Nosocomial pneumonia: importance of the oral environment*

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Abstract
Nosocomial pneumonia, especially ventilator-associated pneumonia, is a common infection in ICUs. The main etiologic factors involve colonizing and opportunistic bacteria from the oral cavity. Oral hygiene measures, including the use of oral antiseptic agents, such as chlorhexidine, have proven useful in reducing its incidence. The objective of this article was to review the literature on the importance of the oral environment in the development of nosocomial pneumonia.

Keywords: Intensive care; Oral hygiene; Cross infection; Pneumonia.

Introduction
Periodontal medicine appeared based on studies that reported the direct relationship between periodontal disease and a number of systemic morbidities, such as atherosclerosis, acute myocardial infarction, preterm birth, low birth weight, respiratory problems, gastritis, endocarditis and bacteremia. 

Within this group of diseases, nosocomial pneumonia has been increasingly studied, and the relationship between nosocomial pneumonia and microorganisms from the oral cavity has been increasingly acknowledged.

Patients submitted to cardiac surgery have a particularly high risk of developing nosocomial pneumonia; in these patients, the incidence of nosocomial pneumonia can be as high as 20%, and the disease is significantly associated with mortality.

The risk of developing nosocomial pneumonia increases with the need for mechanical ventilation and, in addition to prolonging, on average, 5-9 days the length of hospital stay of patients, nosocomial pneumonia markedly increases hospital costs.

The use of oral antiseptic and antimicrobial agents to prevent nosocomial pneumonia has been widely studied and, based on what has been reported, the present study aimed to review the literature focusing on how oral microorganisms can influence the development of nosocomial pneumonia and on how the frequency of nosocomial pneumonia can be reduced by changing the oral environment.

Definitions
Pneumonia is an acute lung infection, which can produce respiratory signs and symptoms, such as cough, short and fast breathing, production of secretion and chest pain, as well as non-specific systemic symptoms, such as fever,
fatigue, muscle pain and loss of appetite. Bacteria are the most frequent cause of this infection, and bacterial pneumonia is usually the type of pneumonia most easily prevented and treated.

Pneumonia and influenza are, together, the sixth leading cause of death in the United States and in most developing countries. Pneumonia is usually divided into two categories: community-acquired pneumonia and nosocomial pneumonia. Community-acquired pneumonia is defined as an infection that occurs in any individual living in a community and is acquired out of institutions. Nosocomial pneumonia is defined as an infection of the lower respiratory tract that is diagnosed at least 48 h after the patient has been admitted to hospital, which is not present or incubating at the time of hospital admission. There is also the healthcare-associated pneumonia category, which refers to pneumonia associated with patients residing in nursing homes or receiving home care, with patients who received i.v. antimicrobial agents or chemotherapy within 30 days before the onset of the infection, with patients receiving renal replacement therapy or with patients who needed emergency treatment and were hospitalized for 2 or more days within the 90 days preceding the onset of the infection.

Because of its different presentation forms and risk factors, nosocomial pneumonia—also known as hospital-acquired pneumonia—was defined, in accordance with the Brazilian Guidelines for Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia of 2007, as follows:

a) Hospital-acquired pneumonia (HAP), which refers to any pneumonia occurring at least 48 h after hospital admission. It is generally treated at the hospital ward (infirmary/apartment) and is not related to orotracheal intubation or mechanical ventilation (MV). Patients might, however, require treatment in the ICU when the severe form of the disease is present or when the disease progresses to the severe form. Because of etiological, therapeutic and prognostic implications, HAP has been classified, according to the time elapsed since hospital admission until its onset, as early (which develops within four days of hospital admission) or late (which develops at least five days after hospital admission).

b) Ventilator-associated pneumonia (VAP), which refers to any pneumonia developing 48-72 h after orotracheal intubation and institution of invasive MV. Similar to HAP, VAP is classified as early (which develops within four days of intubation and institution of MV) or late (which develops at least five days after intubation and institution of MV).

Pathogenesis of nosocomial pneumonia and importance of the oral environment

Nosocomial pneumonia is the second most common hospital infection and the most common cause of death among hospital-acquired infections. In ICUs, most of the hospital-acquired pneumonias are, in fact, cases of VAP, which can affect from 8% to 38% of the patients submitted to MV. The mortality rates of these infections can range from 24% to 76%, especially when the pneumonia is associated with Pseudomonas spp. or Acinetobacter spp., and ICU patients who require ventilation are at a 2-10 times greater risk of death than ICU patients who do not require ventilation.

The risk factors for developing nosocomial pneumonia include: age > 70 years; malnutrition; underlying diseases; a drop in the level of consciousness; lung or heart diseases; MV; manipulation of the patient by the hospital staff; use of probes or nasogastric tube; orotracheal intubation or reintubation; tracheostomy; microaspiration or macroaspiration of tracheobronchial secretion; previous use of antimicrobials; severe trauma; bronchoscopy or bronchial aspiration of microorganisms from the oropharynx; administration of antacids or H$_2$ receptor blockers; supine position and in-hospital transport.

In addition to these factors, in a hospital environment there is a greater possibility of treating patients who are immunocompromised due to diseases or medications and who therefore present reduced salivary flow due to procedures such as drug-induced dehydration (to increase respiratory and cardiac function), reduced cough reflex and decreased hygiene.
ability, factors that increase the risk of developing other diseases.\(^\text{1,3,7,19,20}\)

Evidence has correlated microbial colonization of the oropharynx and of the dental plaque with VAP.\(^\text{1,2,5,7,9,11,12,16,17,19,20-32}\) Almost 50% of the healthy adults present aspiration of oropharyngeal secretion at some point during sleep; this percentage increases to 70% in cases of patients with a drop in the level of consciousness.\(^\text{1,3,19}\) When the respiratory conditions of the patient worsen to the point of requiring intubation, resources such as MV can lead to the risk of microaspiration of pathogens to the lower respiratory tract.\(^\text{16,20}\) The orotracheal tube itself provides an inert surface to which bacteria can adhere and where they can form colonies, resulting in the formation of biofilms, from which bacteria can be aspirated to the lower airways.\(^\text{20}\) All patients in this group might also present periodontal disease, which can further aggravate a preexistent systemic condition and influence the course of respiratory infections, especially pneumonia.\(^\text{1,3,19,20}\)

The mouth is continuously colonized, presenting approximately half of the microbiota observed in the human body; in addition, bacterial plaque serves as a permanent reservoir of microorganisms, which might lead to remote infections.\(^\text{10,25}\) For the development of HAP, pathogens must reach the lower respiratory tract and overcome the respiratory system defense mechanisms, including mechanical mechanisms (glottal reflex, cough reflex, and mucociliary transport system), humoral mechanisms (antibodies and complement) and cellular mechanisms (polymorphonuclear leukocytes, macrophages and lymphocytes).\(^\text{10}\)

In healthy adults, the organism that predominates in the oral cavity is *Streptococcus viridans*; however, in critical patients the oral flora changes and becomes predominantly composed of gram-negative organisms, thus becoming a more aggressive flora. This flora can comprise *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Haemophilus influenza* and *Pseudomonas aeruginosa*.\(^\text{1,8,22}\) In addition, even if the bacteria usually responsible for the development of VAP, such as *P. aeruginosa*, methicillin-resistant *S. aureus*, *Acinetobacter* spp., *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis*, *Klebsiella pneumoniae*, *Streptococcus hemolyticus* and *S. pneumoniae*, are not commonly observed in the oral and oropharyngeal microbiota, these organisms can colonize the oral cavity in certain situations, such as in cases of precarious sanitation, of institutionalized elderly and of ICU patients.\(^\text{6,10,20,22}\)

In such cases, the percentage of these bacteria in the mouth can be as high as 70% in the dental biofilm, 63% on the tongue and 73% on the ventilator tube. When these areas are analyzed as a single system, the population of these organisms might be up to 43% of the total percentage of oral bacteria in patients on MV.\(^\text{6}\)

An additional and concerning finding is the presence of a higher number of resistant strains, such as methicillin-resistant *S. aureus*, 72 h after intubation.\(^\text{7}\)

The level of oral hygiene is related to the number of bacterial species present in the mouth.\(^\text{3,16,25}\) In general, ICU patients present poor oral hygiene; in addition, these individuals are exposed to a number of other factors, such as the reduction in the natural cleansing of the mouth resulting from the ingestion of hard and fibrous foods and from the movement of the tongue and cheeks while speaking. Salivary flow is also reduced due to the use of some medications, which contributes to increase the formation of the biofilm and, therefore, its complexity, favoring the oral colonization by respiratory pathogens.\(^\text{1,3}\) When comparing ICU patients with patients who had adequate oral hygiene, it was shown that poor oral hygiene was, in itself, related to pulmonary infections, to a greater number of episodes of fever and to the development of pneumonia.\(^\text{8,9}\) Identical results were observed in patients residing in nursing homes, which corroborates the fact that these patients and hospitalized patients present the highest risk for the development of pneumonia.\(^\text{6-9}\)

The main entry point for microorganisms to reach the lower respiratory tract consists in the aspiration of oropharyngeal secretion and, in cases of patients on ventilatory support, in the aspiration of secretion that accumulates above the tube cuff.\(^\text{11}\) Biofilm contaminated with bacteria within the orotracheal tube has also been implicated as a source for the inoculation of microorganisms into the lungs through tracheal aspiration or resulting from bronchoscopy. The access of pathogens through the bloodstream,
via catheters or bacterial translocation from the intestinal tract, should also be considered.\(^{(11)}\)

Salivary enzymes and local immunoglobulins act as a defense barrier against these bacteria; however, in addition to the factors mentioned above and to the age of the patients, other factors—such as smoking, alcohol consumption, antibiotic therapy, hospitalization, nutritional state and poor oral hygiene—can increase or reduce the oral microbial flora, facilitating the formation of an oral biofilm.\(^{(8,10,25)}\) The amount of biofilm increases with the length of hospital stay, and respiratory pathogens that colonize this film are the most difficult to be destroyed because of the protection created by the biofilm, which makes the bacteria more resistant. These bacteria are also found in saliva and can be easily aspirated from the oropharynx to the lungs, which might lead to pneumonia.\(^{(3,8-10,16,20,25)}\)

Colonization of the oropharynx with gram-negative bacilli in patients on mechanical ventilation occurs 4–72 h after the patient is admitted to the ICU.\(^{(2,25)}\) Patients under intensive care who require MV cannot close their mouths because of the orotracheal tube, which causes oral dryness, increases contact with the environment and favors even further the colonization of the biofilm.\(^{(3)}\) Additional risk factors to ICU patients are parenteral nutrition support, the position of the patient and insufficient head elevation in bed.\(^{(17)}\) The orotracheal tube and invasive MV increase 6 to 21 times the risk for pneumonia.\(^{(11)}\)

In vitro studies carried out in the 1970s and 1980s showed that \(P.\) aeruginosa and \(K.\) pneumoniae adhered more easily to epithelial cells of hospitalized patients than to epithelial cells of nonhospitalized patients.\(^{(6,22)}\) Dental plaque colonization by respiratory pathogens was investigated in ICU patients and control patients, and the findings suggested that dental surfaces, especially dental plaque, could be a large reservoir of these pathogens, especially in ICU patients.\(^{(9)}\)

It has long been known that pulmonary anaerobic infections can occur through the aspiration of salivary secretion, especially in patients with periodontal disease; however, only recently has colonization by oral and dental bacteria been implicated as the main source of bacteria involved in the etiology of VAP.\(^{(8,20)}\) Anaerobic bacteria frequently colonize the lower respiratory tract in patients on MV,\(^{(27)}\) and oral anaerobic germs such as \(Porphryromonas gingivalis\) can cause severe inflammation when introduced in the lung of laboratory animals.\(^{(10)}\) The presence of respiratory pathogens in the oral biofilm of ICU patients can serve as a reservoir of microorganisms associated with nosocomial pneumonia.\(^{(6)}\) The evaluation of bacterial samples from the orotracheal tube of laboratory animals and from tracheobronchial lavage fluid using molecular methods has shown the presence of a wide variety of bacterial species in the mouth and lung. This evaluation suggested that it was likely that the orotracheal tube acted as a reservoir of bacteria that are pathogenic for the respiratory tract and involved in VAP.\(^{(1,16,17)}\) Isolates of \(S.\) aureus, \(P.\) aeruginosa, \(Acinetobacter\) spp. and enteric species collected from the dental plaque of patients with VAP can be indistinguishable from isolates collected from the bronchoalveolar fluid, which reinforces this observation.\(^{(18)}\)

Periodontal diseases are multifactorial diseases of infectious etiology and inflammatory nature; they are considered the second major cause of oral pathology in the world population.\(^{(3,31)}\) One cubic millimeter of dental plaque contains approximately 100 million bacteria and might act as a permanent reservoir of potential pathogens.\(^{(11)}\) Patients who allow the accumulation of oral biofilm present characteristic blood changes, which might be detected since the initial stages of gingivitis.\(^{(3)}\) The presence of biofilm can trigger an inflammatory reaction, significantly increasing the amount of circulating immunoglobulins and chemical mediators of inflammation, as well as causing harm to local and distant sites, thereby lending credence to the idea that there is a relationship between the periodontal disease and systemic diseases.\(^{(3,10)}\)

Various factors are related to the risk of developing HAP and VAP. The development of VAP is primarily caused by the aspiration of oropharyngeal secretions, of the condensate formed in the ventilator circuit or of gastric contents colonized with pathogenic bacteria. Therefore, the onset of bacterial pneumonia can depend on the colonization of the oral cavity and the oropharynx with potential respiratory pathogens, on the aspiration of these pathogens to the lower airways or on the failure of the host defense mechanisms.\(^{(11,31)}\) Various mechanisms have been proposed to explain how the patho-
Prevention of nosocomial pneumonia: importance of oral hygiene and control of the oral biofilm

According to the Brazilian Guidelines for Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia of 2007, the risk factors for nosocomial pneumonia can be classified as modifiable and non-modifiable. Non-modifiable risk factors include advanced age, greater disease severity score at the time of hospital admission, COPD, neurological disease, trauma and surgery. Modifiable risk factors include the duration of MV, reintubation, tracheostomy, use of a nasogastric tube, enteral feeding, aspiration of gastric contents, use of antacids, paralyzing agents, previous use of antimicrobials, transportation from the ICU and supine position.

Some of the modifiable factors can be changed using relatively simple measures, such as washing and disinfecting the hands; implementing protocols to reduce inadequate prescription of antimicrobials; and maintaining a microbiological vigilance, with periodical information to health professionals regarding the prevalence and resistance of the oral microbiota. Initiative such as the implementation of protocols for sedation and ventilatory weaning, as well as the early removal of invasive devices, can reduce the prevalence of nosocomial respiratory infections.

Various studies have evaluated the efficacy of oral decontamination for the prevention of nosocomial pneumonia. There is, however, considerable variation regarding the places investigated (ICUs and nursing homes), the study design and the intervention methods (including the topical use of non-absorbable antibiotics; the use of oral rinses, such as products containing chlorhexidine gluconate; mechanical debridement and toothbrushing), which partially hinders the interpretation of the results. Nevertheless, it is clear that all preventive methods have proven effective in reducing the oral colonization of respiratory pathogens or the incidence of these pathogens in the oral cavity.

Essentially, dental plaque and associated microorganisms can be removed in two ways: through mechanical interventions or pharmacological interventions. These processes include...
decontamination with the administration of systemic antibiotics, local decontamination with the topical use of oral antiseptic and toothbrushing. The need for one of these methods became clear when studies demonstrated that 48 h after admission to ICU all patients investigated presented oropharyngeal colonization by gram-negative bacilli (common etiological agents of nosocomial pneumonia) and the biofilm came to be considered a major reservoir of respiratory pathogens.\(^{[1,2,22]}\)

There is significant reduction in the levels of VAP in patients decontaminated with systemic antibiotics; however, this type of intervention is limited due to bacterial resistance.\(^{[12]}\) Oral decontamination seems to be a better option, since it requires only a fraction of the medications used for systemic decontamination.\(^{[12]}\) Aiming to establish the best form of intervention in hospital environments, various studies were performed to evaluate the effects of 0.12% chlorhexidine on the dental biofilm and on gingival infection. The results were promising regarding the reduction in plaque accumulation, gingival bleeding and colonization by various bacterial types, especially *Actinomyces* spp.\(^{[16,17,19-21,24-26,30,32]}\)

A number of studies have demonstrated the efficacy of implementing protocols for the control of oral and dental biofilm in order to reduce the number of episodes of nosocomial pneumonia. The investigation of the effects of chlorhexidine in 353 patients submitted to cardiac surgery revealed that the nosocomial infection rate was decreased by as much as 65% in patients treated with chlorhexidine when compared with patients who received placebo.\(^{[24]}\) At St. Luke's Episcopal Hospital in Houston, TX, USA, where, historically, over 50% of the cases of nosocomial pneumonia occurred in cardiovascular patients, chlorhexidine produced better results than another phenolic oral rinse.\(^{[26]}\) A decrease of up to 65% in the occurrence of respiratory infection in patients on MV with the combined use of chlorhexidine and a phenolic oral rinse has produced better effects against gram-negative microorganisms.\(^{[21]}\) Another study showed that chlorhexidine led to a 65% reduction in the risk of developing VAP when compared with placebo.\(^{[31]}\) In addition, the effectiveness of VAP prevention in patients undergoing topical decontamination of the oropharynx with gentamicin/colistin/vancomycin at 2% in orabase was also observed.\(^{[23]}\)

A decrease of up to 40% in cases of pneumonia was observed when oral hygiene of patients was mechanically and chemically improved.\(^{[20]}\) The efficacy of the combination of chlorhexidine and other antimicrobials, such as neomycin sulfate, gentamicin or vancomycin, has also been reported.\(^{[20]}\) A combination of povidone and mechanical care also resulted in a reduced incidence of VAP.\(^{[19]}\) In addition to the use of chlorhexidine, professional cleaning performed by a dental hygienist once a week significantly reduced the prevalence of fever, fatal pneumonia, and the flu in the elderly.\(^{[20]}\) The combination of chlorhexidine and hydrogen peroxide showed antibacterial effect against most pathogens associated with VAP, which reinforces the possibility of using these agents for oropharyngeal decontamination.\(^{[43]}\) An oral protocol using sodium monofluorophosphate at 0.7% and the subsequent application of chlorhexidine at 0.12% twice a day promoted a 46% reduction in the frequency of VAP.\(^{[42]}\)

The literature reports a wide variety of treatment regimens using chlorhexidine, including variations in concentration (0.2%, 0.12% and 2%), site of application, form of presentation (oral rinse or gel) and application techniques.\(^{[32,42,43]}\) Studies involving cardiac surgery patients at a low risk for VAP reported that chlorhexidine at 0.12% was effective; however, higher concentrations might be required for more heterogeneous populations in a hospital environment, since the use of chlorhexidine at 2% in these populations seemed to produce better results.\(^{[12]}\)

The association between oral decontamination using topical antiseptic agents and the time spent in the ICU, mortality or duration of MV is not always evident; however, a reduction in the incidence of pneumonia has been observed in all studies.\(^{[32]}\) Nevertheless, although chlorhexidine reduces bacterial colonization in the oral cavity and consequently the prevalence of VAP\(^{[39,43,45]}\) and postoperative pneumonia,\(^{[46]}\) its influence on the reduction of mortality associated with these conditions has not yet been clearly shown.\(^{[44]}\)

It has been shown that preventive protocols for the control of oral biofilm reduce the risk for nosocomial pneumonia, especially VAP; however, a recent study investigating 59 ICUs in five European countries showed that in approxi-
mately 60% of the ICUs chlorhexidine was routinely used for oral decontamination.\(^{12}\) In a large study of the impact of oral care on VAP, the teams of five hospitals in Chicago, including nurses and respiratory therapists, reported that they adequately brushed the teeth of patients on MV using swabs and toothbrushes. However, it was observed that, in daily practice, these procedures were not considered a priority, and that the frequency of oral care documented was lower than the necessary. A key factor that became evident was the different perception of the meaning of oral care for the nursing staff,\(^{17}\) which showed that without the creation of a standardized oral hygiene protocol, the frequency and the methods implemented for hygiene will not suffice.\(^{16,17}\)

Although the most effective protocol for the control of oral biofilm in order to prevent VAP has yet to be established, there is a consensus that a protocol should be adopted and that the team responsible for oral care in these patients should follow this protocol in order to guarantee the success of preventive measures.\(^{42}\) In addition to the benefit in the quality of life and recovery of the patients, the costs of preventive protocols are much lower, being as low as 10% of the cost for the care of patients with nosocomial pneumonia.\(^{20,22,26,42}\) The prevention of nosocomial pneumonia and VAP should follow a multi-directional strategy, involving interventions aimed at reducing the aerodigestive tract colonization with pathogenic bacteria and the aspiration of these bacteria.\(^{47}\)

**Final considerations**

The current knowledge of the oral and oropharyngeal microbiota, as well as the increasing evidence that this microbiota plays a role in the pathogenesis of respiratory infections in hospitalized patients, shows that negligence of oral care is a risk factor for the development of nosocomial pneumonia. The inclusion of monitoring and decontamination of the oral cavity of hospitalized patients by qualified professionals in the protocol for the prevention of nosocomial pneumonia seems to be an important ally in attempts to reduce pulmonary colonization by oral pathogens and, consequently, the incidence of nosocomial pneumonia.

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