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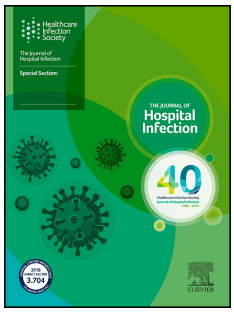

Incidence and impact of hospital-acquired pneumonia: a Portuguese nationwide 4-Year study.

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Incidence and impact of hospital-acquired pneumonia: a Portuguese nationwide 4-Year study.

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Running title: Hospital-acquired pneumonia incidence

Summary

We present the incidence of hospital-acquired pneumonia (HAP) in Portugal during a 4-year period (2014-2017). Data were retrieved from the 100 Portuguese Hospital diagnosis discharge database for adult patients and included gender, age, chronic comorbidities, mortality and hospital length of stay.

We found 28,632 episodes of HAP, an incidence of 0.95 per 100 admissions. HAP patients had both a prolonged hospital length of stay (mean 26.4 days) and high mortality (33.6%). Most episodes occurred in patients aged ≥65 years and in males (76.1% and 61.7%, respectively). Invasive ventilation was required in 18.8%.

Key words: Hospital-acquired pneumonia; Hospital epidemiology; Stroke; Age related disease; Outcome assessment

Introduction

Hospital-acquired infections, especially pneumonia (HAP), remain one of the most important challenges clinicians face in everyday work [1]. Nevertheless, the epidemiology of HAP is uncertain. Epidemiological studies focusing on HAP in non-ventilated patients suggest that the incidence may be twice as high as that of ventilator associated pneumonia [2,3], with similar mortality rate [2] and frequently leading to ICU admission [2].

There is scarce information regarding both HAP risk and incidence outside the ICU, and epidemiological data regarding HAP global incidence is clearly needed.

In this study we addressed the incidence of HAP at a national level. We studied data from four consecutive years (2014-2017) to account for possible seasonal variation. We included all hospitals, both community and university, of the Portuguese mainland health care system. We aimed to determine the burden of HAP nationally, and to identify the sub-groups at higher risk.

Methods.

The Central Administration of the Health System of the Portuguese Ministry of Health records administrative and clinical discharge data for all admissions to the 100 (77 General) National Health System hospitals in mainland Portugal. The anonymized database includes all discharge diagnoses of hospital inpatients, either dead or alive, codified according to the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM), until 2016, and the 10th Revision (ICD-10-CM), from 2017 onwards. The ICD-9 and ICD-10 codes used to identify the different pathologies for this study are described in detail in Supplementary file A.

In 2014 a complementary codification approach was introduced in Portugal. All diagnoses were coded according to their presence or absence on admission. Pneumonia not "present on admission" is, by definition, acquired in the hospital. Consequently, this codification allowed an easier and more accurate identification of HAP episodes.

We retrospectively analyzed data from all adult patients discharged between Jan 1st 2014 and Dec 31st 2017 with HAP, that is a pneumonia "not present on admission". Patients under 18 years of age or with a hospital length of stay (LOS) of less than 48h were excluded. We collected administrative data, namely age and gender, the presence of chronic comorbidities, acute stroke, type of admission (either medical or for a surgical procedure) or ICU admission, along with outcomes, especially mortality, invasive mechanical ventilation and hospital LOS.

We adopted a descriptive statistical analysis approach. Rates of HAP per 100 episodes of hospitalization and per 1000 hospital patient days (with 95% confidence intervals [CI]), according to age and gender, were computed for the whole population, for each year of the study and for the relevant subgroups.

Continuous variables were expressed as mean ± square deviation and/or median [interquartile range] according to data distribution; the discrete variables were expressed as total number (percentage).

The statistical significance analysis was performed using the Chi-square test (for discrete variables), Student's T, Mann Whitney or Kolmogorov Smirnov tests (for continuous variables), according to data distribution. Odds Ratio (OR) with 95% CI were computed.

All the calculations presented were obtained using the statistical software package R statistical computing environment (R Core Team 2020. R: A language and environment

for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) and the Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA).

This study was approved by the Central Administration of the Portuguese National Health System. As all individual patient information was protected and only aggregated data was available, the requirement for patient informed consent was waived.

Results.

Hospital-acquired pneumonia incidence

A total of 3,026,233 hospital discharges were evaluated. We identified 28,632 episodes of HAP. The overall incidence was 0.95% and increased almost 5 times with age (Figure 1). The incidence of HAP per 1000 hospital-days was 1.13 (1.42 in men and 0.85 in women). Male patients represented only 42.3% of all hospital admissions but accounted for 61.9% of HAP cases (figure 1).

Overall, HAP was strongly associated with a prolonged LOS (mean 26.4 days) and with a very high mortality (33.6%), both significantly above the recorded values for general hospitalizations of ≥48h (mean LOS 8.4 days; mortality rate 6.7%; $p<0.0001$). Mortality of patients with HAP also increased with age, attaining 40.1% in patients older than 85 years. Even in patients <30 years, mortality was still 12.4%.

The incidence of HAP was higher in patients admitted for a medical reason (1.1% vs. 0.69% of surgical admissions, $p<0.0001$). As many as 5,383 (12.5%) of all patients ventilated in mainland Portugal during the study period had HAP, either before or as a complication of invasive mechanical ventilation, unveiling a significant burden of HAP in Intensive Care Medicine. Again, these patients had a high mortality rate (42%) and long hospital LOS (29 [17-44.5]).

Comorbidities and hospital-acquired pneumonia

Mortality was consistently higher in patients with HAP and chronic diseases, especially chronic hepatic disease (44.2%). Moreover, mortality rate increased with the cumulative number of comorbidities, from 29.1% in patients without any diagnosed comorbidity to 40.8% in patients with 2 or more (mortality OR for ≥ 1 comorbidity 1.48 95% CI 1.33-1.65).

Acute stroke was strongly associated with HAP (Figure 2). The overall stroke prevalence in HAP patients was 14.3% (with no significant gender difference), well above the reported 3.24% stroke prevalence for the general hospitalizations ≥ 48h. This association increased with age, roughly 1% per each 5 years, being 17.3% in patients older than 85 years, whilst only 6% of all hospitalizations in the same age group had a diagnosis of stroke. Stroke patients (either ischaemic or haemorrhagic) who developed HAP during their hospital stay had a much higher risk of death (OR 4.84, 95% CI 4.53-5.16).

Discussion

The incidence of HAP in mainland Portugal during a consecutive 4-year period, from 2014 to 2017, was 0.95%, which corresponded to 1.13 episodes per 1000 hospital-days. Patients ≥65 years and male gender were significantly more prone to HAP, especially patients with an acute stroke. Hospital mortality was very high, at 33.6% overall, and increased sharply with age. Even patients without significant comorbidities had a mortality rate of roughly 30%, suggesting that attributable mortality may be substantial. Hospital LOS was very long (26.4 days), roughly 3 times higher than that of the general population. Invasive mechanical ventilation was provided to 18.8% of these patients.

An important limitation of retrospective studies addressing HAP is the reliance on clinical diagnoses, especially as 2/3 of HAP may be acquired outside of the ICU [4,5], where classic signs of pneumonia may be missing in as many as half of the patients [6]. Automatic detection of HAP patients, based on oxygenation drop and antibiotic use, has recently been proposed [7] and may facilitate identification.

As a consequence, the reported incidence of HAP seems to be mostly related to the definitions used to identify the cases and the included population. In a recently published European point prevalence study an overall incidence of 1.3% was noted [3] and a Portuguese HAP incidence of 2.7% was reported, much higher than we found in our study [3]. Hospital selection bias and a possible seasonal variation may help to explain these differences.

A large study from the USA, including more than 6 million patients, reported a HAP incidence of 1.6%, corresponding to 3.63 per 1000 hospital-days [8], again higher than our rates. In this study HAP was defined as a discharge secondary diagnosis of pneumonia [8], whilst we only included patients with pneumonia considered to be “not present on admission”. In contrast, a study done in 24 hospitals, using a HAP definition identical to ours [4] reported an incidence of 0.12-2.28 per 1000 hospital-days, very similar to ours. In the same study, LOS was also very long and 37.3% of HAP patients stayed in the hospital for more than 20 days [4].

The impact of HAP on outcome also seems to extend to the ICU. In a large cohort of ICU patients, the incidence of HAP was 5% in ventilated patients and 2% in non-ventilated patients. The 30-day mortality was significantly increased in both groups (adjusted hazard ratio 1.38 [1.24–1.52] in ventilated and 1.82 [1.35–2.45] in non-ventilated) [9].

In our study age was the most important predictor of HAP and more than 75% of HAP occurred in patients older than 65 years, unveiling a relationship between this pathology, senescence and frailty. Along with age, acute stroke may cause swallowing dysfunction and facilitate aspiration, both as a result of direct neurologic insult or as a consequence of oropharyngeal muscle weakness [10]. In our study, an interaction of age and acute stroke on the incidence of HAP, was disclosed (Figure 2).

This study has some limitations: It relates only to Portuguese hospitals, relies on a discharge diagnosis codification system, is retrospective, and limitations of the database do not allow segregation of ventilator associated HAP. Furthermore, the anonymized nature of the database did not allow us to perform discharge diagnosis audits to further validate the data. It also has several strengths. To our knowledge, it is the first HAP incidence study done at a national level, including both large and small community as well as teaching hospitals. Beside it includes data from 4 complete consecutive years, accounting for a potential seasonal variation. A large data base (including more than 3 million hospital admissions) was evaluated, which strengthens our conclusions.

In conclusion, HAP is common in hospital wards as well as in the ICU, and its incidence increased with age, male gender and stroke. It is associated with significant mortality, hospital LOS and health care resource utilization. The strong association with stroke deserves further study.

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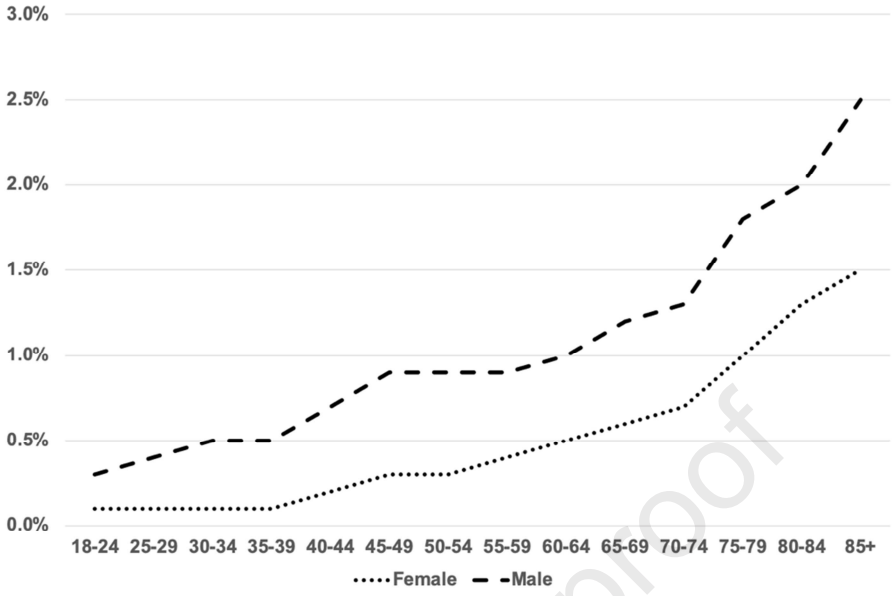

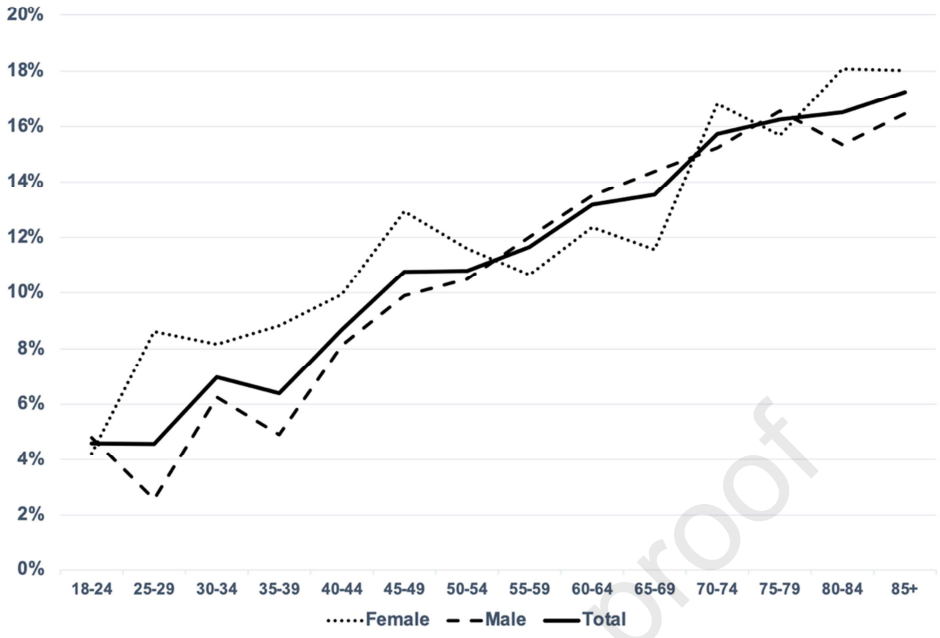

Figure Captions

Figure 1 – **Incidence of hospital-acquired pneumonia**

The incidence of hospital-acquired pneumonia increased almost 5 times with age, mainly after 70 years. The curve trend was similar for both genders, although the incidence was twice as higher in males (OR 2.05, 95% CI 2.0-2.1, $p<0.001$).

Figure 2 – **association of acute stroke and hospital-acquired pneumonia**

A close relationship between age and the presence of stroke in patients with hospital-acquired pneumonia was noted. The incidence of hospital-acquired pneumonia in all patients with stroke increased roughly 1.05% per every 5 years of age ($p<0.001$ for comparisons between 2 time points)

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Conflicts of Interest

Dr. Gonçalves-Pereira reports grants from Merck Sharp and Dohme, during the conduct of the study; grants and personal fees from Merck Sharp and Dohme, grants and personal fees from Angelini Pharmaceuticals, personal fees from Pfizer Pharmaceuticals, personal fees from Atral Pharmaceuticals, personal fees from Biomerieux, outside of the submitted work.

Dr. Mergulhão reports personal fees and non-financial support from MSD, grants and personal fees from Pfizer, personal fees from BioMérieux, personal fees from Accelerate diagnostics, outside the submitted work; and is currently heading the Portuguese Infection and Sepsis Group ("Grupo de Infecção e Sepsis" - www.gis.pt). The group has received financial support during the past 36 months from the following: MSD; Pfizer; Astellas; BioMérieux; Accelerate disgnostics; Maquet; Baxter; Gilead.

Dr. Nunes has nothing to disclose.

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Authors' Contribution

João Gonçalves Pereira acts as guarantor of the integrity and accuracy of the data.

JGP, FF conceived the study; JGP, BN, FF acquired the data; JGP, BN, PM, FF analyse and interpret the data; JGP, PM drafted the manuscript; JGP, BN, PM, FF revised the manuscript for important intelectual content; BN provided the statistical expertise. All authors review and approved the final manuscript.

Supplementary File A

Data requested from the National Health System Hospital database:

1. Anonymized data from all adult hospital admissions (age >=18 years) with a hospitalization longer than 48h between 1st Jan 2014 and 31st Dec 2017
2. Codes from: 2014 to 2016: ICD9-CM; 2017: ICD10-CM
3. Number of all hospital admissions, mortality and mean length of hospital stay according to age and gender

Study population

All admissions with any discharge diagnosis of:

- ICD9-CM: 480-486 (pneumonia) or 997.31 (ventilator associated pneumonia) that was "not present on admission"
- ICD10-CM: J12-J18 (pneumonia), or J95.851 (ventilator associated pneumonia) that was "not present on admission"

Data collected for each included patient:

- Age, gender, hospital, admission and discharge day, outcome, day of first surgical procedure (if any), days in the ICU (if any), days on invasive mechanical ventilation, nosocomial infection, antibiotics;
- 1st to 20th diagnoses with classification "present on admission – yes/no"; Procedures performed (1st to 20th); classification system (Homogeneous Diagnostic Group)

Disease Codification used

A. ICD-9-CM

1. Diabetes mellitus: 250.XX

2. Chronic respiratory disease:

- Obstructive Chronic Bronchitis:

    without exacerbation: 492.20

    with acute exacerbation: 492.21

    with acute bronchitis: 492.22

- Emphysema: 492.8

- Chronic respiratory failure chronic: 518.83

- Acute on chronic respiratory failure: 518.84

3. Chronic neurologic disease:

- Late effects of cerebrovascular disease: 438

- Dementias: 290.XX

- Hereditary and Degenerative Diseases of the Central Nervous System (e.g., Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis): 330.XX a 337.XX

- Multiple sclerosis: 340

4. Chronic renal disease:

- Chronic Kidney Disease (Chronic uremia): 585.X

5. Chronic liver disease:

- Chronic liver disease and cirrhosis: 571.XX

- Viral chronic hepatitis (B or C) with or without mention of hepatitis delta: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54

6. Chronic cardiac disease with chronic heart failure (or acute on chronic):

- Systolic heart failure chronic: 428.22

- Systolic heart failure acute on chronic: 428.23

- Diastolic heart failure chronic: 428.32

- Diastolic heart failure acute on chronic: 428.33

- Combined systolic and diastolic heart failure chronic: 428.42

- Combined systolic and diastolic heart failure acute on chronic: 428.43

7. Acute stroke

- Subarachnoid hemorrhage: 430

- Intracerebral Hemorrhage: 431

- Other and unspecified intracranial hemorrhage: 432.XX

- Occlusion and stenosis of precerebral arteries: 433.X1

- Occlusion of cerebral arteries: 434.X1

8.Invasive mechanical ventilation

- IMV no specified length: 96.79

- IMV <96 consecutive hours: 96.71

- IMV longer than 96 consecutive hours: 96.72

B. ICD-10-CM

1. Diabetes mellitus: E11.XX

2. Chronic respiratory disease:

- Emphysema: J43.X

- Chronic obstructive pulmonary disease: J44.X

- Chronic respiratory failure: J96.1X

- Acute on chronic respiratory failure: J96.2X

3. Chronic neurologic disease:

- Late effects of cerebrovascular disease (sequelae): I69.XX

- Dementias: F02.8X e F03.9X

- Hereditary and Degenerative Diseases of the Central Nervous System (e.g., Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis): G10.XX-G14.XX, G20.XX-G21.XX e G30.XX-G32.XX

- Demyelinating diseases of the CNS (e.g., Multiple sclerosis): G35.XX-G37.XX

4. Chronic kidney disease:

- Chronic Kidney Disease: N18.X

5. Chronic hepatic disease:

- Chronic viral hepatitis: B18.X

- Alcoholic fibrosis and sclerosis of liver: K70.2

- Alcoholic cirrhosis of liver: K70.3X

- Chronic hepatic failure (not elsewhere classified): K72.1X

- Chronic hepatitis (not elsewhere classified): K73.X

- Fibrosis and cirrhosis of liver: K74.XX

6. Chronic heart disease with chronic heart failure or acute on chronic heart failure:

- Systolic heart failure chronic: I50.22

- Systolic heart failure acute on chronic: I50.23

- Diastolic heart failure chronic: I50.32

- Diastolic heart failure acute on chronic: I50.33

- Combined systolic and diastolic heart failure chronic: I50.42

- Combined systolic and diastolic heart failure acute on chronic: I50.43

7. Acute stroke

- Nontraumatic Subarachnoid Hemorrhage: I60.XX

- Nontraumatic intracerebral hemorrhage: I61.XX

- Other and unspecified non traumatic intracranial hemorrhage: I62.XX

- Cerebral Infarction: I63.XX

8. Invasive mechanical ventilation:

- Respiratory Ventilation, less than 24 consecutive hours: 5A1935Z

- Respiratory Ventilation, 24-96 consecutive hours: 5A1945Z

- Respiratory Ventilation, greater than 96 consecutive hours: 5A1955Z