








Factors related to mortality by pneumonia unrelated to mechanical ventilation*

Fatores relacionados com mortalidade por pneumonia não associada à ventilação mecânica

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 Jucinay Phaedra Silva Sanches¹
 Carla Fernanda Tiroli¹
 Erika Bernardo da Silva¹
 Gabriela Machado Ezaias Paulino²
 Gilselena Kerbauy¹
 Renata Aparecida Belei¹
 Flávia Meneguetti Pieri¹

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¹Universidade Estadual de Londrina.
Londrina, PR, Brazil.

²Instituto Federal do Paraná.
Londrina, PR, Brazil.

Corresponding author:

Carla Fernanda Tiroli
Rua José Manoel Ruiz, 52, CEP: 86076-200.
Londrina, PR, Brazil.
E-mail: carla_tiroli@yahoo.com.br

ABSTRACT

Objective: to analyze the factors related to mortality by nosocomial pneumonia unrelated to mechanical ventilation. **Methods:** retrospective cohort study with a sample acquired using the 538 notification forms for health care-related infections. The relative risk was calculated and a multivariable analysis was carried out using Poisson regression with a significance level of 5%. **Results:** the multivariable analysis showed that being under 59 years old and taking only one antimicrobial drug were protective factors against death. The main microorganisms responsible for the increase in the risk of death were: *Acinetobacter baumannii*, *Klebsiella pneumoniae* and species of *Candida* (*Candida* spp). **Conclusion:** the factors related to mortality were being 60 years old or older, using two or more antimicrobial substances, and being affected by the microorganisms *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and species of *Candida* (*Candida* spp).

Descriptors: Pneumonia; Mortality; Cross Infection; Hospital Mortality.

RESUMO

Objetivos: analisar os fatores relacionados com mortalidade por pneumonia hospitalar não associada à ventilação mecânica. **Métodos:** estudo do tipo coorte retrospectiva com amostra obtida por meio das 538 fichas de notificação das infecções relacionadas com a assistência à saúde. Calculado o Risco Relativo e realizada análise multivariável por meio de regressão de Poisson com nível de significância de 5%. **Resultados:** na análise multivariável, percebeu-se que os indivíduos com idade inferior a 59 anos e que receberam apenas um antimicrobiano apresentaram proteção para óbito. Os principais microrganismos responsáveis pelo aumento do risco para óbito foram: *Acinetobacter baumannii*, *Klebsiella pneumoniae* e Espécies de *Candida* (*Candida* spp). **Conclusão:** foram fatores relacionados com a mortalidade os indivíduos com idade maior que 60 anos, em uso de dois ou mais antimicrobianos, assim como a identificação dos microrganismos *Acinetobacter baumannii*, *Klebsiella pneumoniae* e Espécies de *Candida* (*Candida* spp).

Descritores: Pneumonia; Mortalidade; Infecção Hospitalar; Mortalidade Hospitalar.

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Introduction

Acquired nosocomial pneumonia, related or not to mechanical ventilation, is one of the main infections in health services and is responsible for a high level of mortality. According to the World Health Organization, infections in the respiratory tract are highly lethal, causing three million deaths worldwide⁽¹⁾. Brazil is one of the countries with the highest incidence of this type of disease⁽²⁾. Currently, it is seen as an adverse and persistent event, that leads to greater morbidity, increased hospitalization time and high treatment costs, not to mention the need for intensive care including mechanical ventilation, also leading to a higher risk of death⁽³⁾.

A North American multicentric study, involving 21 hospitals, presented a prevalence of nosocomial pneumonia unrelated to mechanical ventilation that varied from 0.12 to 2.28 cases per 1,000 patients/day. 15.8% of these cases were associated with death⁽⁴⁾. Another study in a university hospital, in the Brazilian Northeast, described that, from the total number of infections related to health care, 30.2% were diagnosed as having pneumonia⁽⁵⁾. It should be noted that this infection is considered to be undernotified, since there were no attempts to identify its rates of incidence in the services^(4,6-7).

A narrative review presented a scientific gap in the evaluation of measures to prevent and control nosocomial pneumonia unrelated to mechanical ventilation. Certain risk factors can be considered as unavoidable, including age, nutritional conditions, the presence of comorbidities, while others are avoidable, such as those related to conditions of hospitalization, to the treatment provided, and to environmental contamination⁽⁸⁻⁹⁾.

Pneumonia related to mechanical ventilation was and still is investigated with great interest, especially regarding prevention and control measures. However, the knowledge about preventive measures led its incidence to diminish, and the pneumonia un-

related to mechanical ventilation began to stand out, becoming one of the main preoccupations with the safety of the patient. It is considered to be a persisting adverse event in the health services and, as a consequence, it leads to longer hospitalization times, morbidity and mortality, and increases the cost of treatments⁽⁹⁾.

It should also be highlighted that knowing factors associated to death allows for early diagnosis and treatment, giving support to the development of protocols about the prevention and clinical evolution of these cases and helping to provide the patient with a better prognosis. Considering the above, this study aimed to analyze the factors related to mortality by nosocomial pneumonia unrelated to mechanical ventilation.

Methods

This study is a retrospective cohort. It was carried out in the university hospital of the *Universidade Estadual de Londrina*, in the city of Londrina, Paraná, Brazil.

The inclusion criteria were: patients with nosocomial pneumonia unrelated to mechanical ventilation, who were 18 years old or older; hospitalized in the emergency unit, hospitalization unit, intensive care unit, center for the treatment of burns, or in the intensive care unit for burns; and who were diagnosed with nosocomial pneumonia unrelated with mechanical ventilation, from January 2017 to December 2018. The diagnoses of nosocomial pneumonia unrelated to mechanical ventilation were carried out by the physician from the Commission for the Control of Nosocomial Infections, in accordance with the International Classification of Diseases (CID-10) and the definitions of the National Sanitary Surveillance Agency⁽⁸⁾. Were excluded notified cases whose forms had incomplete data. 540 patients were included, diagnosed with nosocomial pneumonia unrelated to mechanical ventilation. From these, 2 cases were excluded, because the

data from the notification form was incomplete. As a result, the sample used in this research was comprised by 538 patients.

The information was acquired from a source of secondary data using the notification forms for health care related infections, made available by the Commission for the Control of Nosocomial Infections from the university hospital of the *Universidade Estadual de Londrina*.

In the hospital where this study was carried out, pneumonia cases are actively searched and identified, and are seen as an indication for the prescription of antimicrobial substances. These substances are only recommended after the approval from the Commission for the Control of Nosocomial Infections. Therefore, the work of this commission allows for the identification of all patients who were prescribed antimicrobial substances. After the patients with some type of infection were identified, a form of suspected health care-related infection is started. When the infection is confirmed, the records change into a form for the notification of health care-related infections.

The notification form was elaborated by the Commission for the Control of Nosocomial Infections according with the criteria from the National Agency of Health Surveillance, including clinical, laboratory, and imaging items. The form is filled in by undergraduate/interns who volunteer to participate in the commission, and are trained to do so by a nurse, who is PhD in education and responsible for the sector. This happens during the hospitalization of the patient, that is, the interns accompany and update information from notification to discharge or death.

All data from the form to notify nosocomial infections was collected and typed into an Excel spreadsheet. It should be mentioned that this form was already the one used for data collection and was considered to be complete by the team of the Commission for the Control of Nosocomial Infections, concerning data related to nosocomial infections.

The data collection stage took place from December 2019 to March 2020 by two researchers who were trained by the coordinator of the research project and by a nurse who had experience in the Commission for the Control of Nosocomial Infections and a member of the research project. Data collection took place once a week, in the afternoon, in the room of the commission. The following clinical and demographic variables were collected: gender, age, days of hospitalization, unit associated to the pneumonia, days of hospitalization until being diagnosed with pneumonia, blood culture associated with pneumonia, tracheal secretion culture associated to pneumonia, number of antimicrobial medicines used, and death.

The variables were categorized as follows: gender (male or female), age group (up to 59 years old or 60 years old or more), hospitalization days (up to 14 days or ≥ 15), unit associated to the pneumonia (emergency unit + hospitalization unit and intensive care unit + center for the treatment of burns + intensive care unit for burns), days of hospitalization until the diagnosis of pneumonia (up to 14 days or ≥ 15), blood culture and tracheal secretion culture associated with pneumonia (positive, negative, not collected) number of antimicrobial drugs used (1 or 2 or more), and death (yes or no).

The emergency unit was considered together with hospitalization units due to the profile of the institution, since patients from the emergency unit may not be transferred due to the lack of beds available. The center for the treatment of burns and the intensive care unit for the treatment of burns were grouped with the intensive care unit because these units receive severe cases until the clinical framework is stable.

The number of hospitalization days until diagnosis was calculated based on the subtraction between the variables: date of hospitalization, date when the nosocomial pneumonia unrelated to mechanical ventilation was diagnosed, and date of discharge or death. Diagnostic cultures were carried out upon request

of the physician in charge of the patient, considering clinical aspects (hyperthermia, changes in the characteristics of trachea secretions), laboratory aspects (leukogram results), and imaging (x-ray).

Tracheal secretion collection is carried out via the aspiration of airwaves, when the patient is unable to promptly expel catarrh or was using catheters. For cases with no pulmonary secretion, no collection was made.

Blood culture was carried out through two venipunctures or peripheral artery punctures, and blood was stored in aerobic and anaerobic blood culture vials. After collection, the material was sent to the laboratory of clinical analysis of the university hospital from the *Universidade Estadual de Londrina*. There, tracheal secretion and blood culture were analyzed using the Bactec™ automated system. The absence of blood culture analysis is justified when the blood is collected by there is no microbial growth, when the team fails to collect the material and, finally, when the patient dies before there is time to collect a sample.

The data were transcribed into a Microsoft Excel® 2013 spreadsheet. Later, they were transported and analyzed in the IBM software *Statistical Package for the Social Sciences for Windows*, version 20.0® For the bivariate analysis, the variable death was crossed with the following exposition variables: gender, age, unit associated to pneumonia, days of hospitalization prior to the diagnostic of pneumonia, blood culture, and tracheal secretion culture, associated to pneumonia, number of antimicrobial drugs used. The chi-squared test was applied, and the probability of type I error was considered to be significant when at 5%, with the respective confidence interval of 95% (CI 95%).

For the multivariable analysis, Poisson's regression with a robust variance adjustment was used. The selection of adjustment variables considered the following mathematical criteria: $p < 0.20$ in the variate analysis, with the following variables for the multiva-

riable model: age group, hospitalization days prior to the diagnosis of pneumonia, and number of antimicrobial drugs. The magnitude of the association was determined calculating relative risk (RR) with an CI of 95%. The standardized level of reference (RR=1) indicated the best situation possible, that is, no risk.

The research began after being approved by the Ethics Committee for Researches with Human Beings from the *Universidade Estadual de Londrina*, with Certificate for the Submission to Ethical Appreciation No. 00745218.0.0000.5231 and opinion No. 2,978,943/2018, as per Resolution 466/12. To guarantee the secrecy of information, the researchers signed the Confidentiality and Secrecy Form.

Results

Little more than half participants were male (n=331; 61.5%) and 60 years old or older (n=327; 60.8%). Regarding clinical data, most were hospitalized for 15 days or more (n=406; 75.5%) and diagnosed with pneumonia for up to 14 days after hospitalization (n=451; 83.8%). The units associated to pneumonia the most were the emergency unit and hospitalization units (n=374; 69.5%). Most participants used one or more antimicrobial drugs (n=375; 69.7%) and 260 individuals (48.3%) died.

In the multivariable analysis, individuals who were 59 years old or younger (RR=0.60; IC95% = 0.50 - 0.73; $p < 0.001$) and who were applied only one antimicrobial drug (RR=0.35; IC 95% 0.26-0.47; $p < 0.001$) were less likely to die when compared to those who were 60 years old or older and used more than one antimicrobial drug, respectively (Table 1).

398 patients had their tracheal secretion and/or blood collected for bacterial cultures, and in 214 (53.8%) the culture was positive. Bivariate analysis of the bacterial cultures, associated with death, are presented in Table 2.

Table 1 – Bivariate and multivariate analysis of demographic, clinical, and therapeutic factors associated to the death of the 260 patients with pneumonia unrelated to mechanical ventilation. Londrina, PR, Brazil, (2017-2018)

Variables	Death	Bivariate analysis		Multivariable analysis*	
	n (%)	†RR (‡CI 95%)	§p-value	RR (CI95%)	p-value
Gender					
Male	155 (59.6)	0.92 (0.77-1.10)	0.380		
Female	105 (40.4)	1			
Age group					
Up to 59	76 (29.2)	0.64 (0.52-0.79)	<0.001	0.60 (0.50-0.73)	<0.001
> 60	184 (70.8)	1			
Days of hospitalization until the diagnosis of pneumonia					
Up to 14	209 (80.4)	0.79 (0.65-0.97)	0.030	0.85 (0.71-1.02)	0.086
> 15	51 (19.6)	1			
Unit of admission					
Emergency unit and hospitalization unit	236 (90.8)	1.08 (0.79-1.47)	0.640		
Intensive care unit, center for the treatment of burns, and intensive care unit for the treatment of burns	24 (9.2)	1			
Unit associated to the diagnosis of pneumonia					
Emergency unit + hospitalization unit	179 (68.8)	0.97 (0.80-1.17)	0.740		
Intensive care unit, center for the treatment of burns, and intensive care unit for the treatment of burns	81 (31.2)	1			
Number of antimicrobial drugs					
1	35 (13.5)	0.36 (0.26-0.49)	<0.001	0.35 (0.26-0.47)	<0.001
>2	225 (86.5)	1			

*Adjusted by: age group, days of hospitalization until the diagnosis of pneumonia, and number of antimicrobial drugs; †RR: relative risk; ‡IC: confidence interval; §chi-squared test

Table 2 – Bivariate analysis of the 398 bacterial cultures associated to death in patients with pneumonia unrelated to mechanical ventilation. Londrina, PR, Brazil, (2017-2018)

Variables	Yes	No	Bivariate analysis		
	n (%)	n (%)	Relative risk	*CI 95%	†p-value
Positive culture associated with pneumonia					
Yes	135 (63.1)	79 (36.9)	1.51	1.24-1.84	<0.001
No	77 (41.8)	107 (58.2)			
<i>Acinetobacter baumannii</i>					
Yes	47 (74.6)	16 (25.4)	1.52	1.27-1.81	<0.001
No	165 (49.3)	170 (50.7)			
<i>Candida spp</i>					
Yes	22 (73.3)	8 (26.7)	1.42	1.12-1.80	0.020
No	190 (51.6)	178 (48.4)			
<i>Escherichia coli</i>					
Yes	9 (60.0)	6 (40.0)	1.13	0.74-1.73	0.590
No	203 (53.0)	180 (47.0)			
<i>Staphylococcus Coagulase Negativa</i>					
Yes	15 (55.6)	12 (44.4)	1.05	0.74-1.49	0.810
No	197 (53.1)	174 (46.9)			
<i>Klebsiella pneumoniae</i>					
Yes	36 (66.7)	18 (33.3)	1.30	1.05-1.62	0.030
No	176 (51.2)	168 (48.8)			
<i>Pseudomonas aeruginosa</i>					
Yes	16 (64.0)	9 (36.0)	1.22	0.89-1.66	0.270
No	196 (52.5)	177 (47.5)			
<i>Staphylococcus aureus</i>					
Yes	28 (57.1)	21 (42.9)	1.08	0.83-1.41	0.560
No	184 (52.7)	165 (47.3)			
<i>Gram positive cocci</i>					
Yes	16 (45.7)	19 (54.3)	0.85	0.58-1.23	0.350
No	196 (54.0)	167 (46.0)			

*Confidence interval; †chi-squared test

Patients with a positive culture associated with pneumonia had a higher risk of death (RR=1.51; IC95% = 1.24 – 1.84; $p < 0.001$). The increase in the risk of death was associated with positive cultures for the following microorganisms: *Acinetobacter baumannii*, *Candida* spp., and *Klebsiella pneumoniae*.

Discussion

The results of this investigation show the reality of a single local public hospital limiting the possibilities of generalizing the results, despite the sample size. It was also found that many forms are not adequately filled in and there is no indication of the severity of the cases. A limiting factor for this study is the fact that it used data from secondary sources, making it impossible to detect modifiable risk factors such as: environmental microbiota, assistance from the multi-professional team, and unavoidable factors: score of severity at the time of admission and comorbidities.

The results presented here may give support to the care practice in the institution where the research was carried out through the elaboration of bundles, assistance protocols to detect nosocomial pneumonia unrelated to mechanical ventilation and treat it early, in addition to the development of later multicentric studies. Furthermore, it can contribute for teaching and research in nursing in regard with the acquisition of knowledge related to two factors that can provoke the death of patients with pneumonia unrelated to mechanical ventilation. It can also give support to a multifaceted management of care, which must be provided for the hospitalized patient to prevent health care-related infections, reflecting on the quality of attention and, consequently, on the reduction of the deaths associated to it.

The mortality in people with nosocomial pneumonia unrelated with mechanical ventilation is common, and the pneumonia can be a direct or indirect cause of their death. In a study carried out in the United States, the likelihood of death was significantly higher in people with nosocomial pneumonia unrelated

to mechanical ventilation when compared to other groups⁽¹⁰⁾.

The association between death and the number of antimicrobial drugs may be related to the resistance of the microorganisms present in the cultures, since the patient needs wide spectrum therapy and multiple antibiotics to fight against these pathogens. On the other hand, patients whose tests indicate antibiotic sensitivity and who are not in septic shock or have a high risk of death are recommended to undergo a single therapy^(2,11).

The main microorganisms associated to death, are: *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Candida* spp. The airways are naturally colonized, but when there are large aspirations and pathogen agents are absorbed, there is a risk for infection. This is especially true for elders with bad oral hygiene, bacterial biofilm, food residues, and erosion. The insertion of bacteria deteriorates the defense mechanisms, leading to the introduction of virulent pathogens⁽¹²⁾.

Acinetobacter baumannii pneumonia is an increasingly recognized infection in critical patients. High rates of resistance to the most common antimicrobial drugs mean that professionals must empirically choose the adequate treatment for pneumonia from *Acinetobacter baumannii*, which is challenging⁽¹³⁾. Similarly, infections by *Klebsiella pneumoniae* are difficult to treat due to the resistance against antimicrobial drugs and to hyper-virulent strains⁽¹⁴⁾.

Regarding *Candida* spp., a systematic review with meta-analysis showed that the colonization from this microorganism is associated to longer mechanical ventilation, more mortality in 28 days, hospitalization in intensive care units, and, probably, to longer hospitalizations⁽¹⁵⁾. The clinical, therapeutic, and demographic characteristics of the patients with nosocomial pneumonia unrelated to mechanical ventilation also show that the predominance of deaths in the elders can be attributed to the excess of comorbidities in this age group⁽¹⁶⁻¹⁷⁾.

Although there have been many advances in this field regarding prevention, diagnosis and treat-

ment for pneumonia associated to mechanical ventilation, prophylactic measures are insufficient when they are connected to nosocomial pneumonia unrelated to mechanical ventilation, leading to long hospitalizations due to the worsening of clinical conditions, and to the need of transferring into an intensive care unit and staying there^(4,17).

It is also worth reminding the causal relation with the hospitalization sector. Our results showed that the emergency unit and the hospitalization units were responsible for a greater incidence of cases. The precariousness of the care provided, caused by insufficient human resources, is one of the main causes of this health issue in hospital units, since, in intensive care units, the only well-defined protocols are targeted at preventing pneumonia related to mechanical ventilation⁽¹⁸⁾.

The risk of death by nosocomial pneumonia unrelated to mechanical ventilation, in addition to other components, must be investigated and analyzed, as a way to give more visibility to this issue. The knowledge and the ability of the health team and techniques associated to the prevention of infections, such as hand hygiene, are included. In this context, studies are needed that evaluate the assistance provided to the individual, the way in which oxygen therapy devices are stored in the units, the quality of chemical disinfection, not to mention studies that investigate the presence of microorganisms in the hospital environments⁽¹⁹⁾.

Conclusion

This research has found that the number of deaths in patients caused by nosocomial pneumonia unrelated to mechanical ventilation was high. The factors related to mortality were 60-year-old or older people, the use of two or more antimicrobial drugs, and the identification of the following etiologic agents: *Acinetobacter baumannii*, *Klebsiella pneumoniae* e Espécies de *Candida* (*Candida* spp.).

Collaborations

Sanches JPS, Tiroli CF, Silva EB and Pieri FM took part in the conception of the project, data analysis and interpretation, in the writing of the article, and in a relevant critical review of its intellectual content. Paulino GME, Kerbauy G, Belei RA took part in data interpretation, in a relevant critical review of the intellectual content, and in the approval of the final version to be published.

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