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Nursing home-associated pneumonia, hospital-acquired pneumonia and ventilator-associated pneumonia: the contribution of dental biofilms and periodontal inflammation

Krishnan Raghavendran, Joseph M. Mylotte, and Frank A. Scannapieco

Evidence is building that dental plaque and inflammatory periodontal disease may contribute to the initiation and/or progression of certain lung diseases. Pneumonia is an acute infection of the lung, demonstrating the following respiratory signs and symptoms: cough; shortness of breath; increased respiratory rate; sputum production; and chest pain. Pneumonia may also induce nonspecific systemic symptoms, including fever, fatigue, muscle aches, and lack of appetite. Although pneumonia can be caused by viruses or fungi, bacteria are the most frequent cause of this infection and are the most easily treatable.

Pneumonia often affects individuals with impaired host defense systems, for example, conditions with defects in antibody production, phagocytosis, ciliary function, or reduced CD4⁺ T-lymphocyte counts, as seen in acquired immunodeficiency syndrome (AIDS) (7). Other underlying respiratory diseases, such as chronic obstructive pulmonary disease, can also lead to pneumonia.

Community-acquired pneumonia is defined as infection occurring in any individual living in the community (7). The annual cost for the treatment of community-acquired pneumonia exceeds \$9 billion and affects 4 million adults per year in the USA, *c.* 20% of whom are admitted to a hospital for treatment. The rate of pneumonia ranges from 8 to 15 per 1000 persons per year, with infants and the elderly having the greatest risk for infection. Rates of pneumonia are higher for men than for women and for black people than for white people. Risk factors for community-acquired pneumonia include alcoholism, asthma, immunosuppression, and age >70 years. Dementia, seizures, congestive heart failure, cerebrovascular disease, tobacco smoking, alcoholism, and chronic obstructive pulmonary disease are risk factors for pneumococcal pneumonia, the most common cause of community-acquired pneumonia.

Evidence is building that an unhygienic oral environment and resulting oral diseases, such as inflammatory gingivitis and periodontitis, can negatively affect systemic health. A straightforward connection between the oral cavity and a specific systemic disease is that between dental plaque, periodontal disease, and lung disease. Accumulating evidence suggests that poor oral health may influence lung function and increase the risk for bacterial lung infection (pneumonia), especially in high-risk patient populations. Three populations for developing pneumonia are the focus of this review: nursing home residents; people hospitalized with acute illness; and those hospitalized who require mechanical ventilation as a result of respiratory failure.

In the past decade there has been an evolution in the classification of pneumonia. Previously, pneumonia was classified as either community acquired or hospital acquired. Hospital-acquired pneumonia was defined as pneumonia occurring with onset >48 hours after admission to hospital. This classification scheme was straightforward and easy to apply. However, in the past decade the classification scheme has evolved, relating to the shift of care for various conditions from the hospital to the outpatient setting for delivery of services such as antibiotic therapy, cancer chemotherapy, wound management, outpatient dialysis centers, and short-term rehabilitation. This shift in care from the hospital to the outpatient, home setting or nursing

home gives rise to cases of pneumonia that occur outside the hospital setting, but are clearly related to healthcare environments. Thus, such pneumonia has been referred to as healthcare-associated pneumonia (83).

Nursing-home associated pneumonia is the most important of the common infections affecting nursing home residents because of the high morbidity and mortality associated with this infection (58). Pneumonia is also a common reason for transfer of residents from the nursing home to the hospital (55). Hospital-acquired pneumonia and ventilator-associated pneumonia are amongst the most common infections in the hospital and are together a major cause of morbidity, mortality, extended length of stay and excessive cost in this setting.

This article provides an update on present thinking regarding the pathogenesis, epidemiology, risk factors, microbial etiology, diagnosis, and treatment of nursing home-associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia. This is followed by a discussion of the role of poor oral health as a risk factor for these diseases. Finally, questions awaiting answers regarding the role of oral health status and pneumonia are posed.

An overview of nursing home-associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia

Pathogenesis

The pathogenesis of pneumonia depends on the micro-aspiration of oropharyngeal secretions containing bacteria into the lung, and the failure of host defenses to clear the bacteria, which results in a destructive host response and the development of lung infection (85). In the case of ventilator-associated pneumonia, the risk for pneumonia is increased by the presence of a foreign device, such as an endotracheal tube, extending through the trachea into the lower airway and bypassing major impediments to aspiration such as the glottis and the larynx. The seeding of oropharyngeal organisms into the trachea may occur during passage of the tube. In addition, bacteria adhere to the surface of the endotracheal tube, resulting in the growth of a bacterial biofilm that seeds detached bacteria into the lower airway and that is resistant to host defenses and antibiotics (10). The biofilm can also become dislodged and embolize distally to set up foci of infection. The endotracheal tube itself may also facilitate infection by acting as a conduit that bypasses the mucociliary 'blanket', and pooling of secretions around the cuff of the tube can provide an incubator for pathogenic bacteria (10).

In the nursing home population, there are two other disease entities that need to be considered: aspiration pneumonia and aspiration pneumonitis. Aspiration pneumonia is defined as the development of an infiltrate, observed on a chest radiograph, in a person with an increased risk for oropharyngeal aspiration, usually caused by underlying dysphagia (48). Residents at risk for aspiration pneumonia include those with dysphagia secondary to a stroke, often involving the basal ganglia, Parkinson's disease, or dementia (89). However, other factors, such as gastro-esophageal reflux or the presence of a nasogastric feeding tube, also increase the risk of aspiration of oropharyngeal contents (48). The oropharyngeal material that is aspirated includes many species of bacteria and saliva. Saliva itself is a complex mixture of bacteria and of bacterial and host products, including diverse enzymes, cytokines, and other biologically active products (65). As previously discussed (74), several potential mechanisms can be envisioned for oral bacteria and saliva in the pathogenesis of respiratory infection. For example, oral pathogens (such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, etc.), which are abundant in subjects with poor oral hygiene and periodontal disease, can be directly aspirated into the lung to cause disease. In fact, such a polymicrobial inoculum appears to be more pathogenic than individual microbial species alone (36). In addition, periodontal disease-

associated enzyme-laden saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens (74). Cytokines originating from periodontal tissues may promote inflammation of the lower airway following aspiration, and thus alter the respiratory epithelium to promote infection by respiratory pathogens.

In light of this discussion, it seems that the degree of oropharyngeal bacterial colonization and oral inflammation at the time of aspiration may be important factors influencing the development of pneumonia (48). It is postulated that the oral hygiene and periodontal status of these subjects impact the burden and quality of the bacterial flora in the mouth (80), and this relationship will be explored in more detail below.

In contrast to pneumonia, aspiration pneumonitis is broadly defined as acute lung injury after inhalation of regurgitated gastric contents, and it most commonly occurs in people with marked disturbance of consciousness, such as occurs after a drug overdose, seizure, stroke, or general anesthesia (48). However, there is evidence that nursing home residents with dementia and dysphagia, Parkinson's disease, or a feeding tube are also at risk for gastric content aspiration and pneumonitis (67). A common fallacy is that gastric content aspiration has to be witnessed to make a diagnosis of aspiration. In a prospective study of residents in one facility, the use of definitions of witnessed and unwitnessed gastric content aspiration revealed that the incidence was 1.6 episodes per 1000 resident care days over an 8-month study period; only 40% of the 98 aspiration events were witnessed (67). For 54 aspiration events a chest radiograph was performed, and 70% had an infiltrate. Gastric contents do not often contain a large burden of bacteria and therefore when aspiration occurs there is no bacterial infection initially and antibiotic therapy is not required (48). Nevertheless, aspiration of acid, food, or acid plus particulates, results in an acute inflammatory process in the tracheobronchial tree and lung that is mediated by neutrophils (48). The acute inflammatory process in the lung often results in an infiltrate that, when observed on a chest radiograph, is indistinguishable from an infiltrate caused by bacterial infection. A recent study of the epidemiology of aspiration pneumonitis and pneumonia in nursing home residents admitted to the hospital with suspected pneumonia (59,60) found evidence of gastric content aspiration in a substantial proportion of episodes of suspected pneumonia. This suggests that aspiration pneumonitis is much more common than previously recognized in nursing home residents and is frequently misclassified as pneumonia and treated with antibiotics. The importance of these observations is that if one accurately makes the clinical distinction between pneumonitis and pneumonia, there is the potential to reduce the use of antibiotics, because, in the majority of patients, those with pneumonitis do not have bacterial infection.

Epidemiology and risk factors

Nursing home-associated pneumonia—The incidence of nursing home-associated pneumonia varies from 0.3 to 2.3 episodes per 1000 resident care days (58). The variation in incidence is related to differences in multiple methodological approaches used in the various studies, including differences in study design, the number of facilities evaluated (one vs. multiple), intensity of surveillance, and facility affiliation (U.S. Veterans Affairs vs. community nursing homes). There are only two prospective studies of nursing home-associated pneumonia, and in those the incidence was reported to be 1 per 1000 resident care days (33) and 0.7 per 1000 resident care days (43).

Several studies have identified, using multivariate analysis, risk factors for nursing home-associated pneumonia. Among factors found to be associated with pneumonia risk are poor functional status (2,29), presence of a nasogastric tube (2), dysphagia (29,43), occurrence of an unusual event (such as new or increased confusion, agitation, falls, or wandering) (29), chronic lung disease (45), presence of a tracheostomy (45), increasing age (43), and male gender (43). Therefore, it would appear that it is debilitated residents, especially those with a

high risk for aspiration, who are at greatest risk for developing pneumonia. Interestingly, a recent study sought to identify modifiable risk factors for pneumonia in elderly residents of nursing homes (70). Among the candidate risk factors that were evaluated as covariates (i.e. nursing home facility, age, race, co-existing conditions, and immobility), only inadequate oral care and swallowing difficulty were statistically associated with pneumonia.

The case-fatality rate for nursing home residents admitted to hospital with pneumonia has been found to range from 13% to 41%, whereas for those treated in the nursing home the case-fatality rate has been found to range from 7% to 19% (43,49,54,62). Risk factors for mortality have included pre-pneumonia functional status in several studies (54), dementia (62), increased respiratory rate (49,62), increased pulse rate (62), change in mental status (62), witnessed aspiration (86), and use of sedatives (86). Two research groups have defined models for predicting the mortality of nursing home residents with pneumonia. Naughton et al. (62) derived a model for predicting 30-day mortality in residents with nursing home-associated pneumonia, which included the following components: respiratory rate >30 breaths per minute; pulse rate >125 beats per minute; acute change in mental status; and history of dementia. The probability of death among residents with two or more predictors at the onset of nursing home-associated pneumonia was >30%. Other models for predicting mortality in residents with lower respiratory tract infection may also be useful, but require diagnostic testing (50,51).

Hospital-acquired pneumonia and ventilator-associated pneumonia—Pulmonary complications, including various forms of pneumonia, are common in the postoperative period and affect a substantial fraction of patients following surgery with general anesthesia. Ventilator-associated pneumonia is the second most common hospital-acquired infection (4, 71). Ventilator-associated pneumonia is a leading cause of death in critically ill patients in the intensive care unit, with estimated prevalence rates of 10–65% and mortality rates of 25–60%, depending on the study, the patient population, and the medical/surgical conditions involved (9,12,14,15,37,39,87). Ventilator-associated pneumonia and other forms of hospital-acquired pneumonia are independent risk factors for mortality in hospitalized patients, irrespective of the severity and type of underlying illness (22). An episode of hospital-acquired pneumonia adds c. 5–6 days to the length of hospital stay and thousands of dollars in cost to medical care (9,12,14,15,37,39). The risk of developing ventilator-associated pneumonia in the medical and surgical intensive care unit varies from 5 to 21 per 1000 ventilator days (44).

The risk of ventilator-associated pneumonia, or other forms of hospital-acquired pneumonia, is greatly increased by anesthesia and surgery. In one study carried out by the U.S. Centers for Disease Control and Prevention (10), 75% of patients with bacterial pneumonia became infected following surgery. A number of risk factors have important implications for the peri-operative period. Of principal concern is the association of pneumonia with the placement of an endotracheal tube and mechanical ventilation. The incidence of respiratory tract infections in patients requiring an endotracheal tube is substantial, and the risk of acquiring ventilator-associated pneumonia increases by as much as 1–5% per hospital day (11).

The endotracheal tube provides an inert, nonshedding surface to which bacteria adhere and grow to form biofilms, from which bacteria are shed and aspirated into the lower airway. Furthermore, the endotracheal tube induces mechanical abrasion, irritation of the respiratory mucosa, impairment of normal laryngeal function and increased sedation, all of which lead to an increased risk of aspiration of upper respiratory tract secretions. Bacterial flora and/or gastric contents may also be important in the pathogenesis of postoperative pneumonia (15,38). Although ventilators alone are not considered to be an important source of bacterial spread, breathing circuits can become heavily contaminated with microorganisms from the patients' oropharynx and trachea (13).

A number of additional risk factors for the development of pneumonia in the hospital intensive care setting have also been identified (10,37,38). These include patient age >70 years, altered mental status (in particular, closed-head injuries with placement of intracranial pressure monitors), thoracoabdominal procedures, underlying chronic lung disease, history of large-volume aspiration, trauma, peri-operative use of antibiotics, supine position, the use of neuromuscular paralysis, and obesity. Other factors include 24-hour ventilator circuit changes, acute respiratory distress syndrome, contaminated anesthesia or respiratory therapy equipment, and recent bronchoscopy (10,39). Of relevance to the present article, the oral microflora may also contribute to the pathogenesis of pneumonia.

Microbial etiology

Nursing home-associated pneumonia—The microbial etiology of nursing home-associated pneumonia is probably the most controversial issue related to this infection. The main controversy is the role of gram-negative aerobic rods and *Staphylococcus aureus* as causative agents of nursing home-associated pneumonia. Muder (54) found that when strict criteria were used to evaluate the degree of contamination of a sputum culture specimen by oropharyngeal material in those with nursing home-associated pneumonia, gram-negative bacilli were isolated in only 0–12% of episodes. When less strict or no criteria were used to evaluate contamination of the sputum specimen, gram-negative bacilli were isolated in 9–55% of episodes. The presence of gram-negative bacilli in the sputum cultures of residents with pneumonia was a major factor influencing the inclusion of nursing home-associated pneumonia in the category of healthcare-associated pneumonia (83). For example, in a study of nursing home residents with pneumonia who were intubated and placed on mechanical ventilation and had quantitative bronchoalveolar lavage cultures, the most commonly isolated organisms were *S. aureus* (29%), enteric gram-negative rods (15%), *Streptococcus pneumoniae* (9%), and *Pseudomonas* species (4%) (19). A study of 95 episodes of severe aspiration pneumonia in nursing home residents who were mechanically ventilated by the same research group (20) found that the most commonly isolated organisms were gram-negative enteric bacilli (49%) and *S. aureus* (12%). However, the most interesting finding in this latter study was that in 41 (43%) of the 95 cases, the cultures were sterile. The group with sterile cultures may represent episodes of gastric content aspiration and severe aspiration pneumonitis rather than bacterial pneumonia. Alternatively, these cases may be pneumonia caused by as-yet unculturable organisms. In this regard, it is now evident from studies that utilize molecular techniques not requiring microbial culture that a substantial proportion of the endogenous human microbial flora is unculturable and novel (18,42,66). In any case, these studies suggest that gram-negative rods and *S. aureus* are a frequent cause of severe pneumonia in nursing home residents requiring mechanical ventilation. However, residents with pneumonia who are mechanically ventilated represent <5% of all residents with pneumonia.

The etiology of pneumonia among long-term care residents who are not mechanically ventilated continues to be a matter of debate. In this latter group, *S. pneumoniae* may be the most common bacterial pathogen, followed by nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis* (58). Atypical bacteria, such as *Legionella* species, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, rarely cause pneumonia in nursing home residents. The role of viruses as a cause of sporadic cases of pneumonia in nursing home residents is unclear.

Hospital-acquired pneumonia and ventilator-associated pneumonia—

Approximately 60% of cases of hospital-acquired pneumonia are caused by aerobic gram-negative bacteria, in particular, the *Enterobacteriaceae* and *Pseudomonas* species (10). *S. aureus* (10–20% of infections) and *S. pneumoniae* (3–8% of infections) are also important nosocomial bacterial pathogens (41). A significant percentage of cases of ventilator-associated

pneumonia occurring in the peri-operative period are associated with gastric aspiration events and have a bacteriological spectrum that includes *H. influenzae*, *S. pneumoniae*, and methicillin-sensitive *S. aureus* (40,48). The prognosis associated with gram-negative bacteria, particularly *Pseudomonas*, is considerably worse than that associated with gram-positive bacteria which, in turn, is greater again than that associated with viral pneumonia (40). Interestingly, although rare, *Legionella* spp. in some hospitals may cause over 30% of lower respiratory tract infections. Older and immunocompromised patients have a high mortality rate from pneumonias related to this organism (Legionnaire's disease) (10).

Diagnosis

Nursing home-associated pneumonia—The dogma has been that nursing home residents with pneumonia have an 'atypical' presentation, meaning that respiratory symptoms (cough, shortness of breath, pleuritic chest pain, chills) and signs (fever, tachypnea, rales on chest examination) occur less frequently than among age-matched community-dwelling elderly or younger people (58). In a recent study of 378 episodes of nursing home-associated pneumonia occurring among residents of 11 nursing homes, the findings were as follows: fever, 70%; respiratory rate >30 per minute, 23%; pulse >125 per minute, 6%; cough, 61%; and altered mental status, 38% (62). Nonspecific symptoms (e.g. generalized weakness, loss of appetite, falls, delirium, and new or worsening incontinence) were more common presentations of pneumonia in the elderly compared with those <65 years of age; however, this difference was found to be the result of a confounding effect of dementia in the elderly group (34). Mehr et al. (50) studied clinical characteristics associated with radiographic pneumonia in nursing home residents and found that at least one lower respiratory symptom (cough, sputum production, or pleuritic chest pain) was present in >90% of episodes, but none of these was useful as a predictor of pneumonia compared with a respiratory rate of ≥ 30 breaths per minute or the presence of localized crackles on lung auscultation. In a case-control study, a single oxygen saturation of <94% breathing room air had a positive predictive value of 95% for pneumonia in nursing home residents (35). Criteria for the diagnosis of 'probable' pneumonia have been developed by a consensus group and are as follows (31). Pneumonia should be considered a possible diagnosis if two or more of the following signs or symptoms are present: new onset of cough, with or without sputum production; fever (rectal temperature 37.7°C), complaints of shortness of breath, respiratory rate ≥ 25 breaths per minute; heart rate ≥ 100 beats per minute; hypoxemia (oxygen saturation <94% breathing room air); acute change in cognitive or functional status; or localized congestion (rales/ronchi) on chest auscultation. In summary, the diagnosis of pneumonia in nursing home residents will be facilitated if one carefully evaluates residents for signs and symptoms related to the respiratory tract, including respiratory rate, presence of hypoxemia, and auscultatory findings on chest examination.

Hospital-acquired pneumonia and ventilator-associated pneumonia—Although many hospital-acquired pneumonias are polymicrobial in nature, no infectious agent can be identified as the etiologic source in c. 20–30% of cases. Because of the difficulty in diagnosing hospital-acquired pneumonia, guidelines have been formulated that include techniques such as bronchoalveolar lavage and quantitative culture of protected-specimen brushing (41). In addition, a clinical pulmonary infection score is often used to identify patients who require further evaluation for hospital-acquired pneumonia/ventilator-associated pneumonia. The clinical pulmonary infection score takes into account arterial oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio), body temperature (fever), the nature of tracheal secretions, the degree of leukocytosis, and evidence of infiltrates on chest radiography (41). A recent modification of this score is outlined in Table 1. One approach (followed at our institution) is to perform clinical pulmonary infection score evaluations on a daily basis, and if the score reaches 6, a bronchoalveolar lavage (mini-bronchoalveolar lavage) is performed for culture (41). A quantitative culture of lavage fluid

that yields $>10^4$ colony-forming units per ml is considered conclusive evidence of ventilator-associated pneumonia.

Relation of hospital-acquired pneumonia to lung injury syndromes (acute lung injury/acute respiratory distress syndrome)—When ventilator-associated pneumonia or other hospital-acquired pneumonia lead to acute respiratory failure, the functional consequences are frequently defined as clinical acute lung injury or the acute respiratory distress syndrome. Acute lung injury/acute respiratory distress syndrome can occur in patients of all ages, and may arise from multiple direct and indirect etiologies, including not only pulmonary infection but also gastric aspiration, systemic sepsis, hypovolemic shock, chest trauma, head injury, and many others (6,23,57,72,88). Acute lung injury/acute respiratory distress syndrome frequently show multiorgan pathology, but are diagnosed by criteria relating to acute respiratory failure that include acute onset, impaired arterial oxygenation (a $\text{PaO}_2/\text{FiO}_2$ of ≤ 300 mmHg for acute lung injury and ≤ 200 mmHg for acute respiratory distress syndrome, regardless of positive end-expiratory pressure), the presence of bilateral infiltrates on frontal chest radiograph, and pulmonary artery occlusion pressure of ≤ 18 mmHg or no clinical evidence of left atrial hypertension (6). Clinical acute lung injury/acute respiratory distress syndrome include not only acute respiratory failure, but may progress to a ‘fibroproliferative’ phase that involves chronic lung injury with tissue remodeling and the initiation of fibrosis (23,57). Current treatments for acute lung injury/acute respiratory distress syndrome include mechanical ventilation with low tidal volumes and positive end-expiratory pressure, increased concentrations of inspired oxygen, and antibiotic therapy, as indicated. There is, however, a pressing need to develop more specific diagnostic and management paradigms, and improved therapeutic interventions.

Treatment

Nursing home-associated pneumonia—The optimum antibiotic regimen (antibiotic, dose, duration of therapy) for nursing home-associated pneumonia is not known. Few clinical trials have evaluated the treatment of nursing home-associated pneumonia. Thus, treatment recommendations are based on clinical experience (61) or expert opinion in the form of guidelines.

In 2000, the first specific guideline for the treatment of nursing home-associated pneumonia, based on a review of community practice in one region, was published (61). The investigators found that a wide range of oral agents was prescribed for the treatment of nursing home-associated pneumonia in the nursing home setting and there was no clear consensus among practicing physicians as to what agent should be prescribed. Likewise, in the hospital setting, several different regimens were prescribed. The Canadian Infectious Diseases Society published a community-acquired pneumonia treatment guideline (46) that included specific recommendations for nursing home-associated pneumonia. This guideline recommended an oral respiratory quinolone (levofloxacin, gatifloxacin, or moxifloxacin) alone, or amoxicillin/clavulanate plus a macrolide, as the first choice for treatment of nursing home-associated pneumonia in the nursing home, and for treatment in the hospital a respiratory quinolone alone was the first choice and the second choice was a second- or third-generation cephalosporin plus a macrolide. The Infectious Diseases Society of America updated a previous guideline and made recommendations for treatment of nursing home-associated pneumonia that were similar to the Canadian guideline (47). More recently, the American Thoracic Society and the Infectious Diseases Society of America have collaborated on a guideline for hospital-acquired, ventilator-associated, and healthcare-associated pneumonia (63). In this guideline, nursing home-associated pneumonia is included in the healthcare-associated pneumonia group. As previously discussed, the rationale for this grouping appears to be the results of invasive diagnostic testing in the small group of residents with pneumonia who are intubated and in

whom *S. aureus* and enteric gram-negative bacilli were the most commonly isolated pathogens (19,20). However, there are few data about the bacteriology of healthcare-associated pneumonia in those who are not mechanically ventilated, which includes >90% of nursing home residents with pneumonia. Therefore, the appropriateness of recommending antibiotic treatment for nursing home-associated pneumonia, based on the findings of a small group of residents who are severely ill with pneumonia, is unclear. Until randomized trials are performed to provide guidance, the most logical and simple approach is to use a respiratory quinolone (levofloxacin, gatifloxacin, or moxifloxacin) as initial therapy for nursing home-associated pneumonia. The respiratory quinolones provide excellent coverage for the common bacterial pathogens causing nursing home-associated pneumonia, in addition to once-a-day treatment (and therefore better compliance) and a low side-effect profile.

Hospital-acquired pneumonia and ventilator-associated pneumonia—Like nursing home-associated pneumonia, there is no ‘gold standard’ in place to treat hospital-acquired pneumonia/ventilator-associated pneumonia. Over the last decade, several clinical studies have outlined important issues for treatment. Early administration of appropriate antibiotics affect mortality, morbidity, and cost (32). The intensivist may not get a second chance to get it right. Delays in treatment, or treatment with inappropriate antibiotics, lead to increased morbidity and mortality. The institution of broad-spectrum antibiotics, followed by the appropriate use of organism-specific antibiotics, once the organism is identified, is the approach in use in most intensive care units. The bacteriological spectrum varies from one intensive care unit to another. Additionally, the use of prior antibiotic therapy and the time of onset of ventilator-associated pneumonia (early vs. late) dictate the antibiotic regimen employed. For example, for early onset ventilator-associated pneumonia with no prior history of antibiotic usage, a cephalosporin (e.g. ceftriaxone or cefotaxime) or a fluoroquinolone is preferred. For late-onset ventilator-associated pneumonia, an antipseudomonad cephalosporin (e.g. ceftazidime or cefipime), an antipseudomonad penicillin (e.g. piperacillin), carbapenem (e.g. imipenem or meropenem) or aztreonam combined with an aminoglycoside, with or without methicillin-resistant *S. aureus* coverage (e.g. vancomycin or Linezolid, especially if there are gram-positive cocci identified in the sputum Gram stain), appears to be an appropriate combination regimen (64). Overuse or unnecessary use of broad-spectrum antibiotics leads to microbial resistance, increased infection rates, and possibly increased morbidity and mortality. Hence, timely and accurate clinical and microbiological diagnoses are of paramount importance.

Traditionally, the duration of antibiotic therapy can vary from 7 to 15 days. Recent reports have argued for shorter durations of treatment (8,79). Unnecessarily prolonged treatment with antibiotics may promote resistance, superinfection and toxicity, and might increase overall infection rates. Another issue of importance is the recommended rotation of empiric antibiotics. Studies have indicated that antibiotic rotation results in a reduced emergence of resistant pathogens (28). However, it is arguable that this approach may lead to an overall decline in the rate of ventilator-associated pneumonia.

Understanding the pharmacokinetic and pharmacodynamic issues related to antibiotics is also an important issue. The concept of concentration-dependent vs. time-dependent killers, and the avoidance of excessive reduction in the dose related to renal function, are important. Additionally, it is necessary that a high plasma concentration of vancomycin be achieved.

Oral respiratory pathogen colonization of hospitalized, intensive care and nursing-home subjects

As mentioned above, the oral cavity is proximal and contiguous with the trachea and therefore a logical portal for respiratory pathogen colonization. We began to investigate the association of oral health status and oral respiratory pathogen colonization by comparing oral hygiene and parameters of dental plaque and/or buccal mucosal colonization by potential respiratory pathogens in intensive care unit subjects with age- and gender-matched outpatients upon their initial visit to a dental school clinic (76). Dental plaque scores were statistically significantly higher in the intensive care unit patients than in the dental subjects. Furthermore, potential respiratory pathogens were prevalent and abundant on the teeth and/or buccal mucosa of the intensive care unit patients, 65% of whom were colonized at these sites compared with only 16% of ambulatory dental patients colonized at the same sites ($P < 0.005$). The potential respiratory pathogens identified in the oral flora of intensive care unit patients included *S. aureus*, *Pseudomonas aeruginosa*, and a number of enteric species. Several patients had oropharyngeal colonization by two or more potential pathogens, and in some cases the pathogen comprised up to 100% of the culturable aerobic flora. Oral colonization by respiratory pathogens was also statistically associated with antibiotic usage.

A number of other studies have verified that the teeth and other oral surfaces of intensive care unit subjects serve as reservoirs of respiratory pathogen colonization. It has been reported that the relative risk for pneumonia is increased by 9.6-fold when the dental plaque is colonized by a potential respiratory pathogen between days 0 and 5 following intensive care unit admission. In some cases, the pathogen causing pneumonia appeared to first colonize the dental plaque (24).

A recent study assessed dental plaque as a reservoir of respiratory pathogen colonization in hospitalized patients with chronic lung diseases (17). Using a checkerboard DNA–DNA hybridization technique to determine the prevalence of eight respiratory pathogens and eight oral pathogens, species such as *S. aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter cloacae* were detected in dental plaque from 29 of the 34 (85.3%) hospitalized patients, whereas only 12 of 31 (38.7%) nonhospitalized subjects were colonized. These results indicate that dental plaque may serve as a reservoir of infection in hospital patients with chronic lung diseases.

A number of other studies have examined geriatric and nursing home subjects regarding oral hygiene status and oral colonization by potential respiratory pathogens. The literature suggests that respiratory pathogens preferentially colonize the teeth or dentures, rather than soft tissues (53,81,82,84). Diminished salivation and salivary pH may also promote oral colonization by respiratory pathogens; these conditions occur in ill patients and in those receiving various medications (84). One study found that the dental plaque of 43% of elderly patients, recently admitted to a hospital, was colonized by gram-negative pathogens (68). Studies of chronic care nursing-home residents found that the dental plaque scores were significantly higher in the nursing-home residents than in the outpatient controls, and that 14.3% of chronic care subjects showed dental plaque colonization with respiratory pathogens compared to 0% of the control dental outpatients (73). More recently, the relationship among oral hygiene status, the number of oral bacteria in saliva, and pneumonia experience was explored in 145 Japanese nursing home subjects (1). Dentate patients with poor oral hygiene showed significantly higher salivary bacterial counts than those with good oral hygiene. Interestingly, the number of febrile days was significantly higher, and the number of patients developing pneumonia more numerous, in dentate patients with poor oral hygiene.

Evidence has also been presented that demonstrates the genetic identity of respiratory pathogen isolates recovered from the bronchoalveolar lavage fluid of hospitalized institutionalized elderly individuals and isolates from the dental plaques of the same patients (21). These results confirm that dental plaque serves as an important reservoir of respiratory pathogens in this patient cohort.

Oral care in the prevention of nursing home-associated pneumonia, ventilator-associated pneumonia and hospital-acquired pneumonia

The application of appropriate preventive measures, combined with mandatory education programs, are helpful in reducing the incidence of pneumonia in institutionalized patients (11). Measures that have been reported to be helpful in reducing the incidence of ventilator-associated pneumonia are listed in Table 2 (39). Regardless of whether nosocomial infections are pulmonary or extrapulmonary in location, their control in a hospital setting emphasizes the interruption of the infectious cycle. The use of barrier precautions, attention to aseptic technique, and strict compliance with infection control practices (such as hand washing and sterilization or disinfection of equipment) are essential in denying a portal of entry for pathogenic microorganisms. Once infection occurs, recognition of the interactions among surgery/anesthesia, immunology, and inflammation becomes crucial for optimizing patient management and long-term outcomes.

As detailed above, and as recently reviewed (27,52,56,74,75,77), the oral cavity probably serves as an important reservoir for the growth of respiratory pathogens in patients admitted to hospital intensive care units and in the elderly who are debilitated, hospitalized, or living in a nursing home. Inpatients of hospitals and nursing homes often have poorer oral hygiene than community-dwelling individuals, and poor oral hygiene and periodontal inflammation may foster oropharyngeal colonization with respiratory pathogens. These findings suggest that oral hygiene interventions may reduce the rate of oral colonization by respiratory pathogens and, subsequently, the risk for pneumonia in these special patient populations.

Several trials have evaluated the effectiveness of oral decontamination to prevent pneumonia [reviewed in (77)]. Most of these trials, while varying in setting (intensive care unit, nursing homes), design, and in intervention (including topical application of nonabsorbable antibiotics, antiseptics such as chlorhexidine gluconate rinse, and mechanical debridement, e.g. tooth brushing), showed reductions in oral colonization by respiratory pathogens and/or incidence of pneumonia. An analysis of the combined data from five controlled oral hygiene intervention trials was performed (5,16,25,69,90). In all cases the intervention reduced the rate of pneumonia in these populations by *c.* 40%. Thus, oral decontamination appears to hold promise in reducing the carriage of respiratory pathogens on the oropharynx and thus the rate of pneumonia in the high-risk populations.

Since the published systematic review of 2003, several recently reported studies have also addressed this issue. A prospective, randomized, case-controlled clinical trial tested the effectiveness of 0.12% chlorhexidine gluconate oral rinse in decreasing microbial colonization of the respiratory tract and hospital-acquired pneumonia in patients undergoing open heart surgery (30). The results showed that the overall rate of hospital-acquired pneumonia was reduced by 52% (4/270 vs. 9/291; $P = 0.21$) in chlorhexidine gluconate-treated patients when compared to patients treated with Listerine™. In patients at highest risk for pneumonia (intubated for >24 hours, with cultures showing the most growth), the rate was 71% lower in the chlorhexidine gluconate group than in the Listerine group (2/10 vs. 7/10; $P = 0.02$).

Another prospective, multicenter, double-blind, placebo-controlled trial assessed the efficacy of 0.2% chlorhexidine gluconate topical gel against a placebo gel to prevent pneumonia in 228

nonedentulous patients requiring endotracheal intubation and mechanical ventilation, with an anticipated length of stay of ≥ 5 days (26). The active gel or placebo was placed at the gingival margin three times a day for the entire intensive care unit stay. No difference was observed in the incidence of nosocomial bacteremia, bronchitis, or in ventilator-associated pneumonia per ventilator or intubation days, mortality, or length of stay. However, on day 10, the number of dental plaque cultures positive for a target respiratory pathogen was significantly lower in the treated group (29% vs. 66%; $P < 0.05$). While it would appear that these results counter the efficacy of topical oral chlorhexidine gluconate to prevent ventilator-associated pneumonia in this cohort, several caveats must be considered. First, the group size of this study may have been insufficient to detect an effect of the intervention. Second, a significant number of subjects entered into the trial already had a diagnosis of pneumonia or other lung disease. Third, the population entered into the study was very heterogeneous with respect to underlying illness. It seems that these factors would together diminish the possibility that the simple oral intervention would show an effect in reducing pneumonia. Additional large-scale multicenter trials are therefore necessary to answer this question.

Heightened interest in the possibility that improved oral hygiene could prevent ventilator-associated pneumonia has resulted in recognition of oral care as a possible modifiable risk factor for ventilator-associated pneumonia by the U.S. Centers for Disease Control and Prevention (83) and the American Thoracic Society and the Infectious Disease Society of America (3). Some hospitals have implemented formal, organized oral care programs to reduce ventilator-associated pneumonia in high-risk subjects. For example, a retrospective study reported on the impact of implementation of such a program, which involved nurse-administered tooth brushing every 2–4 hours, swabbing with an alcohol-free antiseptic oral rinse, frequent suctioning of oral and pharyngeal secretions, and application of a water-based mouth moisturizer, on ventilator-associated pneumonia-intensive care unit rates (78). The results showed that the ventilator-associated pneumonia rate decreased by 3.4 per 1000 ventilator days (from 9.9 per 1100 ventilator days) following institution of this program, resulting in estimated cost savings of c. \$30,000 per ventilator-associated pneumonia.

Unanswered questions

While progress has been made in understanding the role of dental biofilms and oral health as risk factors for pneumonia, many questions remain to be answered. As a means to stimulate further research in this field, the following questions are offered that deserve rigorous study.

- (1) What is the minimal oral intervention required to reduce the risk for pneumonia? Is a simple oral antiseptic rinse sufficient, or is mechanical disruption of oral biofilms (by tooth brushing) also required to maximize prevention of oral colonization by respiratory pathogens? Is a single daily rinse sufficient, or are multiple rinses required? Which topical antiseptic is most effective in reducing colonization by respiratory pathogens. Indeed, several studies, described above, found that topical oral disinfection may not be sufficient to reduce pathogen colonization below the threshold necessary to prevent disease onset. This could be a result of the fact that the pathogens within the oral biofilms are resistant to the disinfectant. Thus, mechanical debridement may be required to reduce or eliminate the pathogen from the oral cavity and hence reduce risk.
- (2) Must the dental plaque biofilm be completely removed (for example by tooth scaling) to minimize respiratory pathogen colonization? It is well known that biofilms are resistant to antimicrobial agents, and it is possible that respiratory pathogens that emerge in the biofilm ecology would escape killing by such agents, thus requiring physical removal of the biofilm.

- (3) Is oral inflammation itself (e.g. gingivitis, periodontitis, mucositis), and the resulting products released into the secretions (proteases, cytokines), risk factors for respiratory pathogen colonization and pneumonia initiation? It is clear that oral inflammatory diseases, such as gingivitis and periodontitis, release bioactive molecules, such as cytokines and proteases, from the periodontal tissues into the secretions. If aspirated, these molecules may modify the respiratory mucosa in such a way to promote respiratory pathogen adhesion and infection.

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References

1. Abe S, Ishihara K, Adachi M, Okuda K. Oral hygiene evaluation for effective oral care in preventing pneumonia in dentate elderly. *Arch Gerontol Geriatr* 2006;43:53–64. [PubMed: 16271775]
2. Alvarez S, Shell CG, Woolley TW, Berk SL, Smith JK. Nosocomial infections in long-term facilities. *J Gerontol* 1988;43:M9–17. [PubMed: 3121716]
3. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416. [PubMed: 15699079]
4. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med* 2001;135:847–857. [PubMed: 11712875]
5. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van Der Geest S, van Tiel FH, Beysens AJ, de Leeuw PW, Stobberingh EE. Prevention of ventilator-associated pneumonia by oral decontamination. A prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2001;164:382–388. [PubMed: 11500337]
6. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824. [PubMed: 7509706]
7. Braunwald, E.; Fauci, A.; Kasper, D.; Hauser, S.; Longo, D.; Jameson, J. *Harrison's Principles of Internal Medicine*. 16. New York, NY: McGraw-Hill; 2004.
8. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *J Am Med Assoc* 2003;290:2588–2598.
9. Center for Disease Control. National Nosocomial Infections Study Report. Annual Summary. *MMWR* 1984;35:17SS–29SS.
10. Center for Disease Control. Morbidity and Mortality weekly report. 1997;46(RR1):1–79.
11. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;129:433–440. [PubMed: 9735080]
12. Craven DE, Steger KA. Epidemiology of nosocomial pneumonia. New perspectives on an old disease. *Chest* 1995;108(2 Suppl):1S–16S. [PubMed: 7634921]
13. Craven DE, Connolly MG Jr, Lichtenberg DA, Primeau PJ, McCabe WR. Contamination of mechanical ventilators with tubing changes every 24 or 48 hours. *N Engl J Med* 1982;306:1505–1509. [PubMed: 7043269]
14. Craven DE, Barber TW, Steger KA, Montecalvo MA. Nosocomial pneumonia in the 1990s: update of epidemiology and risk factors. *Semin Respir Infect* 1990;5:157–172. [PubMed: 2255802]
15. Craven DE, Steger KA, Barber TW. Preventing nosocomial pneumonia: state of the art and perspectives for the 1990s. *Am J Med* 1991;91:44S–53S. [PubMed: 1928191]
16. DeRiso AJ II, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic

systemic antibiotic use in patients undergoing heart surgery. *Chest* 1996;109:1556–1561. [PubMed: 8769511]

17. Didilescu AC, Skaug N, Marica C, Didilescu C. Respiratory pathogens in dental plaque of hospitalized patients with chronic lung diseases. *Clin Oral Invest* 2005;9:141–147.
18. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. *Science* 2005;308:1635–1638. [PubMed: 15831718]
19. El-Solh AA, Sikka P, Ramadan F, Davies J. Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med* 2001;163:645–651. [PubMed: 11254518]
20. El-Solh AA, Pietrantonio C, Bhat A, Aquilina AT, Okada M, Grover V, Gifford N. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med* 2003;167:1650–1654. [PubMed: 12689848]
21. El-Solh AA, Pietrantonio C, Bhat A, Okada M, Zambon J, Aquilina A, Barbary E. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. *Chest* 2004;126:1575–1582. [PubMed: 15539730]
22. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993;94:281–288. [PubMed: 8452152]
23. Fauci, AS.; Braunwald, E.; Isselbacher, KJ.; Martin, JB.; Kasper, DL.; Hauser, SL.; Longo, DL., editors. *Harrison's principles of internal medicine*. 15. New York: McGraw-Hill; 2001.
24. Fourrier F, Duvivier B, Boutigny H, Roussel-Delvallez M, Chopin C. Colonization of dental plaque: a source of nosocomial infections in intensive care unit patients. *Crit Care Med* 1998;26:301–308. [PubMed: 9468169]
25. Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. *Intensive Care Med* 2000;26:1239–1247. [PubMed: 11089748]
26. Fourrier F, Dubois D, Pronnier P, Herbecq P, Leroy O, Desmettre T, Pottier-Cau E, Boutigny H, Di Pompeo C, Durocher A, Roussel-Delvallez M. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. *Crit Care Med* 2005;33:1728–1735. [PubMed: 16096449]
27. Garcia R. A review of the possible role of oral and dental colonization on the occurrence of health care-associated pneumonia: underappreciated risk and a call for interventions. *Am J Infect Control* 2005;33:527–541. [PubMed: 16260328]
28. Gruson D, Hilbert G, Vargas F, Valentino R, Bebear C, Allery A, Bebear C, Gbikpi-Benissan G, Cardinaud JP. Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. *Am J Respir Crit Care Med* 2000;162:837–843. [PubMed: 10988092]
29. Harkness GA, Bentley DW, Roghmann KJ. Risk factors for nosocomial pneumonia in the elderly. *Am J Med* 1990;89:457–463. [PubMed: 2121031]
30. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *Am J Crit Care* 2002;11:567–570. [PubMed: 12425407]
31. Hutt E, Kramer AM. Evidence-based guidelines for management of nursing home-acquired pneumonia. *J Fam Pract* 2002;51:709–716. [PubMed: 12184969]
32. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002;122:262–268. [PubMed: 12114368]
33. Jackson MM, Fierer J, Barrett-Connor E, Fraser D, Klauber MR, Hatch R, Burkhart B, Jones M. Intensive surveillance for infections in a three-year study of nursing home patients. *Am J Epidemiol* 1992;135:685–696. [PubMed: 1580245]
34. Johnson JC, Jayadevappa R, Baccash PD, Taylor L. Non-specific presentation of pneumonia in hospitalized older people: age effect or dementia? *J Am Geriatr Soc* 2000;48:1316–1320. [PubMed: 11037021]

35. Kaye KS, Stalam M, Shershen WE, Kaye D. Utility of pulse oximetry in diagnosing pneumonia in nursing home residents. *Am J Med Sci* 2002;324:237–242. [PubMed: 12449443]
36. Kimizuka R, Kato T, Ishihara K, Okuda K. Mixed infections with *Porphyromonas gingivalis* and *Treponema denticola* cause excessive inflammatory responses in a mouse pneumonia model compared with mono-infections. *Microbes Infect* 2003;5:1357–1362. [PubMed: 14670448]
37. Kollef MH. The identification of ICU-specific outcome predictors: a comparison of medical, surgical, and cardiothoracic ICUs from a single institution. *Heart Lung* 1995;24:60–66. [PubMed: 7706101]
38. Kollef MH. What's new about ventilator-associated pneumonia. *Anesthesiology* 2001;94:551–553. [PubMed: 11379671]
39. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med* 2004;32:1396–1405. [PubMed: 15187525]
40. Kollef MH, Schuster DP. The acute respiratory distress syndrome. *N Engl J Med* 1995;332:27–37. [PubMed: 7646623]
41. Kollef MH, Bock KR, Richards RD, Hearn ML. The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. *Ann Intern Med* 1995;122:743–748. [PubMed: 7717596]
42. Kroes I, Lepp PW, Relman DA. Bacterial diversity within the human subgingival crevice. *Proc Natl Acad Sci USA* 1999;96:14547–14552. [PubMed: 10588742]
43. Loeb M, McGeer A, McArthur M, Walter S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999;159:2058–2064. [PubMed: 10510992]
44. Lynch J, Lama V. Diagnosis and therapy of nosocomial ventilator associated pneumonia. *AFC* 2000;4:19–26.
45. Magaziner J, Tenney JH, DeForge B, Hebel JR, Muncie HL Jr, Warren JW. Prevalence and characteristics of nursing home-acquired infections in the aged. *J Am Geriatr Soc* 1991;39:1071–1078. [PubMed: 1753044]
46. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Summary of Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. *Can Respir J* 2000;7:371–382. [PubMed: 11058205]
47. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immuno-competent adults. *Clin Infect Dis* 2003;37:1405–1433. [PubMed: 14614663]
48. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001;344:665–671. [PubMed: 11228282]
49. Mehr DR, Zweig SC, Kruse RL, Popejoy L, Horman D, Willis D, Doyle ME. Mortality from lower respiratory infection in nursing home residents. A pilot prospective community-based study. *J Fam Pract* 1998;47:298–304. [PubMed: 9789516]
50. Mehr DR, Binder EF, Kruse RL, Zweig SC, Madsen RW, D'Agostino RB. Clinical findings associated with radiographic pneumonia in nursing home residents. *J Fam Pract* 2001;50:931–937. [PubMed: 11711008]
51. Mehr DR, Binder EF, Kruse RL, Zweig SC, Madsen R, Popejoy L, D'Agostino RB. Predicting mortality in nursing home residents with lower respiratory tract infection: The Missouri LRI Study. *J Am Med Assoc* 2001;286:2427–2436.
52. Mojon P. Oral health and respiratory infection. *J Can Dent Assoc* 2002;68:340–345. [PubMed: 12034069]
53. Mojon P, Budtz-Jørgensen E, Michel JP, Limeback H. Oral health and history of respiratory tract infection in frail institutionalised elders. *Gerodontology* 1997;14:9–16. [PubMed: 9610298]
54. Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. *Am J Med* 1998;105:319–330. [PubMed: 9809694]
55. Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. *Am J Med* 1998;105:319–330. [PubMed: 9809694]
56. Munro CL, Grap MJ. Oral health and care in the intensive care unit: state of the science. *Am J Crit Care* 2004;13:25–33. [PubMed: 14735645]discussion 34

57. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720–723. [PubMed: 3202424]
58. Mylotte JM. Nursing home-acquired pneumonia. *Clin Infect Dis* 2002;35:1205–1211. [PubMed: 12410480]
59. Mylotte JM, Goodnough S, Naughton BJ. Pneumonia versus aspiration pneumonitis in nursing home residents: diagnosis and management. *J Am Geriatr Soc* 2003;51:17–23. [PubMed: 12534840]
60. Mylotte JM, Goodnough S, Gould M. Pneumonia versus aspiration pneumonitis in nursing home residents: prospective application of a clinical algorithm. *J Am Geriatr Soc* 2005;53:755–761. [PubMed: 15877549]
61. Naughton BJ, Mylotte JM. Treatment guideline for nursing home-acquired pneumonia based on community practice. *J Am Geriatr Soc* 2000;48:82–88. [PubMed: 10642027]
62. Naughton BJ, Mylotte JM, Tayara A. Outcome of nursing home-acquired pneumonia: derivation and application of a practical model to predict 30 day mortality. *J Am Geriatr Soc* 2000;48:1292–1299. [PubMed: 11037018]
63. Niederman MS, Craven DE. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Crit Care Med* 2005;171:388–416.
64. Ost DE, Hall CS, Joseph G, Ginocchio C, Condon S, Kao E, LaRusso M, Itzla R, Fein AM. Decision analysis of antibiotic and diagnostic strategies in ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2003;168:1060–1067. [PubMed: 12842855]
65. Ozmeric N. Advances in periodontal disease markers. *Clin Chim Acta* 2004;343:1–16. [PubMed: 15115674]
66. Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, Sahasrabudhe A, Dewhirst FE. Bacterial diversity in human subgingival plaque. *J Bacteriol* 2001;183:3770–3783. [PubMed: 11371542]
67. Pick N, McDonald A, Bennett N, Litsche M, Dietsche L, Legerwood R, Spurgas R, LaForce FM. Pulmonary aspiration in a long-term care setting: clinical and laboratory observations and an analysis of risk factors. *J Am Geriatr Soc* 1996;44:763–768. [PubMed: 8675922]
68. Preston AJ, Gosney MA, Noon S, Martin MV. Oral flora of elderly patients following acute medical admission. *Gerontology* 1999;45:49–52. [PubMed: 9852381]
69. Pugin J, Auckenthaler R, Lew DP, Suter PM. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, double-blind clinical trial. *J Am Med Assoc* 1991;265:2704–2710.
70. Quagliarello V, Ginter S, Han L, Van Ness P, Allore H, Tinetti M. Modifiable risk factors for nursing home-acquired pneumonia. *Clin Infect Dis* 2005;40:1–6. [PubMed: 15614684]
71. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med* 1999;27:887–892. [PubMed: 10362409]
72. Rubenfeld GD. Epidemiology of acute lung injury. *Crit Care Med* 2003;31(Suppl):S276–S284. [PubMed: 12682453]
73. Russell SL, Boylan RJ, Kaslick RS, Scannapieco FA, Katz RV. Respiratory pathogen colonization of the dental plaque of institutionalized elders. *Spec Care Dent* 1999;19:1–7.
74. Scannapieco FA. Role of oral bacteria in respiratory infection. *J Periodontol* 1999;70:793–802. [PubMed: 10440642]
75. Scannapieco FA, Mylotte JM. Relationships between periodontal disease and bacterial pneumonia. *J Periodontol* 1996;67:1114–1122. [PubMed: 8910830]
76. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. *Crit Care Med* 1992;20:740–745. [PubMed: 1597025]
77. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Ann Periodontol* 2003;8:54–69. [PubMed: 14971248]
78. Schleder B, Stott K, Lloyd RC. The effect of a comprehensive oral care protocol on patients at risk for ventilator-associated pneumonia. *J Advocate Health Care* 2002;4:27–30.

79. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162:505–511. [PubMed: 10934078]
80. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol* 2000 2005;38:135–187. [PubMed: 15853940]
81. Sumi Y, Miura H, Sunakawa M, Michiwaki Y, Sakagami N. Colonization of denture plaque by respiratory pathogens in dependent elderly. *Gerodontology* 2002;19:25–29. [PubMed: 12164235]
82. Sumi Y, Kagami H, Ohtsuka Y, Kakinoki Y, Haruguchi Y, Miyamoto H. High correlation between the bacterial species in denture plaque and pharyngeal microflora. *Gerodontology* 2003;20:84–87. [PubMed: 14697018]
83. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing healthcare-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53:1–36. [PubMed: 15048056]
84. Terpenning M, Bretz W, Lopatin D, Langmore S, Dominguez B, Loesche W. Bacterial colonization of saliva and plaque in the elderly. *Clin Infect Dis* 1993;16(S):314–316.
85. Verghese A, Berk SL. Bacterial pneumonia in the elderly. *Medicine (Baltimore)* 1983;62:271–285. [PubMed: 6353130]
86. Vergis EN, Brennen C, Wagener M, Muder RR. Pneumonia in long-term care: a prospective case-control study of risk factors and impact on survival. *Arch Intern Med* 2001;161:2378–2381. [PubMed: 11606155]
87. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *J Am Med Assoc* 1995;274:639–644.
88. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342:1334–1348. [PubMed: 10793167]
89. Yamaya M, Yanai M, Ohru T, Arai H, Sasaki H. Interventions to prevent pneumonia among older adults. *J Am Geriatr Soc* 2001;49:85–90. [PubMed: 11207848]
90. Yoneyama T, Yoshida M, Ohru T, Mukaiyama H, Okamoto H, Hoshiba K, Ihara S, Yanagisawa S, Ariumi S, Morita T, Mizuno Y, Ohsawa T, Akagawa Y, Hashimoto K, Sasaki H. Oral care reduces pneumonia in older patients in nursing homes. *J Am Geriatr Soc* 2002;50:430–433. [PubMed: 11943036]

Table 1**Modified Clinical Pulmonary Infection Score**

Temperature (°C) ≥ 36.5 and ≤ 38.4 = 0 point ≥ 38.5 and ≤ 38.9 = 1 point ≥ 39 and ≤ 36 = 2 points
Blood leukocytes (mm³) ≥ 4000 and $\leq 11,000$ = 0 point < 4000 or $> 11,000$ = 1 point + band forms $\geq 50\%$ = add 1 point
Tracheal secretions Absence of tracheal secretions = 0 point Presence of nonpurulent tracheal secretions = 1 point Presence of purulent tracheal secretions = 2 points
Oxygenation: PaO₂/FiO₂, mmHg ≥ 240 or ARDS (ARDS defined as PaO ₂ /FiO ₂ ; or equal to 200, pulmonary arterial wedge pressure) ≤ 18 mmHg and acute bilateral infiltrates = 0 point ≤ 240 and no ARDS = 2 points
Pulmonary radiography No infiltrate = 0 point Diffuse (or patchy) infiltrate = 1 point Localized infiltrate = 2 points
Progression of pulmonary infiltrate No radiographic progression = 0 point Radiographic progression (after CHF and ARDS excluded) = 2 points
Culture of tracheal aspirate Pathogenic bacteria cultured in rare or light quantity or no growth = 0 point Pathogenic bacteria cultured in moderate or heavy quantity = 1 point Same pathogenic bacteria seen on Gram stain, add 1 point

Adapted from Singh et al. (79).

Table 2**Measures to prevent ventilator-associated pneumonia****Nonpharmacologic**

- Avoidance of endotracheal intubation (noninvasive ventilation)
- Early weaning of mechanical ventilation
- Appropriate staffing levels in the intensive care units
- Subglottic suctioning
- Avoidance of unnecessary changes in the ventilator circuit
- Draining ventilator circuit and using heat and moisture exchangers
- Semi-erect positioning
- Prevention of gastric distension and checking gastric volumes and residual feeds
- Biofilm prevention on endotracheal tube and oral tissue surfaces
- Following rigorous hand washing and disinfection procedures

Pharmacologic

- Use of chlorhexidine or other methods for oral care
- Antibiotic cycling (changing appropriate antibiotic regimen for specific organisms)
- Limiting use of antibiotic prophylaxis
- Using shorter courses of empirical antibiotic therapy when possible
- Following stringent protocols for blood transfusions

Table adapted from Kollef (39).