# Risk Factors of Oropharyngeal Carriage of *Pseudomonas aeruginosa* Among Patients from a Medical-Surgical Intensive Care Unit

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**Oropharyngeal carriage of *Pseudomonas aeruginosa* is associated with increased risk of infection and may provide a source for spread of drug-resistant strains. In order to assess the incidence and risk factors of oropharyngeal carriage, we conducted a retrospective cohort study based on results of surveillance cultures (oropharyngeal swabs) from a medical-surgical intensive care unit, collected from March 2005 through May 2006. Variables investigated included demographic characteristics, comorbid conditions, invasive procedures, use of devices and use of antimicrobials. Thirty case patients with *P. aeruginosa* carriage were identified. Other 84 patients with surveillance cultures negative to *P. aeruginosa* were enrolled as control subjects. Case patients were more likely to have a solid malignancy (Odds Ratio [OR] = 12.04, 95% Confidence Interval [CI] = 1.93-75.09, p=0.008), Acquired Immunodeficiency Syndrome (AIDS, OR = 7.09, 95% CI= 1.11-45.39, p = 0.04), central nervous system disease (OR = 4.51, 95% CI = 1.52-13.39, p = 0.007), or to have a central venous catheter placed (OR = 7.76, 95% CI = 1.68-35.79, p=0.009). The use of quinolones was a protective factor (OR = 0.13, 95% CI = 0.03-0.47, p = 0.002). The predominance of comorbidities as risk factors points out a group of patients to whom preventive measures should be directed.**

**Key-Words: *Pseudomonas aeruginosa*, colonization, oropharyngeal carriage, surveillance cultures, intensive care unit.**

The oropharynx is a reservoir of potentially pathogenic microorganisms, and its colonization has been implicated in the pathogenesis of healthcare acquired pneumonia and other systemic infections [1,2]. Oropharyngeal carriage of *Pseudomonas aeruginosa* is uncommon in the community setting, but it is frequently detected in patients from hospitals and long-term care facilities [3,4]. Besides being associated with infection, *P. aeruginosa* carriage can also provide a continuous source for cross-transmission. This phenomenon is relevant for the hospital spread of multidrug-resistant strains [5].

Patients in Intensive Care Units are particularly susceptible to *P. aeruginosa* colonization and infection [6]. Patients' severity, specific comorbid conditions, invasive procedures, device use and antimicrobials have been implicated in this phenomenon [6,7]. The identification of specific risk factors can help improve infection control strategies. This was the main purpose of our study.

## Maerial and Methods

### Setting

The study was conducted in a medical-surgical Intensive Care Unit (ICU) from Hospital Estadual Bauru. This is one of the teaching hospitals from Faculdade de Medicina de Botucatu. The hospital serves an area with approximately 1,000,000 inhabitants. It has 285 beds and four ICUs. The medical-surgical ICU has 11 beds.

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The study was approved by the Research Ethics Committee.

### Surveillance and Microbiology Methods

During the study period, the Infection Control Committee performed weekly surveillance cultures in ICU patients to identify Gram-negative bacilli. All patients that had a previous stay of at least 48 hours or that were transferred from another hospital setting were eligible for surveillance cultures.

Briefly, oropharyngeal swabs were collected and transported in Stuart media. Later, they were inoculated in MacConkey media. For *P. aeruginosa* identification, a manual kit for non-fermenters (NF II, PROBAC Inc.) was employed. Disk diffusion tests for antimicrobial susceptibility were performed according to standards from the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) [8].

### Study Design

The study had a retrospective cohort design. We analyzed results from surveillance cultures performed from March 2005 through May 2006. Patients that had at least one culture positive for *P. aeruginosa* were selected as case patients. Those that had all culture results negative for *P. aeruginosa* were selected as controls.

### Investigation of Risk Factors

Patient data were recovered from medical charts and laboratory files. Underlying conditions were defined following the guidelines in the *International Classification of Diseases* [9]. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [10]. Hospital admissions in the previous year and transfers from other hospitals were also recorded. All other data were

analyzed from the day of admission to our hospital up to the isolation of *P. aeruginosa* for case patients and up to the last negative culture for control subjects. Data included performance of surgery or other invasive procedures; use of steroids or other immune-suppressing drugs and use of antimicrobials (with or without antipseudomonal activity). Time at risk was assessed using two different variables: "time in the hospital" (defined as time from admission to the hospital up to the isolation of *P. aeruginosa* for case patients and up to the last negative culture for control subjects) and "time in the ICU" (defined in a similar fashion, but counting from the day of admission to the ICU).

Statistical Analysis

Data were recorded using the EPI INFO software for Windows, version 3.2 (Centers for Disease Control and Prevention) and analyzed using the SPSS version 15.0 (SPSS inc). Each variable was submitted to univariate analysis. Fischer's exact test (for binomial variables) and Student's T test (for numeric variables) were used to calculate p values. For multivariate analysis, we used a stepwise backward selection process. All variables for which $p<0.2$ were included in a first model. Variables were excluded from the model based on the magnitude of their effect. A p value of 0.05 was required for staying in the models. The same limit was set for significance in the final model. To assess the effect of severity of illness and time at risk, we forced APACHE II and "time in the hospital" into all models, regardless of their significance.

**Results**

A total of 263 surveillance cultures (oropharyngeal swabs) were collected from 114 patients in the study period. *P. aeruginosa* was recovered from 30 (26.3%) patients, which were selected as case patients. Resistance rates for commonly used antipseudomonal agents were: amikacin, 26.7%; ciprofloxacin, 26.7%; ceftazidime, 16.7%; piperacillin-tazobactam 10.0%; imipenem, 3.3%.

Eight case patients had one or more clinical cultures positive to *P. aeruginosa* after its recovery from surveillance cultures. The cultured specimens were: urine (three patients), blood (two), central venous catheter (two), tracheal aspirate (quantitative cultures, two) and pleural effusion (one). This finding, altogether with clinical pictures, confirmed the diagnosis of healthcare-acquired infections (HAI) in the following sites: urinary tract (three patients), respiratory tract (two) and bloodstream (two). Time from surveillance cultures detection until HAI diagnosis ranged from four to 28 days (average, 13 days).

Results from the univariate analysis of risk factors for *P. aeruginosa* carriage are listed in Table 1. Table 2 presents results from the multivariate analysis. Case patients were more likely to have a solid malignancy, AIDS, central nervous system (CNS) disease or the placement of central venous catheter (CVC). On the other hand, the use of quinolones (ciprofloxacin and/or levofloxacin) was a protective factor for *P. aeruginosa* carriage.

**Discussion**

Oropharyngeal carriage of Gram-negative bacilli is a matter of interest for healthcare epidemiologists. Fillius et al. describe a continuous increase in colonization rates during hospitalization [11]. Interestingly, those authors report the maintenance of increased rates three months after discharge. Oropharyngeal colonization may be due to individual patient's susceptibility, as well as to changes in the ecologic conditions of the mouth. Endotracheal and nasogastric tubes have been implicated in those changes, mainly because they provide an ideal environment for bacterial adherence and biofilm formation [5,12]. In our study, however, the presence of nasogastric tubes did not increase the risk for *P. aeruginosa* carriage. Mechanical ventilation, though significantly related to carriage in univariate analysis, lost significance when multivariate models included comorbid conditions. Those conditions are worth attention.

Patients with solid malignancies were usually admitted to the ICU in an advanced stage. The same applies to AIDS patients – all of whom were admitted due to severe opportunistic diseases. A greater susceptibility to *P. aeruginosa* in AIDS patients has been proposed by some authors [13]. Others suggest that apparent increase in *P. aeruginosa* infections in those patients is in fact due to frequent hospitalization [14]. Immune suppression, AIDS-related disorders and the use of antimicrobials may have impact in oropharyngeal ecology.

Besides contributing to general morbidity burden, central nervous system diseases may impair mechanical cleaning of the mouth through chewing and swallowing. The presence of central venous catheter is possibly a marker for increased patient manipulation.

The potential clinical and epidemiological implications of oropharyngeal colonization with *P. aeruginosa* are yet to be fully elucidated. Leibovitz et al. emphasize that elderly patients carrying *P. aeruginosa* in the oropharynx are also a group especially at risk for aspiration pneumonia and systemic infections [5]. The same can be said about ICU patients – who usually have additional risk factors for infection.

It has also been stated that the oropharynx may be a "reservoir of resistance" and a source for cross-transmission [5,6]. The implementation of surveillance cultures in our hospital aimed at the identification and isolation of patients colonized with imipenem or ceftazidime-resistant strains. However, resistance rates to antipseudomonal antimicrobials in colonizing strains were low. This may account for the finding of quinolones use as a protective factor against *P. aeruginosa* carriage.

Two quinolones – ciprofloxacin and levofloxacin – were routinely prescribed in the ICU. We found no protective effect for each particular quinolone – only for the class as a whole. This may reflect some lack of statistical power in our analysis. However, though the spectrum of action of quinolones against *P. aeruginosa* varies, both ciprofloxacin and levofloxacin have some antipseudomonal activity [16].

**Table 1.** Results of univariate analysis of risk factors for oropharyngeal carriage of *Pseudomonas aeruginosa*.

| Risk factor | Case patients (n=30) | Control subjects (n=84) | OR (95% CI) | p |
|---|---|---|---|---|
| **Demographic characteristics** | | | | |
| Age, mean | 60.5 | 64.2 | - | 0.27 |
| Male | 21 (70.0) | 46 (54.8) | 1.92 (0.79-4.69) | 0.11 |
| Comorbidities | | | | |
| Cardiac disease | 6 (20.0) | 19 (22.6) | 0.86 (0.30-2.39) | 0.49 |
| Pulmonary disease | 7 (23.3) | 21 (25.3) | 0.89 (0.33-2.39) | 0.52 |
| Renal disease | 1 (3.3) | 8 (9.5) | 0.32 (0.03-2.74) | 0.26 |
| Liver disease | 7 (23.3) | 10 (11.9) | 2.25 (0.77-6.58) | 0.12 |
| CNS disease | 15 (50.0) | 28 (33.3) | 2.00 (0.86-4.67) | 0.06 |
| Diabetes mellitus | 9 (30.0) | 27 (32.1) | 0.90 (0.37-2.24) | 0.51 |
| AIDS | 4 (13.3) | 4 (4.8) | 3.07 (0.72-13.18) | 0.12 |
| Tumor (solid) | 4 (13.3) | 4 (4.8) | 3.07 (0.72-13.18) | 0.12 |
| Trauma-related disease | 0 | 2 (2.4) | - | 0.54 |
| APACHE II, median (range) | 20 (6-41) | 23.5 (2-46) | - | 0.41 |
| **Data related to hospitalization** | | | | |
| Admission(s) during previous year | 13 (44.8) | 42 (50.0) | 0.82 (0.35-1.89) | 0.39 |
| Transfer from other hospital | 23 (76.7) | 68 (81.0) | 0.77 (0.28-2.11) | 0.39 |
| Surgery | 5 (17.2) | 16 (19.0) | 0.89 (0.29-2.68) | 0.53 |
| Neutropenia | 0 1 (1.2) | - 0.74 | | |
| Use of steroids | 12 (40.0) | 40 (47.6) | 0.73 (0.31-1.71) | 0.31 |
| Use of other immuno-supressing drug(s) | 0 1 (1.2) | - 0.74 | | |
| Placement of central venous catheter | 27 (90.0) | 59 (70.2) | 3.81 (1.06-13.73) | 0.02 (a) |
| Placement of urinary catheter | 29 (96.7) | 80 (95.2) | 1.45 (0.16-13.51) | 0.6 |
| Mechanical ventilation | 29 (96.7) | 66 (78.6) | 7.91 (1.01-62.09) | 0.02 (a) |
| Nasogastric tube | 28 (93.3) | 71 (84.5) | 2.56 (0.54-12.09) | 0.18 |
| Parenteral nutrition | 5 (16.7) | 3 (3.6) | 5.40 (1.20-24.20) | 0.03 (a) |
| Pressure ulcer | 18 (60.0) | 43 (51.2) | 1.43 (0.61-3.33) | 0.26 |
| *Time at risk* | | | | |
| Time in the hospital, mean | 20.4 | 18.1 | - | 0.52 |
| Time in the ICU, mean | 16.9 | 13.1 | - | 0.23 |
| **Use of antimicrobials** | | | | |
| *Agents with antipseudomonal activity* | | | | |
| Carbapenems | 5 (16.7) | 11 (13.1) | 1.33 (0.42-4.19) | 0.41 |
| Cefalosporins (b) | 15 (50.0) | 36 (42.9) | 1.33 (0.58-3.08) | 0.32 |
| Piperacillin-Tazobactam | 2 (6.7) | 14 (16.7) | 0.36 (0.08-1.67) | 0.14 |
| Aminoglycosides | 2 (6.7) | 6 (7.1) | 0.93 (0.18-4.87) | 0.65 |
| Quinolones (c) | 6 (20.0) | 36 (42.9) | 0.33 (0.12-0.90) | 0.02 (a) |
| *Agents without antipseudomonal activity* | | | | |
| Cefalosporins (d) | 5 (16.7) | 9 (10.7) | 1.67 (0.51-5.44) | 0.28 |
| Penicillins (e) | 16 (53.3) | 40 (47.6) | 1.26 (0.55-2.89) | 0.37 |
| Glicopeptides | 8 (27.6) | 16 (19.0) | 1.55 (0.58-4.09) | 0.65 |
| Clindamycin | 3 (10.0) | 15 (17.9) | 0.51 (0.14-1.91) | 0.24 |
| Metronidazole | 5 (16.7) | 19 (22.6) | 0.68 (0.23-2.03) | 0.34 |

Note. Data are in number (%), unless otherwise specified. AIDS, acquired immunodeficiency syndrome; APACHE II, acute physiology and chronic health evaluation II; CNS, central nervous system; ICU, intensive care unit; OR, odds ratio; CI, confidence interval. (a) Statistically significant; (b) Cefipime and Ceftazidime; (c) Ciprofloxacin and Levofloxacin; (d) Ceftriaxone, Cefuroxime, Cefazolin and Cefalotin; (e) Ampicillin, Ampicillin-Sulbactam, Amoxicillin, Amoxicillin-Clavulanate, Oxacillin.

**Table 2.** Results of multivariate analysis of risk factors for oropharyngeal carriage of *Pseudomonas aeruginosa*.

| Risk factors | OR (95% IC) | P |
|---|---|---|
| Tumor (solid) | 12.04 (1.93-75.09) | 0.008 |
| AIDS | 7.09 (1.11-45.39) | 0.04 |
| CNS disease | 4.51 (1.52-13.39) | 0.007 |
| Placement of central venous catheter | 7.76 (1.68-35.79) | 0.009 |
| Use of quinolones (a) | 0.13 (0.03-0.47) | 0.002 |

AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; OR, odds ratio; CI, confidence interval. (a) Ciprofloxacin and Levofloxacin.

It is possible that our study design has had some influence over results. The requirements for eligibility for surveillance cultures might have selected a subset of patients with greater severity of illness. It is worth noting that APACHE II scores were similarly high for case patients and control subjects. Also, "time in the hospital" and "time in ICU" did not differ between case and controls. In a case-control study of factors for acquisition of resistant *P. aeruginosa*, Harris et al. compared results using different control groups [16]. Those authors suggest that requiring negative cultures for enrolling patients as controls might lead to underestimation of the impact of specific risk factors. This might have happened in our study, and can account for the absence of significance for mechanical ventilation or other factors. However, allowing only patients with negative surveillance cultures to be enrolled in the control group prevented us from erroneously including individuals with unidentified oropharyngeal carriage of *P. aeruginosa* in that group. Of course, focusing solely on oropharyngeal cultures makes it possible to include in the study control subjects that harbour *P. aeruginosa* in other sites, such as the gastrointestinal tract. Though this may also lead us to underestimate risk factors, this minor bias is not an argument against the validity of our findings. Again, we must emphasize that our study specifically addresses oropharyngeal colonization. Further studies focusing on *P. aeruginosa* carriage in lower respiratory or gastrointestinal tracts would complement our findings and help elucidate this pathogen's epidemiological behaviour.

Surveillance cultures were not obtained on patients' admission. Thus we cannot rule out previous colonization of case patients. However, neither previous admissions nor transfer from other hospital were significantly associated with *P. aeruginosa* carriage. Besides, as we previously mentioned, colonization is uncommon in healthy, non-hospitalized individuals. These findings suggest that most patients acquired *P. aeruginosa* in our ICU.

We conclude that oropharyngeal carriage of *P. aeruginosa* is frequent in our ICU.

This phenomenon is potentially harmful, and the predominance of comorbidities as risk factor points out a group of patients to whom preventive measures should be directed.

## References


1. Garrouste-Orgeas M., Chevert S., Arlet G. et al. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult Intensive Care Unit patients. Am J Respir Crit Care Med **1997**;156:1647-55.
2. Limeback H. Implications of oral infections on systemic diseases in the institutionalized elderly with a special focus on pneumonia. Ann Periodontol **1998**;3:262-75.
3. Morrison, Jr. A.J., Wenzel R.P. Epidemiology of infections due to *Pseudomonas aeruginosa*. Rev Infect Dis **1984**;6(Suppl 3):S627-S42.
4. Murthy S.K., Baltch A.L., Smith R.P. et al. Oropharyngeal and fecal carriage of *Pseudomonas aeruginosa* in hospital patients. J Clin Microbiol **1989**;27:35-40.
5. Leibovitz A., Dan M., Zinger J. et al. *Pseudomonas aeruginosa* and the oropharyngeal ecosystem of tube-fed patients. Emerg Infect Dis **2003**,9:956-9.
6. Bonten M.J.M., Bergmans D.C.J.J., Speijer H., Strobbering E.E. Characteristics of polyclonal endemicity of *Pseudomonas aeruginosa* colonization in Intensive Care Units. Am J Respir Crit Care Med **1999**,160:1212-9.
7. Ortega B., Groenvald J., Schultsz C. Endemic multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. Infect Control Hosp Epidemiol **2004**,25:825-31.
8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial disk susceptibility tests; approved standard, 8th ed. Pennsylvania: CLSI; **2003**.
9. World Health Organization. International Classification of Diseases. tenth revision, 2005 update. Geneva, Switzerland: WHO; **2005**.
10. Knaus W.A., Draper E.A., Wagner D.R., Zimmerman J.E. APACHE II: a severity of disease classification system. Crit Care Med **1985**;13:818-29.
11. Fillius P.M.G., Gyssens I.C., Kershof I.M. et al. Colonization and resistance dynamics of Gram-negative bacteria in patients during and after hospitalization. Antimicrob Agents Chemother **2005**;49:2879-86.
12. Berthelot P., Grattard F., Mahul P. et al. Prospective study of nosocomial colonization and infection due to *Pseudomonas aeruginosa* in mechanically ventilated patients. Intensive Care Med **2001**;27:503-12.
13. Asboe D., Gant V., Aucken H.M. et al. Persistance of *Pseudomonas aeruginosa* strains in respiratory infection in AIDS patients. AIDS **1998**;12:1771-5.
14. Sorvillo F., Beall G., Turner P.A. et al. Incidence and determinants of *Pseudomonas aeruginosa* infection among persons with HIV: association with hospital exposure. Am J Infect Control **2001**;29:79-84.
15. Bonfiglio G. Is Levofloxacin as active as Ciprofloxacin against *Pseudomonas aeruginosa*? Chemotherapy **2001**;47:239-42.
16. Harris A.D., Carmeli Y., Samore M.H. et al. Impact of severity of illness bias and control group misclassification bias in case-control studies of antimicrobial resistant organisms. Infect Control Hosp Epidemiol **2005**;26:342-5.