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Ventilator-Associated Pneumonia Caused by *Pseudomonas aeruginosa* in Intensive Care Unit: Epidemiology and Risk Factors

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Abstract

Purpose: We studied the risk factors for the acquisition of Ventilator-associated Pneumonia (VAP) caused by *Pseudomonas aeruginosa* in two Intensive Care Units (ICU).

Methods: We carried out a case-control study, from January 1, 2006 through June 30, 2008. We defined as CASES patients with *Pseudomonas aeruginosa* VAP and CONTROLS patients with VAP caused by other Gram-negative bacteria.

Results: The study of risk factors for the development of VAP by *Pseudomonas aeruginosa* showed that three of them are referred to the pre-ICU admission history of the patient: hospitalization during previous 6 months, admission from other wards/hospitals instead of domicile provenance ($p<0.01$) and duration of pre-ICU hospitalisation ($p<0.01$, at multivariate analysis: OR 2.09 IC95% 1.18-3.72). Analysis of antibiotic prescription before the development of VAP showed as independent risk factor the number of different antibiotic classes prescribed to patients or rather the complexity of antibiotic exposure (OR 2.3 IC95% 1.14-4.67). Analysis of mortality revealed a non-significant difference between VAP caused by Pseudomonas or other Gram-negative bacteria, although our data suggest an association between MDR Pseudomonas infection and higher mortality ($p=0.03$).

Conclusion: Our study offers points that can contribute to improve the empiric antibiotic prescription in ICU. In presence of in-hospital patients presenting with a previous history of antibiotic prescription, with a complex clinical condition preceding ICU admission or with a prolonged ventilatory assistance, presenting with signs or symptoms of infection, should be advisable to prescribe a therapy with a specific activity against *Pseudomonas aeruginosa*.

Keywords: Intensive care unit; Venrilator-associated Pneumonia; Gram-negative; *Pseudomonas aeruginosa*; Infection; Risk factor

Introduction

Considering the particular tendency of *Pseudomonas aeruginosa* to acquire antibiotic resistance mediated by intrinsic factor or by the acquisition of resistance genes [1–12], it is easily understood the increasing concern about infections caused by this pathogen, particularly in complex patients. In fact, *Pseudomonas aeruginosa* is commonly associated with respiratory tract infections in different clinical contests: nosocomial infections in hospitalized patients, patients with prolonged mechanical ventilation, immuno-compromised patients or patients with cystic fibrosis [9–16].

For this reason we studied the epidemiology and distribution of risk factors for the acquisition of Ventilator-associated Pneumonia (VAP) caused by *Pseudomonas aeruginosa* in two polyvalent Intensive Care Units, assuming as control group the patients with VAP caused by other Gram-negative bacteria.

We excluded from the analysis patients with Gram-positive VAP because they corresponds to well codified risk factors such as neurological impairment or coma and because these ICUs since years adopted effective strategies con control the diffusion of methicillin-resistant *Staphylococcus aureus* (MRSA) [17–20].

Materials and Methods

Study design

We carried out a case-control study without matching, from January 1, 2006 through June 30, 2008. It has been retrospective from January 1, 2006 to October 31, 2007 and prospective from October 31, 2007 through June 30, 2008.

The study was performed at two different ICUs of two different Italian hospitals. The first centre is the *2° Servizio di Anestesia e Rianimazione of the Spedali Civili di Brescia* and the second one is the *Unità Operativa di Rianimazione, Terapia Intensiva e Neuroanestesia of the Istituti Ospitalieri di Cremona.* Both ICUs have 10 beds and admit about 450 medical/surgical patients per year.

Definitions

For definitions of infection, systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock, we referred to the

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [21].

For the definition of VAP we referred to the 2005 American Thoracic Society – Infectious Disease Society of America guidelines [22]. VAP was defined as any lower respiratory tract infection that developed after 2 days of MV. Clinical suspicion of VAP was defined as a new, progressive, or persistent (>24 h) infiltrate on the chest radiograph, with two or more of the following criteria: 1) fever>38.3°C or hypothermia<36°C; 2) purulent endotracheal aspirate; 3) leukocytes count>10,000/mm^3 or<4,000/mm^3. Every patient suspected of having pneumonia underwent, within 24 hours, lower respiratory tract microbiologic sampling. To establish a microbiological diagnosis we performed, whenever feasible, a broncho-alveolar lavage (BAL); as an alternative method, when bronchoscopy was not immediately available, we used a blind sampling technique (blind mini-BAL) whose diagnostic accuracy has been widely established. A case of VAP was defined as microbiologically confirmed when bacteria were isolated in significant quantities from BAL samples (≥ 10^4 CFU/ml). We defined "early onset VAP" (EOP) as those occurring during the first 5 days of MV and "late onset VAP" (LOP) as those occurring after 5 days of MV.

Those patients who developed VAP caused by *Pseudomonas aeruginosa* were defined as CASES; those who developed VAP caused by other Gram-negative bacteria were defined as CONTROLS.

To evaluate antibiotic sensibility spectrum we tested: aminoglycosides (amikacin), 3rd and 4th generation cephalosporins, β-lactams (piperacillin/tazobactam), carbapenems (imipenem, meropenem), fluoroquinolones (ciprofloxacin, levofloxacin). We defined as Multi Drug Resistant (MDR) *Pseudomonas aeruginosa* those strains which were resistant toward two or more antibiotic classes. We also considered as MDR *Stenotrophomonas maltophilia* and Extended Spectrum β-Lactamase (ESBL) producing *Enterobacteriaceae* [23].

Collected data

We collected demographical, clinical and microbiological data related to study patients, in particular:

ICU admission diagnosis, Simplified Acute Physiology Score (SAPS), predicted in-hospital mortality.

Patient's characteristics preceding ICU admission, patient's provenance, length of hospital stay before ICU, coexisting diseases expressed by the Charlson Comorbidity Index, prior immunosuppressive or antimicrobial therapies and MDR pathogens isolation.

Use of invasive devices like central Venous Catheters (CVC), duration of mechanical ventilation (MV), surgical interventions, renal replacement therapies.

Microbiological isolations and their antimicrobial susceptibility spectrum.

Main outcomes like infection severity, length of hospital stay and in-hospital mortality.

Antibiotic prescription

In both study centres there were a written internal protocol for the empirical antibiotic treatment of VAP which was based on local microbiological flora as well as on international guidelines. In case of EOP, without risk factors for MDR germ infection, an association between semi-synthetic non anti-pseudomonas penicillin and β-lactamase inhibitor (e.g. ampicillin-sulbactam) was administered. In case of LOP, the therapy of choice was a semi-synthetic anti-pseudomonas penicillin with β-lactamase inhibitor (usually piperacillin-tazobactam) associated with a fluoroquinolone or an aminoglycoside, eventually with the addition of a glycopeptide or linezolid in the suspect of a Gram-positive multi-resistant infection.

Antimicrobial drugs procurement was not limited, with the exception of linezolid, whose supply required medical justification to the hospital pharmacy.

Every empirical therapy was re-evaluated at 48-72 hours considering the patient's clinical condition and the microbiological results and, if appropriated, the antibiotic was continued, suspended or de-escalated. Antibiotic therapy duration for the confirmed VAP was 7 to 14 days, considering the type of microbiological isolation and the patient's clinical condition. Serum drug levels were monitored for those antibiotics with limited therapeutic range (i.e. aminoglycosides and glycopeptides) so that the dose was modulated without toxic effects.

Both ICUs applied a protocol for the prevention of VAP, according to the American Thoracic Society guidelines [22], an infection surveillance programme, providing periodical reports on the local microbial flora and an active control of MRSA infections or colonization. Selective Digestive Decontamination (SDD) or subglottic secretions aspiration with dedicated endotracheal tubes was not performed during the study.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation; dichotomously variables are expressed as percentage values. We used logistic regression analysis to study risk factors involved in the acquisition of VAP caused by *Pseudomonas aeruginosa*. We reported p-values for univariate models relative to *likelihood ratio* tests between models with or without clinical variable of interest. The variables to be included in multivariate models were selected by a stepwise selection based on AIC criteria after the imputation of missing; missing data were not considered in the final model. All the statistical tests were considered significant when $p<0.05$ and Confidence Interval (CI) fixed to 95%.

The same type of analysis was used to identify variables involved in the determination of mortality for the studied patients.

The SAPS2 was used during 2006 and 2008; the SAPS3 was used during 2007. These two parameters have been compared by calculating the predicted in-hospital mortality associated with each SAPS value.

The statistical analysis was conducted using the *R* software (*R* Development Core Team 2008).

Results

Study Population

We enrolled a total of 76 patients who developed VAP caused by Pseudomonas aeruginosa or another Gram-negative pathogen, microbiologically documented. Within the study patients there were 38 cases and 38 controls.

We diagnosed 32 EOP (12 within cases, 20 within controls) and 44 LOP (26 within cases, 18 within controls). The mean onset time of VAP since ICU admission was 10.26 10.23 days within cases and 7.03 6.77 days within controls.

Micro-organisms associated with VAP are described in Figure 1. Among MDR germs we had: 14 *Pseudomonas aeruginosa*, 3 *Stenotophomonas maltophilia* and 1 *Escherichia coli* ESBL.

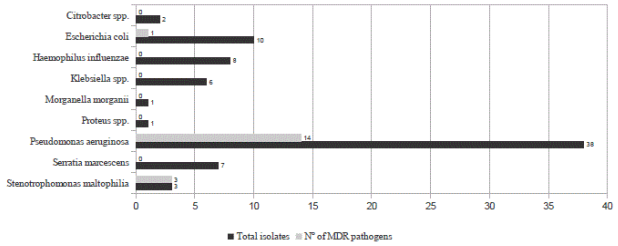

Figure 1: Microorganisms associated with VAP

During the study 16 patients developed severe sepsis or septic shock, 12 within cases and 4 within controls (p=0.05, OR 3.29 IC95% 1.13-13.58).

Risk Factors for VAP Caused by *Pseudomonas aeruginosa*

Risk factors for Pseudomonas-VAP are summarized in Table 1. Those factors that reached statistical significance at univariate analysis were: patient's morbility represented by Charlson Comorbility Index (p=0.04, OR 2,04 IC95% 0.97–4.28), hospitalization during previous 6 months (p=0.03, OR 3,04 IC95% 1.11–8.32), provenance from other wards (p<0.01, OR 5,30 IC95% 1,88–14,9), duration of pre-ICU hospitalisation (p<0.01, OR 2,09 IC95% 1,18–3,72), presence of tracheostomy at time of VAP diagnosis (p=0.03, OR 3,04 IC95% 1,11–8,32). Evaluating the main pathologies causing ICU admission, cardio-circulatory insufficiency revealed to be more frequently associated to Pseudomonas VAP, at the contrary neurological insufficiency was less frequently associated (p=0.05, OR 0.09 IC95% 0.09-0.96). At multivariate analysis the only variable that maintained the statistical significance was the duration of pre-ICU hospitalisation (p<0.01, OR 2.09 IC95% 1.18-3.72).

Risk factors for *Pseudomonas* VAP	**Cases (n=38)**	**Controls (n=38)**	***p* value**
Age, years	54.03 ± 18.82	55.9 ± 17.62	0,65
Female Sex (%)	9 (23,68)	10 (26,32)	0,08
Patients baseline conditions (%)			
Alcohol	3 (7,89)	2 (5,26)	0,64
Drugs abuse	1 (2,63)	1	1
Cirrhosis	2 (5,26)	0	0,09
Diabetes	6 (15,79)	3 (7,89)	0,28
COPD	10 (26,32)	5 (13,16)	0,15
Chronic steroid therapy (%)	7 (18,42)	4 (10,53)	0,32
HIV	0	1 (2,63)	0,24
Surgery (%)	20 (52,63)	22 (57,89)	0,64
Charlson Comorbidity Index	2,10 ± 2,34	1,47 ± 2,12	0,04
Previous 6 months hospitalisation (%)	17 (44,74)	5 (13,16)	0,03
Provenance from other wards (%)	25 (65,79)	12 (31,58)	<0,01
Predicted mortality by SAPS			0,54
SAPS II	46,8 ± 16,95	46,65 ± 14,09	
SAPS III	59,87 ± 24,83	66 ± 15,04	
Admission pathology (%)			
Neurologic	6 (15,79)	13 (34,21)	
Cardiocirculatory	10 (26,32)	2 (5,26)	0.04
Respiratory	7 (18,42)	5 (13,16)	
Trauma	12 (31,58)	18 (47,37)	

Central venous catheter (%)	36 (94,74)	36 (94,74)	0,64
Number of catheter-days	10,31 ± 10,41	7 ,35 ± 7,71	0,19
Dialysis (%)	3 (7,89)	3 (7,89)	1
Length of mechanical ventilation, days	9,90 ± 10,28	7,19 ± 7,89	0,26
Tracheostomy (%)	30 (78,95)	21(55,26)	0,03
NOTE: Cases: Patients with Pseudomonas-VAP; controls: Patients with VAP caused by other Gram-negative.			

Table 1: Univariate analysis of risk factors for VAP caused by *Pseudomonas aeruginosa*

Use of antimicrobial agents before the diagnosis of VAP is analysed in Table 2. Univariate analysis showed statistical significance for: glycopeptides (p=0.04 OR 3,46 IC95% 1,05–13,62), carbapenems (p=0.04, OR 4,8 IC95% 1,1–33,44), aminoglycosides (p=0.02, OR 5,59 IC95% 1,12–27,9) and the number of antibiotic classes administered to the patient during the period preceding the diagnosis of VAP (p=0.01). Multivariate analysis confirmed the association between Pseudomonas-VAP and number of antibiotic classes administered to the patient (p=0.01, OR 2.31 IC95% 1.14-4.67).

Antibiotic class	**Cases (n= 38)**	**Controls (n=38)**	**p value**
Glicopeptydes, n (%)	11 (28,95)	4 (10,53%)	0,04
Glicopeptydes-days	13,54 ± 11,55	7,5 ± 8,27	0,76
Antifungines, n (%)	7 (18,42)	2 (5,26)	0,07
Carbapenems, n (%)	8 (21,05)	2 (5,26)	0,04
Carbapenems-days	17,37 ± 12,55	20 ± 5,66	0,69
β-lactams, n (%)	26 (68,42)	23 (60,53)	0,16
β-lattams-days	8,42 ± 10,27	8,65 ± 7,26	0,94
Fluoroquinolones, n (%)	3 (7,89)	6 (15,79)	0,17
Fluoroquinolones-days	12,83 ± 10,04	7,5 ± 7,29	0,20
Aminoglycosides, n (%)	10 (26,32)	2 (5,26)	0,02
Aminoglycosides-days	11,2 ± 10,84	13 ± 8,72	0,66
Cephalosporins, n (%)	3 (7,89)	3 (7,89)	1
Cephalosporins-days	5,67 ± 6,43	12 ± 9,16	0,08
N° of administered antibiotic classes	2,03 ± 1,88	1,18 ± 1,56	0,01
NOTE. Values express the number of patients receiving a specific antibiotic class. Cases: Patients with Pseudomonas-VAP; Controls: Patients with VAP caused by other Gram-negative.			

Table 2: Use of antimicrobial agents before the diagnosis of VAP

Outcomes

Risk factors for ICU mortality are summarized in Table 3. Overall ICU mortality of the study patients was 21.05%. Mortality within Cases was 28.94%, while within controls it was 13.16% (p=0.16). Those factors that reached statistical significance at univariate analysis were: female sex (p<0,01, OR 6.43 IC95% 1.94–21.31), dialysis (p=0.01, OR 9,67 IC95% 1,59 - 58,93), length of MV (p<0,01, OR 1,80 IC95% 1,14 – 2,83), days of central venous catheterization (p=0.03, OR 1,64 IC95% 1,05 – 2,56), use of steroid therapy (p=0.05, OR 4,09 IC95% 1,06–15,82). Those factors that appear to be independently associated with mortality at multivariate analysis are: female sex (p<0,01, OR 7 IC95% 1.88-26.1) and length of MV (p<0,01, OR 1.89 IC95% 1.14-3.13).

Finally the development of severe sepsis or septic shock was present in 62% of deceased patients, revealing a significant association with mortality (p<0,01, OR6.67 IC95% 2.02-21.99).

Risk factors for ICU mortality	Survived (n=60)	Deceased (n=16)	*p* value
Age, years	53,79 ± 18,95	59,37 ± 14,36	0,26
Female sex (%)	10 (16,67)	9 (56,25)	<0,01
Patients baseline conditions (%)			
Alcohol abuse (%)	3 (5)	2 (12,5)	0,32
Cirrhosis (%)	1 (1,67)	1 (6,25)	0,36
COPD (%)	11 (18,33)	3 (43,7)	0,91
Diabetes (%)	6 (10)	3 (43,75)	0,36
Surgery (%)	30 (50)	11 (68,75)	0,22
Charlson Comorbidity Index	1,36 ± 2,04	1,94 ± 1,73	0,51
Previous 6 months hospitalisation (%)	19 (31,67)	6 (37,5)	0,66
Provenance from other wards (%)	26 (43,33)	11 (68,75)	0,10
Days of pre-ICU hospitalisation	2,57 ± 8,86	5,87 ± 6,56	0,15
Predicted mortality by SAPS			0,24
SAPS II	44,64 ± 15,19	51 ± 16,04	
SAPS III	62.42 ± 20,40	60,33 ± 17,27	
Duration of antibiotic therapy, days	18,46 ± 11,63	20,75 ± 23,64	0,64
Central venous catheter (%)	57 (95)	16 (100)	0,95
Number of catheter-days	20 ± 13,49	31,57 ± 26,25	0,03
Length of mechanical ventilation, days	17,42 ± 10,79	31,25 ± 26,73	<0,01
Pseudomonas infection (%)	27(45)	11 (68,75)	0,88
Multi Drug Resistant pathogen infection (%)	13 (21,67)	5 (31,25)	0,072
MDR-Pseudomonas VAP (%)	9 (69,23)	5(100)	
Dialysis (%)	2 (3,33)	4 (25)	0,01
Duration of dialysis, days	1,36 ± 6,21	2,25 ± 5,98	0,12
Steroid therapy (%)	14 (23,33)	7 (43,75)	<0,01
Days with steroid therapy	2,08 ± 5,46	4,57 ± 9,21	0,93
Tracheostomy (%)	54 (90)	12 (75)	0,11
Days of hospital stay preceding VAP	7,87 ± 7,61	13,06 ± 12,34	0,48
Length of hospital stay, days	23,76 ± 13,57	28,87 ± 24,83	0.10

Table 3: Univariate analysis of risk factors for ICU mortality

Discussion

The study of risk factors for the development of VAP by *Pseudomonas aeruginosa* showed that three of them are referred to the pre-ICU admission history of the patient: hospitalisation during previous 6 months, admission from other wards/hospitals instead of domicile provenance ($p<0.01$) and duration of pre-ICU hospitalisation ($p<0.01$). At multivariate analysis the length of hospital stay before the admission to ICU appears to be independently associated with the development of VAP by *Pseudomonas aeruginosa* (OR 2.09 IC95% 1.18-3.72). This is easily explainable when we think that as longer is hospitalisation, as higher are risks for the development of complications or worsening clinical conditions, with a major exposition to Pseudomonas due to a prolonged hospital stay [23–26].

The relationship between the number of patient's comorbilities and the predisposition to develop a Pseudomonas infection is well-known in literature. Various studies report an increased incidence of

Pseudomonas infections in patients with immunosuppression (e.g. haematologic malignancies) or chronic diseases like cystic fibrosis [15,25,27–29]. Nevertheless our study seems to not confirm these data, in fact Charlson Comorbility Index is at limit of significativity (OR 2.04 IC95% 0.97-4.28), but this variable is lost at multivariate analysis.

Regarding the cause of ICU admission, cardio-circulatory insufficiency seems to be related to an increased risk for Pseudomonas infection, probably because splancnic hypo-perfusion may facilitate a perturbation of the normal intestinal flora, leading to an extensive Pseudomonas colonisation, thus facilitating an endogenous diffusion of this germ toward the respiratory tract [30]. Contrarily, patients with neurological impairment are known to be more easily colonised by Gram-positive cocci, especially Staphylococcus which may represent an antagonist factor to Pseudomonas colonisation or infection. Similar results were reported in a study by Rello et al. where the absence of coma was considered an high risk factor for the development of Pseudomonas VAP (p<0.01, OR 8.3 IC95% 2.68-26) [31]. It seems that patients with coma have elevated levels of fibronectin expression above the above the respiratory tract which may promote the adhesion of Staphylococcus to the epithelial cells, thus contrasting Pseudomonas growth [32,33].

Well-known in literature is the association with tracheostomy and Pseudomonas colonisation. Tracheostomy in fact is often correlated with prolonged MV or difficult respiratory weaning; however this variable is not significant in multivariate analysis [34,35].

Analysis of antibiotic prescription before the development of VAP, showed as independent risk factor the number of different antibiotic classes prescribed to patients or rather the complexity of antibiotic exposure (OR 2.3 IC95% 1.14-4.67). Use of some specific classes like carbapenems or aminoglycosides appears to be associated with an increased risk of Pseudomonas VAP [26,36–41] but this results are not confirmed by multivariate analysis. We do not exclude that an higher study population would clarify this relationship.

All these data agree with ATS guidelines for hospital-acquired pneumonia diagnosis, prevention and treatment, particularly: number of previous hospital admissions, hospital stay more than 5 days, past antibiotic exposure or immunosuppression.

We did not find a relationship between Pseudomonas VAP and severity score (SAPS) at ICU admission and probably would be more interesting to collect a clinical severity score at the time of VAP diagnosis, but actually we do not dispose of this data. Analysis of mortality revealed a non-significant difference between VAP caused by Pseudomonas or other Gram-negative, although our data suggest an association between MDR Pseudomonas infection and higher mortality (p=0.03) [24,42–44].

The main limitations of this study are:

The small dimension of patients population, which did not allow a case-control study with patients matching, this may have induced analysis errors, like the unclear association between female sex and higher risk of mortality; therefore some trends would have become statistically significant if the samples would have been more consistent.

We did not performed molecular typisation of Pseudomonas isolates; this is a useful method to establish the pathogens "epidemiological kinetics" and to define which hospital procedures could facilitate Pseudomonas spread.

We did not evaluate the relationship between appropriateness of antibiotic therapy prescription and outcome.

Conclusion

Our study offers points that can contribute to improve the empiric antibiotic prescription in ICU. In presence of in-hospital patients presenting with a previous history of antibiotic prescription, with a complex clinical condition preceding ICU admission or with a prolonged ventilatory assistance, presenting with signs or symptoms of infection, should be advisable to prescribe a therapy with a specific activity against *Pseudomonas aeruginosa.*

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