Oropharyngeal colonization as a risk factor for ventilator-associated pneumonia by *Staphylococcus aureus,* use of antimicrobials and multidrug-resistance

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Ventilator-associated pneumonia (VAP) is the most frequent infection acquired in intensive care unit (ICU). It is associated with increased morbidity, prolonged hospitalization, and increased healthcare costs. Oropharyngeal colonization plays a central role in the pathogenesis of VAP, once virulent microorganisms can reach the alveolar space via microaspiration of secretions from that region. Each antibiotic prescription has an environmental and ecological consequence. Antimicrobial resistance is an increasing threat in hospitalized patients, and inappropriated empirical antimicrobial therapy is known to adversely affect outcomes in VAP.

Keywords Oropharingeal colonization, *Staphylococcus aureus,* Ventilator-associated pneumonica, Multidrug-resistance.

Hospital acquired infections (HAIs) are a serious public health problem in both developing countries, where human and financial resources are very limited and the minority of hospitals have infection control committees active, as in developed countries, causing increased significant morbidity, mortality and hospital costs [1-5]. In Brazil, the average prevalence rate is 15% in tertiary care hospitals [1]. In the United States (U.S.)., they affect about 9% of hospitalized patients and rates of infections acquired in intensive care units (ICUs) are 5-10 times higher than in the other units, so at least 45% of HAIs occurring in hospitalized patients in these units, which corresponds to less than 10% of the hospital beds [6]. In ICUs, patients are more susceptible to these infections due to immunocompromise due to old age, co-morbidities, as well as increased use of invasive devices and exposure to antibiotics [2,3,7]. Earlier this century, the incidence of HAIs was estimated at 1.7 million in the U.S., with approximately 6% mortality (100.000/year) and a financial cost of US$ 35-45 billion / year [4,5].

Among the HAIs, pneumonia is the second most common and the first in ICU patients, which account for about 50% of infections [7,8]. Most of these infections is represented by "Ventilator-associated pneumonia" (VAPs) [4]. They occur in 9-24% of patients on mechanical ventilation, increase the length of stay and contribute to increased mortality in ICUs [4,9-11]. In developed countries, the incidence rate of VAP ranges from 1 to 4 cases per 1,000 days of ventilation [12,13] and is around 13 cases per 1,000 days of ventilation in developing countries [3,13], and in the adult ICU of the Uberlândia Federal University Hospital Clinic (UFU-HC) the incidence rate of VAP was 24.59 cases per 1000 ventilator days [14]. It is estimated that 52,000 patients / year in the U.S. are afflicted [5]. VAPs are defined as hospital acquired after 48 hours when the presence of mechanical ventilation [15]. This invasive procedure is associated with 83% of hospital-acquired pneumonias [7], undertakes the defense mechanisms, including the role of cough and mucociliary barrier [9], favoring micro-aspiration of oropharyngeal secretions colonized by potentially pathogenic microorganisms [7,16].

Although mechanical ventilation is identified as a risk factor itself, the duration of ventilation is also important [5,15]. The risk of VAP is 1% to 3% per day of mechanical ventilation [17]. Other risk factors include: decreased level of consciousness, advanced age, chronic obstructive pulmonary disease (COPD), head trauma, burns, stress ulcer prophylaxis, gastro-thoracic surgery, parenteral nutrition and antibiotics [5,8,9,13].

The etiologic agents of PAVs vary according to geographic region, hospital, unit and population [15], however, in general, *Staphylococcus aureus* and the non-fermenting gram-negative bacilli are the most important agents [4,5,11,15,18,19]. In Brazil, data from the "SENTRY" surveillance program show that *Pseudomonas aeruginosa* is the most frequent agent associated with pneumonia in hospitalized patients, followed by *S. aureus* and *Acinetobacter baumannii* [18], as revealed in a study in an adult ICU in Uberlândia-MG-Brazil [14,20]. In Porto Alegre-RS-Brazil, a study conducted at four clinical-surgical ICUs showed that *S. aureus* was the main agent PAVs, followed by *P. aeruginosa* or *A. baumannii* [17].

Although staphylococci are common inhabitants of the skin and mucous membranes, the nares are the major reservoir of microorganisms, being the site most investigated [21]. The colonization of these seems to play an important role in the epidemiology and pathogenesis of many infections [22]. The nasal colonization by *S. aureus* significantly increases the rate of surgical site infection after cardiac surgery, and is an independent risk factor for surgical wound infections [23]. With regard to infections related to central venous catheter, Luzar (1991) [24] reported that 45% of patients had nasal colonization prior to insertion of the catheter. Infections of the catheter insertion site occurred at a rate of 0.4 episodes per patient per year in patients colonized but are less frequent in patients not colonized with 0.1 episodes per patient per year. In a study conducted by Pujol et al. (1996) [25], nasal colonization by *S. aureus* was a risk factor for the development of nosocomial bacteremia in an intensive care unit, with a rate of 38% of bacteremia for

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patients colonized with oxacillin resistant *S. aureus* (ORSA) vs. 9.5% for those colonized with oxacillin sensitive *S. aureus* (OSSA) and 1.7% for those not colonized. However, recent studies show that colonization of the oropharyngeal mucosa is also important to the nasal mucosa [26-30] and has an important role in the pathogenesis of VAPs [31-32]. Additionally, intubation, in respiratory failure is more common orally than nasal due to iatrogenic aspects [33,34], therefore, the investigation of the oropharyngeal colonization as the source of microorganisms involved in the etiology of PAVs appears to be more rational.

The micro-aspiration of oropharyngeal secretions is a common event, even in healthy individuals [35], with 45% of them aspiring secretions during sleep [36]. The colonization of the mucosa of the upper respiratory tract by potentially pathogenic microorganisms is particularly common in critically ill patients in the ICU for prolonged periods, and using of antibiotics and invasive devices, with emphasis on ventilation support, especially in patients with decreased level of consciousness [7,16]. The colonization of the oropharynx is independent predictor for tracheo-bronchial colonization and subsequent aspiration of this secretion containing a bacterial inoculum in mechanically ventilated patients is the main route of acquiring VAP [16].

Some specific risk factors predispose to ORSA colonization / infection, including durations of mechanical ventilation and prolonged ICU stay, age, proximity to patients with this bacterial infection and prior use of broad-spectrum antibiotics, particularly cephalosporins and fluoroquinolones [37,38]. On the other hand, colonization / infection by oxacillin sensitive *S. aureus* (OSSA) occur more often in younger patients with traumatic brain injury [39].

The hospital mortality rate for VAP is high, ranging from 20% to 70% depending on the population studied [5,11,35], and its financial cost is substantial, ranging from US$ 10,000 to US$ 40,000 per episode [5-9].

The diagnosis of nosocomial pneumonia is complex and envolves clinical, radiological, laboratory and microbiological criteria [9]. The clinical and radiological data are linked to low specificity, and the use of quantitative microbiological criteria increases the specificity [40,41]. The specimens used in clinical microbiological evaluation include: endotracheal aspirate, bronchoalveolar lavage and protected brush, the last two being considered minimally contaminated by secretions from the upper respiratory tract, but more expensive and invasive, and can rarely lead to cardiac arrhythmias, hypoxemia and bronchospasm [4,15,40,41]. The endotracheal aspirate is a lower cost alternative, with good sensitivity but with poorer specificity when compared with the results obtained with other clinical specimens [9,40,42,43]. However, the analysis of endotracheal aspirate by quantitative technique with a cutoff of 10^6 CFU / ml (colony forming units per milliliter) shows good correlation with the results obtained with the minimally contaminated specimens [9,41,43-46].

The PAVs are classified into early and late, the latter occurring after four days of mechanical ventilation and related more often with resistant bacteria, as ORSA [9,43,47].

Antimicrobial resistance is a growing threat to hospitalized patients and both morbidity and mortality are greater when caused by microorganisms resistant to antibiotics [9,48]. Brazil and other Latin American countries in general, have higher rates of bacterial resistance in hospitals compared with Europe and the United States, particularly among non-fermenting gram-negative bacilli and representatives of the Enterobacteriaceae family, in this last group standing out members producers of extended spectrum beta-lactamase (ESBL) but also among gram-positive microorganisms, especially *S. aureus* [49].

The increased prevalence of these pathogens resistant to antibiotics in hospitals is often related to high selective pressure exerted by antimicrobials traditionally used in hospitalized patients, particularly extended-spectrum cephalosporins, beta-lactam combinations with beta-lactamase inhibitors, carbapenems, fluoroquinolones and aminoglycosides [48].

Due to its severity, the treatment of PAVs should be initiated quickly, and empirically with broad-spectrum antibiotics until culture results and antimicrobial susceptibility testing are available, they may have many agents, be polymicrobial or involve multidrug-resistant (MDR) bacteria to antibiotics [47,50,51], which are most often associated with late-onset VAP, prior hospitalization or prior use of antimicrobials (JOSEPH et al., 2010a). After defining the causal agent, specific therapy should be adopted with the use of narrow-spectrum antibiotics, promoting the descalonamento empirical antimicrobial therapy [50], even when patients responding well to initial treatment, in order to limit the risk of super infection, bacterial resistance, adverse reactions, and limit costs [7].

The inappropriate empirical antimicrobial therapy negatively affects the outcome of patients with VAP [52], therefore, must be adapted according to the local microbial ecology and the length of stay prior to the development of VAP [4]. Appropriate antibiotic use in hospital entails find a middle road between their potent ability to reduce the mortality and morbidity of patients with infectious diseases and their potentially hazardous effects, that is, serious adverse events, drug interactions, and induction of resistant strains [53].

Overuse or inappropriate use of broad-spectrum antibiotics and the difficulties in implementing measures to control hospital infections are seen as responsible for the emergence and spread of agents increasingly resistant, especially in environments that have high density of use of such drugs, as in ICUs [20,54].

Previous studies show that there are great variations in antibiotic use among European countries as well as in American hospitals. These differences can be explained mainly on the basis of patient populations studied, but cultural, behavioral, financial and administrative also has influence [53,55]. In Brazil there are data, considering only patients critics, pointing use much more intense when compared to American and European hospitals [20].

Understanding the mechanism of spread of MDR pathogens such as ORSA is essential for planning measures for prevention and control and, given the limitations of conventional typing methods, there is a preference for the use of molecular techniques for a better understanding and characterization of nosocomial pathogens [56].

The typing techniques commonly used for *S. aureus* are the Pulsed Field Gel Eletrophoresis (PFGE), the sequencing of the polymorphic region of the X gene encoding protein A, the typing of SCCmec and the Multilocus sequence typing (MLST) [57].

Genotypic characterization by macrorestriction techniques are widely used by its greater reproducibility and discriminatory power of the samples [58]. The PFGE is most commonly used for a variety of microorganisms including gram-positive bacteria like *S. aureus* and *Enterococcus* and gram-negative bacteria, such as species of *Enterobacteriaceae*, *P. aeruginosa* e *A. baumannii* [56,57,59].

The importance of PAVs in ICUs of hospitals in developing countries with limited resources in healthcare hospital is clear, requiring more and better epidemiological studies, and research on strategies easier and less costly in its prevention.

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