

## Mortality due to respiratory infections: an alert study before COVID-19 pandemic

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### Summary

**Objective.** Respiratory tract infections remain a common problem in clinical practice with high morbidity and mortality worldwide. In Portugal, pneumonia was the third leading death cause in 2018. Due to COVID-19 pandemic, there is a growing concern about the burden of respiratory diseases and preventable risk factors. The present study started before the pandemic and its aim was to determine the occurrence of pneumonia/bronchopneumonia in a postmortem series and to characterize its circumstantial context.

**Methods.** A retrospective anatomopathological study was performed on cases with acute pneumonia/bronchopneumonia at the Medicolegal Portuguese Institute (2011-2017).

**Results.** In an autopsy series of 737 patients, 521 were male and 675 presented comorbidities. The mean age was  $63.87 \pm 19.8$  years. The most common acquisition site was community (65.1%), as natural death (65.5%). Concerning the manner of death, most cases (48.0%) were sudden deaths, followed by accidents (29.2%). A statistically significant association was observed between the medicolegal etiology and the place of infection acquisition, with higher prevalence of natural obitus (91.0%) in community-acquired pneumonia/bronchopneumonia versus higher prevalence of violent obitus in hospital-acquired pneumonia/bronchopneumonia (82.1%) ( $p < 0.001$ ).

**Conclusions.** Forensic anatomopathological postmortem data may contribute to better understand community and hospital pulmonary infections.

**Key words:** pneumonia, bronchopneumonia, postmortem study

### Introduction

Although lower respiratory tract infections are potentially preventable, incidence and health resource consumption have been increasing <sup>1</sup>. Portugal presents the highest rates of pneumonia mortality in the European Union <sup>2</sup>. According to the National Statistical Institute, pneumonia was the third leading cause of death in Portugal, in 2018, registering an increase of 2.5% compared to the previous year <sup>3</sup>. The emergence of SARS-CoV-2 may change these statistics significantly.

In the present context, high hospitalization rates, admission to Intensive Care Unit and death <sup>4</sup> may contribute to end the neglect of respiratory infections by focusing on human-to-human transmission and health education <sup>5</sup>. Prior studies have identified multiple variables that contribute to community- and hospital-acquired pulmonary infections <sup>6-8</sup> but, to date, the circumstances around death are poorly characterized. Autopsy studies can enhance our understanding of these diseases <sup>9,10</sup>, providing use-

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ful information about the cause and manner of death. The present study started before COVID-19 pandemic and aims to determine the occurrence of acute pneumonia and bronchopneumonia in a postmortem series and to characterize its circumstantial context; expecting that the data collected might contribute to highlight health preventive measures and/or patient outcome improvements.

## Materials and methods

### STUDY DESIGN

Our study was designed as a population-based retrospective study in the Centre of Portugal (area = 31,334 km<sup>2</sup>, population = 2,749,108 inhabitants) between 1 January 2011 and 31 December 2017. Based on the final cause of death as determined by the pathologist, we selected cases in which the primary cause of death was acute pneumonia or bronchopneumonia. Ethical approval was obtained from the Central Branch of the Portuguese National Institute of Legal Medicine and Forensic Sciences.

### DATA COLLECTION

To establish trends and identify the circumstances underlying death, the following data was collected for each case: deceased person's demographics, clinical and medicolegal information available in the request for histopathological examination and final anatomopathological report. Variables analyzed included age, sex, comorbid conditions, medication, history of alcohol, tobacco or illicit drugs use, timing of the most recent contact with the healthcare system before death (which allowed pulmonary infection classification according to site of acquisition) and factors related to the medicolegal manner of obitus, as natural death (sudden or non-sudden) and violent death (accident, homicide or suicide).

Cases without patient related information (such as age), deaths in neonates associated with placental rather than independently acquired infection, and deaths caused by interstitial pneumonia or pneumonia due to aspiration events were excluded.

### DEFINITIONS

Community-acquired pneumonia/bronchopneumonia: acute pulmonary infection acquired outside of a healthcare establishment.

Hospital-acquired pneumonia/bronchopneumonia: acute pulmonary infection occurring 48 hours or more after hospital admission.

Sudden death: defined as an unexpected non-violent

(natural) death, which occurred instantly or within 1 hour after the onset of symptoms. If unwitnessed, it is defined as an unexpected non-violent (natural) death within a period of 24 hours of an apparently healthy person or of an individual whose disease did not present as a short-term death risk.

Violent death: includes homicide, suicide and accidents.

### DATA ANALYSIS

Statistical analysis was performed in SPSS, version 22. In the descriptive analysis, means (M) and standard deviations (SD) were used for continuous variables and absolute (n) and relative (%) frequencies for categorical variables. The association of categorical variables was assessed using the chi-square test or Fisher's test; in the continuous variables, the t-test was used. We used Kolmogorov-Smirnov test to evaluate normal distribution of continuous variables. The Levene test was used to assess the homogeneity of variances.

Logistic regression was used to measure the multivariate association between outcomes and potential predictors. The odds ratio (OR) and the respective 95% confidence interval were calculated. The level of significance for H0 rejection was 5%.

## Results

A series of 737 cases was identified: 342 (46.4%) cases concerning victims with pneumonia and 395 (53.6%) cases concerning victims with bronchopneumonia, over the 7-year period of the study. Registrations indicated predominance of males; median age was 63.87 years (range 0-97). Comorbidities were present in 675 cases (91.6%). The most common site of infection acquisition was community (65.1%) and the most frequent medicolegal etiology was natural death (65.5%). The deceased persons' characteristics and circumstances of death are summarized in Table I. In regard to the manner of death, the majority of these cases (48.0%) was sudden deaths, followed by accidents (29.2%) (Tab. II).

When stratifying for age, we identified that in the 20-39-year age cohort, violent death was more frequent than natural death and hospital was more common than community as site of infection acquisition. Community-acquired pneumonia/bronchopneumonia reached its maximum in the 40-64-year age cohort and hospital-acquired pneumonia/bronchopneumonia increased with age (Tab. III).

The association observed between the medicolegal etiology and the place where the pulmonary infection had been acquired was statistically significant, with higher

**Table I.** Demographic characteristics of series.

	<b>Pneumonia (n = 342)</b>	<b>Bronchopneumonia (n = 395)</b>	<b>p-value</b>
<b>Age, mean (SD)</b>	61.84 (21.16)	65.63 (18.45)	p = 0.010
<b>Sex, n (%)</b>			p = 0.134
Female	91 (26.6%)	125 (31.6%)	
Male	251 (73.4%)	270 (68.4%)	
<b>Site of acquisition, n (%)</b>			p = 0.230
Community	215 (62.9%)	265 (67.1%)	
Hospital	127 (37.1%)	130 (32.9%)	
<b>Medicolegal etiology, n (%)</b>			p = 0.984
Natural death	224 (65.5%)	259 (65.6%)	
Violent death	118 (34.5%)	136 (34.4%)	
<b>Presence of comorbidities, n (%)</b>			p = 0.054
No	36 (10.5%)	26 (6.6%)	
Yes	306 (89.5%)	369 (93.4%)	

**Table II.** Distribution between natural death (sudden or non-sudden) and violent death (accident, homicide or suicide).

	<b>Pneumonia (n = 342)</b>	<b>Bronchopneumonia (n = 395)</b>	<b>p-value</b>
<b>Natural, n (%)</b>			p = 0.203
Non-sudden	66 (19.3%)	63 (15.9%)	
Sudden	158 (46.2%)	196 (49.6%)	
<b>Violent, n (%)</b>			p = 0.844
Accident	101 (29.5%)	114 (28.9%)	
Homicide	4 (1.2%)	4 (1.0%)	
Suicide	13 (3.8%)	18 (4.6%)	

**Table III.** Distribution of cases according to age groups.

Age, n (%)	<b>Pneumonia</b>				<b>Bronchopneumonia</b>			
	<b>Natural death</b>		<b>Violent death</b>		<b>Natural death</b>		<b>Violent death</b>	
	<b>Community-acquired</b>	<b>Hospital-acquired</b>	<b>Community-acquired</b>	<b>Hospital-acquired</b>	<b>Community-acquired</b>	<b>Hospital-acquired</b>	<b>Community-acquired</b>	<b>Hospital-acquired</b>
0-9 yrs	6 (85.7%)	1 (14.3%)	1 (100.0%)	0 (0.0%)	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10-19 yrs	4 (100.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
20-39 yrs	15 (93.8%)	1 (6.3%)	1 (5.3%)	18 (94.7%)	9 (100.0%)	0 (0.0%)	0 (0.0%)	9 (100.0%)
40-64 yrs	78 (91.8%)	7 (8.2%)	8 (21.6%)	29 (78.4%)	91 (90.1%)	10 (9.9%)	9 (32.1%)	19 (67.9%)
65-79 yrs	42 (82.4%)	9 (17.6%)	3 (9.1%)	30 (90.9%)	84 (93.3%)	6 (6.7%)	11 (23.4%)	36 (76.6%)
≥ 80 yrs	56 (91.8%)	5 (8.2%)	1 (3.8%)	25 (96.2%)	42 (85.7%)	7 (14.3%)	9 (17.6%)	42 (82.4%)

prevalence of natural etiology (91.0%) in community-acquired pneumonia/bronchopneumonia versus higher prevalence of violent etiology in hospital-acquired pneumonia/bronchopneumonia (82.1%) ( $p < 0.001$ ) (Tab IV).

On multivariate analysis, the presence of comorbidities was significantly associated with natural sudden deaths (OR = 3.44, 95% CI: 1.25-9.45,  $p = 0.017$ ).

**Table IV.** Association between the medicolegal etiology and site of infection acquisition.

Medicolegal etiology, n (%)	Community (n = 480)	Hospital (n = 257)	p-value
Natural	<b>437 (91.0%)</b>	<b>46 (17.9%)</b>	<b>p &lt; 0.001*</b>
Non-sudden	101 (21.0%)	28 (10.9%)	
Sudden	336 (70.0%)	18 (7.0%)	
Violent	<b>43 (9.0%)</b>	<b>211 (82.1%)</b>	
Accident	27 (5.7%)	188 (73.2%)	
Homicide	2 (0.4%)	6 (2.3%)	
Suicide	14 (2.9%)	17 (6.6%)	

\*statistically significant.

## Discussion

Most of the deceased were male septuagenarians with comorbidities, a fact favored by several studies that reported a higher male susceptibility to pulmonary infections and a higher risk of death due to sepsis<sup>11</sup>. In high-income countries, mortality due to pulmonary infections is usually related to older age and medical comorbid conditions<sup>12-14</sup>. In our study, the primary cause of death generally appeared to be community-acquired pulmonary infections. This represented 94.9% of natural sudden death cases, which led to consider that most people in this study died before exposure to the healthcare system. That fact presents a potential opportunity for intervention. In a German study assessing knowledge of sepsis among the elderly population (aged 65 or older), only 18.2% of respondents knew that infections such as influenza or community-acquired pneumonia could cause sepsis<sup>15</sup>. Therefore, general population sanitary education may be the key to save lives, namely of elderly and to avoid delaying medical care.

At the same time, community-acquired pneumonia incidence presents a U-shaped distribution and it is the leading-cause of death in children under 5 years old, worldwide<sup>8,16,17</sup>. Older children are also vulnerable. In our study, 2.9% of the deceased with community-acquired pneumonia/bronchopneumonia had less than 10 years of age. In a multicenter study in South Wales about why children hospitalized for pneumonia were not submitted to general practitioner consultation before the day of hospitalization, most carers reported that they simply had not considered it and/or did not think their child's initial symptoms were serious or unusual. This lack of early general practice consultation was strongly associated with rapid evolution of pneumonia<sup>18</sup>. These results highlight the need to advise parents or carers about signs of deterioration, dehydration, and complications of pneumonia.

In addition to the above findings, our study showed that hospital-acquired pneumonia/bronchopneumonia was more common in patients who suffered an accident. As demonstrated by A.J. Mangram et al.<sup>19</sup>, pneumonia can develop in any trauma patient, but patients injured in motor vehicle collisions are more likely to be affected by infections than patients injured by other mechanisms.

Furthermore, in our data, when medicolegal etiology was violent, 83.1% of the deceased victims acquired pneumonia/bronchopneumonia in a hospital setting. Of these, 16.6% had less than 40 years old. This finding may be related to the fact that younger individuals are more often implicated in road accidents and thus more prone to acquire pneumonia while hospitalized. For this reason, preventive measures are essential and must be emphasized in healthcare institutions. Concerning this issue, Baker D. et al.<sup>20</sup> found that in the 24 hours prior to diagnosis, most of the patients did not have hospital care measures associated with pneumonia prevention. This is a call to action: reducing the incidence of hospital-acquired pneumonia could make a difference in functional outcomes and decrease mortality<sup>21,22</sup>.

Multiple risk factors for community- and hospital-acquired pneumonia are modifiable and amenable to effective interventions. A recent systematic review established that active smoking, environmental exposures, malnutrition, poor oral health, use of immunosuppressive therapy, oral steroids and proton pump inhibitors or H2 antagonists, among others, are preventable risk factors for community-acquired pneumonia in adults<sup>8</sup>. The role of 23-valent pneumococcal polysaccharide (PPSV23) and influenza vaccination as protective factors against community-acquired pneumonia remains unclear<sup>8</sup>. Yet, in Portugal, 13-valent pneumococcal conjugate vaccine (PCV13) and PPSV23 vaccine are recommended in adults at increased risk for invasive pneumococcal disease<sup>23</sup>.

Literature reports that the most studied preventive measure in hospital-acquired pneumonia is oral hygiene<sup>24</sup>. However, there are several recommendations for pneumonia prevention issued by international guideline committees and professional societies that also include: hand hygiene, bed elevation, use of orogastric tubes, avoidance of endotracheal intubation, promotion of non-invasive ventilation and early mobilization<sup>25-27</sup>. Clinicians, nurses and other health professionals should be aware of these measures to reduce pneumonia mortality among hospitalized patients.

The authors recognize a few limitations in this study. First, it is a retrospective database analysis, and so there is the possibility of information bias. In addition, autopsy data presents the inherent bias due to the selection of fatal cases. Moreover, some important patient characteristics (such as personal and family medical history) could not be analyzed because they were not always available for consultation, which also happened with history of alcohol, tobacco or drugs use. In fact, in some cases, consumption was reported, but in general, these lifestyle habits were not mentioned. Lastly, one of the main difficulties of this study is the unavoidable heterogeneity of population, risk factors and comorbid conditions analyzed. However, this can also be seen as an advantage, since the sample correspond to a real autopsy series.

Despite the aforementioned limitations, this work contributed to a more accurate identification and better understanding of circumstances underlying death by pulmonary infections in Portugal, filling a gap in the literature, since there have been few autopsy studies on pneumonia/bronchopneumonia, and none of them specifically on this setting. Lessons learned from this work can be used to recognize the threat of pneumonia/bronchopneumonia and to explore new strategies of systematic preventive measures in the community as well as in hospitals or other health institutions.

## Conclusions

There is much to be explored and understood about severe respiratory tract infections, especially in the context of COVID-19. Preventing these deaths requires standard strategies to reduce infection susceptibility and transmission. The COVID-19 pandemic played a significant role in raising awareness about the relevance of hygiene measures and respiratory etiquette among the general public and healthcare providers, which may hopefully change the course of deadly infectious diseases.

## CONFLICTS OF INTEREST

The Authors declare no conflict of interest.

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