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Individualizing antibiotic therapy for community-acquired pneumonia

J. Vasco Barreto

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José Vasco Soares da Conceição Tavares Barreto

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SEDE ADMINISTRATIVA INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

JOSÉ VASCO SOARES DA CONCEIÇÃO TAVARES BARRETO

Individualizing antibiotic therapy for community-acquired pneumonia

Thesis applying for **Doctoral Degree** in **Medical Sciences** submitted to **School of Medicine and Biomedical Sciences (ICBAS), University of Porto**

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LIST OF FIGURES

ABBREVIATIONS

ACES	Agrupamento dos Centros de Saúde
aOR	Adjusted Odds Ratio
ATB	Antibiotic
ATS	American Thoracic Society
AUROC	Area Under the Receiver Operating Characteristics
BP	Blood Pressure
BTS	British Thoracic Society
BUN	Blood Urea Nitrogen
CAP	Community-Acquired Pneumonia
CD4+TL	T-Lymphocytes with Cluster Differentiation 4
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COP	Community-Onset Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CRB-65	Conscience, Respiratory rate, Blood pressure, age 65 years-old
CT	Computed Tomography
CURB-65	Conscience, Urea, Respiratory rate, Blood pressure, age 65 years-old
DRIP	Drug Resistance In Pneumonia
DRP	Drug Resistant Pathogen
ECDC	European Centers for Disease Control and Prevention
ECTS	European Credit Transfer and Accumulation System
EPIC	Etiology of Pneumonia in the Community
EPOPEIA	Estudo Prospetivo Observacional de Pneumonias Em Internamento de Agudos
ERS	European Respiratory Society
ESBL	Extended-Spectrum ß-Lactamase
ESBLpE	Extended-Spectrum ß-Lactamase producing *Enterobacteriaceae*
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FiO2	Fraction of Inspired Oxygen
GLIMP	Global Initiative for Methicillin-Resistant *Staphylococcus aureus* Pneumonia
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAP	Hospital-Acquired Pneumonia

HCAP	Healthcare-Associated Pneumonia
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
ICBAS	School of Medicine and Biomedical Sciences
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IQR	Inter-Quartile Range
IV	Intra-Venous
LOS	Length of Stay
MEDCIDS	Department of Community Medicine, Information and Health Decision Sciences
MIC	Minimal Inhibitory Concentration
MR	Methicillin-Resistant
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MS	Methicillin-Sensitive
nfGNB	Non-Fermenting Gram-negative Bacteria
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds Ratio
Pa	*Pseudomonas aeruginosa*
PaO2	Arterial Oxygen Pressure
PCR	Polymerase Chain Reaction
PES	*Pseudomonas aeruginosa*, extended-spectrum ß-lactamase producing *Enterobacteriaceae* and MRSA
PSI	Pneumonia Severity Index
qSOFA	Quick Sequential Organ Failure Assessment
RCT	Randomized Controlled Trial
RF	Risk Factor
RR	Respiratory Rate
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCAP	Severe Community-Acquired Pneumonia
SMART-COP	Systolic blood pressure, Multilobar, Albumin, Respiratory rate, Tachycardia, Confusion, Oxygenation, arterial pH
SOFA	Sequential Organ Failure Assessment
Sp	*Streptococcus pneumoniae*
SPMI	Sociedade Portuguesa de Medicina Interna

SPSS	Statistical Package for the Social Sciences
SSC	Surviving Sepsis Campaign
TInA	Timing of Initial Antibiotic Administration
UP	University of Porto
USA	United States of America

OUTLINE OF THE THESIS

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The main objectives of this thesis are:

- To determine which patients with community-acquired pneumonia (CAP) have increased risk of having a drug resistant pathogen (DRP) and benefit from a wider spectrum empirical antibiotic treatment.

- To determine the impact of identifying the etiological agent on clinical outcomes.

- To determine the impact of timing of initial antibiotic administration (TInA) on CAP outcomes.

- To determine the impact of the initial antibiotic choice (in particular, the empirical use of macrolides) on CAP outcomes.

In Chapter 1, we present a theoretical background about CAP, including a review of the state of the art, ending with the main knowledge gaps that originated our research questions.

In Chapter 2, the research questions and the objectives are presented.

In Chapter 3, the general methodology is described.

Chapter 4 is constituted by the publication "Risk factors for community-onset pneumonia caused by drug-resistant pathogens: A prospective cohort study" (1).

Chapter 5 is constituted by the publication "Does etiological investigation have an impact on the outcomes of community-acquired pneumonia? – A prospective cohort study" (2).

Chapter 6 is constituted by the publication "Impact of the Timing of Initial Antibiotic Administration on Community-Onset Pneumonia Hospital Mortality – a Prospective Cohort Study".

Chapter 7 presents data relative to the empirical use of macrolides in our sample.

In Chapter 8, we present a general discussion of the results and the main conclusions of the thesis.

In Chapter 9, future directions for research are presented.

LIST OF PUBLICATIONS AND ADDITIONAL ACADEMIC AND DOCTORAL WORK

LIST OF PUBLICATIONS

PUBLICATION 1

Barreto JV, Dias CC, Cardoso T. **Risk factors for community-onset pneumonia caused by drug-resistant pathogens: A prospective cohort study**. Eur J Intern Med. 2022 Feb;96:66-73. doi: 10.1016/j.ejim.2021.10.005. Epub 2021 Oct 18. PMID: 34670681.

In 2021, the European Journal of Internal Medicine Impact Factor was 7.749. It was ranked as the 26th journal in the area of General and Internal Medicine, in a total of 172 (1st Quartile).

PUBLICATION 2

Barreto JV, Dias CC, Cardoso T. **Does etiological investigation have an impact on the outcomes of community-acquired pneumonia? - A prospective cohort study**. Eur J Intern Med. 2023 Feb;108:85-92. doi: 10.1016/j.ejim.2022.11.034. Epub 2022 Dec 7. PMID: 36494307.

In 2022, the European Journal of Internal Medicine Impact Factor was 8.0. It was ranked as the 23rd journal in the area of General and Internal Medicine, in a total of 323 (1st Quartile).

PUBLICATION 3

Barreto JV, Dias CC, Cardoso T. **Impact of the Timing of Initial Antibiotic Administration on Community-Onset Pneumonia Hospital Mortality – a Prospective Cohort Study**.

Submitted for publication, 2023.

ADDITIONAL ACADEMIC AND DOCTORAL WORK

- Academic position

Invited associated Professor at School of Medicine and Biomedical Sciences (ICBAS), University of Porto.

- Divulgation in classes

Professor at ICBAS-UP, since 2017. Responsible for teaching pneumonia and healthcare-associated infections to the 6th year students.

- Taskforces

"Terapêutica Ambulatória Empírica para doentes pertencentes ao ACES de Matosinhos com diagnóstico de Infeção das Vias Aéreas Inferiores" – co-author of local guidelines for the treatment of low respiratory tract infections in outpatients at Matosinhos Local Health Unit, 2023.

- Lectures

1. "Atualização – Pneumonia da Comunidade". Second Global Summit of Internal Medicine. Mexico City, May 2022.
2. "Is Pneumonia Still a Challenge?". First Global Summit of Internal Medicine, XLIII International Meeting of Internal Medicine. December 2020 (virtual congress).
3. "Pneumonias na Comunidade - Dados Portugueses e Experiência em Matosinhos". Second Meeting of the Respiratory Diseases Working Group of the Portuguese Society of Internal Medicine (SPMI). Porto, October 2019.

- Member of the jury of a Master degree dissertation

Arguer at the Master in Medicine degree dissertation "Community-acquired pneumonia: a cohort study on risk factors for infection by drug resistant pathogens and prognosis", student Ana Antunes Albuquerque, at ICBAS-UP, July 2020.

- Training and development

"**Blended Learning Introduction to Clinical Studies**" – B-learning course of 162 hours, equivalent to 6 ECTS credits. Final classification: 19 values (in 20). Faculty of Medicine, University of Porto, 2020.

ABSTRACT

ABSTRACT

Background

Pneumonia is the eighth leading cause of death, and the first among infectious causes. Worldwide incidence of community-acquired pneumonia (CAP) varies between 1.5 and 14 cases per 1000 person-year, with 3.5 admissions per 1000 person-year. Microbial etiology of CAP remains unknown in at least 60% of the cases. The role of viruses and atypical agents, risk factors for drug-resistant pathogens (DRP) and the importance of etiological investigation are some of the knowledge gaps in CAP. Antibiotic treatment is based on typical and atypical bacteria coverage, but there is uncertainty about the need to cover atypical agents in low and moderate severity CAP, about the indications to cover DRP and about the ideal timing of initial antibiotic administration.

Objectives

1- To develop a model to identify patients with increased risk of CAP by DRP
2- To determine the impact of identifying the etiological agent on clinical outcomes
3- To analyze the impact of timing of initial antibiotic administration (TInA) on CAP outcomes

Methods

This was a prospective cohort study, conducted over a two years' period, in all medical wards, in a high dependency unit and in the intensive care unit of a community-based hospital. Inclusion criteria were: adult patients (age ≥ 18 years) primarily observed at our Hospital; new onset *or* worsening pulmonary infiltrate on chest radiography (or CT scan) with no alternative explanations; and at least 2 of the following: a) Fever (T > 38 ºC) (without alternative explanation); b) Leukocytosis (> 11500 / mm^3) (without alternative explanation); c) Purulent respiratory secretions; *or* one of a), b) and c), in the presence of: severe sepsis (defined as in "Sepsis 2"); hemodynamic instability; or refractory hypoxemia. Exclusion criteria: absence of vital signs, mental status and arterial blood gases record on admission; Hospital Acquired Pneumonia. Data collection addressed extensive information

about demographic, epidemiological, clinical, analytical, microbiological and imagiological data, as well as antibiotic therapy, and follow-up until 30 days after discharge (mortality and readmission), comorbidities and selected scores (CURB-65, Pneumonia Severity Index (PSI), Charlson's index, Katz score). Infection by a DRP was defined as infection by a PES agent: *Pseudomonas aeruginosa*, or Extended-Spectrum β-Lactamase-producing *Enterobacteriaceae*, or Methicillin-Resistant *Staphylococcus aureus*. We classified antibiotic therapy modification as being motivated by results of the microbiological investigation or by other reasons. In order to have a more thorough understanding of the factors associated with our outcomes (infection by a DRP, hospital mortality, 30-day mortality and length of stay), univariable and multivariable logistic regression modeling were used. The significance level used was 0.05. Statistical analysis was performed using the software SPSS v. 26.0.

Results

During the study period, there were 1624 patients admitted with lower respiratory tract infection, of which 1171 were pneumonias; 660 met the inclusion criteria, with a mean±sd age of 74±15 years, 58.9% male. The overall identification rate was 33%, and the percentage of CAP that were caused by a DRP was 5.6% (18.8% of the patients with etiological identification). Being bed-ridden (aOR 5.492, p<0.001) and having had antibiotics in the previous 90 days (aOR 4.411, p=0.002) were independently associated with the identification of a DRP. A multivariable model including these two risk factors had a discriminative power of 0.832 to predict CAP by a drug-resistant pathogen. In a patient with both these risk factors, an initial antibiotic therapy with carbapenem plus vancomycin would guarantee adequate initial antibiotic therapy in 92% of the cases; this rate would drop to 72% if piperacillin/tazobactam was used instead of a carbapenem.

Etiologic identification was not associated with better outcomes, namely hospital mortality (aOR 1.360, p=0.200). This remained unchanged when considering subgroups of patients with risk factors for infection by a DRP. There was a limited influence of the results of etiology investigation in clinical management: antibiotic modification based on microbiological results was only decided in 7.7% of all cases (4.1% escalated and 3.6% de-escalated) and, in some situations (3.0% of all cases), the antibiotic was not de-escalated, despite, based solely on microbiology, it could

have been. There was not an association of antibiotic modification based on microbiological findings with mortality (OR 0.632, p=0.272).

The median (IQR) Timing of Initial Antibiotic Administration (TInA) was 4.9 h (3.2-7.4); 35.7% of the patients had a TInA ≤4h. Earlier timing of initial antibiotic administration was not independently associated with reduced hospital mortality (aOR 0.986, p=0.648). This was verified for different severity subgroups, and after adjusting for the variables previously identified as being independently associated with mortality (Charlson's index and being bed-ridden).

Conclusions

Patients with CAP who have had antibiotics in the previous 90 days and are bed-ridden should be empirically treated with DRP coverage and be subjected to etiological investigation, and de-escalate antibiotics if there are no DRP identification at 48 to 72 hours. This decision does not have an impact on mortality, but it has the potential to reduce antibiotic pressure and toxicity. Patients without any of the two DRP risk factors do not seem to benefit from etiological investigation, unless it is integrated in a surveillance program aimed at continuously updating local antibiotic therapy guidelines, or for exclusion of problematic agents in selected situations. Patients with sepsis or shock should have the first antibiotic administration immediately (within the first hour). The remaining patients do not seem to benefit of a specific timing for initial antibiotic, and they should have the first administration when the diagnosis of pneumonia is established, and still at the emergency department.

Keywords: Community-acquired pneumonia; Community-onset pneumonia; drug resistant pathogens; risk factors; etiological investigation; antibiotic precocity; outcomes; mortality.

RESUMO

RESUMO

Introdução

A Pneumonia é a oitava causa de morte e é a primeira entre as doenças infeciosas. A incidência mundial da Pneumonia Adquirida na Comunidade (PAC) varia entre 1,5 e 14 casos por 1000 pessoas-ano, com 3,5 internamentos por 1000 pessoas-ano. A etiologia microbiana da PAC permanece desconhecida em pelo menos 60% dos casos. O papel dos vírus e dos agentes atípicos, os fatores de risco para patogéneos resistentes e a importância da investigação etiológica são algumas das lacunas de conhecimento na PAC. O tratamento antibiótico é baseado na cobertura de bactérias típicas e atípicas, mas há incerteza acerca da necessidade de cobrir agentes atípicos na PAC de gravidade baixa ou moderada, acerca das indicações para cobrir patogéneos resistentes e acerca do momento ideal para início da antibioterapia.

Objetivos

1- Desenvolver um modelo para identificar doentes com risco aumentado para PAC por patogéneos resistentes
2- Determinar o impacto de identificar o agente etiológico nos resultados clínicos
3- Analisar o impacto do *timing* da administração inicial de antibiótico nos resultados clínicos da PAC

Métodos

Foi realizado um estudo de coorte prospetivo, por um período de 2 anos, em todas as enfermarias médicas, numa Unidade de Cuidados Intermédios e numa Unidade de Cuidados Intensivos de um hospital distrital. Os critérios de inclusão foram: doentes adultos (idade ≥ 18 anos) primariamente observados no nosso Hospital; instalação inaugural ou agravamento de infiltrados em radiografia do tórax (ou tomografia computorizada) sem explicação alternativa; e pelo menos 2 dos seguintes: a) Febre (T > 38 ºC) (sem explicação alternativa); b) Leucocitose (> 11500 / mm^3) (sem explicação alternativa); c) Secreções respiratórias purulentas; *ou* um de a), b) e c), na presença de: sépsis grave (definida como em "Sepsis 2"); instabilidade hemodinâmica; ou hipoxemia refratária. Critérios de exclusão:

ausência de registo de sinais vitais, estado mental e gasimetria arterial à admissão; Pneumonia Adquirida no Hospital. A colheita de dados incluiu extensa informação sobre dados demográficos, epidemiológicos, clínicos, analíticos, microbiológicos e imagiológicos, assim como a antibioterapia, e o seguimento até aos 30 dias após a alta (mortalidade e reinternamento), comorbilidades e *scores* selecionados (CURB-65, *Pneumonia Severity Index* (PSI), Índice de Charlson, *score* de Katz). Infeção por um patogéneo resistente foi definido como infeção por um agente PES: *Pseudomonas aeruginosa*, ou Enterobacteriáceas produtoras de β-Lactamases de espetro alargado, ou *Staphylococcus aureus* Meticilina-Resistente. Classificámos a modificação da antibioterapia como sendo motivada pelos resultados da investigação microbiológica ou por outros motivos. Para melhor compreender os fatores associados com os resultados (infeção por um patogéneo resistente, mortalidade hospitalar e aos 30 dias e duração do internamento), foram utilizadas regressões logísticas uni e multivariável. O nível de significância utilizado foi 0,05. A análise estatística foi feita utilizando o *software* SPSS v. 26.0.

Resultados

Durante o período do estudo, houve 1624 doentes internados com infeções respiratórias baixas, das quais 1171 eram pneumonias; 660 cumpriam os critérios de inclusão, com uma idade média±dp de 74±15 anos, e 58,9% do sexo masculino. A taxa de identificação global foi de 33%, e a percentagem de PAC que foram causadas por um patogéneo resistente foi 5,6% (18,8% dos doentes com identificação etiológica). Alectuamento (aOR 5,492, p<0,001) e antibioterapia nos 90 dias prévios (aOR 4,411, p=0,002) tiveram associação independente com a identificação de um patogéneo resistente. Um modelo multivariável incluindo estes 2 fatores de risco teve um poder discriminativo de 0,832 na predição de um patogéneo resistente. Num doente com ambos os fatores de risco, uma antibioterapia inicial com um carbapenemo e vancomicina garantiria adequação do espetro em 92% os casos; esta taxa diminuiria para 72% de fosse utilizado piperacilina/tazobactam em vez do carbapenemo.

A identificação etiológica não teve associação independente com melhores resultados, nomeadamente a mortalidade hospitalar (aOR 1,360, p=0,200). Isto permaneceu inalterado considerando subgrupos de doentes conforme os fatores de risco para infeção por um patogéneo resistente. Houve uma influência limitada dos resultados da investigação etiológica na gestão clínica: a modificação do

antibiótico com base nos resultados microbiológicos apenas foi decidida em 7,7% de todos os casos (4,1% escalaram e 3,6% desescalaram) e, em algumas situações (3,0% de todos os casos), o antibiótico não foi desescalado, apesar de que, apenas com base na microbiologia, poderia ter sido. Não houve associação entre a modificação da antibioterapia motivada pelos achados microbiológicos e a mortalidade (OR 0,632, p=0,272).

O *timing* de início da antibioterapia (TInA) mediano (AIQ) foi 4,9 h (3,2-7,4); 35,7% dos doentes tiveram TInA ≤4h. Um *timing* mais precoce de início da antibioterapia não teve associação independente com redução da mortalidade (aOR 0,986, p=0,648). Isto verificou-se em diferentes subgrupos de gravidade e após ajuste às variáveis previamente identificadas como estando independentemente associadas com a mortalidade (índice de Charlson e alectuamento).

Conclusões

Doentes com PAC que tenham sido submetidos a antibioterapia nos 90 dias prévios e que estejam acamados devem ser empiricamente tratados com cobertura de patogéneos resistentes e devem ser submetidos a investigação etiológica, e desescalar a antibioterapia se não houver identificação de patogéneos resistentes às 48 a 72 horas. Esta decisão não tem impacto na mortalidade, mas tem o potencial de reduzir a pressão antibiótica e a toxicidade associada. Doentes sem nenhum dos 2 fatores de risco para patogéneos resistentes parecem não necessitar de ser submetidos a investigação etiológica, salvo se integrados em programa de vigilância destinado a atualização contínua de recomendações locais de antibioterapia, ou para exclusão de agentes-problema em situações selecionadas. Doentes com sépsis ou choque devem ter a primeira administração de antibiótico imediatamente (na primeira hora). Os restantes doentes não parecem beneficiar de um *timing* específico de antibioterapia inicial, e devem ser medicados com a primeira dose de antibiótico quando o diagnóstico de pneumonia for estabelecido, e ainda no Serviço de Urgência.

Palavras chave: pneumonia adquirida na comunidade; pneumonia de instalação na comunidade; patogéneos resistentes; fatores de risco; investigação etiológica; precocidade antibiótica; resultados; mortalidade.

CHAPTER 1 – BACKGROUND

CHAPTER 1 – BACKGROUND

A) STATE OF THE ART

1. Definitions

Pneumonia is an acute infection of the lung parenchyma. According to the site of acquisition, it can be classified as community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP), if it has installed 48 hours or more after admission, and it was not incubating at the time of admission (3).

At the beginning of the century, along with the recognition of healthcare-associated infections (4), a third entity was defined: healthcare-associated pneumonia (HCAP). This classification included patients coming from the community but with risk factors for an infection by a drug-resistant pathogen (DRP), namely patients who fulfilled any of the following criteria: were hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received intravenous antibiotic therapy, chemotherapy, chronic haemodialysis or wound care within the 30 days previous to the current infection; or had a family member with a DRP. However, the term HCAP has been abandoned in the latest CAP (5) and HAP guidelines (6), as will be further explained.

Aspiration pneumonia is considered to be part of a continuum with CAP and HAP, in which aspiration of colonized oropharyngeal or upper gastrointestinal contents plays a major role in the physiopathology. It is estimated to account for 5 to 15% of all CAP cases (7).

2. Pathophysiology

Pathogens enter the low respiratory tract through direct mucosal extension (shedding from the nasopharynx of a colonized individual), micro aspiration or from inhalation of infecting droplets or aerosols (8) (9). The “success” of the infection depends on environmental conditions, pathogen characteristics and host factors, like ciliary clearance and immunity.

There have been recent advances in the understanding of pneumonia pathophysiology, mainly related to the description of a lung microbiota (7) (8) (9)

(10). More than 100 different taxa have been identified in the lungs. The constitution of this flora is determined by three factors: microbial entry into the lungs, microbial elimination, and regional growth conditions for bacteria. It has been hypothesized that pneumonia develops as a consequence of epithelial or endothelial injury, with release of cytokines and chemokines that create a state of dysbiosis, with changes in the microbiota constitution and positive feedback loops, some of which may promote the growth of certain bacteria.

3. Epidemiology

Estimated worldwide incidence of CAP varies between 1.5 and 14 cases per 1000 person-years (11). In the Unites States, more than 5 million cases occur annually (14.7 cases per 1000 person-years), resulting in more than 1.2 million hospitalizations (3.5 per 1000 person-years) (10). The EPIC study (12), an American multicenter study supported by the Centers for Disease Control and Prevention (CDC), showed 2.5 hospitalizations per 1000 person-years, with a higher incidence in older people (16.4/1000 in patients ≥80 years old). In Western Europe, an incidence of 1.07-1.2 per 1000 person-years has been described (13).

The Portuguese observatory of respiratory diseases identified more than 150.000 cases per year (15 per 1000 person-years), with more than 40.000 admissions per year, of which around 35.000 in adults (3.5 per 1000 person years) (14). A retrospective study of 10 years determined an incidence of 3.61 admissions per 1000 person-years (1.02 / 1000 in patients with 65 years-old or less, and 13.4 / 1000 in patients older than 65) (15).

Pneumonia is the eighth leading cause of death, and the first among infectious causes (8) (11). In outpatients, mortality is described as lower than 1%, but it ranges from 4% to 18% in the general ward and up to 50% in the ICU (8). In Portugal, a global mortality of around 20% has been determined, and 44.3% if mechanical ventilation is needed (14) (15).

4. Severity Stratification

British (16) and American (17) societies have created severity scores that have been widely validated as predictors of mortality and as tools to help in the decision of the site of treatment (admission *versus* outpatient).

CURB-65 (16) is a simple score, based on 4 clinical and 1 analytical characteristics (level of Conscience, Urea, Respiratory Rate, Blood Pressure and age). Each contribute with one point. Patients with 0 or 1 point have a low mortality (less than 3%) and can be treated as outpatients. Patients with CURB-65 of 2 have a 9% mortality and should be considered for short-stay inpatient treatment or hospital-supervised outpatient treatment. Patients with a CURB-65 of 3 to 5 have a higher mortality and should be admitted to the hospital.

The Pneumonia Severity Index (PSI) is the reference prognostic model of the American CAP guidelines (17). It consists of a 20 variable score, composed of demographic, clinical (including laboratorial and radiological findings) and comorbidities. It stratifies patients into 5 mortality risk classes (I to V). Patients in class I and II have low mortality and can be treated as outpatients. Patients in risk class III should be treated in an observation unit or with a short hospitalization, and classes IV and V suggest the need for admission.

Very recently, a predictive model based on machine learning was compared with the traditional scores of mortality prediction (18). This model showed an AUROC of 0.832 in the validation cohort, which was significantly higher than CURB-65, SOFA, PSI, and qSOFA.

Based on the fact that PSI and CURB-65 have limited ability to identify patients that will require treatment in an intensive care unit (ICU) (19), new scores were developed. The SMART-COP includes eight variables (low systolic blood pressure, multilobar involvement, low serum albumin, high respiratory rate, tachycardia, confusion, poor oxygenation and low arterial pH). This score, with a threshold of ≥3 points, performed better than CURB-65 and PSI in predicting the need for invasive respiratory or vasopressor support, with an AUROC of 0.87 (IQR 0.83-0.91) in the derivation cohort. One other score (SCAP), which also includes 8 variables (pH < 7.30, systolic blood pressure < 90 mm Hg, respiratory rate (RR) > 30 breaths/min, altered mental status, blood urea nitrogen (BUN) > 30 mg/dL, oxygen arterial pressure (PaO_2) < 54 mm Hg or ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) < 250 mm Hg, age ≥ 80 and multilobar involvement), showed a similar performance (AUROC 0.83) (20). However, based on further works and two meta-analysis (21) (22), the 2019 IDSA/ATS guidelines (5) still recommend the use of the ATS 2007 criteria for admission in the ICU: one major criterium (need for invasive mechanical ventilation or vasopressor support) or three minor criteria from nine: RR ≥30 breaths/min, PaO_2/FiO_2 <250, multilobar

infiltrates, confusion/disorientation, BUN ≥20 mg/dL, leukopenia (<4000 cells/mm^3), thrombocytopenia (<100,000 cells/mm^3), hypothermia (core temperature <36ºC) and hypotension requiring aggressive fluid resuscitation (17).

5. Etiology

In clinical practice, microbial etiology of CAP remains unknown in at least 60% of the cases (12). It is usually assumed that the most common causal micro-organisms in CAP are *Streptococcus pneumoniae*, respiratory viruses, *Haemophilus influenzae* and atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*) (8) (23). It is estimated that 10 to 15% of CAP are polymicrobial (10). Clinical severity and site of treatment influence the relative probability of etiological agents. Notably, in more severe CAP, the importance of *Legionella*, Gram negative bacilli and MRSA is higher (24). The opposite happens with *M. pneumoniae* and viruses (24) (25).

The importance of viral etiology has been progressively recognized. A big American study revealed Influenza, Parainfluenza, Respiratory Syncytial Virus, Coronavirus, Rhinovirus and others as the sole agents of CAP in up to 22% of the cases (12), although the authors recognize that molecular detection of viruses in the upper airways does not necessarily indicate a role in pneumonia causation, and could represent infection that is limited to the upper respiratory tract. The more recent SARS-CoV-2 pandemic further reinforced our notion of the importance of viruses as CAP agents.

A retrospective single center Portuguese study, including hospitalized patients over a period of 3 years (2013-2015), showed *S. pneumoniae* as the most prevalent agent (45.7% of the patients with etiology identification), followed by *H. influenzae* (19.8%), Gram negative bacilli (10%), Influenza (9%), *L. pneumophila* (7.6%) and *S. aureus* (4.3%) (26). This study recognizes the limitation of having very scarce investigation for atypical agents and viruses.

The global initiative for methicillin-resistant *Staphylococcus aureus* pneumonia (GLIMP), a multicenter point prevalence study that included 222 hospitals in 54 countries, found *Streptococcus pneumoniae* as the most prevalent pathogen, accounting for 8.2% of the cases. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the second and the third most prevalent pathogens (4.1% and

3.4% respectively), and MRSA was responsible for 3.0% of CAP episodes (6.9% in the ICU vs 2.1% in non-ICU, p<0.01) (27).

Some patients with CAP have an increased risk for DRP. Some of these risk factors are immunosuppression, previous antibiotic use, prior hospitalization, use of gastric acid-suppressing agents, tube feeding and non-ambulatory status (8). Various scoring systems have been developed to help determine this risk (28) (29) (30) (31) (32) (33) (34), but this subject is still an area of uncertainty. In a multinational study, the prevalence of *Pseudomonas aeruginosa* in CAP was 4.2% (35). In another study, the MRSA prevalence was 1.0% (36).

In another publication from the GLIMP project, the prevalence of atypical bacteria was analyzed (37). In a total of 3702 admitted patients, atypicals were actively searched for in 1250: *Mycoplasma* serologies were positive in 26 out of 251 tests; *Chlamydophila* serologies were positive in 8 out of 228 tests; and *Legionella pneumonia* serologies or urine antigen were positive in 30 out of 1186 tests. Globally, at least one atypical agent was found in around 5% of tested patients. Another study (38) prospectively analyzed the relative importance of *Mycoplasma pneumoniae* in CAP. In 4532 patients (35% outpatients), there were 307 with positive *Mycoplasma* PCR or serology, corresponding to 6.8% of all cases. Compared to other bacterial agents, the proportion of outpatients was significantly higher in *Mycoplasma* (56% vs 22%, p<0.001).

5.1 The role of etiological investigation

Although there is lack of evidence that etiological identification improves individual patient outcomes in CAP, there are some arguments in favor of an active investigation: the possibility of finding a resistant pathogen or an agent with public health implications (e.g. SARS-CoV-2, *Mycobacterium tuberculosis*); the possibility of narrowing antibiotic spectrum; and the ongoing knowledge of local epidemiology (5), which is essential for producing regional recommendations.

One argument against the need for etiological investigation is that CAP has a limited number of possible pathogenic agents, which are mostly covered by the usual recommended antibiotics. In fact, a reference study showed that only 3.3 to 7.6% of CAP patients with etiology identification (0.9 to 2.4% of all CAP patients) had an DRP (39).

Many studies have demonstrated the lack of impact of etiological investigation in CAP outcomes, whether for blood cultures (40) (41), for sputum (42) (43) (44) or for etiological investigation in general (45) (46) (47) (48).

Based on this, the IDSA/ATS 2019 Guidelines (5) recommend that respiratory secretions and blood cultures should only be obtained in patients: with clinical severity; that will be empirically treated for MRSA or *Pseudomonas aeruginosa*; that had a previous infection by one of these pathogens; or that were hospitalized and received antibiotics in the previous 90 days. As for urinary antigen tests, the recommendation is only for severe pneumonia and, for *Legionella*, in risk epidemiological scenarios. In other reference guidelines, however, a different position has been defended, consisting in obtaining blood cultures and respiratory secretions examination in all admitted patients (16) (49). In a panel of experts that published an appraisal of the American guidelines, 7 out of 14 experts also defended a more aggressive etiological investigation strategy (50), as well as other reference authors (8).

6. Antibiotic therapy

One of the most important aspects of the treatment of bacterial pneumonia is antibiotic therapy (ATB). Precocity has an impact on prognosis, so it is unacceptable to delay the initiation of ATB until the timespan of traditional microbiological results, which is at least 48 hours (5) (16) (49). Therefore, virtually all the initial ATB regimens are empirical and directed at the most frequent etiological agents.

Over the last 20 years, medical societies from many countries have been producing clinical guidelines about CAP treatment. In Figures 1 to 4, we present three reference ones: Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) (5), European Respiratory Society (ERS) (49) and British Thoracic Society (BTS) (16). The Portuguese guidelines were published in 2003 (51) and, with respect to outpatients, are in accordance with the 2001 ATS guidelines (52), recommending macrolide monotherapy for patients without comorbidities and an association of a ß-lactam and a macrolide for patients with comorbidities.

As said before, etiology varies according to clinical severity, so the ATB recommendations are mainly based on severity and site of treatment. As a general principle, the more severe the clinical picture, the less margin there is for error. So, for inpatients with moderate or high clinical severity, all the guidelines recommend

an association of a ß-lactam and a macrolide (or a respiratory fluoroquinolone), to assure typical and atypical coverage.

6.1 Outpatients

For outpatients, there is less consensus than for inpatients. Because of the belief that atypical agents should always be covered, and also because of a favorable macrolide sensitivity profile of *Streptococcus pneumoniae*, the previous IDSA/ATS guidelines (17) used to recommend macrolide monotherapy for outpatients without comorbidities. However, *Streptococcus pneumonia* resistance to macrolides has increased up to 30%, so this recommendation was changed. In the 2019 guidelines (5), amoxicillin or doxycycline are recommended as monotherapy in this group of patients. Patients with comorbidities tend to have more contact with healthcare and are more prone to *Haemophilus influenzae*. Also, the margin for error is smaller in these patients. So, a ß-lactamase inhibitor is added to the recommendation, as well as association with a macrolide (Fig 1). The BTS guidelines recommend amoxicillin monotherapy in these patients (Fig 3), and ERS has an open recommendation (ß-lactam ±macrolide) (Fig 4).

Figure 1: ATS/IDSA 2019 guidelines for initial treatment of outpatients with CAP (5)

	Standard Regimen
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa**	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%)†
With comorbidities±	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline§ OR monotherapy with respiratory fluoroquinolone¶

MRSA= methicillin-resistant *Staphylococcus aureus*.

*Risk factors: prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics (in the last 90 d).

†Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin extended release 1 g daily.

±Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.

§Amoxicillin/clavulanate 500 mg/125 mg three timed daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily; AND azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin extended release 1 g daily, or doxycycline 100 mg twice daily.

¶Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or Gemifloxacin 320 mg daily.

Figure 2: ATS/IDSA 2019 guidelines for initial treatment strategies for inpatients with CAP by level of severity and risk for drug resistance (5)

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia*	ß-Lactam + macrolide† or respiratory fluoroquinolone±	Add MRSA coverage§ and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add *P. aeruginosa* coverage¶ and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia*	ß-Lactam + macrolide† or ß-Lactam + fluoroquinolone±	Add MRSA coverage§ and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add *P. aeruginosa* coverage¶ and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Add MRSA coverage§ and obtain nasal PCR and cultures to allow de-escalation or confirmation of need for continued therapy	Add *P. aeruginosa* coverage¶ and obtain cultures to allow de-escalation or confirmation of need for continued therapy

*As defined by 2007 ATS/IDSA CAP severity criteria guidelines.

†Ampicillin + sulbactam 1.5-3 g every 6 hours, cefotaxime 1-2 g every 8 hours, ceftriaxone 1-2 g daily, ceftaroline 600 mg every 12 hours AND azithromycin 500 mg daily or clarithromycin 500 mg twice daily.

±Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.

§Per the 2016 ATS/IDSA HAP/VAP guidelines: vancomycin (15 mg/Kg every 12 h, adjust based on serum levels) or Linezolid (600 mg every 12 h).

¶Per the 2016 ATS/IDSA HAP/VAP guidelines: Piperacillin/tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), meropenem (1 g every 8 h), or aztreonam (2 g every 8 h). Does not include coverage for extended-spectrum ß-lactamase-producing *Enterobacteriaceae*, which should be considered only on the basis of patient or local microbiological data.

Figure 3: BTS 2009 guidelines for initial empirical treatment regimens for CAP in adults (16)

Pneumonia severity (based on clinical judgement supported by CURB65 severity score	**Treatment site**	**Preferred treatment**	**Alternative treatment**
Low severity (e.g., CURB65 = 0-1 or CBR65 = 0, <3% mortality)	Home	Amoxicillin 500 mg tds orally	Doxycycline 200 mg loading dose then 100 mg orally *or* clarithromycin 500 mg bd orally
Low severity (e.g., CURB65 = 0-1, <3% mortality) but admission indicated for reasons other than pneumonia severity (e.g., social reasons/unstable comorbid illness)	Hospital	Amoxicillin 500 mg tds orally If oral administration not possible: Amoxicillin 500 mg tds IV	Doxycycline 200 mg loading dose then 100 mg orally *or* clarithromycin 500 mg bd orally
Moderate severity (e.g., CURB65 = 2, 9% mortality)	Hospital	Amoxicillin 500 mg – 1 g tds orally *plus* clarithromycin 500 mg bd orally If oral administration not possible: Amoxicillin 500 mg tds IV *or* Benzylpenicillin 1.2 g qds IV *plus* clarithromycin 500 mg bd IV	Doxycycline 200 mg loading dose then 100 mg orally *or* levofloxacin 500 mg od orally *or* moxifloxacin* 400 mg od orally
High severity (e.g., CURB65 = 3-5, 15-40% mortality)	Hospital (consider critical care review)	**Antibiotics given as soon as possible** Co-amoxiclav 1.2 g tds IV *plus* clarithromycin 500 mg bd IV (If *Legionella* strongly suspected, consider adding levofloxacin§)	Benzylpenicillin 1.2 g qds IV *plus* levofloxacin 500 mg bd IV *or* ciprofloxacin 400 mg bd IV **OR** Cefuroxime 1.5 g tds IV *or* cefotaxime 1 g tds IV *or* ceftriaxone 2 g od IV *plus* clarithromycin 500 mg bd IV (If *Legionella* strongly suspected, consider adding levofloxacin§)

od, once daily; bd, twice daily; tds, three times daily; qds, four times daily

* the European Medicines Agency (EMEA) recommended that moxifloxacin ''should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection''.

§Caution – risk of QT prolongation with macrolide-quinolone combination.

Figure 4: ERS Recommendations for inpatients with CAP (49)

Clinical severity	Antibiotic recommendation	
Low severity inpatients	Aminopenicillin ± macrolide[a,b] Aminopenicillin/ß-lactamase inhibitor[a] ± macrolide[b] Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone ± macrolide[b] Levofloxacin[a] Moxifloxacin[a,c] Penicillin G ± macrolide	
High severity inpatients	**No risk factors for *P. aeruginosa***	**Risk factors for *P. aeruginosa***
	Non-antipseudomonal cephalosporin III + macrolide[b] or Moxifloxacin or levofloxacin ± Non-antipseudomonal cephalosporin III	Antipseudomonal cephalosporin[d] or Acylureidopenicillin/ß-lactamase inhibitor or Carbapenem (meropenem preferred, up to 6 g possible, 3 x 2 in 3-h infusion) PLUS Ciprofloxacin[e] OR PLUS Macrolide[b] ± aminoglycoside (gentamicin, tobramycin or amikacin)

[a] Can be applied as sequential treatment using the same drug.

[b] New macrolides preferred to erythromycin.

[c] Within the fluoroquinolones, moxifloxacin has the highest antipneumococcal activity

In patients at risk for GNEB, particularly strains with ESBL, but without risk (or after exclusion of) of *P. aeruginosa*, ertapenem may be used.

[d] Ceftazidime has to be combined with penicillin G for coverage of *S. pneumoniae*.

[e] Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative and also covers Gram-positive bacteria if treatment is empirical.

6.2 The rationale for macrolides

As said before, the need to cover atypical agents is not consensual. A Cochrane systematic review included 28 trials comparing antibiotic regimens with and without atypical coverage in hospitalized adults with CAP. No advantage was found for atypical coverage on mortality or clinical efficacy (53). However, another meta-analysis including almost 10,000 critically ill patients with CAP showed that macrolide use was associated with a 18% relative reduction in mortality, compared with therapies without a macrolide (54). One third meta-analysis suggested that macrolides were associated with a statistically significant lower failure rate, but with no difference in other outcomes (mortality, bacteriologic failure, and adverse

events requiring ATB discontinuation) (55). A more recent narrative review states that the available evidence suggests a possible but small reduction of adverse outcomes in favor of atypical coverage, recognizing that the mechanisms of the risk reduction remain unclear (56).

Some years before, the same author conducted an important trial, in which he compared ß-lactam monotherapy with ß-lactam-macrolide association in moderate severity CAP. The trial failed to prove non-inferiority of ß-lactam monotherapy: patients with monotherapy had delayed clinical stability. However, mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms (57).

One large observational study analyzed 30-day mortality with a β-lactam plus macrolide compared with a fluoroquinolone alone or with a β-lactam. The combination of β-lactam plus macrolide had a protective effect on mortality only in patients with high inflammatory response (C-reactive protein, > 15 mg/dL) and pneumococcal CAP (58).

In fact, the immunomodulatory effects of macrolides have been known for a long time (59) and have been pointed as one of the possible explanations for its benefits in more severe cases. A recent Portuguese publication presents the results of a retrospective multicenter study of 797 patients with pneumococcal CAP (60). In comparison with ß-lactam monotherapy, the combination of a ß-lactam plus a macrolide significantly reduced 30-day all-cause mortality, but only for patients with bacteremia. Another recent study found that macrolide-based treatment reduced the risk of dying at 6 and 12 months, in patients with CAP admitted to an ICU (61), and another previous Portuguese publication based on an ICU study showed a significant reduction in hospital and 6 month mortality associated with macrolide therapy (62).

Using a very large international database, a group of investigators used machine learning to build a prediction rule that could be able to identify which hospitalized patients with CAP would benefit the most of macrolide combination therapy (63). By testing all combinations of all variables, machine learning produced the following rule: treat the patient with macrolides if they have no chronic respiratory disease and no cardiovascular comorbidity or if they have a chronic respiratory disease and show high or medium leukocyte counts in the respiratory secretions (this last variable was the one with most impact as a single rule). The odds ratio for

survival for the rule “always give macrolides” was considerably lower than this one. The authors speculate that this rule may traduce the benefit of macrolides for patients with high pulmonary inflammation and a possible risk in patients with cardiovascular comorbidities, because of the potential of these drugs to induce dysrhythmia. They also state that this rule may be a step towards personalized treatment decisions, by contrast to randomized controlled trials, whose results represent the average effect, failing to reflect the situation of individual patients and their complexity.

In face of these conflicting results, major guidelines suggest a macrolide/β-lactam combination for severely ill patients (5) (16) (49), but some leave it at the discretion of the treating physician for inpatients with CAP of low to moderate severity (16) (49).

6.3 Drug-resistant pathogen coverage

One other question is the indication to empirically cover DRP. The BTS guidelines do not address this subject, and ERS only recommends that severe patients with risk factors for *Pseudomonas* should have empirical double coverage (Fig 4). The latest IDSA/ATS document proposes two individual risk factors for MRSA or *Pseudomonas aeruginosa*: prior isolation of these organisms (especially from the respiratory tract), and/or recent hospitalization and exposure to parenteral antibiotics. If any of these, or another locally validated risk factor is present, it is recommended that cultures are obtained (sputum and blood). In severe cases, empirical therapy should be started, and interrupted if cultures are negative at 24h. In non-severe cases, empirical coverage is only recommended if previous respiratory identification of that agent is present (Fig 2).

6.3.1 The rise and fall of Healthcare-Associated Pneumonia

The inclusion of the concept of risk for DRP in CAP ATB therapy guidelines is recent, and is a result of the abandonment of the concept of Healthcare-Associated Pneumonia (HCAP).

In 2005, the concept of HCAP was introduced in the American guidelines for the treatment of Hospital-Acquired Pneumonia (HAP) (3). The concept of healthcare-associated infections was then recent (4) and there was a dominant idea that

patients who fulfilled HCAP criteria (hospitalization in an acute care hospital for two or more days within 90 days of the infection; residence in a nursing home or long-term care facility; recent intravenous ATB therapy, chemotherapy, chronic haemodialysis or wound care within the past 30 days of the current infection; or having a family member with a DRP) had a microbial etiology more similar to that of HAP than to CAP. For these patients, it was recommended to use empirical wide spectrum ATB regimens.

ERS and BTS guidelines never incorporated the concept of HCAP, and in the 2011 ERS recommendations the authors actually stated that, in their opinion, the evidence does not support the use of this term as "being clinically relevant in Europe", and therefore it was no further discussed (49). In 2014, Chalmers *et al* conducted a meta-analysis and concluded that the concept of HCAP did not accurately identify patients with CAP by DRP (64). Finally, even IDSA and ATS recognized, in their 2016 guidelines (6), that there was increasing evidence that many patients defined as having HCAP were not at high risk for DRP, and that, although interaction with the healthcare system is potentially a risk for DRP, underlying patient characteristics are also important determinants of risk.

So, as we have left HCAP behind, CAP now includes a group of patients different from the former CAP concept. For that reason, some authors have started to call it community-onset pneumonia (COP), instead of CAP.

A number of studies tried to define a predictive rule to decide which patients benefit the most of empirical wide-spectrum ATB (28) (29) (30) (31) (32) (33) (34). The DRIP score (29) is represented in Fig 5. With a threshold of ≥4 points, it has an area under the receiver operating characteristic (AUROC) of 0.88 (0.82-0.93), revealing to be more accurate than HCAP criteria for DRP prediction (AUROC 0.72 (0.64-0,79)) (p=0.02). Also, Prina *et al* (34) defined a prediction rule for identification of the so-called PES agents (*Pseudomonas aeruginosa*, extended-spectrum ß-lactamase producing *Enterobacteriaceae* and MRSA) (Fig 6). The AUROC was 0.754 (0.708-0.801) for a score of ≥5 points.

Figure 5: DRIP score (29)

Characteristic	No. of points
Major risk factors	
Antibiotic use within previous 60 days	2
Residence in a long-term-care facility	2
Tube feeding	2
Prior infection with a DRP (1 yr)	2
Minor risk factors	
Hospitalization within previous 60 days	1
Chronic pulmonary disease	1
Poor functional status	1
Gastric acid suppression	1
Wound care	1
MRSA colonization (1 yr)	1
Total no. of points possible	**14**

Figure 6: Score to assess the risk of pneumonia due to PES pathogens (34)

Score to PES Pathogen	Points
Age, yr	
<40	0
40-65	1
>65	2
Male	1
Previous antibiotic use	2
Chronic respiratory disorder	2
Chronic renal disease	3
At emergency	
Consciousness impairment	2
Fever	-1

In Portugal, there is a 2007 consensus statement about Nosocomial Pneumonia (65). In this document, 7 out of 12 experts did not agree with the 2005 IDSA/ATS recommendation of treating HCAP with wide spectrum antibiotics similar to those with late onset HAP. It was recommended that, until Portuguese epidemiological data were known, decisions should be made case by case.

6.4 Timing of initiation of antibiotic

In clinical practice, early ATB administration in pneumonia is a common-sense objective. Earlier ATB administration has the potential to reduce inflammatory response and organ damage, by reducing bacterial load (66) (67). Timely administration of appropriate antibiotics is considered to be very important for treatment success in severe infections (68). Although the last Surviving Sepsis Campaign recommendations have decreased the strength of the recommendation for ATB precocity in relation to the previous ones (69) (especially in the absence of sepsis or septic shock), in more severe patients it is still considered a strong recommendation. However, the association between timing of initial antibiotic administration (TInA) and outcomes in CAP is still debated.

A well-known systematic review from 2016 (70) included 8 studies, 4 of which showed an association between earlier TInA and reduced mortality. These were all retrospective cohort studies. The other 4 (3 of which were prospective) did not show any impact of TInA on mortality. Other prospective studies also did not show any association between TInA and mortality, even when sub analysis were made for more severe patients (66) (71) (72).

On the other side, there has been growing concern about the potential harms of excessively early ATB administration, including allergic reactions, kidney injury, thrombocytopenia, *Clostridioides difficile* infection and antimicrobial resistance (68) (71). A study found that delivering ATB within 4 h to all patients resulted in an excessive number of patients in whom an infection was later not confirmed (73).

In face of these conflicting results, the IDSA/ATS guidelines reduced the importance of TInA in 2007 and recommended that the first ATB dose should be administrated while the patient is still in the emergency department, with no defined time frame (17). The 2019 guidelines do not even mention this issue as a specific recommendation (5). The 2019 NICE guidelines, however, still recommend ATB treatment as soon as possible, within 4 hours, for patients admitted with CAP (74).

In summary, the evidence available for the importance of TInA is weak. It would be unethical to delay TInA in a clinical trial, so the available evidence is based on observational studies (67).

6.5 Duration of therapy

In face of studies that have shown safety and non-inferiority of shorter treatment courses (75), IDSA/ATS recommend that ATB therapy should be continued until the patient achieves clinical stability (according to a validated measure - normalization of vital signs and mental state and ability to eat), and for no less than 5 days (5). It is also recommended that MRSA and *Pseudomonas aeruginosa* be treated for 7 days, and that ATB duration should be longer when there are complications (empyema, meningitis, endocarditis) or in the presence of less common pathogens (e.g. fungi, *Mycobacterium tuberculosis*).

7. Antimicrobial resistances

As previously exposed, a limited number of bacterial pathogens are responsible for the vast majority of CAP cases (8). In this section, we describe the most important problems relative to antimicrobial resistance in the most common CAP etiological agents.

7.1 *Streptococcus pneumoniae*

The prevalence of penicillin resistance in *Streptococcus pneumoniae* has been stable over time (10). The prevalence of non-susceptibility has artificially decreased in the years following 2008, when EUCAST adjusted the resistance MIC cutoff for non-meningitis infections (8) (10) (76). In 2020, the CDC 2020 reported 1.7% of resistance (77). In 2021, the ECDC reported 6.8% resistance in Portugal (78). A Portuguese multicenter study published in 2018 showed high-level resistance in 1% of the isolates (79).

Macrolide resistance is a heterogeneous phenomenon. It can be the result of a target-site modification caused by ribosomal methylation encoded by the *ermB* gene, which results in high-level resistance (MIC ≥64 μg/mL), known as the MLS_B phenotype; or happen in the context of an efflux mechanism, encoded by the *mef* gene (M phenotype), usually associated with low-level resistance (MIC 1–32 μg/mL)

(8) (10). The first one is more frequent in Europe, while the latest prevails in the USA.

Macrolide resistance has been increasing. The CDC reported a 29.3% resistance in 2020. Portuguese data from the ECDC (2021) reveal 19.1%, whereas the previously mentioned Portuguese study showed 21.7%, of which 79.1% by the *ermB* gene mechanism and 20.9 by the *mef* gene.

Levofloxacin resistance was reported to be 0.0% by the CDC. A Portuguese 2014 study also revealed a low prevalence of 1.3% (80).

The prevalence of doxycycline resistance has been shown to be 5 to 20% in a Canadian study (81). A large USA pediatric database showed 11% resistance (82).

7.2 *Haemophilus influenzae*

Haemophilus influenzae is a frequent ß-lactamase producer, with up to a 17.6% prevalence (49). A study of invasive infections by this agent showed a 28.1% frequency of ampicillin resistance (83). In the same study, macrolide resistance was 6.3%, but 39.9% of the isolates had intermediate susceptibility, rendering a 46.2% prevalence of reduced susceptibility. In a Portuguese study, from 1999 to 2007, ampicillin resistance has been described to be 12%, and azithromycin resistance was 0.0% (84).

7.3 *Moraxella catarrhalis*

Moraxella catarrhalis is an almost universal ß-lactamase producer (97.6%). On the other side, it has a 99.2% susceptibility to azithromycin (84) (85).

7.4 *Mycoplasma pneumoniae*

Macrolide-resistant *Mycoplasma pneumoniae* has been reported in some countries: Germany (3%), Japan (30%), China (95%), and France and the USA (5–13%) (8) (10) (49). In a meta-analysis, it is described that the proportion of this phenomenon was highest in the Western Pacific (53.4%), followed by the South East Asia (9.8%), the American continents (8.4%), and Europe (5.1%) (86).

B) KNOWLEDGE GAPS

Having reviewed the state of the art, we identified some knowledge gaps that are good research targets. We defined our objectives and research questions based on these gaps.

1- There is still uncertainty as to which individual patient characteristics constitute risk factors for having a community-acquired pneumonia caused by a drug-resistant pathogen.
2- It is not clear in which patients etiological investigation has an impact in antibiotic treatment decisions and in outcomes, namely hospital and 30-day mortality and length of stay.
3- There is still debate on whether a specific timing for the initiation of antibiotic treatment has an impact on CAP outcomes, and in which patients it is most important.
4- In moderate severity CAP (general ward), it is not clear which patients benefit the most of an antibiotic therapy with inclusion of a macrolide.
5- In low severity CAP, there is scarce knowledge about the most common etiological agents and in relation to what is the best antibiotic treatment choice.

C) PERSONALIZED MEDICINE – A CHALLENGE TO SCIENTISTS

As William Osler said, *Medicine is a science of uncertainty and an art of probability* (87).

One of the reasons for *uncertainty* is that every individual is unique – in fact, variability is the essence of biology, and also of biomedical sciences. The heterogeneity of individuals calls for personalized decisions to benefit individual patients (88). However, we ground much of our practice in clinical guidelines, which in turn are based on data from randomized controlled trials (RCT). The results of RCT constitute a *corpus* of generalizable knowledge that, in theory, is applicable to "average patients" (88) (89).

But there are no "average patients". So, the challenge to researchers and to clinicians is to develop *the art of probability*, that is, to develop research in the area of patient centered medicine and to achieve applicability of guidelines to individuals (88) (90). As a reference author in this area said, "predicting the effects of a treatment for individual patients may enable doctors to practice individualized medicine in an evidence based manner" (90).

One of the purposes of this thesis is to identify individual patient characteristics that can contribute to a more individualized approach to patients with CAP, regarding management and treatment decisions relative to aspects that remain controversial.

In the next chapter, we present the research questions we defined. They are based on the above described knowledge gaps and they were built to find individualized answers for each question.

CHAPTER 2 – RESEARCH QUESTIONS AND OBJECTIVES

CHAPTER 2 – RESEARCH QUESTIONS AND OBJECTIVES

The objectives of this thesis were the following. For each objective, a research question was formulated.

a) To develop a model to identify patients with increased risk of CAP by DRP

Research question 1: Which patients with CAP need to be empirically treated with wider spectrum antibiotics?

b) To determine the impact of identifying the etiological agent on clinical outcomes

Research question 2: In which patients does the identification of an etiological agent have an impact on CAP outcomes?

c) To analyze the impact of timing of initial antibiotic administration (TInA) on CAP outcomes

Research question 3: In which patients is there an impact of TInA on CAP outcomes?

d) To analyze the impact of the initial antibiotic choice on CAP outcomes

Research question 4: In which patients is there a benefit of empirical macrolide treatment on CAP outcomes?

CHAPTER 3 – METHODS

CHAPTER 3 – METHODS

a) Study Design

Prospective (concurrent data collection), cohort study, conducted over a two years' period, between January 1st 2012 and December 31st 2013, in all medical wards (120 beds general ward), in a high dependency unit (HDU) with 13 beds and in the intensive care unit (ICU) with 10 beds of a community-based hospital (350 beds).

The research project (Prospective Observational Study of Pneumonias in the Acute Setting – EPOPEIA) was approved by the Hospital Ethics Committee and by the National Data Protection Commission (*Appendix 3*). Informed consent was obtained for every protocol and data were coded, in order to guarantee anonymization.

b) Inclusion and Exclusion Criteria

All adult patients (age ≥ 18 years) with community-onset pneumonia primarily observed at our Hospital were enrolled in the study. Pneumonia diagnosis was made by the presence of [new onset *or* worsening pulmonary infiltrate on chest radiography (or CT scan) with no alternative explanations (ex: heart failure, neoplasm, chronic interstitial disease, pulmonary embolism); *and at least 2 of the following criteria*: a) Fever (T >38 ºC) (without obvious alternative focus of infection or non-infectious explanations); b) Leukocytosis (>11500 / mm^3) (without obvious alternative focus of infection or non-infectious explanation); c) Purulent respiratory secretions; *or one of a), b) and c)*, in the presence of: severe sepsis (defined as in "Sepsis 2": sepsis with acute end-organ dysfunction (91)); hemodynamic instability; or refractory hypoxemia (PaO_2 / FiO_2 < 100 in spontaneous ventilation)].

All inclusions in the study were validated by an internal medicine consultant, namely chest x-ray and/or CT scan observation.

Absence of vital signs, mental status and arterial blood gases record on admission were considered to be exclusion criteria, as well as Hospital Acquired Pneumonia, defined as pneumonia diagnosed 48h or more after hospital admission and not incubating at the time of hospital admission (3).

c) Data Collection and variables definition

A data collection protocol was created (*Appendix 1*), addressing extensive information about demographic, epidemiological, clinical, analytical,

microbiological and imagiological data, as well as antibiotic therapy, and follow-up until 30 days after discharge (mortality and readmission). Comorbidities (92) (93) (94) (95) and selected scores (CURB-65 (16), Pneumonia Severity Index (PSI) (17), Charlson's index (96), Katz score (97)) were defined according to the current definitions. Immunosuppression was a composite definition that included: chemotherapy less or equal to 90 days before; or HIV infection with CD4 TL count <500/mm^3; or chronic glucocorticoids equivalent to prednisolone ≥ 0,5 mg / Kg / day; or solid organ transplant; or treatment with immunosuppressive drugs; or liquid neoplastic disease (Hodgkin's or non-Hodgkin's Lymphoma or Chronic or Acute Leukemia or Multiple Myeloma or Waldenström Macroglobulinemia).

Data were collected concurrently by a group of investigators, according to a set of instructions (*Appendix 2*).

MRSA colonization was defined as the presence of MRSA on nasal swab by molecular biology. This variable was dichotomized as "documented", if there was a positive test, or "not documented", if negative or absent test.

The microbial isolates were considered clinically significant when they were identified by culture in samples of respiratory secretions or blood. Urine antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were also considered, as well as Polymerase Chain Reaction (PCR) assays for respiratory viruses in pharyngeal swabs. Secretions from the lungs, bronchi, or trachea were considered a valid sample only if it contained ≥25 neutrophils and ≤10 squamous epithelial cells per low power field (x100). In respiratory samples, criteria for rejecting results as non-relevant included a semi-quantitative method for interpretation of cultures and the type of agent identified. Coagulase negative *Staphylococci*, *Corynebacterium* spp and *Candida* were never considered relevant, as well as most Enterococci and *viridans* group Streptococci. Mixed respiratory flora was usually not valued.

Infection by a DRP was defined as infection by a PES agent: *Pseudomonas aeruginosa*, or Extended-Spectrum β-Lactamase-producing *Enterobacteriaceae*, or Methicillin-Resistant *Staphylococcus aureus* (34). We also included non-fermenting Gram-negative bacteria (nfGNB) other than Pa in the definition, namely other *Pseudomonas spp, Acinetobacter baumannii, Stenotrophomonas maltophilia, Burkholderia cepacia and Ralstonia picketii*.

We classified antibiotic therapy modification as being motivated by results of the microbiological investigation or by other reasons, namely: pneumonia complication or additional infectious focus; adverse effect of the antimicrobial; or empirical modification.

Being bed-ridden was defined as being chronically confined to bed, with no gait capability, due to disabling disease or age-related multifactorial frailty and disability.

A specific database was built in Statistical Package for the Social Sciences (SPSS) for data introduction. All data were coded, for personal data protection.

d) Statistical Analysis

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, interquartile (IQR) range, and minimum and maximum, when appropriate.

Hypotheses were tested regarding the distribution of continuous variables with non-normal distribution using the nonparametric Mann–Whitney and Kruskal–Wallis tests, depending on the nature of the hypothesis, or T test for independent samples or One Way Anova for variables with normal distribution. When testing a hypothesis regarding categorical variables, a chi-square test or a Fisher's exact test were used, as appropriate.

In order to have a more thorough understanding of the factors associated with our outcomes (infection by a DRP, hospital mortality, 30-day mortality and length of stay), univariable and multivariable logistic regression modeling were used. Odds ratio (OR) and 95% confidence intervals (95% CI) were presented. The variables were chosen for the multivariable analysis according to their statistical significance in the univariable analysis and also because of their clinical relevance. All selected variables were included in the model (enter method).

Model goodness-of-fit was assessed using the Hosmer-Lemeshow statistic. When appropriate, discriminative power was evaluated by receiver-operator curve (ROC) curve analysis.

The significance level used was 0.05.

Statistical analysis was performed using the software SPSS v. 26.0.

CHAPTER 4 - "Risk factors for community-onset pneumonia caused by drug-resistant pathogens: A prospective cohort study"

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Risk Factors for Community-Onset Pneumonia caused by Drug-Resistant Pathogens: a Prospective Cohort Study

Abstract

Introduction

There is no consensual definition of risk factors for drug resistant pathogens (DRP) in community-onset pneumonia (COP). Healthcare-associated pneumonia criteria have been abandoned because they were found to have weak discriminative power. Our aim was to identify risk factors for DRP in COP.

Methods

Prospective cohort study, conducted over a two years' period, in a community-based hospital, including all adult patients with COP criteria. Univariate and multivariate logistic regression modelling were performed to understand the association of risk factors (demographic, clinical and epidemiological) with COP by a DRP (PES: *Pseudomonas aeruginosa*, extended-spectrum ß-lactamase producing *Enterobacteriaceae*, Methicillin-resistant *Staphylococcus aureus*; and other non-fermenting gram-negative bacteria, namely *Acinetobacter baumannii*).

Results

A total of 660 cases of COP were included, with a mean (±SD) age of 74±15 years and 58.9% of males. Microbiological documentation was possible in 32.6% of the cases. There were 197 cases selected for further analysis, of which 37 were cases of PES. The multivariate logistic regression model retained antibiotic use in the previous 90 days (adjusted OR=4.411, 95%CI [1.745–11.148]) and being bed-ridden (adjusted OR=5.492, 95%CI [2.121–14.222]), adjusted for Charlson's Index, CURB 65 and provenience from a long-term care facility. The area under the ROC curve for this model was 0.832, 95%CI [0.756–0.908], higher than the application of the HCAP criteria (AUROC = 0.676, 95%CI [0.582–0.770]).

Conclusion

In this study, antibiotic use in the previous 90 days and being bed-ridden were independently associated with COP caused by DRP, after adjustment for Charlson's Index, CURB 65 and provenience from a long-term care facility.

Keywords

Community-onset pneumonia; drug resistant pathogens; *Pseudomonas aeruginosa*; extended-spectrum ß-lactamase producing *Enterobacteriaceae*; Methicillin-resistant *Staphylococcus aureus;* risk factors.

Introduction

It is presumed that 70% of Community-Acquired Pneumonias (CAP) are caused by bacteria [1], but, in clinical practice, microbial etiology remains unknown in at least 60% of the cases [2]. One of the most important aspects of the treatment of bacterial pneumonia is antibiotic therapy. Precocity has such a decisive impact on prognosis that it is unacceptable to delay the initiation of antibiotics until microbiological results are available [1] [3] [4]. Therefore, virtually all the initial antibiotic regimens are empirical. But antibiotics must cover the causative bacteria, which makes it essential to identify patients who are at risk for infection by drug-resistant pathogens (DRP).

Over the last 20 years, medical societies from many countries have been producing clinical guidelines about Community-Acquired Pneumonia (CAP) treatment. The most well-known and more discussed are the North American (Infectious Diseases Society of America and American Thoracic Society – IDSA/ATS, 2007 and 2019) [3] [5], the European (European Respiratory Society – ERS, 2011) [1] and the British (British Thoracic Society – BTS, 2009) [4] guidelines.

One of the most debated aspects is the definition of risk factors for infection by DRP. In their 2005 guidelines [6], based on studies that showed an increased prevalence of DRP in certain patient populations [7] [8], IDSA/ATS proposed a new classification, "healthcare-associated pneumonia" (HCAP), that would comprise those patients, and recommended the use of empirical wide spectrum antibiotic regimens for these situations. ERS and BTS guidelines never incorporated the concept of HCAP, and in the 2011 ERS recommendations the authors actually state that, in their opinion, the evidence does not support the use of this term as "being clinically relevant in Europe", and therefore it is no further discussed [1]. In 2014, Chalmers conducted a meta-analysis and concluded that the concept of HCAP did not accurately identify resistant pathogens [9]. Finally, even IDSA and ATS

recognized, in their 2016 guidelines, that there is increasing evidence that many patients defined as having HCAP are not at high risk for resistant pathogens, and that, although interaction with the healthcare system is potentially a risk for DRP, "underlying patient characteristics are also important independent determinants of risk" [10].

There has been an effort to develop risk assessment tools in order to identify patients at higher risk of having DRP infections. Some of them have better performance than the original HCAP criteria [11] [12] [13] [14] [15] [16] [17] [18]. Prina et al [18] created a new acronym (PES) to identify the CAP pathogens that would require an antibiotic treatment different from the guidelines recommendations (*Pseudomonas aeruginosa* [Pa], extended-spectrum ß-lactamase producing *Enterobacteriaceae* [ESBLpE], and methicillin-resistant *Staphylococcus aureus* [MRSA]). In the editorial of that journal, Dean concluded that "HCAP criteria are mostly dead" [19].

In Portugal, there are guidelines for the management of community-acquired pneumonia published in 2003 [20] and a 2007 consensus statement about Nosocomial Pneumonia [21]. The first are very similar to the 2001 ATS CAP guidelines [22]. In the 2007 document, 7 in 12 experts did not agree with the 2005 IDSA/ATS recommendation of treating HCAP with wide spectrum antibiotics similar to those with late onset hospital-acquired pneumonia. It was recommended that, until Portuguese epidemiological data were known, decisions should be made case by case. To our knowledge, there are no consistent Portuguese studies documenting the microbial etiology of CAP or associated risk factors for DRP infection.

Our goal was to identify risk factors associated with Community-Onset Pneumonia (COP) caused by DRP.

d) Study Design

This was a prospective (concurrent data collection), cohort study, conducted over a two years' period, between January 1st 2012 and December 31st 2013, in all medical wards (general ward with 120 beds), in a high dependency unit (HDU) with 13 beds and in the intensive care unit (ICU) with 10 beds of a community-based hospital (350 beds).

The study was approved by the Hospital Ethics Commission and by the National Data Protection Committee. Informed consent was obtained for every protocol and data were coded, in order to guarantee anonymization.

e) Inclusion and Exclusion Criteria

All adult patients (age ≥ 18 years) with community-onset pneumonia primarily observed at our Hospital were enrolled in the study. Pneumonia diagnosis was made by the presence of [new onset *or* worsening pulmonary infiltrate on chest radiography (or CT scan) with no alternative explanations (ex: heart failure, neoplasm, chronic interstitial disease, pulmonary embolism); *and at least 2 of the following criteria*: a) Fever (T > 38 ºC) (without obvious alternative focus of infection or non-infectious explanations); b) Leukocytosis (> 11500 / mm^3) (without obvious alternative focus of infection or non-infectious explanations); c) Purulent respiratory secretions; *or one of a), b) and c)*, in the presence of: severe sepsis; hemodynamic instability; or refractory hypoxemia (PaO_2 / FiO_2 < 100 in spontaneous ventilation)].

All inclusions in the study were validated by an internal medicine senior consultant, namely chest x-ray and/or CT scan observation.

Absence of vital signs, mental status and arterial blood gases record on admission were considered to be exclusion criteria, as well as Hospital Acquired Pneumonia, defined as pneumonia diagnosed 48h or more after hospital admission and not incubating at the time of hospital admission [6].

f) Data Collection

The protocol addressed extensive information about demographic, epidemiological, clinical, analytical, microbiological and imagiological data, as well as antibiotic therapy, and follow-up until 30 days after discharge (mortality and readmission). Comorbidities [23] [24] [25] [26] and selected scores (CURB 65 [4], Pneumonia Severity Index (PSI) [3], Charlson's index [27], Katz score [28]) were defined according to the current definitions. Immunosuppression was a composite definition that included: chemotherapy less or equal to 90 days before; or HIV infection with CD4 TL count <500/mm^3; or chronic glucocorticoids equivalent to prednisolone ≥ 0,5 mg / Kg / day; or solid organ transplant; or treatment with immunosuppressive drugs; or liquid neoplastic disease (Hodgkin's or non-Hodgkin's Lymphoma or Chronic or Acute Leukemia or Multiple Myeloma or Waldenström Macroglobulinemia).

MRSA colonization was defined as the presence of MRSA on nasal swab by molecular biology. This variable was dichotomized as "documented", if there was a positive test, or "not documented", if negative or absent test.

The microbial isolates were considered clinically significant when they were identified by culture in samples of respiratory secretions or blood. Urine antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were also considered, as well as Polymerase Chain Reaction (PCR) assays for respiratory viruses in pharyngeal swabs. Secretions from the lungs, bronchi, or trachea were considered a valid sample only if it contained ≥25 neutrophils and ≤10 squamous epithelial cells per low power field (x100).

Infection by a DRP was considered the primary outcome and was defined as infection by a PES agent: Pa, or ESBLpE, or MRSA [18]. We also included non-fermenting Gram-negative bacteria (nfGNB) other than Pa in the definition, namely other *Pseudomonas spp, Acinetobacter baumannii, Stenotrophomonas maltophilia, Burkholderia cepacia and Ralstonia picketii*.

A specific database was built in Statistical Package for the Social Sciences (SPSS) for data introduction. All data were coded, for personal data protection.

d) Statistical Analysis

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, interquartile (IQR) range, and minimum and maximum, when appropriate.

Hypotheses were tested regarding the distribution of continuous variables with non-normal distribution using the nonparametric Mann–Whitney and Kruskal–Wallis tests, depending on the nature of the hypothesis, or T test for independent samples or One Way Anova for variables with normal distribution. When testing a hypothesis regarding categorical variables, a chi-square test or a Fisher's exact test were used, as appropriate.

In order to have a more thorough understanding of the factors associated with our outcome, univariate and multivariate logistic regression modeling were used. Odds ratio (OR) and 95% confidence intervals (95% CI) were presented. The variables were chosen for the multivariate analysis according to their statistical significance in the univariate analysis and also because of their clinical relevance (antibiotic use in the previous 90 days, being bed-ridden, and provenience from a long-term care facility). CURB 65 and Charlson's index were used for adjustment to clinical severity. All selected variables were included in the model (enter method).

Model goodness-of-fit was assessed using the Hosmer-Lemeshow statistic and discriminative power was evaluated by receiver-operator curve (ROC) curve analysis.

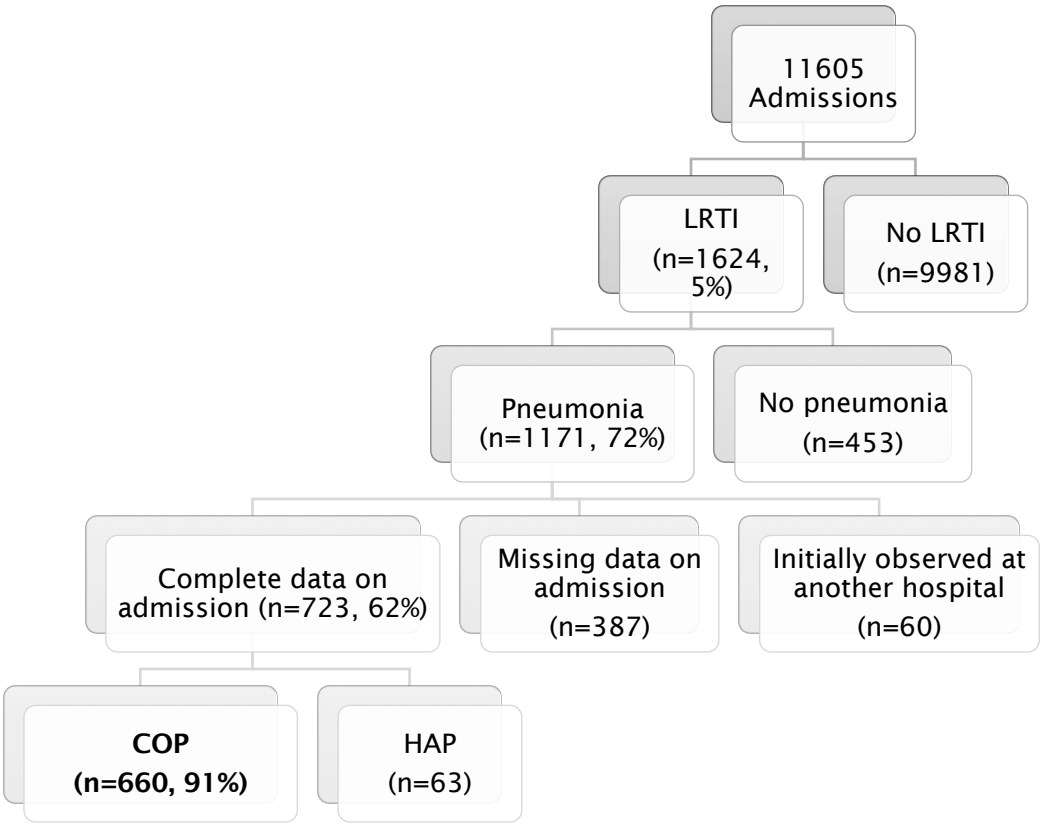
The significance level used was 0.05.

Statistical analysis was performed using the software SPSS v. 26.0.

Results

During the study period, 11605 patients were admitted into the department, 1624 with lower respiratory tract infection, of which 1171 were pneumonias; 660 were community-onset pneumonias (Fig 1). Chest imaging included a CT scan in 152 patients (23.0%). The remainder had a clear new onset pulmonary infiltrate on chest radiography.

Figure 1: Flow chart of admitted patients, with criteria for inclusion and exclusion



LRTI: lower respiratory tract infection; COP: community-onset pneumonia; HAP: hospital-acquired pneumonia

The mean (±sd) age of included patients was 74±15 years, and 58.9% were males. Detailed characteristics of the study population are described in table 1.

Table 1: Characterization of the study population and severity of pneumonia (n=660)

Characteristics	
Comorbidities and functional status	
Charlson's Index, median (P25-P75)	*2 (1-4)*
Neoplastic disease, n (%)	128 (19,4)
Neoplastic disease (Active)	80 (62.5)
Neoplastic disease (Past)	48 (37.5)
COPD, n (%)	124 (28.2)
COPD GOLD 1-2	38 (30.6)
COPD GOLD 3-4	51 (69.4)
Pulmonary Fibrotic Sequelae, n (%)	28 (20.9)
Bronchiectasis, n (%)	70 (15,7)
Long duration oxygen therapy, n (%)	64 (13.7)
Chronic non-invasive ventilation, n (%)	2 (0.3)
Chronic Heart Failure, n (%)	213 (32.5)
Chronic Heart Failure (NYHA Class II or more)	171 (92.5)
Chronic Renal Disease, n (%)	107 (16.3)
Chronic Dialysis	7 (6.7)
Chronic Liver Disease, n (%)	19 (2.9)
Child-Pugh A	15 (83.3)
Child-Pugh B	3 (16.7)
Dementia, n (%)	202 (54.0)
Diabetes, n (%)	155 (23.6)
With target-organ dysfunction	84 (13.4)
Autoimmune Disease, n (%)	17 (2.6)
HIV infection, n (%)	19 (4.0)
with CD4+TL ≥200	10 (52.6)
with CD4+TL <200	9 (47.4)
Chronic glucocorticoids (>0,5mg/Kg/d), n (%)	24 (3.6)
Immunosuppressive medication, n (%)	14 (2.2)
Splenectomy, n (%)	2 (0.3)
Smoking habits (Active), n (%)	96 (15.5)
Smoking habits (Past), n (%)	153 (24.7)
Active alcoholic habits, n (%)	80 (12.9)
Drug abuse (cannabis), n (%)	7 (1.1)
Drug abuse (Other drugs), n (%)	11 (1.7)
Katz score, n (%)	
0	162 (25.4)
1	26 (4.1)
2	41 (6.4)
3	35 (5.5)
4	43 (6.8)
5	26 (4.1)
6	304 (47.7)
Other Risk Factors	
Male Sex, n (%)	389 (58.9)
Age (years), mean ±sd	*74 ± 15*
MRSA colonization, n (%)	50 (7.6)
Household contact with DRP carrier, n (%)	19 (5.2)
Recent travelling, n (%)	13 (2.1)
Household contact with children at kindergarden, n (%)	55 (9.9)
Flu epidemic, n (%)	118 (18.3)
Anti-flu vaccination, n (%)	228 (42.1)
Anti-*Streptococcus pneumoniae* vaccination, n (%)	49 (9.1)
Surgery in the last 90 days, n (%)	13 (2.1)
Hospital stay ≥ 2 days in the last 90 days, n (%)	153 (23.5)
Antibiotic use in the last 90 days, n (%)	234 (40.8)
Wound treatment in the last 30 days, n (%)	70 (11.0)
Treatment at the outpatient clinic in last 30 days, n (%)	21 (3.3)
Provenience from a long-term care facility, n (%)	79 (12.0)

Immunosuppression (composite definition), n (%)	68 (10.3)
Being bed-ridden, n (%)	205 (31.2)
Invasive devices, n (%)	
Nasogastric tube	71 (14.3)
Percutaneous Gastrostomy	45 (9.2)
Percutaneous Colostomy	37 (7.6)
Percutaneous Urostomy	37 (7.5)
JJ catheter	36 (7.3)
Tracheostomy	37 (7.5)
Urinary catheter	89 (17.6)
Transient Pacemaker	33 (6.6)
Clinical Severity	
Admission to the ICU, n (%)	31 (4.7)
Admission to the HDU, n (%)	77 (11.7)
CURB 65 Class, n (%)	
0	61 (9.2)
1	129 (19.5)
2	207 (31.4)
3	222 (33.6)
4	41 (6.2)
5	0 (0.0)
PSI Class, n (%)	
I	21 (3.3)
II	31 (4.8)
III	79 (12.2)
IV	262 (40.6)
V	252 (39.1)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NYHA: New York Heart Association; HIV: human immunodeficiency virus; CD4TL: CD4 T-lymphocytes; ICU: Intensive Care Unit; HDU: High Dependency Unit.

The median Charlson's index of this sample was 2. With a Katz score of 2 or less, 35.9% of the patients had severe functional impairment, and 31.2% were bed-ridden. Traditional healthcare-associated risk factors were present in a proportion of the patients: 40.8% had used antibiotics in the previous 90 days, 23.5% had a hospital stay of 2 or more days in the previous 90 days and 12.0% came from a long-term care facility. Severity scores were mostly those associated with need of hospital admission (71.2% had CURB 65 class of 2 or higher, and 91.9% had PSI class of III or higher). In 31 cases, there was admission to the ICU, and in 77 cases there was admission to the HDU.

The median length of stay (LOS) of the global sample was 9 days (IQR 7-15). The LOS in the general ward (9 days [IQR 7-14]) was lower than that observed at the ICU and HDU subgroups (22 days [IQR 13-41], $p<0.001$, and 12 days [IQR 9-22], $p<0.001$, respectively).

The global mortality rate was 18.8%: 19.4% in patients admitted directly to the ward, 25.8% in those admitted to the ICU ($p=0.381$) and 11.7% in those admitted to the HDU ($p=0.102$).

There were 215 patients (32.6% of 660) with microbiological documentation of COP; the microbiological documentation rate was 29.9% among patients admitted in the ward, 51.9% in the HDU (p<0.001) and 61.3% in the ICU (p<0.001). Of these 215 patients, 14 had infections caused by microorganisms other than bacteria and 4 did not have adequate antibiogram information, leaving 197 cases for analysis. From 345 samples of non-invasive respiratory secretions, in 160 (46.4%) a significant pathogen was identified, as well as in 14 out of 25 samples obtained by bronchofibroscopy (56.0%). In 44 cases (22.3%), there was documented bacteremia. The infection was polymicrobial in 9% of the cases (n=18).

There were 37 cases of COP caused by a PES agent (18.8% of all isolates). The percentage of COP by a PES agent was 19.9% among patients admitted to the general ward, compared with 14.7% among those admitted to the HDU (p=0.485) and 12.5% to the ICU (p=0.740). The involved pathogens are described in table 2. The median length of stay in PES patients was higher than that found in patients with identification of non-PES pathogens (13 days [IQR 10-20] vs 9 days [IQR 7-14], p=0.005). The mortality rate in PES patients was 32.4%, compared to 18.8% in patients with non-PES pathogens (p=0.067) and 17.1% in patients without a pathogen identification (p=0.243).

Table 2: Identified microorganisms

Bacteria	As a single agent	In co-infection	Total
*Streptococcus pneumoniae**	79	9	**88**
Haemophilus influenzae not B	22	4	**26**
Pseudomonas aeruginosa	16	1	**17**
Legionella pneumophila	15		**15**
Staphylococcus aureus (Methicillin-Resistant)	5	3	**8**
Haemophilus influenzae type B	7		**7**
Proteus mirabilis	5	2	**7**
Staphylococcus aureus (Methicillin-Sensitive)	5	1	**6**
Acinetobacter baumannii	3	2	**5**
Escherichia coli	3	2	**5**
Klebsiella pneumonia	3	1	**4**
Klebsiella oxytoca	3		**3**
Klebsiella pneumoniae ESBL+	3		**3**
Enterobacter cloacae		2	**2**
Enterococcus faecalis (Methicillin-Sensitive)		2	**2**
Moraxella catarrhalis	1	1	**2**
Morganella morganii	2		**2**
Streptococcus agalactiae Group B		2	**2**
Streptococcus mitis	2		**2**
Capnocytophages spp	1		**1**
Enterobacter (Klebsiella) aerogenes	1		**1**
Escherichia coli ESBL+	1		**1**
Pseudomonas fluorescens		1	**1**
Pseudomonas stutzeri		1	**1**
Ralstonia picketii		1	**1**
Stenotrophomonas maltophilia		1	**1**
Streptococcus pyogenes	1		**1**
Streptococcus salivarius		1	**1**

36 only in urinary antigen

In table 3 we present the association of potential risk factors with COP caused by PES. The univariate analysis showed an association of COP by PES with: higher

median Charlson's index (4 vs 2, p=0.002); diabetes with target-organ dysfunction (16.7% vs 5.9%, p=0.039); being bed-ridden (56.8% vs 20.1%, p<0.001); lower median Katz's score (2 vs 6, p=0.001); higher CURB 65 [median (IQR) = 2 (2-3) vs 2 (1-3), p=0.038] and PSI scores (142 vs 117, p=0.003); MRSA colonization (24.3% vs 8.8%, p=0.011); household contact with DRP carrier (15.8% vs 3.2%, p=0.043); absence of anti-*Streptococcus pneumoniae* vaccination (3.4% vs 9.4% vaccinated, p=0.046); hospital stay ≥ 2 days in last 90 days (47.2% vs 20.9%, p=0.002); antibiotic use in the last 90 days (72.7% vs 30.7%, p<0.001).

Table 3: Association of potential risk factors with COP caused by PES

			Patients with microbiological identification					
	Total		**PES**		**No PES**		**Crude OR**	**p-value[1]**
Age, mean (sd)	73	(17)	78	(9)	72	(18)	1.023	0.085
Male Sex, n (%)	134	(68.0)	29	(78.4)	105	(65.6)	1.897	0.138
Charlson's Index, median (P25-P75)	**2**	**(1-4)**	**4**	**(2-5)**	**2**	**(1-3)**	**1.217**	**0.002**
Active Neoplastic Disease, n (%)	24	(63.2)	6	(85.7)	18	(58.1)	4.329	0.198
DPOC GOLD 3 or 4, n (%)	22	(62.9)	5	(83.3)	17	(58.6)	3.529	0.276
Bronchiectasis, n (%)	29	(20.4)	8	(30.8)	21	(18.1)	2.011	0.153
Pulmonary Fibrotic Sequelae, n (%)	28	(20.9)	7	(29.2)	21	(19.1)	1.745	0.275
Long Duration Oxygen therapy, n (%)	20	(13.4)	5	(19.2)	15	(12.2)	1.714	0.562
Chronic non-invasive ventilation, n (%)	2	(1)	0	(0)			-	-
Chronic Heart failure NYHA II or more, n (%)	42	(91.3)	8	(100.0)	34	(89.5)	-	-
Chronic Renal Disease, n (%)	24	(12.4)	6	(16.2)	18	(11.5)	1.495	0.432
Chronic dialysis, n (%)	3	(4.1)	1	(9.1)	2	(3.2)	3.000	0.388
Chronic liver disease, n (%)	10	(5.2)	0	(0)	10	(6.4)	-	-
Dementia, n (%)	50	(45.5)	17	(58.6)	33	(40.7)	2.061	0.100
Diabetes with TO dysfunction, n (%)	**15**	**(7,9)**	**6**	**(16.7)**	**9**	**(5.9)**	**3.200**	**0.039**
Autoimmune disease, n (%)	6	(3.0)	2	(5.4)	4	(2.5)	2.229	0.366
HIV infection, n (%)	9	(6.1)	1	(3.8)	8	(6.6)	0.570	0.604
Chronic glucocorticoids (>0,5mg/Kg/d), n (%)	7	(3.6)	2	(5.4)	5	(3.1)	1.771	0.330
Immunosuppressive medicat, n (%)	4	(2.1)	1	(2.8)	3	(1.9)	1.486	0.150
Splenectomy, n (%)	2	(1.0)	1	(2.9)	1	(0.6)	4.559	0.288
Being bed-ridden, n (%)	**53**	**(27.0)**	**21**	**(56.8)**	**32**	**(20.1)**	**5.209**	**<0.001**

Katz score, median (P25-P75)	**6**	**(1-6)**	**2**	**(0-6)**	**6**	**(2-6)**	**0.794**	**0.001**
CURB 65, median (P25-P75)	**2**	**(1-3)**	**2**	**(2-3)**	**2**	**(1-3)**	**1.466**	**0.038**
PSI, median (P25-P75)	**122**	**(97-150)**	**142**	**(119-162)**	**117**	**(95-145)**	**1.016**	**0.003**
Smoking habits, n (%)								0,689
No	93	(49.5)	17	(53.1)	76	(48.7)	1.000	
Active	41	(21.8)	5	(15.6)	36	(23.1)	0.621	0.384
Past	54	(28.7)	10	(31.3)	44	(28.2)	1.016	0.971
Active alcoholic habits, n (%)	35	(18.6)	3	(8.3)	32	(21.1)	0.341	0.090
Drug abuse (cannabis), n (%)	3	(1.6)	0	(0)	3	(1.9)	-	-
Drug abuse (other drugs), n (%)	7	(5.7)	0	(0)	7	(4.6)	-	-
MRSA colonization, n (%)	**23**	**(11.7)**	**9**	**(24.3)**	**14**	**(8.8)**	**3.352**	**0.011**
Recent travelling, n (%)	5	(2.6)	0	(0)	5	(3.2)	-	-
Household contact with children at kindergarden, n (%)	14	(8.3)	0	(0)	14	(10.1)	-	-
Flu epidemic, n (%)	31	(16.1)	9	(25.0)	22	(14.1)	2.030	0.843
Household contact with DRP carrier, n (%)	6	(5.3)	3	(15.8)	3	(3.2)	5.688	**0.043**
Anti-flu vaccination, n (%)	69	(41.1)	14	(48.3)	55	(39.6)	1.425	0.387
Anti-*Streptococcus pneumoniae* vaccination, n (%)	14	(8.3)	1	(3.4)	13	(9.4)	0.346	**0.046**
Surgery in the last 90 days, n (%)	5	(2.7)	0	(0)	5	(3.3)	-	-
Hospital stay ≥ 2 days in last 90 days, n (%)	**50**	**(25.8)**	**17**	**(47.2)**	**33**	**(20.9)**	**3.389**	**0,002**
Antibiotic use in the last 90 days, n (%)	**66**	**(38.8)**	**24**	**(72.7)**	**42**	**(30.7)**	**6.032**	**<0.001**
Wound treatment in the last 30 days, n (%)	19	(9.8)	5	(13.5)	14	(9.0)	1.585	0.480
Treatment at the outpatient clinic in last 30 days, n (%)	5	(2.6)	0	(0)	5	(3.2)	-	-
Provenience from a long-term care facility, n (%)	28	(14.4)	8	(22.2)	20	(12.6)	1,986	0.142
Immunosuppression (composite definition), n (%)	23	(11.7)	6	(16.2)	17	(10.6)	1.628	0.343
Invasive devices, n (%)								
Nasogastric tube	**27**	**(18.8)**	**13**	**(40.6)**	**14**	**(12.5)**	**4.789**	**0.001**
Percutaneous Gastrostomy	12	(8.8)	1	(3.6)	11	(10.1)	0.330	0.299
Percutaneous Colostomy	10	(7.4)	1	(3.7)	9	(8.3)	0.423	0.424
Percutaneous Urostomy	11	(8.1)	0	(0)	11	(10.2)	-	-
JJ catheter	11	(8.1)	0	(0)	11	(10.1)	-	-
Tracheostomy	10	(7.3)	1	(3.7)	9	(8.2)	0.432	0.435
Urinary catheter	28	(19.2)	9	(31.0)	19	(16.2)	2.321	0.075
Transient Pacemaker	9	(6.4)	0	(0)	9	(7.9)	-	-

Differences in percentage calculation are due to different number of missings in each variable

Among patients with hospital stay in the previous 90 days, 84% (42 out of 50) had antibiotic use in the same period, and among patients who used antibiotic in the previous 90 days, 63,6% (42 out of 66) had a hospital stay during that same period.

Based on the results of the univariate analysis, two models were developed, including five variables: Charlson's Index, CURB 65 score, provenience from a long-term care facility, being bed-ridden and antibiotic use in the previous 90 days or hospital stay ≥ 2 days in the previous 90 days. The first model (table 4) retained antibiotic use in the previous 90 days (adjusted OR=4.411, 95%CI [1.745-11.148]) and being bed-ridden (adjusted OR=5.492, 95%CI [2.121-14.222]); in the second model, only "being bed-ridden" was retained with an adjusted OR=4.955, 95%CI [2.081-11.797] (data not shown).

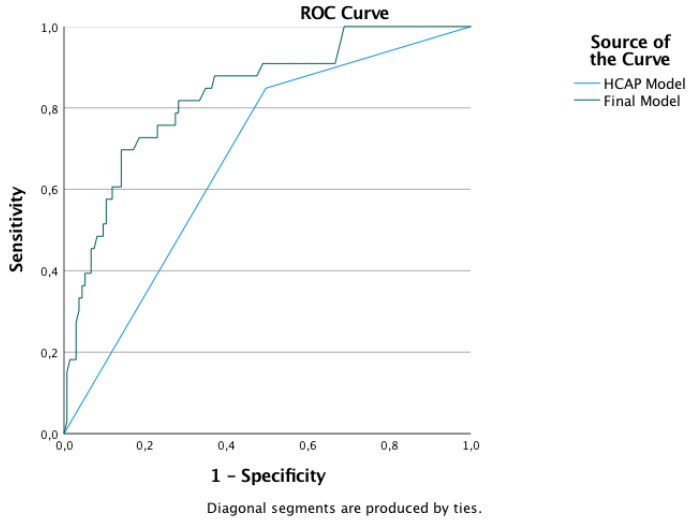
Table 4: Factors associated with COP caused by PES: multivariable analysis

	aOR	95% CI for aOR		p
Charlson's Index	1.174	0.994	1.387	0.059
CURB 65	1.278	0.826	1.977	0.271
Long-term care facility	0.668	0.180	2.477	0.546
Antibiotic in previous 90 days	**4.411**	**1.745**	**11.148**	**0.002**
Bed-ridden	**5.492**	**2.121**	**14.222**	**<0.001**

aOR: adjusted odds-ratio; Hosmer-Lemeshow: p = 0.144; AUROC = 0.832 (CI95% [0.756-0.908])

The model's performance is expressed by an AUROC curve of 0.832, 95%CI [0.756-0.908]. The use of the classic "HCAP criteria" in this group of patients produces an AUROC curve = 0.676, 95%CI [0.582-0.770]) (Fig 2).

Figure 2: AUROC of the final model compared to the "HCAP model"



There were 90 patients that had both risk factors (bed-ridden and previous antibiotic) for COP by DRP. In this group of patients, the identification rate was 27.8% (n=25). Pathogens identified were: *Pseudomonas aeruginosa* in 32% (6 in respiratory secretions and 2 in broncho-alveolar lavage), MRSA in 24% (3 in respiratory secretions and 3 blood cultures), *Streptococcus pneumoniae* in 20% (3 in urinary antigen, 1 in respiratory secretions and 1 in blood culture), *Haemophilus influenzae* in 8% (2 in respiratory secretions) and the remaining 16% were 1 ESBL *Klebsiella pneumoniae* in blood cultures, 1 *Acinetobacter baumannii* in respiratory secretions, 1 non-resistant *E. coli* in respiratory secretions and 1 polymicrobial with an MSSA and a *Proteus mirabilis* in respiratory secretions.

Regarding the antibiotic susceptibility of the more prevalent agent (Pa), we found 50% (n=4) susceptibility to Piperacillin + Tazobactam, Ceftazidime and Cefepime, 75% (n= 6) to Ciprofloxacin, and 87.5% (n= 7) to Imipenem, Meropenem and Amikacin.

Discussion

In this study, we identified two very simple independent risk factors for infection by PES in COP: antibiotic use in the previous 90 days and being bed-ridden.

Antibiotic use is associated with selection of resistant agents in commensal flora, increasing the risk of DRP infection. Similar to other studies, we found this variable to be independently associated with infection by a DRP. In Webb's study [12], antibiotic use in the last 60 days showed an aOR of 5.32, 95% CI [1.86-15.26] for Gram-negative DRP. In Shindo's work [17], previous antibiotic use showed an aOR of 2.45, 95% CI [1.51–3.98] for DRP. And in Prina's study [18], antibiotic use in the last month showed an aOR of 2.48, 95% CI [1.56-3.94] for PES.

As to being bed-ridden, it is not clear whether this and other variables, related to clinical frailty, are surrogates of one another. We could consider that being bed-ridden would be a surrogate of provenience from a long-term care facility or of a recent hospital stay, but our results show that being bed-ridden is still significant after adjustment for these variables and comorbidities. The clinical meaning of this association is not clear. This variable is also present at Shindo's model [17], with an aOR of 2.45, 95% CI [1.40–4.30]. As a functional evaluation, we chose to use "bed-ridden" instead of Katz's score, because it is more intuitive in daily practice.

In our study, previous hospital stay was not an independent risk factor for DRP, even though most of the patients with previous hospital stay also used antibiotics. In Webb's and Prina's studies, the same result was observed [12] [18]. In Gross's study, it also was not significant: only the number of days of the hospital stay was a predictor of infection by a DRP [29]. On the other hand, some works identified this variable as an independent risk factor: Aliberti [16] (aOR of 4.87, 95% CI [1.90-12.4]) and Shindo [17] (aOR of 2.06, 95% CI [1.23–3.43]). It is possible that antibiotic use, and not hospital stay (which is also known to contribute to changes in commensal flora), is the most important factor. Provenience from long-term care facilities was also not an independent risk factor for infection by DRP in our study, unlike the results in Webb [12] (aOR 7.45, 95% CI [1.85 to 30.0]) and in Aliberti [16] (aOR 3.55, 95% CI [1.12-11.24]).

Although the variable "MRSA colonization" was associated with infection by PES, we decided not to include it in the multivariate model, due to the high risk of introducing a selection bias, considering that as investigators we did not interfere

with the decision of performing a nasal swab for MRSA screening, and that the patients that were submitted to it were probably those in which there was the perception of greater risk of DRP colonization and/or infection.

The presence of a nasogastric tube was also associated with COP by PES in the univariate analysis. Some studies found this variable to be associated with infection by DRP (Webb [12]: aOR 12.93, 95% CI [2.28 to 73.37] for Gram-negative DRP; Shindo [17]: aOR 2.43, 95% CI [1.18–5.00]). In our study, the inclusion of this variable in the model instead of "bed-ridden" revealed a much weaker aOR, suggesting that it could be a surrogate of being bed-ridden, and not the opposite (data not shown). Nasogastric tube could be a risk factor for aspiration mechanisms in pneumonia, and not particularly for DRP.

Charlson's index was used to adjust for multimorbidity. In multivariate analysis, as was expected, it did not reveal to be an independent risk factor. Although it was significant in univariate analysis, we did not include diabetes with target-organ dysfunction in the models, because it is one of Charlson's index's variables.

Severity scores (CURB 65 and PSI) were also used for adjustment. Most studies do not identify clinical severity as an independent risk factor for DRP in COP [12][13][16][17][18].

Household contact with DRP carrier is one of the HCAP criteria [6]. In our sample, there were a small number of cases, so we decided not to include this risk factor in the multivariate analysis.

Anti-Streptococcus pneumoniae (Sp) vaccination has been shown to reduce the number of infections by resistant strains of Sp [30]. It is not obvious why it would reduce DRP infections. In our sample, we had a small number of patients with Sp vaccination, so we decided not to include it in the final model.

The performance of our model (AUROC 0.832) is comparable to that of other studies (table 5). In this sample, our model is more discriminative than the HCAP definition (0.676), which was similar to that described in the Chalmers meta-analysis (0.64 to 0.70) [9]. It also has a higher discriminative power than most other published models, with the advantage of being more simple to determine than the majority of them.

Table 5: Other risk models for COP caused by DRP

Risk model	Retained variables	AUROC (95% CI)
Webb [12]	Antibiotic in previous 60 days Tube feeding DRP in last year Long-term care facility Chronic pulmonary disease	0.880 (0.820-0.930)
Falcone [13]	One risk factor for HCAP Bilateral pulmonary infiltrates Pleural effusion PaO2/FiO2 ratio	0.760 (0.710-0.820)
Aliberti [16]	Hospitalization in previous 90 days Long term care facility	0.790 (0.710-0.870)
Shindo [17]	Hospitalization in previous 90 days Antibiotic in previous 90 days Immunosuppression Use of gastric acid–suppressive agents Tube feeding Being bed-ridden	0.790 (0.740-0.840)
Prina [18]	Age >65 yr Male sex Antibiotic in previous month COPD or bronchiectasis Chronic kidney disease Altered mental status Temperature >37.8˚C	0.759 (0.713-0.806)

The rates of Pa and MRSA infection in CAP (2.6% and 1.2%) were similar to the ones described in larger cohorts. In an American Veteran's Affairs database, rates of 1.9% and 1.0%, respectively, were observed [31]. In a multinational study, the prevalence of Pa and antibiotic-resistant Pa in COP was 4.2% and 2.0%, respectively (USA: 4.3% and 2.5%; Europe 3.8% and 1.6%) [32].

Among patients bed-ridden and with previous antibiotic use, the identification rate of *Pseudomonas aeruginosa* and MRSA justifies the initial coverage of these agents. An empirical antibiotic regimen with a carbapenem and vancomycin would guarantee adequate initial antibiotic therapy in 92% of the agents identified in this group. If the choice is piperacillin/tazobactam instead of a carbapenem, this rate drops to 72%.

The main limitation of our study was the fact that in some variables there was a great amount of missing data: more than 30% of the identified pneumonias did not have complete record of vital signs on admission at the emergency department (mainly the respiratory rate). Due to the relatively small number of PES cases we could only use a small number of variables in the logistic regression. The radiological criteria for study inclusion was validated by a single senior consultant, which can represent a selection bias, although the initial selection of patients for inclusion in the study was made by other doctors from the research group, which decreases the risk of bias.

Some relevant variables were underrepresented, like MRSA colonization. This has been described as an important risk factor [33], and it could have impacted the risk model. The same can be said about colonization by other agents, such as Pa [32]. Nonetheless, it is controversial if it is cost effective to screen all hospitalized patients for DRP [34] [35].

The strengths of this study are the exhaustive analysis of risk factors and the continuous and systematic auditing of the prospective data collection, increasing its reliability. It is also appealing that our model is very easy to apply and does not require any analytical or radiographic results.

Conclusions

In this study, antibiotic use in the previous 90 days and being bed-ridden were independently associated with community-onset pneumonia caused by drug resistant pathogens, namely Pseudomonas aeruginosa, other non-fermenting Gram-negative bacteria, extended-spectrum ß-lactamase producing *Enterobacteriaceae* and Methicillin-resistant Staphylococcus aureus, after adjustment for Charlson's Comorbidity Index, CURB 65 and provenience from a long term care facility. A multicenter study would help in a more comprehensive knowledge of the microbiological profile involved in these high risk patients and allow more robust conclusions on initial treatment recommendations.

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CHAPTER 5 - "Does etiological investigation have an impact on the outcomes of community-acquired pneumonia? – A prospective cohort study"

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Does Etiological Investigation Have an Impact on the Outcomes of Community-Acquired Pneumonia? – A Prospective Cohort Study

Abstract

Introduction: There is lack of evidence that etiological investigation influences outcomes in community-acquired pneumonia (CAP). Guidelines recommend diverse approaches to this matter. Our aim was to find if etiological investigation has an impact on CAP management and outcomes.

Methods: Prospective cohort study, conducted over a two years' period, in a community-based hospital, including all adult patients with CAP. Univariate and multivariate logistic regression modeling were performed to understand the association of etiological identification with CAP outcomes, particularly hospital mortality.

Results: A total of 660 cases of CAP were included, with a mean±sd age of 74±15 years and 58.9% of males. Etiology was documented in 33% of cases. Antibiotic (ATB) was modified in 148 patients, in 51 (34%) motivated by microbiological results. There was no significant impact on hospital mortality of microbiological documentation (35.5% vs 31.2%, p=0.352), or the fact that ATB was modified due to microbiological findings (27.0% vs 36.9%, p=0.272). When stratified by 3 subgroups of risk for drug-resistant pathogens (zero, one or two risk factors: being bed-ridden and/or ATB use within 90 days), etiology identification still did not influence mortality. When adjusted for CURB-65, Charlson's index, being bed-ridden, having had ATB or hospitalization within 90 days or coming from long-term care facilities, microbial identification was not associated with lower mortality.

Conclusion: Etiological investigation of patients with CAP does not have an association with hospital mortality, irrespective of the risk for drug-resistant pathogens.

Keywords

Community-acquired pneumonia; Etiological investigation; Outcomes; Mortality

Introduction

In clinical practice, microbial etiology of Community-Acquired Pneumonia (CAP) remains unknown in at least 60% of the cases [1]. Although there is a lack of scientific evidence that etiological identification improves individual patient outcomes, there are some reasons why we tend to investigate (the possibility of finding a resistant pathogen or an agent with public health implications; the aim of narrowing the treatment spectrum; and the ongoing knowledge of local epidemiology) [2].

One argument against the need for etiological investigation is that CAP has a limited number of possible pathogenic agents, which are mostly covered by the usual recommended antibiotics. In fact, a reference study showed that only 3.3 to 7.6 of CAP patients with etiology identification (0.9 to 2.4% of all CAP patients) had identification of a multidrug-resistant pathogen [3]. In more recent works, the prevalence of *Pseudomonas aeruginosa* (Pa) in CAP was 4.2% [4] and the MRSA prevalence was 3% [5].

Many studies have demonstrated the lack of impact of etiological investigation in community pneumonia outcomes, whether for blood cultures [6,7], for sputum [8,9,10] or for etiological investigation in general [11,12,13,14].

Based on this, the IDSA/ATS 2019 Guidelines recommend that respiratory secretions (RS) and blood cultures (BC) should only be obtained in patients: with clinical severity; that will be empirically treated for MRSA or Pa; that had a previous infection by one of these pathogens; or that were hospitalized and received antibiotics in the previous 90 days. As for urinary antigen tests, the recommendation is only for severe pneumonia and, for *Legionella*, in risk epidemiological scenarios [2]. In other reference guidelines, however, a different position has been defended, consisting in obtaining BC and RS examination in all admitted patients [15,16]. In a panel of experts that published an appraisal of the American guidelines, 7 out of 14 experts also defended a more aggressive etiological investigation strategy [17], as well as other reference authors [18].

Our goal was to find if, in a population of patients with CAP, the fact that an etiological agent is identified has an impact on the outcomes, particularly in hospital mortality. Secondarily, we wanted to describe how etiological investigation and its results influence the management of these patients.

Patients and Methods

a) Study design

This was a prospective (concurrent data collection), cohort study, conducted over a two years' period, between January 1st 2012 and December 31st 2013, in all medical wards (general ward with 120 beds), in a high dependency unit (HDU) with 13 beds and in the intensive care unit (ICU) with 10 beds of a community-based hospital (350 beds).

The study was inserted in a prospective registry, alongside with other studies: the Prospective Observational Study of Pneumonias in the Acute Setting (EPOPEIA). It was approved by the Hospital Ethics Committee and by the National Data Protection Committee. Informed consent was obtained for every protocol and data were coded, in order to guarantee anonymization.

b) Inclusion and exclusion criteria

All adult patients (age ≥ 18 years) with community-onset pneumonia primarily observed at our Hospital were enrolled in the study. Pneumonia diagnosis was made by the presence of [new onset or worsening pulmonary infiltrate on chest radiography (or CT scan) with no alternative explanations (ex: heart failure, neoplasm, chronic interstitial disease, pulmonary embolism); and at least 2 of the following criteria: a) Fever (T > 38 ◦C) (without obvious alternative focus of infection or non-infectious explanations); b) Leukocytosis (> 11,500 / mm3) (without obvious alternative focus of infection or non-infectious explanations); c) Purulent respiratory secretions; or one of a), b) and c), in the presence of: severe sepsis [19]; hemodynamic instability [19]; or refractory hypoxemia (PaO2 / FiO2 < 100 in spontaneous ventilation)].

The term "severe sepsis" was defined as sepsis with acute end-organ dysfunction [19].

All inclusions in the study were validated by an internal medicine senior consultant, namely chest x-ray and/or CT scan observation.

Absence of vital signs, mental status and arterial blood gases record on admission were considered to be exclusion criteria, as well as Hospital Acquired Pneumonia,

defined as pneumonia diagnosed 48 h or more after hospital admission and not incubating at the time of hospital admission [20].

c) Data collection

The protocol addressed extensive information about demographic, epidemiological, clinical, analytical, microbiological and imagiological data, as well as antibiotic therapy, and follow-up until 30 days after discharge (mortality and readmission). Comorbidities [21,22,23,24] and selected scores (CURB 65 [16], Pneumonia Severity Index (PSI) [25], Charlson's index [26], Katz score [27]) were defined according to the current definitions. Immunosuppression was a composite definition that included: chemotherapy less or equal to 90 days before; or HIV infection with CD4 TL count <500/mm3; or chronic glucocorticoids equivalent to prednisolone ≥ 0,5 mg / Kg / day; or solid organ transplant; or treatment with immunosuppressive drugs; or liquid neoplastic disease (Hodgkin's or non-Hodgkin's Lymphoma or Chronic or Acute Leukemia or Multiple Myeloma or Waldenström Macroglobulinemia).

The microbial isolates were considered clinically significant when they were identified by culture in samples of respiratory secretions or blood. Urine antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were also considered, as well as Polymerase Chain Reaction (PCR) assays for respiratory viruses in pharyngeal swabs. Secretions from the lungs, bronchi, or trachea were considered a valid sample only if it contained ≥25 neutrophils and ≤10 squamous epithelial cells per low power field (x100). In respiratory samples, criteria for rejecting results as non relevant included a semi-quantitative method for interpretation of cultures and the type of agent identified. Coagulase negative *Staphylococci*, *Corynebacterium* spp and *Candida* were never considered relevant, as well as most *Enterococci* and *Viridans* group *Streptococci*. Mixed respiratory flora was usually not valued.

Infection by a drug-resistant pathogen was defined as infection by a PES agent: *Pseudomonas aeruginosa*, or Extended-Spectrum β-Lactamase-producing *Enterobacteriaceae*, or Methicillin-Resistant *Staphylococcus aureus* [28]. We also included non-fermenting Gram-negative bacteria other than Pa in the definition, namely other *Pseudomonas* spp, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Ralstonia picketii*.

We classified antibiotic therapy modification as being motivated by results of the microbiological investigation or by other reasons, namely: pneumonia complication or additional infectious focus; adverse effect of the antimicrobial; or empirical modification.

The primary evaluated outcome was in-hospital mortality. We also evaluated 30-day mortality and hospital length of stay.

To evaluate the independent impact of etiological investigation on the outcomes, we built a multivariable model to adjust for clinical severity (CURB 65), co-morbidities (Charlson's index) and risk factors for drug resistant pathogens (antibiotics in the previous 90 days (28), being bed-ridden [29], hospitalization in the previous 90 days [30] and provenience from a long-term care facility [30]). Being bed-ridden was defined as being chronically confined to bed, with no gait capability, due to disabling disease or age-related multifactorial frailty and disability.

A specific database was built in Statistical Package for the Social Sciences (SPSS) for data introduction. All data were coded, for personal data protection.

d) Statistical analysis

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, interquartile (IQR) range, and minimum and maximum, when appropriate.

Hypotheses were tested regarding the distribution of continuous variables with non-normal distribution using the nonparametric Mann–Whitney and Kruskal–Wallis tests, depending on the nature of the hypothesis, or T test for independent samples or One Way Anova for variables with normal distribution. When testing a hypothesis regarding categorical variables, a chi-square test or a Fisher's exact test were used, as appropriate.

In order to have a more thorough understanding of the factors associated with hospital mortality, univariate and multivariate logistic regression modeling were used. Odds ratio (OR) and 95% confidence intervals (95% CI) were presented. The variables were chosen for the multivariate analysis according to their statistical significance in the univariate analysis and also because of their clinical relevance

(hospitalization or antibiotic use in the previous 90 days, being bed-ridden, provenience from a long-term care facility and etiology identification). CURB 65 and Charlson's index were used for adjustment to clinical severity. All selected variables were included in the model (enter method). Model goodness-of-fit was assessed using the Hosmer-Lemeshow statistic.

The significance level used was 0.05.

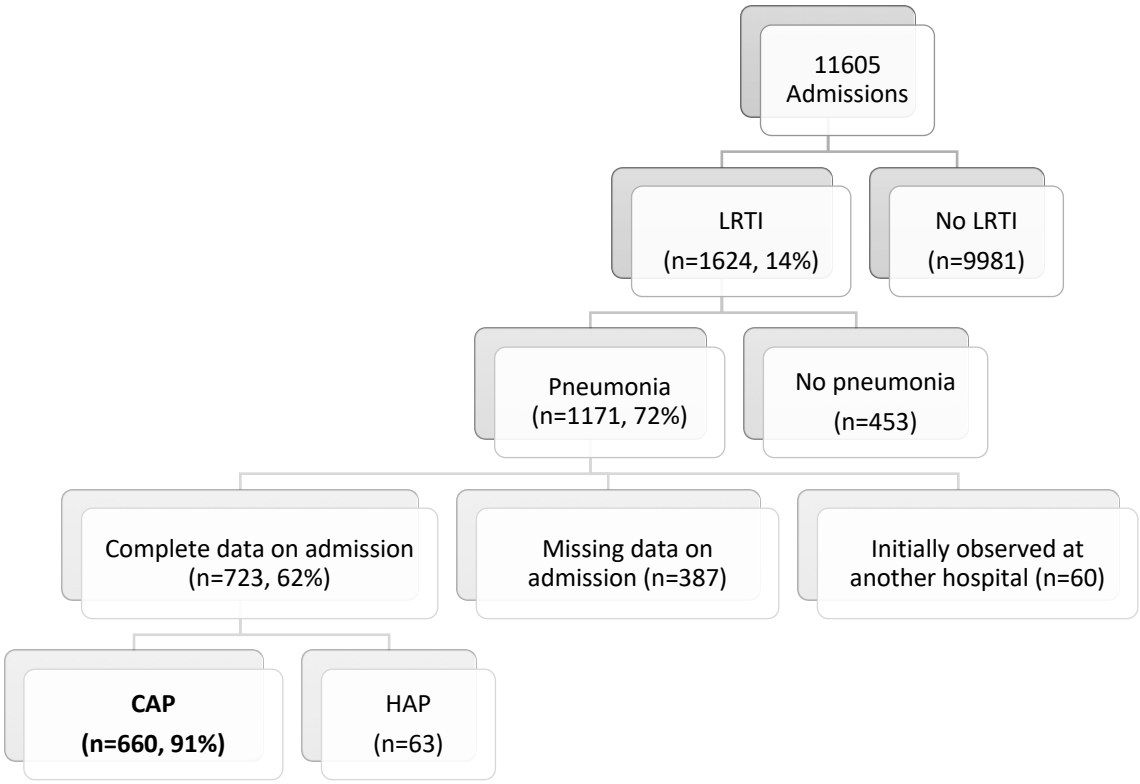
Statistical analysis was performed using the software Statistical Package for the Social Sciences v. 27.0.

Results

General description of the sample

During the study period, there were 11 605 patients admitted into the department, 1 624 with lower respiratory tract infection, of which 1 171 were pneumonias; 660 were community-acquired pneumonias **(Fig 1)**. Chest imaging included a CT scan in 152 patients (23.0%). The remainder had a clear new onset pulmonary infiltrate on chest radiography.

Figure 1: Flow chart of admitted patients, with criteria for inclusion and exclusion



Detailed characteristics of the study population are described in table 1. The mean±sd age of included patients was 74±15 years, and 58.9% were males. The median Charlson's index of this sample was 2. With a Katz score of 2 or less, 35.9% of the patients had severe functional impairment, and 31.2% were bed-ridden. Traditional healthcare-associated risk factors were present in a proportion of the patients: 40.8% had used antibiotics in the previous 90 days, 23.5% had a Hospital

stay of 2 or more days in the previous 90 days and 12.0% came from a long-term care facility. Severity scores were mostly those associated with need of hospital admission (71.2% had CURB 65 class of 2 or higher, and 91.9% had PSI class of III or higher). In 77 cases there was admission to the HDU and 31 cases to the ICU.

The median (IQR) length of stay (LOS) of the global sample was 9 (7-15) days: 9 (7-14) days in those admitted to the general ward, 12 (9-22) in those admitted to HDU and 22 (13-41) in the group admitted to the ICU, $p<0.001$.

The global mortality rate was 18.8%; 19.4% in patients admitted directly to the ward, 11.7% in those admitted to the HDU ($p=0.102$) and 25.8% in those admitted to the ICU ($p=0.381$). Thirty-day mortality was 28.0%.

There were 215 patients (33.0% of 660) with etiological identification; the microbiological documentation rate was 30.0% among patients admitted in the ward, 52.0% in the HDU ($p<0.001$) and 61.0% in the ICU ($p<0.001$). Of these 215 patients, 4 did not have adequate antibiogram information, leaving 211 cases for analysis.

Blood cultures were obtained in 622 patients (94%) and yielded a pathogen in 7%. Spontaneous respiratory secretions were obtained in 340 patients (52%), with 33% of positive results. In respiratory secretions obtained by bronchoscopy (40 samples), the identification rate was 25%. The infection was polymicrobial in 9% of the cases (n=20). There were 37 cases of CAP caused by a PES agent (18% of all identified agents).

Table 1. General characterization of the study population according to hospital outcome

	Hospital mortality							
	Total (n=660)		**No (n=536)**		**Yes (n=124)**		**p-value[1]**	**Crude OR**
Age, mean (sd)	74	(15)	74	(16)	78	(13)	0489[2]	0.917
Male Sex, n (%)	388	(58.8)	313	(58.4)	75	(60.5)	0.670	1.091
Length of hospital stay	8	(6-14)	8	(6-13)	8	(4-17)	0.373[3]	1.016
Charlson's Index, median (P25-P75)	**2**	**(1-4)**	**2**	**(1-4)**	**3**	**(1-6)**	**<0.001**[3]	**1.138**
Active Neoplastic Disease, n (%)	80	(62.5)	52	(57.1)	28	(75.7)	0.050	2.333
DPOC GOLD 3 or 4, n (%)	51	(56.7)	47	(56.0)	4	(66.7)	0.694	1.574
Bronchiectasis, n (%)	70	(15.7)	62	(17.3)	8	(9.3)	0.068	0.491
Pulmonary Fibrotic Sequelae, n (%)	88	(21.4)	71	(21.6)	17	(20.5)	0.817	0.932
Long Duration Oxygen therapy, n (%)	64	(13.7)	56	(14.9)	8	(9.0)	0.148	0.566
Chronic non-invasive ventilation, n (%)								
Chronic Heart failure NYHA II or more, n (%)	171	(92.4)	145	(91.2)	26	(100.0)	0.224	-
Chronic Renal Disease, n (%)	107	(16.3)	80	(15.0)	27	(22.0)	0.078	1.584
Chronic dialysis, n (%)	7	(2.6)	4	(2.0)	3	(5.0)	0.194	2.645
Chronic liver disease, n (%)	11	(5.3)	10	(6.4)	1	(2.0)	0.300	0.292
Dementia, n (%)	202	(54.0)	149	(51.7)	53	(61.6)	0.106	1.498
Diabetes with TO dysfunction, n (%)	84	(37.5)	66	(37.3)	18	(38.3)	0.899	1.044
Autoimmune disease, n (%)	17	(2.6)	16	(3.0)	1	(0.8)	0.219	0.262
HIV infection, n (%)	19	(4.0)	16	(4.2)	3	(3.3)	>0.999	0.782
Chronic glucocorticoids (>0,5mg/Kg/d), n (%)	24	(3.6)	18	(3.4)	6	(4.8)	0.427	1.458
Immunosuppressive medication, n (%)	14	(2.2)	13	(2.5)	1	(0.8)	0.488	0.322
Splenectomy, n (%)	2	(0.3)	2	(0.4)	0	(0.0)	>0.999	-
Being bed-ridden, n (%)	**205**	**(31.2)**	**137**	**(25.7)**	**68**	**(54.8)**	**<0.001**	**3.519**
Katz score, median (P25-P75)	**5**	**(0-6)**	**6**	**(2-6)**	**2**	**(0-5)**	**<0.001**[3]	**0.774**
CURB 65, median (P25-P75)	**2**	**(1-3)**	**2**	**(1-3)**	**3**	**(2-3)**	**<0.001**[3]	**1.391**
PSI,								
Class I	21	(3.3)	21	(4.0)	0	(0)	-	-
Class II	31	(4.8)	29	(5.5)	2	(1.6)		Ref
Class III	79	(12.2)	74	(14.1)	5	(4.1)	0.981	0.980
Class IV	262	(40.6)	211	(40.3)	51	(41.8)	0.093	3.505
Class V	**252**	**(39.1)**	**188**	**(35.9)**	**64**	**(52.5)**	**0.032**	**4.936**
Smoking, n (%)							0.401	
No	370	(59.8)	293	(58.5)	77	(65.3)		Ref
Yes	96	(15.5)	80	(16.0)	16	(13.6)		0.761
Past	153	(24.7)	128	(25.5)	25	(21.3)		0.743
Active alcoholic habits, n (%)	**80**	**(12.9)**	**77**	**(15.4)**	**3**	**(2.5)**	**<0.001**	**0.138**
Any inhaled drug addiction, n (%)	7	(1.1)	3	(0.7)	4	(1.9)	0.208	2.545

Any IV drug addiction, n (%)	**11**	**(1.8)**	**2**	**(0.5)**	**9**	**(4.2)**	**<0.001**	**8.800**
MRSA colonization, n (%)	61	(21.7)	47	(20.6)	14	(26.4)	0.356	1.382
Recent travelling, n (%)	13	(2.1)	12	(2.3)	1	(0.8)	0.480	0.349
Household contact with children at kindergarden, n (%)	55	(9.9)	48	(10.7)	7	(6.4)	0.176	0.570
Flu epidemic, n (%)	118	(18.3)	101	(19.2)	17	(14.2)	0.198	0.695
Household contact with DRP carrier, n (%)	19	(5.2)	13	(4.3)	6	(9.1)	0.116	2.200
Anti-flu vaccination, n (%)	228	(42.1)	193	(42.7)	35	(38.9)	0.504	0.854
Anti-*Streptococcus pneumoniae* vaccination, n (%)	49	(9.1)	41	(9.3)	8	(8.6)	0.843	0.923
Surgery in the last 90 days, n (%)	13	(2.1)	11	(2.2)	2	(1.7)	>0.999	0.775
Hospital stay ≥ 2 days in last 90 days, n (%)	**153**	**(23.5)**	**115**	**(21.7)**	**38**	**(31.1)**	**0.027**	**1.629**
Antibiotic use in the last 90 days, n (%)	234	(40.8)	184	(39.7)	50	(45.0)	0.307	1.243
Wound treatment in the last 30 days, n (%)	**70**	**(11.0)**	**48**	**(9.3)**	**22**	**(18.2)**	**0.005**	**2.157**
Treatment at the outpatient clinic in last 30 days, n (%)	**21**	**(3.3)**	**13**	**(2.5)**	**8**	**(6.5)**	**0.043**	**2.690**
Provenience from a long-term care facility, n (%)	79	(12.0)	60	(11.2)	19	(16.4)	0.197	1.443
Immunosuppresion (composite definition), n (%)	68	(10.3)	53	(9.9)	15	(12.1)	0.466	1.254
Invasive devices, n (%)								
Nasogastric tube	**71**	**(14.3)**	**51**	**(12.8)**	**20**	**(20.8)**	**0.042**	**1.801**
Percutaneous Gastrostomy	45	(9.2)	32	(8.1)	13	(13.7)	0.091	1.798
Percutaneous Colostomy	37	(7.6)	28	(7.1)	9	(9.5)	0.434	1.368
Percutaneous Urostomy	37	(7.5)	28	(7,1)	9	(9.4)	0.447	1.356
JJ catheter	36	(7.3)	28	(7.1)	8	(8.4)	0.650	1.209
Tracheostomy	37	(7.5)	29	(7.3)	8	(8.4)	0.711	1.167
Urinary catheter	**89**	**(17.6)**	**62**	**(15.2)**	**27**	**(27.0)**	**0.006**	**2.058**
Transient Pacemaker	33	(6.6)	25	(6.2)	8	(8.2)	0.455	1.370
ATB modification	**148**	**(22.0)**	**111**	**(20.7)**	**37**	**(29.8)**	**0.029**	**1.628**
ATB covered pathogen	178	(30.4)	147	(31.1)	31	(27.7)	0.482	0.849
ATB modification for MB result	51	(34.5)	41	(36.9)	10	(27.0)	0.272	0.632
Initial ATB for community agents	458	(70.0)	380	(83.0)	78	(17.0)		Ref
Initial ATB for Pseudomonas or Ps + MRSA	196	(30.0)	151	(77.0)	45	(23.0)	1.452	0.076
Etiology identification	211	(32.0)	167	(31.2)	44	(35.5)	0.352	1.215
Gram positive	92	(43.6)	78	(46.7)	14	(31.8)	0.076	0.532
Gram negative	86	(40.8)	65	(38.9)	21	(47.7)	0.290	1.433
Polymicrobial	19	(9.0)	12	(7.2)	7	(15.9)	0.081	2.444
Other agents	14	(6.6)	12	(7.2)	2	(4.5)	0.739	0.615
PES	37	(18.8)	25	(16.1)	12	(28.6)	0.077	2.080

P25 – 25 Percentile; P75 – 75 Percentile; 1 – Chi Square Test; 2 – T-Test for Independent Samples; 3 – Mann-Whitney Test

Table 2 shows the microbiological profile in 181 (32.0%) patients that had microbiological identification among the 573 patients that had PES risk factors documented. Pathogens are presented with their frequencies in 3 different groups: patients with 0, 1 or 2 of the PES risk factors identified in our previous study (being bed-ridden and ATB use in the previous 90 days) [29].

Table 2: Microbial identification in products from patients with 0, 1 and 2 risk factors for a PES agent

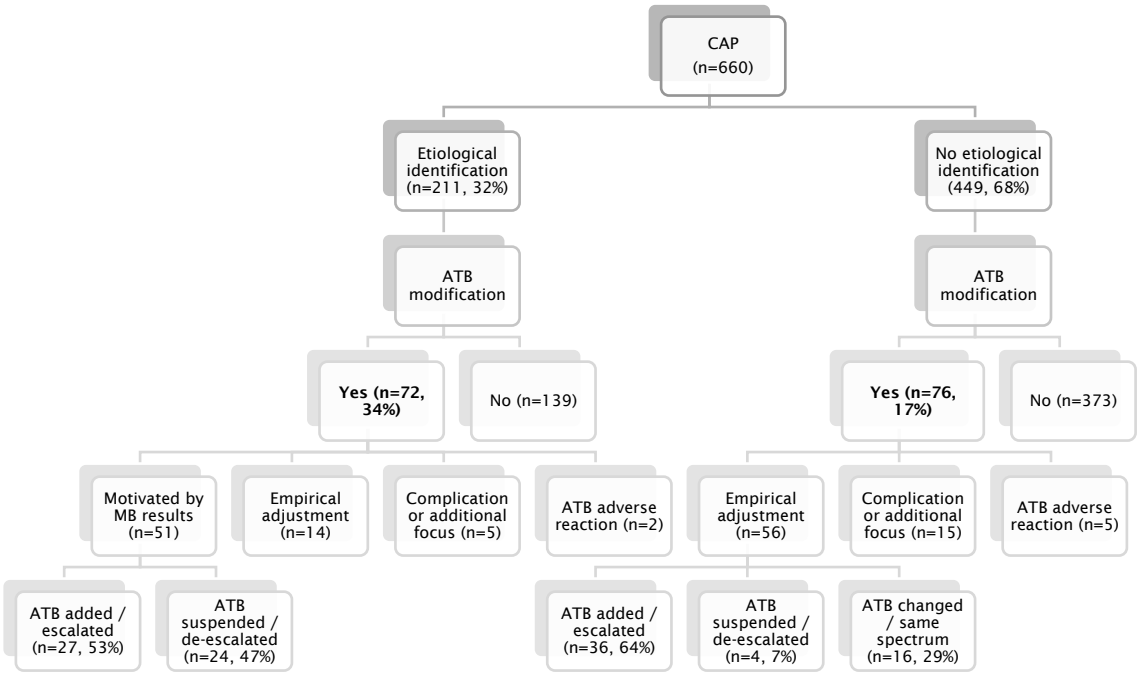
Pathogen	0 Risk Factors (245 pts, 87 with identification - 115 isolates)		1 Risk Factor (238 pts, 69 with identification - 86 isolates)		2 Risk Factors (90 pts, 25 with identification - 34 isolates)	
	n	%	n	%	n	%
Acinetobacter baumanii	2	1.7	4	4.7	2	5.9
*Actinomyces meyeri**			1	1.2		
Aspergillus fumigatus	2	1.7				
Bordetella pertussis			1	1.2		
*Capnocytophages spp**			1	1.2		
Citomegalovirus			1	1.2		
Enterobacter aerogenes	1	0.9	1	1.2		
Enterobacter cloacae			1	1.2		
*Enterococcus faecalis MS**					1	2.9
Escherichia coli (wild)			1	1.2		
Escherichia coli ESBL+	2	1.7			2	5.9
Escherichia coli (drug resistant)			1	1.2		
Haemophilus influenzae not B	10	8.7	9	10.5	2	5.9
Haemophilus influenzae type B	1	0.9	5	5.8		
Influenza A			4	4.7		
Klebsiella oxytoca	2	1.7				
Klebsiella pneumoniae (wild)	2	1.7	1	1.2		
Klebsiella pneumoniae ESBL+			2	2.3	1	2.9
Legionella pneumophila serotype 1	11	9.6	1	1.2		
Moraxella catarrhalis	1	0.9	1	1.2		
Morganella morganii	2	1.7				
Mycobacterium tuberculosis	3	2.6	1	1.2		
Pneumocystis jiroveccii	2	1.7	1	1.2		
Proteus mirabilis	1	0.9	4	4.7	1	2.9
Pseudomonas aeruginosa	2	1.7	4	4.7	9	26.5

Pseudomonas fluorescens	1	0.9				
Pseudomonas stutzeri			1	1.2		
Ralstonia pickettii			1	1.2		
Syncytial Respiratory Virus			1	1.2		
Staphylococcus aureus MR			1	1.2	7	20.6
Staphylococcus aureus MS	5	4.3			2	5.9
Stenotrophomonas maltophilia	1	0.9				
*Streptococcus agalactiae gr B**	1	0.9			1	2.9
Streptococcus mitis	1	0.9	1	1.2		
Streptococcus pneumoniae	59	51.3	36	41.9	6	17.6
Streptococcus pyogenes	2	1.7				
*Streptococcus salivarius**	1	0.9				
Gram +	47	54.0	25	36.2	9	36.0
Gram -	29	33.3	31	44.9	13	52.0
Polymicrobial	7	8.0	5	7.2	3	12.0
Other	7	8.0	8	11.6		
PES	5	6.0	12	19.7	16	64.0

*** patients with these low pathogenicity organisms had their infection confirmed by in-depth note review by the authors**

In 148 cases, the initial antibiotic therapy was modified (72 [34%] in patients with and 76 [17%] in patients without etiology identification). The different motives of modification are shown in Fig 2.

Figure 2: Antibiotic modification in patients with and without etiological identification



From the 139 patients with etiology identification that did not modify ATB, in 86% the decision was based on clinical improvement or identification of a sensitive agent. In 20 cases (14%), the ATB spectrum could have been narrowed based on microbiology results. The reasons for not de-escalating ATB in these cases were: clinical impression of bacterial superinfection in viral pneumonia (n=3); clinical suspicion of co-infection with a DRP because of recent admission (n=10), recent ATB (n=3), bronchiectasis and colonization with *Acinetobacter* (n=1); recent chemotherapy with neutropenia (n=2); death before microbiological results (n=1).

An initial prescription of an ATB regimen with *Pseudomonas* or MRSA coverage was significantly more frequent in patients that had ATB in the previous 90 days (54.1% vs. 16.9%, p<0.001), hospital admission in the previous 90 days (73.2% vs. 17.0%, p<0.001) and in those living in a long-term care facility (41.2% vs. 28.4%, p=0.012). There was no significant difference between those that were bed-ridden and those that were not (35.1% vs. 27.8%, p=0.60).

Patients that died during hospital stay presented a higher Charlson's index (3 vs. 2 p<0.001), lower Katz score (2 vs. 6, p<0.001), a higher proportion were bed-ridden (55% vs. 26%, p<0.001), had a higher CURB-65 (3 vs. 2, p<0.001), a lower

proportion had active alcoholic habits (3.0% vs. 15.0%, p<0.001), a higher proportion had IV drug addiction (4% vs. 0,5%, p<0.001), had hospital stay for 2 or more days in the previous 90 days (31.0% vs. 22.0%, p=0.027), wound treatment in the last 30 days (18.0% vs. 9.0%, p= 0.005), treatment at the outpatient clinic in the last 30 days (6.5% vs. 2.5%, p=0.043), nasogastric tube (21.0% vs. 13.0%, p=0.042), urinary catheter (27.0% vs. 15.0%, p=0.006) and a higher proportion had antibiotics modified (29.8% vs. 20.7%, p=0,029). There were no significant differences in hospital mortality between the group in whom ATB modification was motivated by microbiological results by comparison to those in whom it was motivated by other reasons (27.0% vs. 36.9%, p=0.272); there were also no significant differences in hospital mortality in the group that had initial adequate ATB by comparison to those that did not (27.7% vs. 31.1%, p=0.482), nor in patients that had initial empirical "community" ATB by comparison to ATB with *Pseudomonas* or *Pseudomonas* and MRSA coverage (17.0% vs 23.0%, p=0.076).

In Fig 3, we present the hospital mortality of patients with and without DRP identification, according to the initial ATB ("Community" versus Pa or Pa and MRSA coverage). In Fig 4, we show the Kaplan-Meier mortality curves for these 2 subgroups.

Figure 3: Hospital Mortality in patients with and without DRP identification according to initial ATB

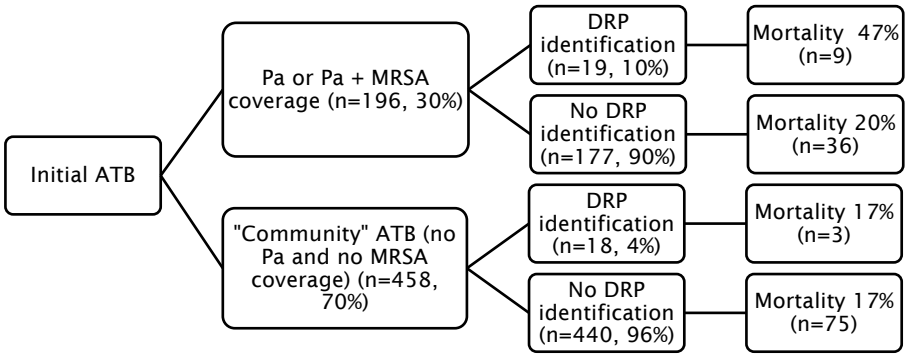
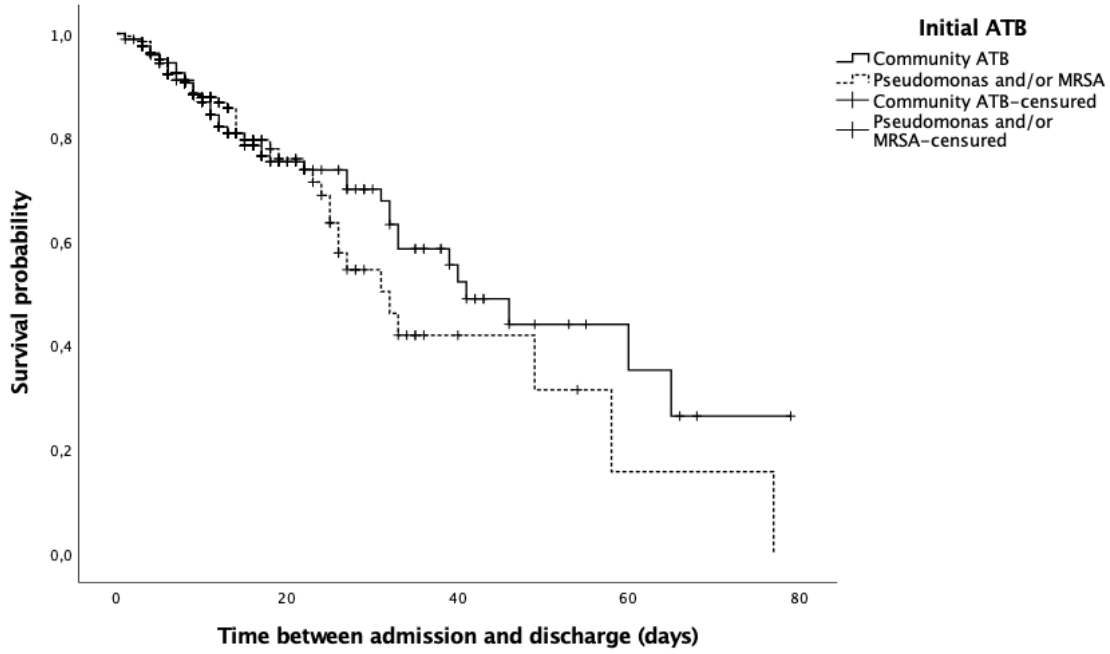


Figure 4: Kaplan-Meier mortality curves in patients with and without initial ATB coverage of *Pseudomonas* or *Pseudomonas* and MRSA



p=0.445 (log-rank test)

The presence of risk factors for PES was not associated with different outcomes, namely hospital LOS and hospital mortality, when comparing the group with microbiological documentation of infection with the group in whom no pathogen was identified, stratified by the presence of risk factors for PES infection (table 3). In the subgroup of patients with 2 PES risk factors, those who had etiology identification of CAP had higher 30-day mortality than those who did not.

Table 3: Association of CAP outcomes with obtaining an etiological identification, in different PES-risk groups

	Etiology identification								
	PES RF=0 (n=245)			PES RF=1 (n=238)			PES RF=2 (n=90)		
	Yes	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**
Hospital mortality	13.8%	9.5%	0.304*	20.3%	24.9%	0.452*	44.0%	26.2%	0.129*
30 days mortality	14.9%	13.3%	0.720*	33.3%	35.5%	0.750*	64.0%	38.5%	0.029*
LOS (median, P25-75)	9 (7-16)	9 (6-13)	0.123#	10 (7-17)	9 (7-15)	0.777#	11 (9-21)	12 (8-18)	0.996#

***Chi-square; #Mann-Whitney-U; RF: risk factors (being bed-ridden; ATB use in the previous 90 days); LOS: Length of stay**

In multivariable analysis, etiology identification (OR=1.360, p=0.200) was not independently associated with mortality, after adjustment for Charlson's index, being bed-ridden, provenience from a long term care facility, having had antibiotics or a hospitalization in the previous 90 days and CURB 65 (Table 4). A higher Charlson's index (OR=1.096, p=0.018), being bed-ridden (OR=3.023, p<0.001) and a higher CURB-65 (OR=1.276, p=0.034) were independently associated with higher hospital mortality.

Table 4 – Factors associated with Hospital Mortality: multivariable analysis

	aOR	95% CI		p
Charlson's index, per point	**1.096**	**1.016**	**1.182**	**0.018**
Bed-ridden	**3.023**	**1.898**	**4.817**	**<0.001**
Long term care facility	.858	.449	1.639	0.643
ATB last 90 days	.992	.600	1.638	0.974
Hospitalization ≥2d last 90 days	1.137	.660	1.959	0.644
CURB-65	**1.276**	**1.019**	**1.599**	**0.034**
Etiology identification	1.360	.849	2.178	0.200

Hosmer-Lemeshow p = 0.200

Discussion

In our study, etiologic identification in patients admitted with CAP to hospital care was not associated with better outcomes, namely in-hospital or 30-day mortality. This conclusion seems to remain unchanged even when considering subgroups of patients with risk factors for infection by a DRP, which are one of the groups of patients in whom the IDSA/ATS 2019 guidelines recommend etiologic investigation.

The overall identification rate was modest (33%), in line with published data, as well as the poor blood culture yield [2,6,14].

The most represented pathogen was *Streptococcus pneumoniae*, with a higher frequency in lower PES risk patients. The very small number of viral agents, especially *Influenza*, is explained by the fact that, at our hospital and at the time of data collection, respiratory viruses identification was not routinely performed. As expected, *Pseudomonas spp* and MRSA were more prevalent in higher PES risk patients.

Antibiotic modification was more frequent in patients with etiological identification than in those without (34% vs 17%). ATB modification based on microbiological results was only decided in 51 patients (7.7% of all cases). There were some situations (20 patients, 3.0% of all cases) in which, despite the ATB could have been de-escalated based on microbiology, it was not, and all these were well justified. This reveals that there was a limited influence of etiology investigation in clinical management. Actually, initial empiric therapy in CAP often turns out to be appropriate.

Variables found to have a significant association with higher hospital mortality were the ones reflecting severity of acute illness (CURB-65 and PSI), complexity (Charlson's index and, indirectly, previous hospital stay) and frailty (Katz, being bed-ridden, nasogastric tube and urinary catheter). Whereas IV drug addiction can be understood as a global risk factor for bad prognosis, the inverse relationship between active alcoholic habits and mortality is bizarre and difficult to explain. It is possible that unmeasured confounders, like the sickest alcoholics not presenting to hospital (possibly dying in the community) may contribute to this phenomenon.

The association of global ATB modification with higher mortality could reflect the number of patients that changed ATB because they were having an unfavorable

clinical course. When we analyzed patients in which ATB was modified based on microbiological findings, this association was no longer present.

Curiously, the patients that had empirical coverage of DRP and had a DRP identification were the subgroup with higher mortality. Even patients with empirical "community" ATB that had identification of a DRP had a mortality that was similar to the general mortality and to other subgroups, including those that did not have identification of a DRP. This is in favor of the idea that the patients in which broad spectrum ATB were empirically prescribed were very vulnerable patients, with more comorbidities, more dependency, and that their increased mortality does not have a relationship with the etiology. The Kaplan-Meier mortality curves for these 2 subgroups are not significantly different. There seems to be a tendency to later mortality (after 20 days) in patients with initial broader spectrum ATB, that could also suggest the importance of frailty and comorbidities, rather than acute sepsis, in these patients' deaths.

For multivariable analysis, we adjusted for variables that represent clinical severity (CURB-65), comorbidities (Charlson's index), the PES risk factors identified in our previous study (being bed-ridden and previous ATB) [29] and two classical risk factors for drug resistant pathogens (previous hospitalization and provenience from a long-term care facility) [30]. As expected, clinical severity and comorbidities were independently associated with mortality.

One limitation of this study is the lack of representation of viral and atypical agents (with the exception of *Legionella*). There was no control over the etiological investigation clinicians performed, so we could not influence their practice. In future studies, it can be useful to define a panel of mandatory microbiological studies. The publication delay in relation to data collection is also a limitation: in the past decade, there have been changes in the microbiological profile and rises in antimicrobial resistance rates that could bring more data to discuss.

Another limitation is that this was a particularly vulnerable population, which can compromise the generalizability of our findings: 31% were bed-ridden, 14% had a nasogastric tube, 23% had a recent hospitalization. Probably, a general prognostic score, like PROFUND [31], would be more accurate than Charlson's index predicting this. Unfortunately, we did not record end-of-life decisions (like withhold or withdraw of therapy), that could further enlighten this question. As a matter of fact, patients at the HDU had a lower mortality than those at the general ward (11.7% versus 19.4%), suggesting that therapy limitation may have played an important

role here. The PES risk subgroups were small, rendering the sub analysis of outcomes in these subgroups difficult to value.

The strengths of our study are the analysis of a big number of variables, the detailed analysis of antibiotic decisions, the differential analysis of subgroups according to PES risk factors and the adjustment for clinical severity, comorbidities and PES risk factors.

Given the progressively stronger demonstration that etiological investigation and its results does not have an association with clinical management and outcomes of CAP, we can ask if it is worthy to do it systematically. One reason to do it is the importance of knowing our local epidemiology in order to update recommendations based on local data. As the American guidelines underline, one other motive is the possibility of ATB de-escalation, which was possible in nearly 50% of the patients in whom ATB therapy was changed due to microbiology results, with the anticipated benefit on resistant strains development and/or selection. Reduction in antimicrobial toxicity is another factor to consider. Molecular diagnostic methods will most certainly change our view about this subject in the future [14,32,33].

To answer the important question of which patients will benefit the most from microbiological investigation, apart from the consensual groups, like immunosuppressed patients, a randomized controlled trial including a general population admitted to hospital with CAP submitted to a standard microbiological panel and the analysis of the impact in clinical outcomes, could help in the definition of the subgroups that could benefit the most from standard microbiological evaluation.

Conclusion

Our study adds scientific evidence that the etiological investigation of the general population of patients admitted with community-acquired pneumonia does not have an association with outcomes, namely hospital length of stay and hospital and 30-day mortality. This also seems to be true for the subgroup of patients with risk factors for PES. Additionally, empirical antibiotic therapy is usually appropriate, results of etiological investigation have a limited yield and they seem to have a limited influence in the management of these patients, particularly antibiotic modification.

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CHAPTER 6 - "Impact of the Timing of Initial Antibiotic Administration on Community-Onset Pneumonia Hospital Mortality – a Prospective Cohort Study"

Submitted to publication

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Impact of the Timing of Initial Antibiotic Administration on Community-Onset Pneumonia Hospital Mortality – a Prospective Cohort Study

Abstract

Introduction: In community-onset pneumonia (COP), early antibiotic administration can reduce inflammation and organ damage. However, the association of the timing of initial antibiotic administration (TInA) and outcomes is still subject of debate. Our goal is to find if, in a population of patients with COP, the timing of initial antibiotic administration has an impact on hospital mortality, and if that impact is different according to different clinical severity subgroups.

Methods: Prospective cohort study, conducted over a two years' period, in a community-based hospital, including all adult patients with COP. Univariate and multivariate logistic regression modeling were performed to understand the association of the timing of initial antibiotic administration with hospital mortality.

Results: A total of 660 cases of COP were included in this study, with a mean±sd age of 74±15 years and 58.9% of males. TInA was ≤4 h in 35.7% of the patients, [4 -8h] in 44.6% and > 8 h in 19.7%, with a median (IQR) of 4.9 h (3.2-7.4). Hospital mortality rate according to TInA was 17.2% in the first group (≤4 h), 21.3% in the second [4 -8h] and 17.2% in the third (>8h), p=0.520. In patients with higher severity COP (PSI III-IV) hospital mortality in the three groups of TInA was 21.5%, 23.1% and 11.3%, respectively (p=0.936). The association of TInA with hospital mortality after adjustment to Charlson's index and being bed-ridden, showed an aOR (95% CI) = 0.985 (0.929-1.047). Similar results were found for the lower severity group (PSI = I-III) with an aOR (95% CI) = 1.071 (0.860-1.333) and high severity (PSI = IV-V) with an aOR (95% CI) = 0.983 (0.923-1.048).

Conclusion: In our study, earlier antibiotic administration was not independently associated with reduced hospital mortality. This was verified for different COP severity subgroups, and sustained after adjusting for Charlson's comorbidity index and being bed-ridden.

Keywords

Community-acquired pneumonia; Antibiotic precocity; Outcomes; Mortality

Introduction

Timely administration of appropriate antibiotics (ATB) is critical for treatment success in severe infections (1). Although the last Surviving Sepsis Campaign (SSC) recommendations have decreased the strength of the recommendation for ATB precocity in relation to the previous ones (2) (especially in the absence of sepsis or septic shock), in more severe patients it is still considered a strong recommendation.

In clinical practice, early ATB administration in pneumonia is a common-sense objective. Earlier ATB administration has the potential to reduce inflammatory response and organ damage, by reducing bacterial load (3) (4). However, the association between timing of initial antibiotic administration (TInA) and outcomes in community-acquired pneumonia (CAP) is still debated.

A well-known systematic review from 2016 (5) included 8 studies, 4 of which showed an association between earlier TInA and reduced mortality. These were all retrospective cohort studies. The other 4 (3 of which were prospective) did not show any impact of TInA on mortality. Other prospective studies also did not show any association between TInA and mortality, even when sub analysis were made for more severe patients (3) (6) (7).

On the other side, there has been growing concern about the potential harms of excessively early ATB administration, including allergic reactions, kidney injury, thrombocytopenia, *Clostridioides difficile* infection and antimicrobial resistance (1) (6). A study found that delivering ATB within 4 h for all patients would force many patients to have ATB before a secure diagnosis could be made (8).

In face of these conflicting results, the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) reduced the importance of TInA in their 2007 guidelines and recommended that the first ATB dose should be administrated while the patient is still in the emergency department, with no defined time frame (9). The 2019 guidelines do not even mention this issue as a specific recommendation (10). The 2019 NICE guidelines, however, still recommend ATB treatment as soon as possible, within 4 hours, for patients admitted with CAP (11).

The evidence available for the importance of TInA is weak. It would be unethical to delay TInA in a clinical trial, so the available evidence is based on observational studies. (4)

Our goal is to find if, in a population of patients with Community-Onset Pneumonia (COP), the timing of the initial antibiotic administration has an impact on hospital mortality. Secondarily, the impact of TInA in different clinical severity subgroups will be evaluated.

Patients and Methods

a) Study design

This was a prospective (concurrent data collection), cohort study, conducted over a two years' period, between January 1st 2012 and December 31st 2013, in all medical wards (general ward with 120 beds), in a high dependency unit (HDU) with 13 beds and in the intensive care unit (ICU) with 10 beds of a community-based hospital (350 beds).

The study was approved by the Hospital Ethics Commission and by the National Data Protection Committee. Informed consent was obtained for every protocol and data were coded, in order to guarantee anonymization.

b) Inclusion and exclusion criteria

All adult patients (age ≥ 18 years) with community-onset pneumonia primarily observed at our Hospital were enrolled in the study. Pneumonia diagnosis was made by the presence of [new onset or worsening pulmonary infiltrate on chest radiography (or CT scan) with no alternative explanations (ex: heart failure, neoplasm, chronic interstitial disease, pulmonary embolism); and at least 2 of the following criteria: a) Fever (T > 38 ºC) (without obvious alternative focus of infection or non-infectious explanations); b) Leukocytosis (> 11,500 / mm^3) (without obvious alternative focus of infection or non-infectious explanations); c) Purulent respiratory secretions; or one of a), b) and c), in the presence of: severe sepsis; hemodynamic instability; or refractory hypoxemia (PaO_2 / FiO_2 < 100 in spontaneous ventilation)].

All inclusions in the study were validated by an internal medicine senior consultant, namely chest x-ray and/or CT scan observation.

Absence of vital signs, mental status and arterial blood gases record on admission were considered to be exclusion criteria, as well as Hospital Acquired Pneumonia, defined as pneumonia diagnosed 48 h or more after hospital admission and not incubating at the time of hospital admission (12).

c) Data collection

The protocol addressed extensive information about demographic, epidemiological, clinical, analytical, microbiological and imagiological data, as well as antibiotic therapy, and follow-up until 30 days after discharge (mortality and readmission). Comorbidities [13] [14] [15] [16] and selected scores (CURB 65 [17], Pneumonia Severity Index (PSI) [9], Charlson's index [18], Katz score [19]) were defined according to the current definitions. Immunosuppression was a composite definition that included: chemotherapy administered in the previous 90 days; or HIV infection with CD4 TL count <500/mm3; or chronic glucocorticoids equivalent to prednisolone ≥ 0,5 mg / Kg / day; or solid organ transplant; or treatment with immunosuppressive drugs; or liquid neoplastic disease (Hodgkin's or non-Hodgkin's Lymphoma or Chronic or Acute Leukemia or Multiple Myeloma or Waldenström Macroglobulinemia).

A specific database was built in Statistical Package for the Social Sciences (SPSS) for data introduction. All data were coded, for personal data protection.

d) Statistical analysis

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, interquartile (IQR) range, and minimum and maximum, when appropriate.

Hypotheses were tested regarding the distribution of continuous variables with non-normal distribution using the nonparametric Mann–Whitney and Kruskal–Wallis tests, depending on the nature of the hypothesis, or T - test for independent samples or One-Way Anova for variables with normal distribution. When testing a hypothesis regarding categorical variables, a chi-square or Fisher's exact test were used, as appropriate.

Timing of Initial Antibiotic Administration (TInA) was evaluated as a continuous variable and as a categorical variable with cutoffs at 4 and 8 hours after registration at the Emergency Department.

Clinical severity subgroups were created for analysis of the impact of TInA in in-hospital mortality: PSI I to III and PSI IV and V.

In each PSI subgroup and for total data, we performed a multivariable logistic regression of the impact of TInA in hospital mortality, with adjustment for Charlson's comorbidity index and being bed-ridden (the variables that were significantly associated with mortality in the multivariable model of our previous paper [20]). Odds ratio (OR) and 95% confidence intervals (95% CI) were presented. All selected variables were included in the model (enter method).

Model goodness-of-fit was assessed using the Hosmer-Lemeshow statistic.

The significance level used was 0.05.

Statistical analysis was performed using the software SPSS v. 26.0.

Results

During the study period, there were 11 605 patients admitted into the department, 1 624 with lower respiratory tract infection, of which 1 171 were pneumonias; 660 were community-onset pneumonias. Chest imaging included a CT scan in 152 patients (23.0%). The remainder had a clear new onset pulmonary infiltrate on chest radiography.

Detailed characteristics of the study population are described in table 1. The mean±sd age of included patients was 74±15 years, and 58.9% were males. The median Charlson's index of this sample was 2. With a Katz score of 2 or less, 35.9% of the patients had severe functional impairment, and 31.2% were bed-ridden. Traditional healthcare-associated risk factors were present in a proportion of the patients: 40.8% had used antibiotics in the previous 90 days, 23.5% had a hospital stay of 2 or more days in the previous 90 days and 12.0% came from a long-term care facility. Severity scores were mostly those associated with need of hospital admission (71.2% had CURB 65 class of 2 or higher, and 91.9% had PSI class of III or higher). In 77 cases, patients were admitted to the HDU and 31 cases to the ICU.

The overall etiological identification rate was 33.0% (215 of 660 patients).

The global mortality rate was 18.8%; 19.4% in patients admitted directly to the ward, 11.7% in those admitted to the HDU (p=0.102) and 25.8% in those admitted to the ICU (p=0.381). Thirty-day mortality was 28.0%.

Timing of Initial Antibiotic Administration (TInA) was ≤4h in 35.7% of the patients, between 4 and 8h in 44.6% and higher than 8h in 19.7% of the patients. The median (IQR) TInA was 4.9 h (3.2-7.4).

Table 1. General characteristics and association of each variable with hospital mortality

	Hospital mortality							
	Total (n=660)		No (n=536)		Yes (n=124)		p-value[1]	Crude OR
Age, mean (sd)	74	(15)	74	(16)	78	(13)	0.489[2]	0.917
Male Sex, n (%)	388	(58.8)	313	(58.4)	75	(60.5)	0.670	1.091
Length of hospital stay, median (P25-P75)	8	(6-14)	8	(6-13)	8	(4-17)	0.373[3]	1.016
Charlson's Index, median (P25-P75)	2	(1-4)	2	(1-4)	3	(1-6)	<0.001[3]	1.138
Being bed-ridden, n (%)	205	(31.2)	137	(25.7)	68	(54.8)	<0.001	3.519
CURB-65, median (P25-P75)	2	(1-3)	2	(1-3)	3	(2-3)	<0.001[3]	1.391
PSI, n (%)								
Class I	21	(3.3)	21	(4.0)	0	(0)	-	-
Class II	31	(4.8)	29	(5.5)	2	(1.6)		Ref
Class III	79	(12.2)	74	(14.1)	5	(4.1)	0.981	0.980
Class IV	262	(40.6)	211	(40.3)	51	(41.8)	0.093	3.505
Class V	252	(39.1)	188	(35.9)	64	(52.5)	0.032	4.936
Hospital stay ≥ 2 days in last 90 days, n (%)	153	(23.5)	115	(21.7)	38	(31.1)	0.027	1.629
Antibiotic use in the last 90 days, n (%)	234	(40.8)	184	(39.7)	50	(45.0)	0.307	1.243
Wound treatment in the last 30 days, n (%)	70	(11.0)	48	(9.3)	22	(18.2)	0.005	2.157
Treatment at the outpatient clinic in last 30 days, n (%)	21	(3.3)	13	(2.5)	8	(6.5)	0.043	2.690
Provenience from a long-term care facility, n (%)	79	(12.0)	60	(11.2)	19	(16.4)	0.197	1.443
Immunosuppression (composite definition), n (%)	68	(10.3)	53	(9.9)	15	(12.1)	0.466	1.254
ATB modification	148	(22.0)	111	(20.7)	37	(29.8)	0.029	1.628
ATB covered pathogen	178	(30.4)	147	(31.1)	31	(27.7)	0.482	0.849
TInA							0.520	
≤4h	169	(35.7)	140	(82.8)	29	(17.2)		
>4 ≤8h	211	(44.6)	166	(78.7)	45	(21.3)		
>8h	93	(19.7)	77	(82.8)	16	(17.2)		

TInA - Timing of Initial Antibiotic Administration; ATB – antibiotic; P25 – 25 Percentile; P75 – 75 Percentile; [1] – Chi Square Test; [2] – T-Test for Independent Samples; [3] – Mann-Whitney Test

Table 2: Association of TInA with hospital mortality in different PSI class subgroups

	PSI subgroup							
	PSI class I-III (n=97)				PSI class IV-V (n=392)			
	TInA ≤4h (n=30)	TInA >4 ≤8h (n=44)	TInA >8h (n=23)	p	TInA ≤4h (n=144)	TInA >4 ≤8h (n=173)	TInA >8h (n=75)	p
Hospital mortality n (%)	1 (3.3)	3 (6.8)	1 (4.3)	0.833*	31 (21.5)	40 (23.1)	16 (21.3)	0.936*

*Chi-square; PSI: Pneumonia Severity Index; TInA: timing of initial antibiotic administration

As shown in Table 2, TInA as a categorical variable with cutoffs at 4 and 8 hours was not significantly associated with hospital mortality, nor in low severity patients (p=0.833) nor in higher severity pneumonias (p=0.936).

Considering only patients with high severity pneumonia, defined by a PSI class of IV-V, hospital mortality rate in the group of patients receiving antibiotic therapy in the first hour vs. those who received ATB > 1h was 16.7% (n=2) and 22.4% (n=85), respectively (p>0.999).

Table 3 – Association of cTInA with Hospital Mortality according to pneumonia severity index subgroups after adjustment to Charlson's comorbidity index and being bed-ridden

	Total (n=493)				**PSI I-III (n=96)**				**PSI IV-V (n=391)**			
	aOR	**95% CI**		**p**	**aOR**	**95% CI**		**p**	**aOR**	**95% CI**		**p**
Charlson's index, per point	**1.101**	**1.018**	**1.190**	**0.016**	**1.538**	**1.030**	**2.295**	**0.035**	1.043	0.958	1.135	0.334
Bed-ridden	**3.510**	**2.179**	**5.653**	**<0.001**	4.111	0.399	42.413	0.235	**3.101**	**1.885**	**5.101**	**<0.001**
cTInA, per hour	0.986	0.929	1.047	0.648	1.071	0.860	1.333	0.539	0.983	0.923	1.048	0.602

aOR – adjusted odds ratio; CI – confidence interval; cTInA: timing of initial antibiotic administration, as a continuous variable.

For low and high severity pneumonia defined by a PSI group I to III vs. IV and V, a multivariable analysis was performed of the impact of continuous TInA on hospital mortality, with adjustment for Charlson's comorbidity index and being bed-ridden (the variables independently associated with hospital mortality in the multivariable analysis previously published [19]) (table 3). TInA was not independently associated with hospital mortality.

Discussion

Our results are in line with other prospective observational studies (3) (7) (21), in which TInA did not show an independent association with reduced mortality in CAP patients.

Two large studies have shown an association of TInA with improved outcomes, but they were retrospective and did not include younger patients nor less severe pneumonias (5) (22) (23). One possibility is that these studies selected more severe patients, in which an earlier TInA could have more benefit. Another hypothesis is that delayed administration of ATB can be related with patient characteristics (3). Older patients, with worse physiological reserve, could have been managed with a less aggressive approach. So, age and clinical frailty could be confounders in those studies, falsely attributing the worse outcomes of those patients to later TInA.

A prospective study showed that adherence to antibiotic guidelines was lower in patients with cancer, a higher Charlson's index and with confusion on presentation (24). Nonetheless, in one further publication of the same project, TInA did not have an independent association with hospital mortality (25). Earlier TInA could also be a surrogate of general quality of care, instead of having a direct biological impact on CAP outcomes (3).

In the current study, when comparing different severity subgroups, TInA is still not associated with hospital mortality, even when adjusting for Charlson's index and being bed-ridden. We could expect a bigger impact in more severe patients (1) (2), but, in this population, this was not verified. Multimorbidity and frailty were independently associated with hospital mortality, and these factors, along with clinical severity, were previously identified as the more important determinants of mortality in this population (20).

The strengths of our study are the analysis of a big number of variables, the differential analysis of subgroups according to clinical severity and the adjustment for recognized independent risk factors.

The main limitation of our study is that it is single center and represents a particularly vulnerable population, which can compromise the generalizability of our findings. Another limitation is the fact that we did not take into account the adequacy of initial ATB selection. This could more accurately evaluate the impact

of the ATB therapy, but it would be restricted to a smaller group of patients (the 215 who had etiological identification), reducing statistical power.

A multicenter study that would prospectively evaluate the impact of TInA and ATB adequacy on hospital and 30-day mortality, as well as on length of stay, with adjustment for clinical severity, frailty and multimorbidity, could further clarify the role of ATB precocity in COP outcomes.

Conclusion

In our study, earlier TInA was not independently associated with reduced hospital mortality in COP patients. This was verified for different COP severity subgroups, as defined by the PSI class, after adjusting for Charlson's index and being bed-ridden.

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CHAPTER 7 – Impact of Empirical Macrolide Treatment on Community-Onset Pneumonia Outcomes

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The need to cover atypical agents is not consensual. Several studies and meta-analysis showed that, in low and moderate severity situations, the addition of a macrolide had the advantages of lower failure rate or shorter time to clinical stability, but not lower mortality; macrolides only proved to have an impact on mortality in patients with high severity pneumonia, bacteremia and more intense inflammation (53) (54) (55) (56) (57) (58) (60) (61) (62) (63). This is thought to be related to the immunomodulatory effects of this class of antibiotics (59). Major guidelines suggest a macrolide/β-lactam combination for severely ill patients (5) (16) (49), but some leave it at the discretion of the treating physician for inpatients with CAP of low to moderate severity (16) (49).

We were aiming to analyze the impact of macrolide treatment (in association with a β-lactam) on the outcomes of our population of COP patients, by comparison of two groups of patients: those treated with an association of a β-lactam plus a macrolide; and those with β-lactam monotherapy.

The group of patients treated with an association of a β-lactam plus a macrolide included 342 patients and those with β-lactam monotherapy, 15 patients. In face of the small size of the latest group, we decided not to proceed with statistical analysis.

CHAPTER 8 – DISCUSSION AND CONCLUSIONS

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1. Synthesis of the most important results

1- The overall agent identification rate in community-onset pneumonia was 33%.
2- The overall percentage of community-onset pneumonias caused by a drug-resistant pathogen was low, 5.6% (18.8% of the patients with etiological identification).
3- Being bed-ridden and having had antibiotics in the previous 90 days were independent risk factors for community-onset pneumonia caused by a drug-resistant pathogen. A multivariable model including these two risk factors had a discriminative power of 0.832 to predict a drug-resistant pathogen.
4- In a patient with both these risk factors, an initial antibiotic therapy with a carbapenem plus vancomycin would guarantee adequate initial antibiotic therapy in 92% of these cases; this rate would drop to 72% if piperacillin/tazobactam was used instead of a carbapenem.
5- Etiologic identification was not associated with better outcomes, namely in-hospital or 30-day mortality. This remained unchanged, even when considering subgroups of patients with risk factors for infection by a drug-resistant pathogen.
6- There was a limited influence of the results of etiology investigation in clinical management: antibiotic modification based on microbiological results was only decided in 7.7% of all cases (4.1% escalated and 3.6% de-escalated) and, in some situations (3.0% of all cases), the antibiotic was not de-escalated, despite, based solely on microbiology, it could have been.
7- The median (IQR) Timing of Initial Antibiotic Administration (TInA) was 4.9 h (3.2-7.4); 35.7% of the patients had a TInA ≤4h.
8- Earlier timing of initial antibiotic administration was not independently associated with reduced hospital mortality. This was verified for different severity subgroups, and after adjusting for the variables previously identified as being independently associated with mortality (Charlson's index and being bed-ridden).

2. Results Interpretation

In the following pages, we will discuss how these results help answering our research questions.

We identified two very simple independent risk factors for infection by a drug-resistant pathogen (DRP, here defined as PES (34) - *Pseudomonas aeruginosa*, extended-spectrum ß-lactamase producing *Enterobacteriaceae*, Methicillin-resistant *Staphylococcus aureus*; and other non-fermenting gram-negative bacteria, namely *Acinetobacter baumannii*). Those risk factors are: antibiotic use in the previous 90 days (aOR=4.411, 95%CI [1.745-11.148]) and being bed-ridden (aOR=5.492, 95%CI [2.121-14.222]).

Previous antibiotic use has been associated with increased risk of DRP infection. In one study (29), antibiotic use in the previous 60 days showed an aOR of 5.32, 95% CI [1.86–15.26] for Gram-negative DRP. In one other work (33), previous antibiotic use showed an aOR of 2.45, 95% CI [1.51-3.98] for DRP. And in a third study (34), antibiotic use in the previous month showed an aOR of 2.48, 95% CI [1.56–3.94] for PES.

Being bed-ridden is also a present variable at Shindo's model (33), with an aOR of 2.45, 95% CI [1.40 4.30]. In another study, Karnofsky's index <70 was found to be independently associated with DRP (aOR 3.7, 95% CI [1.6-8.6]) (98). Being bed-ridden is related to loss of function and clinical frailty, and they can be considered surrogates of one another. Although we could think that being bed-ridden could be a surrogate of provenience from a long-term care facility, or of a recent hospital stay, our results show that being bed-ridden is still significant after adjustment for these variables and comorbidities. The clinical meaning of this association is not clear. A meta-analysis identified a number of mechanisms of high risk for pneumonia in long-term bed-ridden patients (steroid administration, consciousness disorders, nasal feeding, ventilator use, invasive procedures, duration of hospitalization) (99). These factors tend to be perpetuated over time, so they increase the risk of repeated infections and antibiotic cycles. It is possible that this is a determinant mechanism for DRP risk.

Nasal feeding was associated with PES in the univariable analysis. Some studies found this variable to be associated with infection by DRP (Webb *et al* (29): aOR 12.93, 95% CI [2.28-73.37] for Gram-negative DRP; Shindo *et al* (33): aOR 2.43, 95% CI [1.18–5.00]). In our study, the inclusion of this variable in the model instead of

"bed-ridden" revealed a much weaker aOR, suggesting that it could be a surrogate of being bed-ridden, and not the opposite (data not shown). But it is difficult to independently analyze these 2 variables. Nasogastric tube could be a risk factor for aspiration mechanisms in pneumonia, and not particularly for DRP.

In our study, previous hospital stay was not an independent risk factor for DRP, even though most of the patients with previous hospital stay also used antibiotics. In Webb's and Prina's studies, the same result was observed (29) (34). In another study, only the number of days of the hospital stay was a predictor of infection by a DRP (100). On the other hand, some works identified this variable as an independent risk factor: Aliberti *et al* (32) (aOR of 4.87, 95% CI [1.90–12.4]) and Shindo *et al* (33) (aOR of 2.06, 95% CI [1.23-3.43]). It is possible that the duration of the previous hospitalization is more important after a number of days greater than 2. Another hypothesis is that antibiotic use, and not hospital stay, is the most important factor.

Provenience from long-term care facilities, a classical HCAP criterium (3), was also not an independent risk factor for infection by DRP in our study, unlike the results in other studies (29) (32). A recent Portuguese study showed that patient's origin, particularly from a nursing home, was not independently associated with treatment failure (aOR 1.083, 95% CI [0.726–1.616]), which seems to be in line with our results (101).

Household contact with a DRP carrier is one of the HCAP criteria (3). In our sample, there were a small number of cases, so we decided not to include this risk factor in the multivariable analysis.

The performance of our model (AUROC 0.832) was more discriminative than the HCAP definition (0.676), which was similar to that described in the Chalmers' meta-analysis (0.64 to 0.70) (64). It also has a higher discriminative power than most other published models, with the advantage of being more simple to determine than the majority of them.

The rates of Pa and MRSA infection in CAP (2.6% and 1.2%) were similar to the ones described in larger cohorts (1.9% and 1.0%, respectively) (36). In a multinational study, the prevalence of Pa and antibiotic-resistant Pa was 4.2% and 2.0%, respectively (USA: 4.3% and 2.5%; Europe 3.8% and 1.6%) (35).

Among patients bed-ridden and with previous antibiotic use, the identification rate of *Pseudomonas aeruginosa* and MRSA justifies the initial coverage of these agents.

An empirical antibiotic regimen with a carbapenem and vancomycin would guarantee adequate initial antibiotic therapy in 92% of the agents identified in this group. If the choice is piperacillin/tazobactam instead of a carbapenem, this rate drops to 72%.

In our study, etiologic identification in patients admitted with CAP was not associated with better outcomes, namely in-hospital or 30-day mortality. This conclusion remained unchanged when considering subgroups of patients with risk factors for infection by a DRP, which are one of the groups of patients in whom the IDSA/ATS 2019 guidelines recommend etiologic investigation (5).

The overall identification rate was modest (33%), in line with published data, as well as the poor blood culture yield (5) (40) (48).

The most represented pathogen was *Streptococcus pneumoniae*. The very small number of viral agents, especially *Influenza*, is explained by the fact that, at our hospital and at the time of data collection, respiratory viruses identification was not routinely performed. In fact, a study performed at our Department showed that, between October and March of 2013-2014, Influenza was as prevalent as *Streptococcus pneumoniae* (102). As expected, *Pseudomonas spp* and MRSA were more prevalent in higher PES risk patients.

There was a limited influence of the results of etiology investigation in clinical management. Antibiotic modification was more frequent in patients with etiological identification than in those without (34% vs 17%), but only in 7.7% of all cases there was a modification based on microbiological results. According to microbiology, 44 patients could have been de-escalated, but only in 24 cases this decision was taken. All the remaining 20 cases had well justified clinical reasons not to de-escalate. In fact, it is recognized that initial empiric therapy in CAP often turns out to be appropriate (103), and even more if using a DRP prediction model (104).

The association of global ATB modification with higher mortality probably reflects the number of patients that changed ATB because they were having an unfavorable clinical course. When we analyzed patients in which ATB was modified based on microbiological findings, this association was no longer present.

Patients that had empirical coverage of a DRP and had DRP identification were those with higher mortality. Even patients with empirical “community” ATB that had identification of a DRP had a mortality that was similar to the general mortality.

This favors the idea that patients in which broad spectrum ATB were empirically prescribed were very vulnerable patients, with multimorbidity, and that their increased mortality derives from these characteristics, and not from microbial etiology or acute sepsis.

Given the progressively stronger demonstration that etiological investigation and its results does not have an association with clinical management and outcomes of CAP, we can ask if it is worthy to do it systematically. Nonetheless, there are arguments in favor of etiology investigation: the importance of knowing our local epidemiology in order to update local recommendations; the possibility of ATB de-escalation (5) (104), with reduction of ATB pressure and side effects, and with no deleterious effects on CAP outcomes (105); the identification of problem microorganisms like SARS-CoV-2 and *Mycobacterium tuberculosis*. Molecular diagnostic methods will most certainly change our view on this subject in the future, although they will bring some uncertainty relative to false positive results and difficulties in distinguishing colonizing from pathogenic agents (48) (104) (106) (107) (108) (109). Particularly important can be the capability to detect genes associated with DRP, like MRSA, *Pseudomonas* and other drug-resistant Gram negatives (110).

In what concerns TInA, our results are in line with other prospective observational studies (66) (72) (111), in which ATB timing did not show an independent association with reduced mortality in CAP.

Two large studies have shown an association of TInA with improved outcomes, but they were retrospective and did not include younger patients nor less severe pneumonias (70) (112) (113). One possibility is that these studies selected more severe patients, in which an earlier TInA could have had more benefit. Another hypothesis is that delayed administration of ATB can be related to patients' characteristics (66). Older patients, with worse physiological reserve, could have been managed with a less aggressive approach. So, age and clinical frailty could be confounders in those studies, falsely attributing the worse outcomes of those patients to later TInA. The opposite can be observed in another study, where patients that had an earlier TInA were those with higher clinical severity, and were more frequently admitted to the ICU (111).

A prospective study showed that adherence to antibiotic guidelines was lower in patients with cancer, a higher Charlson's index and with confusion on presentation (114). Nonetheless, in one further publication of the same research project, TInA did not have an independent association with hospital mortality (115). Earlier TInA could also be a surrogate of general quality of care, instead of having a direct biological impact on CAP outcomes (66).

So, it is difficult to isolate TInA as a determinant influential factor for outcomes.

In our study, when comparing different severity subgroups, and adjusting for Charlson's index and being bed-ridden, TInA is still not associated with hospital mortality. We could expect a higher impact on more severe patients (68) (69), but, in this population, this hasn't been verified. Multimorbidity and frailty were independently associated with hospital mortality, and these factors, along with clinical severity, were previously identified, in our second publication, as the most important determinants of mortality in this population.

A multicenter study that would prospectively evaluate the impact of TInA and ATB adequacy on hospital and 30 day mortality, as well as on length of stay, with adjustment for clinical severity, frailty and multimorbidity, could further clarify the role of ATB precocity in COP outcomes.

3. Limitations

One limitation of this thesis is the lack of representation of viral and atypical agents (with the exception of *Legionella*). There was no control over the etiological investigation clinicians performed, so we could not influence their practice. In future studies, it can be useful to define a panel of mandatory microbiological studies.

Another limitation was the fact that, in some variables, there was a great amount of missing data. As an example, more than 30% of the identified pneumonias did not have complete record of vital signs on admission at the emergency department (mainly the respiratory rate) – otherwise, the sample size would be around 1000 patients. Some other relevant variables were underrepresented, like MRSA colonization. This has been described as an important risk factor for infection by a DRP (116), and it could have impacted the risk model of the first publication. The same can be said about colonization by other agents, such as Pa (35). It is

controversial if it is cost effective to screen all hospitalized patients for DRP (117) (118), but for the purpose of our investigation, it would have been relevant.

The publication delay in relation to data collection is also a limitation: in the past decade, there have been changes in the microbiological profile and rises in antimicrobial resistance rates, namely a rise in carbapenemase-producing Gram negatives (119) (120) (121), that could bring more data to discuss.

The patients included in our study represent a particularly vulnerable population: 31% were bed-ridden, 14% had a nasogastric tube, 23% had a recent hospitalization. This can compromise the generalizability of our findings. Probably, a general prognostic score, like PROFUND (122) or CHRONIBERIA (123), would be more accurate than Charlson's index to describe our patients' profile. Unfortunately, we did not record end-of-life decisions (like withhold or withdraw of therapy). As a matter of fact, patients at the HDU had a lower mortality than those at the general ward (11.7% versus 19.4%), suggesting that therapy limitation may have played an important role in the clinical management of these patients.

The fact that the sample is from a single center is also a limitation. First, because it may be an additional factor that compromises data generalizability. Second, because the sample size did not allow us to perform some subgroup analysis, like PES risk subgroups, PSI risk subgroups, the adequacy of initial ATB selection, or the impact of initial treatment with macrolides in CAP outcomes.

4. Conclusions

As discussed above, our research adds knowledge relative to risk factors for drug-resistant pathogens, reinforces the limited role of etiological investigation in the clinical management and outcomes, and confirms that timing of the initial antibiotic administration is not a relevant performance measure for most of the patients admitted to hospital with community-onset pneumonia.

As for the question of how does this thesis contribute to an individualization of antibiotic therapy in community-onset pneumonia, we further present the most relevant topics.

a) **Patients with COP who have had antibiotics in the previous 90 days and are bed-ridden should be empirically treated with DRP coverage**. In patients with 2 DRP risk factors: MRSA was present in 20.6% of all samples and 24% of all patients who had etiology identification; *Pseudomonas spp* was present in 26.5% of all isolates and in 32% of the patients who had etiology identification.

b) Our results support the American 2019 guidelines (5): **patients with the two DRP risk factors should be subjected to etiological investigation, and de-escalate antibiotics if there are no DRP identification at 48 to 72 hours**. This decision does not have an impact on mortality, but it has the potential to reduce antibiotic pressure and toxicity.

c) **Patients without any of the two DRP risk factors do not need to be subjected to etiological investigation**, unless it is integrated in a surveillance program aimed at continuously updating local antibiotic therapy guidelines, or for exclusion of problematic agents in selected situations.

d) **Patients with sepsis or shock should have the first antibiotic administration immediately (within the first hour)**, according to the surviving sepsis campaign guidelines (68).

e) **The remaining patients do not benefit of a specific timing for initial antibiotic**, and they should have the first administration when the diagnosis of pneumonia is established, and still at the emergency department, as recommended in the 2007 IDSA/ATS guidelines (17).

CHAPTER 9 – FUTURE DIRECTIONS

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As previously discussed, this sample was relatively small for the purpose of some important sub analysis. So, it would be very useful to expand data collection to other Hospitals (even at a national or regional level). This could enable us to further understand the importance of certain risk factors for DRP, like previous hospitalization, vaccination status, as well as the role of MRSA and other DRP colonization. It would also help in sub analysis of the impact of etiological investigation in more severe patients, as well as the impact of TInA.

Another study that could be accomplished with a multicenter registry would be the impact of macrolide therapy in two subgroups of patients: those with intermediate severity (admitted to general ward) and those with low severity (outpatient regimen) CAP. This is still a subject of debate, and it would be very important to further enlighten our knowledge about it.

In future studies, most probably we will include a protocol of mandatory etiological investigation, including virus and atypical agents. Since this is not part of the clinical routine, we will have to find research funding to support the associated costs.

One other area of uncertainty, with few studies, is the management of outpatients. It would be important to know the etiology of these less severe pneumonias and to evaluate outcomes in relation to different antibiotic options and duration. This would require a more developed structure, since it would imply enrolling researchers from the primary care area and, once again, increasing the amount of laboratory procedures that are not routinely performed in clinical practice.

The inclusion of real time polymerase chain reaction in future research could be very informative as to the impact of this kind of etiological investigation on clinical outcomes and antibiotic therapy decisions.

The inclusion of new research tools and methodologies, like artificial intelligence and big data analysis, may open new possibilities in medical sciences, and we are looking forward to keep up with the evolution in these fields.

APPENDIX 1 – EPOPEIA data collection protocol

EPOPEIA - REGISTO PROSPECTIVO DE PNEUMONIAS

NÚMERO DE ORDEM:_____

DADOS GERAIS (*COLHER NO LOCAL DO DIAGNÓSTICO)*

Local da recolha	SU ☐	DM ☐	SEMI ☐
Sexo	Masculino ☐	Feminino ☐	
Idade (anos)	_____		
Data de internamento	-------/-------/--------		
Hora de inscrição no SU *(se diagnóstico no SU)*	-----:-----	Hora da 1ª avaliação médica no SU *(se diagnóstico no SU)*	-----:-----

1.Dados clínicos

TAS (mmHg)	_____	**TAD** (mmHg)	_____
FC (bpm)	_____	**Temperatura** (ºC)	_____
FR (cpm)	_____	**pH arterial**	_____
PaO2	_____	PaCO2 (mmHg)	_____
HCO3 (mmol/L)	_____	FiO2 (0-1)	_____
Lactato(mmol/L)	_____		
Ventilação	esp ☐	VI ☐	VNI ☐
Creatinina (mg/dL)	_____	**Ureia** (mg/dL)	_____
Na (mmol/L)	_____	**K**(mmol/L)	_____
Glicemia (mg/dL)	_____	**Hemoglobina** (g/dL)	_____
Hematócrito(%)	_____	**Leucócitos** (cel/mm^3)	_____
PMN (%)	_____	**PCR** (mg/L)	_____
Albumina (g/dL)	_____	**DHL**(UI/L)	_____
Derrame pleural	Sim ☐	Não ☐	Não sei ☐
Infiltrado multilobar	Sim ☐	Não ☐	Não sei ☐
Cavitação	Sim ☐	Não ☐	Não sei ☐
Abcessos	Sim ☐	Não ☐	Não sei ☐
Confusão *de novo*	Sim ☐	Não ☐	Não sei ☐

Score de Glasgow **O - _____** **V- _____** **M:_____**

***Número de respostas certas a 10 perguntas (>8/≤8), em casos duvidosos de alteração da consciência*:**

Idade	Sim☐	Não ☐
Data de nascimento	Sim☐	Não ☐
Que horas são	Sim☐	Não ☐
Ano corrente	Sim☐	Não ☐
Nome do hospital	Sim☐	Não ☐
Reconhece 2 pessoas (médico. Enfermeiro, …)	Sim☐	Não ☐
Morada	Sim☐	Não ☐
Data da 1ª ou 2ª guerra mundial ou 25 de Abril	Sim☐	Não ☐
Presidente da república	Sim☐	Não ☐
Contar em escala decrescente	Sim☐	Não ☐

Hora da toma do 1º ATB **-----:-----**

AGRADECEMOS A COLABORAÇÃO. ESTA FOLHA, DEVIDAMENTE PREENCHIDA, DEVE SER ANEXADA AO PROCESSO DO DOENTE OU ENTREGUE AO GRUPO DE INVESTIGADORES (J. Vasco Barreto, José Ribeiro Almeida, Raquel Calisto, Isabel Jesus Pereira, Marta Soares, João Gil, Sara Beça, Ricardo Pereira, Marta Pereira, Liliana Carneiro, Luís Afonso, Mário Tadeu)

2. Comorbilidades e factores de risco

A) Comorbilidade

Neoplasia nos últimos 10

anos Sim☐ Não ☐ Não sei ☐

Mama Sim☐ Não ☐ Data DX: ___/___/____

Colo-rectal Sim☐ Não ☐ Data DX: ___/___/____

Pulmão Sim☐ Não ☐ Data DX: ___/___/____

Próstata Sim☐ Não ☐ Data DX: ___/___/____

Útero Sim☐ Não ☐ Data DX: ___/___/____

Estômago Sim☐ Não ☐ Data DX: ___/___/____

Bexiga Sim☐ Não ☐ Data DX: ___/___/____

Rim Sim☐ Não ☐ Data DX: ___/___/____

Fígado Sim☐ Não ☐ Data DX: ___/___/____

Tiróide Sim☐ Não ☐ Data DX: ___/___/____

Mesotelioma Sim☐ Não ☐ Data DX: ___/___/____

Osso Sim☐ Não ☐ Data DX: ___/___/____

SNC Sim☐ Não ☐ Data DX: ___/___/____

Melanoma Sim☐ Não ☐ Data DX: ___/___/____

LNH Sim☐ Não ☐ Data DX: ___/___/____

LH Sim☐ Não ☐ Data DX: ___/___/____

Leucemia crónica Sim☐ Não ☐ Data DX: ___/___/____

Leucemia Aguda Sim☐ Não ☐ Data DX: ___/___/____

MM Sim☐ Não ☐ Data DX: ___/___/____

Macroglobulinemia

Waldenstrom Sim☐ Não ☐ Data DX: ___/___/____

Policitemia vera Sim☐ Não ☐ Data DX: ___/___/____

Estado atual Activa ☐ Remissão☐ Metastização conhecida Sim☐ Não ☐

Data da última sessão QT Data: ___/___/____ Há ____ dias (preencher se <=90 dias)

Doença Pulmonar Crónica Sim☐ Não ☐ Não sei ☐

Doença do interstício Sim☐ Não ☐ NS☐

Sequelas fibróticas Sim☐ Não ☐ NS☐

DPOC Sim☐ Não ☐ NS☐

Estadio De Gold (I a IV) _____

Asma Sim☐ Não ☐ NS☐

Gravidade Intermitente ☐ Persistente ligeira ☐ Persistente grave ☐

Bronquiectasias Sim☐ Não ☐ NS☐

FQ Sim☐ Não ☐ NS☐

Síndrome hipoventilação Sim☐ Não ☐ NS☐

Insuficiência Respiratória

Crónica Sim☐ Não ☐ NS☐

OLD Sim☐ Não ☐ NS☐

VNI domiciliaria Sim☐ Não ☐ NS☐

Nr de internamentos no último ano por agudizaçao de DPOC 0 ☐ 1-2 ☐ 3-5 ☐ >5 ☐

IC Sim☐ Não ☐ Não sei ☐

Classe NYHA I☐ II ☐ III☐ IV ☐

HTA Sim☐ Não ☐ NS☐

FA Sim☐ Não ☐ NS☐

Fármacos brdicardizantes (Amiodarona, Digoxina, BetaB, BCC, Ivabradina) Sim☐ Não ☐ NS☐

Medicado com estatina Sim☐ Não ☐ NS☐

História de SCA com subida de MNM Sim☐ Não ☐ NS☐

IRC Sim☐ Não ☐ Não sei ☐

Creat basal (mg/dL) _____

TFG basal (mL/min) _____

Diálise crónica Sim☐ Não ☐ NS☐

Doença Hepática Crónica Sim☐ Não ☐ Não sei ☐

Child A ☐ B ☐ C☐

HTP Sim☐ Não ☐ NS☐

Hx de hemooragia de varizes Sim☐ Não ☐ NS☐

Hx de doença ulcerosa péptica Sim☐ Não ☐ NS☐

Doença do SNC Sim☐ Não ☐ Não sei ☐

Sequelas de AVC Sim☐ Não ☐ NS☐

Hemi ou paraplegia Sim☐ Não ☐ NS☐

História de AIT Sim☐ Não ☐ NS☐

Demência Sim☐ Não ☐ NS☐

Outra Sim☐ Não ☐ NS☐ Quais:_____ _____

Diabetes Sim☐ Não ☐ Não sei ☐

Medicada Sim☐ Não ☐ NS☐

Dx até aos 18 anos Sim☐ Não ☐ NS☐

Com atingimento em orgãos alvo Sim☐ Não ☐ NS☐

Hx complicação aguda Sim☐ Não ☐ NS☐

Doença vascular periférica Sim☐ Não ☐ NS☐

Doenças auto imunes Sim☐ Não ☐ Não sei ☐

LES Sim☐ Não ☐ NS☐

AR Sim☐ Não ☐ NS☐

SSjogren Sim☐ Não ☐ NS☐

Esclerodermia Sim☐ Não ☐ NS☐

PM Sim☐ Não ☐ NS☐

DM Sim☐ Não ☐ NS☐

DMTC Sim☐ Não ☐ NS☐

Espondiloartropatia Sim☐ Não ☐ NS☐

Behçet Sim☐ Não ☐ NS☐

Vasculite Sim☐ Não ☐ NS☐

PMR Sim☐ Não ☐ NS☐

Outra Sim☐ Não ☐ NS☐ Qual:_____ _____

VIH Sim☐ Não ☐ Não sei ☐

Sida Sim☐ Não ☐ NS☐

CD4 (células/mm^3) _____

TARV Sim☐ Não ☐ NS☐

Corticoterapia crónica

(>0.5mg/kg/d) Sim☐ Não ☐ Não sei ☐

Transplante Sim☐ Não ☐ Não sei ☐

Renal Sim☐ Não ☐ NS☐

Hepático Sim☐ Não ☐ NS☐

Pancreático Sim☐ Não ☐ NS☐

Cardiaco Sim☐ Não ☐ NS☐

Pulmonar Sim☐ Não ☐ NS☐

Imunossupressão Sim☐ Não ☐ Não sei ☐

antiTNF Sim☐ Não ☐ NS☐

antiCD20 Sim☐ Não ☐ NS☐

Ciclofosfamida Sim☐ Não ☐ NS☐

MMF Sim☐ Não ☐ NS☐

Ciclosp Sim☐ Não ☐ NS☐

MTX Sim☐ Não ☐ NS☐

AZA Sim☐ Não ☐ NS☐

Leflunomida Sim☐ Não ☐ NS☐

Mercaptopurina Sim☐ Não ☐ NS☐

Outro Sim☐ Não ☐ NS☐ Qual:_____ _____

Esplenectomia Sim☐ Não ☐ Não sei ☐

Asplenia funcional Sim☐ Não ☐ NS☐

Cáries Sim☐ Não ☐ Não sei ☐

IMC (Kg/m^2) _____

B) Factores de risco

Estado funcional

Acamado Sim☐ Não ☐ NS☐ **Dificuldade de locomoção** Sim☐ Não ☐ NS☐

Cadeira de rodas Sim☐ Não ☐ NS☐ **Dificuldade de deglutição** Sim☐ Não ☐ NS☐

Depressão da conciência basal Sim☐ Não ☐ NS☐

Em quantas das seguintes actividades Não tem autonimia TOTAL (0-6)

Tomar banho (excepto lavar as costas) _____

Vestir-se (excepto atacadores) _____

Higiéne diária _____

Entrar e sair da cama (bengala aceitável) _____

Continência de esfíncteres _____

Comer de um prato _____

Hábitos/epidemiologia

Fumador Sim☐ Não☐ NS☐ EF☐

UMA (nº de maços/dia*nº de anos que fumou) _____

Hábitos etílicos activos Sim☐ Não ☐ NS☐ g/dia _____

Canabinóides Sim☐ Não ☐ NS☐

Hábitos toxicómanos Sim☐ Não ☐ NS☐

Her EV Sim☐ Não ☐ NS☐

Her inal Sim☐ Não ☐ NS☐

Coca EV Sim☐ Não ☐ NS☐

Coca inal Sim☐ Não ☐ NS☐

Coca+her Ev Sim☐ Não ☐ NS☐

Coca+her inal Sim☐ Não ☐ NS☐

Colonização actual da pele ou mucosas por SAMR Sim☐ Não ☐ NS☐

Colonização prévia da pele ou

mucosas por SAMR Sim☐ Não ☐ NS☐ Data da última confirmação ___/___/____

Viagens recentes Sim☐ Não ☐ NS☐

Europa Ocidental Sim☐ Não ☐ NA☐

Europa de leste Sim☐ Não ☐ NA☐

Norte África Sim☐ Não ☐ NA☐

África sub-sahariana Sim☐ Não ☐ NA☐

América do norte Sim☐ Não ☐ NA☐

Ásia Sim☐ Não ☐ NA☐

Oceania Sim☐ Não ☐ NA☐

Transportes

Carro Sim☐ Não ☐ NS☐

Camioneta Sim☐ Não ☐ NS☐

Comboio Sim☐ Não ☐ NS☐

Avião Sim☐ Não ☐ NS☐

Barco Sim☐ Não ☐ NS☐

Outro Sim☐ Não ☐ NS☐ Qual:_____ _____

Contactos com crinaças que frequentam infantário (profission ou co-habitação) Sim☐ Não ☐ NS☐

Epidemia de Gripe Sim☐ Não ☐ NS☐

Co-habita com individuo inf por MMR Sim☐ Não ☐ NS☐

Surto de Legionelose Sim☐ Não ☐ NS☐

Tem pássaros Sim☐ Não ☐ NS☐

Vacinação anti-gripal Sim☐ Não ☐ NS☐

Vacinação anti-pneumocócica Sim☐ Não ☐ NS☐

Dt de fim

VNI Sim☐ Não ☐ NS☐ Dt de inicio___/___/___ ___/___/___

Cirurgia <=90 dias Sim☐ Não ☐ Urgente ☐ Electiva ☐ Nºdias após _____

Dispositivos invasivos (presentes ao Dx ou até 3d antes) (indicar duração de presença do dispositivo)

SNG 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

PEG 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Colostomia 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Urostomia 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Duplo J 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Traqueostomia 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Algaliação 0-2d ☐ 3-7d ☐ 7-30d ☐ >30 ☐

Sim☐ Não ☐ ☐

CVC de longa duração NS

Sim☐ Não ☐ ☐

CVC de curta duração NS

PM provisório 0-2d ☐ 3-7d ☐ >7 ☐

Sim☐ Não ☐ ☐

PM definitivo NS

Sim☐ Não ☐ ☐

CDI NS

Sim☐ Não ☐ ☐

Catéter de diálise peritoneal NS

Outro dispositivo de longa duração _____

C1) Contacto com cuidados de saúde

Nos últimos 90 dias

Teve internamento >=2 dias Sim☐ Não ☐ NS☐ Data de alta __/___/____

Hospital

Hospital Pedro Hispano ☐ Hospital de São João☐ HGSA ☐ CHPVVC☐

Vale do Sousa ☐ Famalicão☐ Sto Tirso ☐ Braga ☐

Guimarães ☐ Viana ☐ Vila Real ☐ Chaves ☐

Bragança ☐ Outro ☐ Qual:_____ Privado ☐

Usou algum antibiótico Sim☐ Não ☐ NS☐ Qual:_____ _____

Data de fim __/___/____

Motivo

Pneumonia ☐ Traqueobronquite ☐ Inf ORL ☐ ITU ☐

DIP ☐ GEA ☐ Partes moles ☐ SNC ☐

Endocardite ☐ Inf abdominal ☐ osteartic ☐ Proteses e catéteres ☐

Profilaxia ☐

Via EV ☐ IM ☐ PO☐

Nos últimos 30 dias

Realizou hemodiálise Sim☐ Não ☐ NS☐ CVC ☐ FAV☐

Centro HD Área do HPH ☐ Fora da área ☐

Se não pertencente ULSM

Realizou QT Sim☐ Não ☐ NS☐ qual: _____ _____

Tratamento de feridas Sim☐ Não ☐ NS☐

Se não pertencente ULSM

Tratamento no Hospital de dia Sim☐ Não ☐ NS☐ qual: _____ _____

Instit de cuidados prolongados Sim☐ Não ☐ NS☐

Onde:

Lar ☐ RNCC ☐ Centro de dia ☐

Outro ☐ Nome:_____ _____ _____

C2) Se diagnóstico feito no internamento atual

Motivo de internamento _____ _____

Serviço em que está internado SEMI ☐ UCIP ☐ Enfermaria ☐

Serviços em que esteve <=90d antes

Med Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Cirurgia Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Ortopedia Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

ORL Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Oftalmologia Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

CI Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Ginecologia/Obstetricia Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Urologia Sim☐ Não ☐ NS☐ Nº de dias desde a saida _____

Se o internamento não foi por penumonia

ATB já feitos Sim☐ Não ☐ NS☐

Dt de fim

Qual 1:_____ Duração_____ Bact. Isoladas_____ ___/___/___

			Dt de fim
Qual 2:_____	Duração_____	Bacteria Isoladas_____	___/___/___
			Dt de fim
Qual 3:_____	Duração_____	Bacteria Isoladas_____	___/___/___
			Dt de fim
Qual 4:_____	Duração_____	Bacteria Isoladas_____	___/___/___
			Dt de fim
Qual 5:_____	Duração_____	Bacteria Isoladas_____	___/___/___

				Dt de fim
Ventilação invasiva	Sim☐ Não ☐ NS☐	Dt de inicio___/___/___		___/___/___
Alimentação entérica ou parentérica	Sim☐ Não ☐	NE☐	NP☐	Dt de inicio__/___/__
Profilaxia úlcera de stress	Sim☐ Não ☐	IBP☐	AH1☐ Sucr☐	

3. Diagnóstico

Data de dignóstico ____/____/___

Critérios utilizados para o diagnóstico

Infiltrado radiográfico *de novo* ou agravado Sim☐ Não ☐ NS☐

Explicações alternativas para os infiltrados Sim☐ Não ☐

Fibrose ☐	IC ☐	ARDS ☐	Derrame ☐
Doença interstício ☐	Hemorrágica ☐	Trauma ☐	TEP ☐
TP activa ☐	Neoplasia ☐		

Febre (>38ºC) Sim☐ Não ☐ NS☐ **Leucocitose** (>11500/mm^3) Sim☐ Não ☐ NS☐

Explicações alternativas para a

febre e leucocitose Sim☐ Não ☐ NS☐ **Secreções respiratórias** Sim☐ Não ☐ NS☐

Sépsis grave Sim☐ Não ☐ NS☐ **Instabilidade hemodinâmica** Sim☐ Não ☐ NS☐

Hipoxemia refractária (Pa/Fi<100 Vesp) Sim☐ Não ☐ NS☐

Aspiração provável, prévia ao quadro de pneumonia Sim☐ Não ☐ NS☐

Suspeita de foco infeccioso adicional Sim☐ Não ☐ NS☐

ITU ☐ DIP ☐ partes moles ☐ SNC ☐

endocardite ☐ inf abdominal ☐ Osteoartic ☐ prótese e catéter ☐

4. Investigação etiológica

Antes do inicio da antibioterapia

Antigénios na Urina Sim☐ Não ☐ Data: ____/____/___ Leg☐ Pneumo ☐

Liquido Pleural Sim☐ Não ☐ Data: ____/____/___

Que tipo de agentes foi pesquisado nas SR

PCR virus Sim Não☐ ☐ IF Virus Sim☐ Não☐ PCR atípicos Sim☐ Não☐ Gram Sim ☐ Não ☐

Cult Aer Sim Não☐ ☐ ED BAAR Sim ☐ Não☐ Cult Anaer Sim ☐Não ☐ Fungos Sim ☐ Não ☐

Outros Sim Não☐ ☐

NOTA: Hemoculturas e secrecções respiratorias assim como agentes identificados utilizar tabela na página seguinte

4- Investigação etiológica

Antes do inicio da antibioterapia

Hemoculturas

Por acesso central	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Por ac periférico	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____

Secreções Respiratórias

Expectoração	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Secreções brônquicas	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Aspirado Traqueal	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Aspirado Brônquico por broncoscopia	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Lavado brônquico	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Lavado broncoalveolar	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Escovado protegido	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Liquido Pleural	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Antigénico Urinário Pneumococo	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____
Antigénico Urinário Legionella	Sim ☐ Não ☐	Data __/___/____	Agente identificado Sim ☐ Não ☐ Qual: _____

4. Investigação etiológica

Após o inicio da antibioterapia

Antigénios na Urina Sim☐ Não ☐ Data: ____/____/___ Leg☐ Pneumo ☐

Liquido Pleural Sim☐ Não ☐ Data: ____/____/___

Que tipo de agentes foi pesquisado nas SR

PCR atípicos Sim☐ ☐

PCR virus Sim Não☐ Il☐rus Sim☐ Não☐ Não Gram Sim ☐ Não ☐

Cult Aer Sim Não☐ El☐AAR Sim ☐ Não☐ Cult Anaer Sim ☐Não ☐Fungos Sim ☐ Não ☐

Outros Sim Não☐ ☐

NOTA: Hemoculturas, secrecções e agentes identificados: utilizar anexo I (igual à tabela de "antes do ATB")

5. Antibioterapia empírica da pneumonia

Data de internamento **-------/-------/--------** Hora **-----:-----**

Antibiótico inicial _____ Dose: _____

Via PO ☐ EV ☐ IM ☐

Duração da ATB inicial? _____

Motivo interrupção

Cura ☐ Óbito ☐ Causa não infecciosa ☐ Outra ☐

Foi alterado o antibiótico Sim☐ Não ☐

Motivo de alteração Ausência de resposta sem agente isolado ☐

Ausência de resposta com agente isolado ☐ Boa resposta mas agente resistente ☐

Adição de ATB para sinergismo ☐ Adição de ATB por infecção respiratória mista ☐

Infecção extra pulmonar ☐ Reacção 2ª fármaco ☐

Motivos farmacocinéticos ☐

Outro ☐ **Qual:**_____

O ATB inicial cobria o agente isolado Sim☐ Não ☐ NS☐

Foi desescalado ATB Sim☐ Não ☐ NS☐

Se não

Boa resposta ATB actual ☐ Suspeita de outro ou mais agentes envolvidos ☐

Outra infecção associada ☐ Razões farmacocinéticas ☐

Sinergismo ☐ Motivos pouco claros ☐

Se macrólido, foi suspenso Sim☐ Não ☐ NA☐

Quando? (nr de dias após inicio do mesmo) _____

Porquê? Considerado suficiente (5-6d)☐ AgU Leg neg ☐ AgU Pn pos ☐ Ef lateral ☐ Identificação agente alternativo ☐

Passagem do ATB para via oral (dias após inicio)

_____

Duração da ATB considerada eficaz (em dias; inclui tomas após alta) _____

6. Evolução

Instalação de infecção por microrganismo MR até 30 dias após o final do tratamento da pneumonia

Sim☐ Não☐ NS☐

Foco Respiratório ☐ Urinário ☐ Endocardite nativa ☐ abcesso não respiratório ☐ Clostridium ☐ Partes moles ☐ Associada a cateter venoso ☐ Bacteriémia sem foco ☐ Associada a prótese ☐

Ocorreram complicações Sim☐ Não ☐ NS☐

Quais Empiema ☐ Abcesso pulmão ☐ Abcessos distância ☐

Endocardite ☐ Sepsis grave ou choque séptico ☐ Ventilação invasiva ☐

Houve resolução da pneumonia Sim☐ Não ☐ NS☐

Se não coincide com a data de alta, qual o motivo Social ☐ Nova infecção ☐

Outro motivo clinico ☐ Qual:_____

Óbito no internamento Sim☐ Não ☐ NS☐

Se sim, causa Penumonia referente a este protocolo☐ Outro ☐

Data da morte ____/___/____ DNR Sim☐ Não ☐ NS☐

Se não faleceu

Data da alta ____/___/____

Aos 30 dias após a alta (consulta externa ou outra observação programada)

Óbito Sim☐ Não ☐ NS☐

Reinternamento Sim☐ Não ☐ NS☐ **Por pneumonia** Sim☐ Não ☐ NS☐

Resolução dos sintomas Sim☐ Não ☐ NS☐

Resolução radiológica Sim☐ Não ☐ NS☐

Lesão pulmonar subjacente Sim☐ Não ☐ NS☐

<u>NOTA FINAL</u>: CADA PROTOCOLO DIZ RESPEITO A UMA PNEUMONIA, DEVENDO SER PREENCHIDO MAIS DO QUE UM SE O MESMO DOENTE TIVER MAIS DO QUE UMA PNEUMONIA NO MESMO INTERNAMENTO

APPENDIX 2 – Instructions for data collection

PROTOCOLO PROSPECTIVO DE PNEUMONIAS

MANUAL DE PREENCHIMENTO

NOTA: COMEÇAR O PREENCHIMENTO PELO PONTO 3.DIAGNÓSTICO, ONDE SE ENCONTRAM OS CRITÉRIOS DE INCLUSÃO (Dx DE PNEUMONIA)

NÚMERO DE ORDEM: não preencher.

DADOS GERAIS: colher no local do diagnóstico (SU / DM / SEMI); dados pessoais no autocolante; registar sempre data de internamento; se Dx no SU, registar também hora de inscrição no SU e hora da 1ª avaliação médica por qualquer médico no SU.

1. DADOS CLÍNICOS: NUNCA ESQUECER DE REGISTAR FR NO MOMENTO DO DIAGNÓSTICO

(avaliar no mínimo 30seg, idealmente 1min); **consciência**: se há confusão ou depressão de consciência *de novo* evidente, registar "sim"; se claramente não, registar "não"; na dúvida, aplicar o questionário do MMTE; **GSA**: registar sempre o modo ventilatório e a FiO2; registar a primeira disponível após o Dx de pneumonia, excepto se esta for feita em pós-paragem cardio-respiratória; **bioquímica**: se não estiver colhido, pedir ao laboratório para acrescentar DHL e Albumina (a seu tempo vai ser criado um perfil analítico de pneumonia no sistema informático); os restantes dados são universalmente obtidos (restantes sinais vitais, hemograma, restante bioquímica, Rx do tórax, GSA).

(ATÉ AQUI, OS DADOS VÃO SER PREENCHIDOS POR QUEM FAZ O DIAGNÓSTICO; DAQUI EM DIANTE, PELOS INVESTIGADORES DO GRUPO)

2. COMORBILIDADES E FACTORES DE RISCO

A) COMORBILIDADES

Neoplasia: Diagnóstico (S/N/NA) – registar "N" se não houver evidência clínica (história, exame físico, exames auxiliares simples). Estado actual (activa/remissão/NS) – registar o que estiver reconhecido pelo oncologista ou médico hospitalar assistente; na ausência de reconhecimento, registar "activa" se for actualmente óbvio; na dúvida, registar "NS". Metastização conhecida (S/N/NS) – os mesmos princípios.

Doença Pulmonar Crónica: na dúvida sobre determinada doença, discutir comigo (assumir-se-á que "sim" ou "não" se estiver bem estudado – imagem, biópsia ou outros estudos; "NS" se dados insuficientes); Estadio de GOLD: I – IT<70% e FEV1≥80%, II – FEV1 50-80%, III – FEV1 30-50%, IV – FEV1<30% ou <50% e IResp crónica); Gravidade da asma: intermitente – sintomas < 2x/semana; persistente ligeira – sintomas <1x/d e ≥2x/semana; moderada – sintomas diários, por vezes nocturnos; grave – sintomas persistentes,

frequentemente nocturnos; internamentos por agudização de DPOC: contar os que forem mesmo por isso, e não por outras intercorrências.

IC: classe NYHA basal; considerar toda a FA (permanente, intermitente, etc).

IRC: Para a TFG basal, registar peso, o resto (idade, sexo e Cr basal) já está.

Doença do SNC: Sequelas de AVC refere-se a sequelas que não plegias; hemi ou paraplegia de qualquer causa; Demência: défice cognitivo crónico; Outra: qualquer doença que comprometa a deglutição ou a protecção das VAS (extra-piramidais, ELA…).

Diabetes: medicada inclui insulina; atingimento de órgãos-alvo inclui retino, nefro, neuropatia.

Dça auto-imune: dizer qual.

VIH: SIDA se CD4<200 ou doença definidora actualmente (Candidose das vias aéreas inferiores ou esófago, CA do colo do útero invasivo, Coccidioidomicose, Criptococose, Criptosporidiose, Microsporidiose, doença citomegálica, Encefalopatia (HIV-related), Herpes simplex (com duração >1 mês ou em localização não cutânea), Histoplasmose, Isosporiase, Kaposi, Linfoma, MAC, Pneumocistose, Pneumonias recorrentes, Leucoencefalopatia multifocal progressiva, sépsis recorrente por Salmonella,Toxoplasmose cerebral, Tuberculose, wasting syndrome); **NÃO inclui doenças "B"** (angiomatose bacilar, candidose oral ou vulvovaginal, dça inflamatória pélvica, displasia cervical ou CA in situ, tricoleucoplaquia oral, PTI, sintomas constitucionais, neuropatia periférica, herpes zoster).

B) FACTORES DE RISCO

Hábitos / epidemiologia: Epidemia de Gripe: segundo autoridades de saúde; Surto Legionelose: idem; Vacinação anti-gripal refere-se a menos de 1 ano antes; Vacinação anti-pneumocócica refere-se a menos de 5 anos antes.

C1) CONTACTO COM CUIDADOS DE SAÚDE

- **Nos últimos 90 dias**: Usou algum antibiótico: segundo código anexo.

- **Nos últimos 30 dias**: Centro HD da área do HPH: Uninefro; nome do local não pertencente à área do HPH: lista anexa.

- **Instit. de cuid. Prolongados** Nomes em lista anexa.

C2) SE DIAGNÓSTICO FEITO NO INTERNAMENTO ACTUAL

Motivo de internamento (folha de rosto): por extenso, texto livre.

ATB já feitos e **Bactérias isoladas:** anexar folha com a referência **"2-C2"**.

Cirurgia ≤90d antes: exclui pequena cirurgia.

Profilaxia úlcera de stress: referir "sim" se fizesse qualquer dos fármacos no dia do diagnóstico.

3. DIAGNÓSTICO

Este ponto é fundamental porque define inclusão como pneumonia; se não se cumprirem os critérios, exclui-se o caso.

Critérios: infiltrado radiográfico *de novo* ou agravado **e** 2 ou mais dos seguintes: febre, leucocitose ou secreções respiratórias purulentas (excluídos focos extrapulmonares de infecção e causas não infecciosas – considerar se forem fortes possibilidades; ex: sépsis urinária com ARDS, infecção respiratória e infiltrados iguais aos prévios, trauma torácico, etc; na dúvida discutir comigo); **se sépsis grave, instabilidade hemodinâmica ou hipoxemia refractária**: infiltrado radiográfico *de novo* ou agravado **e** 1 ou mais dos mesmos critérios.

4. INVESTIGAÇÃO ETIOLÓGICA

A) Produtos colhidos para microbiologia (para estudo da pneumonia): conforme indicado, registar TUDO o que foi colhido antes e depois de iniciar antibioterapia.

Agentes identificados: anexar folha com a referência "**4.**"; anexar antibiogramas.

5. ANTIBIOTERAPIA EMPÍRICA DA PNEUMONIA

Data e Hora: de administração do antibiótico (registo de enfermagem).

Foi alterado o antibiótico? Registar em folha anexa, com a referência, **"5."**, se várias sequências. ATB conforme código anexo.

Motivo da alteração: registar o motivo que estiver expresso como mais importante no registo clínico. O mesmo é válido para as restantes decisões relativas a ATB.

ATB considerada eficaz: aquela a que é assumido que o doente respondeu.

6. EVOLUÇÃO

Definição de microrganismo MR: a combinar com Dra. Valquíria.

Resolução da pneumonia: assumir se se decidiu suspender ATB perante melhoria, e não por aspectos radiológicos.

Óbito no internamento : Causa: pneumonia a que se refere este protocolo, se assumido pelos médicos assistentes; DNR: se explicitamente registado no processo ou ordens médicas.

Aos 30 dias após a alta: todos os doentes devem ficar com OBSERVAÇÃO PROGRAMADA combinada para esta data, seja em regime de consulta externa ou outro (SU, hospital de dia, vinda à Ala…). Nessa observação, averiguar se houve resolução dos sintomas de pneumonia, resolução radiológica e lesão pulmonar subjacente (obriga a fazer Rx do tórax). Na dúvida, discutir comigo.

FOLHA ANEXA

LISTA DE ATB

1. Amicacina
2. Amoxicilina
3. Amoxicilina/Ác. Clavulânico
4. Ampicilina
5. Azitromicina
6. Aztreonam
7. Cefalotina
8. Cefazolina
9. Cefepime
10. Cefotaxima
11. Cefoxitina
12. Cefixima
13. Ceftazidima
14. Ceftriaxone
15. Cefuroxima
16. Ciprofloxacina
17. Claritromicina
18. Clindamicina
19. Colistina
20. Cotrimoxazol
21. Daptomicina
22. Doxiciclina

23. Eritromicina
24. Estreptomicina
25. Ertapenem
26. Etambutol
27. Flucloxacilina
28. Gentamicina
29. Imipenem
30. Isoniazida
31. Levofloxacina
32. Linezolide
33. Meropenem
34. Metronidazol
35. Moxifloxacina
36. Nitrofurantoína
37. Ofloxacina
38. Penicilina G
39. Piperacilina – Tazobactam
40. Pirazinamida
41. Prulifloxacina
42. Rifabutina
43. Rifampicina
44. Teicoplanina
45. Telitromicina
46. Tigeciclina
47. Tobramicina
48. Vancomicina

LISTA DE MICRORGANISMOS

1. Acinetobacter baumanii
2. Adenovírus
3. Aeromonas spp
4. Anaeróbios
5. Aspergillus fumigatus
6. Bordetella spp
7. Burkholderia cepacia
8. Burkholderia pseudomallei
9. Blastomyces
10. Candida albicans
11. Candida (outras)
12. Chlamydophila pneumoniae
13. Chlamydophila psittaci
14. Citomegalovírus
15. Citrobacter freundii
16. Coccidioides immitis
17. Corynebacterium spp
18. Coxiella burnetti
19. Cryptococcus neoformans
20. Cryptosporidium
21. Echerichia coli
22. Echerichia coli MR
23. Echerichia coli ESBL+
24. Enterobacter aerogenes
25. Enterobacter chloacae
26. Enterococcus faecalis
27. Enterococcus faecalis MR

28. Enterococcus faecalis VR
29. Enterococcus faecium
30. Enterococcus faecium MR
31. Enterococcus faecium VR
32. Francisella tularensis
33. Haemophilus influenzae
34. Histoplasma capsulatum
35. Influenza A
36. Influenza B
37. Klebsiella pneumonia
38. Klebsiella pneumonia MR
39. Klebsiella pneumonia ESBL+
40. Klebsiella (outras)
41. Legionella pneumophila serotipo 1
42. Legionella pneumophila (outro serotipo)
43. Metapneumovírus
44. Moraxella catarrhalis
45. Morganella morgani
46. Mycobacterium tuberculosis
47. Mycobacteria não tuberculosis
48. Mycoplasma pneumoniae
49. Neisseria spp
50. Nocardia spp
51. Outra bactéria
52. Outro fungo
53. Outro protozoário
54. Outro vírus
55. Parainfluenza 1, 2 ou 3

56. Pneumocystis jiroveci
57. Proteus mirabilis
58. Proteus vulgaris
59. Pseudomonas aeruginosa
60. Salmonella typhi
61. Serratia marcescens
62. Serratia (outras)
63. Staphylococcus aureus MS
64. Staphylococcus aureus MR
65. Staphylococcus epidermididis MS
66. Staphylococcus epidermididis MR
67. Staphylococcus coagulase negativo MS (outros)
68. Staphylococcus coagulase negativo MR (outros)
69. Stenotrophomonas maltophilia
70. Streptococcus beta hemolíticos
71. Streptococcus grupo milleri
72. Streptococcus pneumoniae
73. Streptococcus viridans
74. Varicella zóster vírus
75. Vírus sincicial respiratório

LISTA DE INSTITUIÇÕES DE SAÚDE FORA DA ÁREA

LISTA DE LARES E UNIDADES DA RNCCI

MOTIVO DE INTERNAMENTO (FOLHA DE ROSTO, POR EXTENSO)

_____

2-C2.

- ATB JÁ FEITOS (E DATAS DE INÍCIO E FIM)

- BACTÉRIAS ISOLADAS PREVIAMENTE À PNEUMONIA (DATA DA COLHEITA; EM QUE PRODUTO)

4. AGENTES IDENTIFICADOS

- MICRORGANISMO, PRODUTO, DATA DE COLHEITA, DATA DE IDENTIFICAÇÃO, ANTES / DEPOIS DE INÍCIO ATB

- ANEXAR ANTIBIOGRAMAS DE CADA BACTÉRIA

- DISCRIMINAR, PARA TODOS OS AGENTES, SE A AMOSTRA TINHA SIDO COLHIDA ANTES OU DEPOIS DO INÍCIO DO ANTIBIÓTICO

5. SEQUÊNCIA DE ANTIBIÓTICOS

- ATB, DATA DE INÍCIO, DATA DE ALTERAÇÃO, MOTIVO DE ALTERAÇÃO

APPENDIX 3 – Approval letters from Hospital Ethics Committee and National Data Protection Commission

UNIDADE LOCAL DE SAÚDE DE MATOSINHOS HOSPITAL PEDRO HISPANO	INFORMAÇÃO	Nº 07/CE / SR Data: 12-01-2010

Para: **Presidente Conselho de Administração**
De: **Comissão de Ética**

Assunto: **Pedido de autorização para recolha de dados**

INFORMAÇÃO

Exmos. Senhores,

A Comissão de Ética analisou na sua reunião de 08 de Janeiro de 2010, o seguinte trabalho: Estudo Prospectivo de Pneumonias, proponente Dr. J. Vasco Barreto.

Decidido nada opor à realização do estudo.

Com os melhores cumprimentos,

Dr. José Alberto Silva
(Presidente da Comissão de Ética da U. L. S. – Matosinhos

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Processo n.º 2635/2011

AUTORIZAÇÃO N.º 3114 /2011

O Departamento de Medicina da Unidade Local de Saúde de Matosinhos notificou à CNPD um tratamento de dados pessoais com a finalidade de elaborar um estudo observacional de Pneumonias em Internamento de Agudos (EPOPEIA).

Serão incluídos no estudo os indivíduos com pneumonias, diagnosticadas no Departamento de Medicina do Hospital Pedro Hispano da Unidade Local de Saúde de Matosinhos. O médico assistente, investigador no estudo, solicitará consentimento informado, cuja declaração deverá ser arquivada no processo clínico do doente.

O estudo é prospectivo, estimando-se o seguimento dos participantes durante um período de um a três anos.

No "caderno de recolha de dados" não há identificação nominal dos titulares, sendo aposto um código de doente. A chave desta codificação só pode ser conhecida dos investigadores.

Os destinatários deverão ser ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento.

A CNPD já se pronunciou na sua Deliberação n.º 227 /2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correcto cumprimento da Lei de Protecção de Dados, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para esta finalidade.

No caso em apreço, a notificação enquadra-se no âmbito tipificado por aquela Deliberação.

A informação tratada é recolhida de forma lícita (art.º 5º, n.º1 al. a) da Lei 67/98), para finalidades determinadas, explícitas e legítimas (cf. al. b) do mesmo artigo) e não é excessiva.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
geral@cnpd.pt www.cnpd.pt

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Assim, de acordo com as disposições conjugadas do n.º 2 do artigo 7.º, n.º1 do artigo 27º, al. a) do n.º 1 do artigo 28º e art. 30º da Lei de Protecção de Dados, autoriza-se o tratamento, com as condições supra referidas, nos seguintes termos:

Responsável pelo tratamento: Departamento de Medicina da Unidade Local de Saúde de Matosinhos
Finalidade: Estudo observacional de Pneumonias em Internamento de Agudos (EPOPEIA).
Categoria de Dados pessoais tratados: código do doente, dados demográficos (idade e sexo), história da doença, história médica, história médica familiar, hábitos tabágicos, sintomas e sinais da doença, resultados de testes analíticos, terapêuticas e medicação.
Entidades a quem podem ser comunicados: Não há.
Formas de exercício do direito de acesso e rectificação: Junto do médico assistente, ou do investigador principal.
Interconexões de tratamentos: Não há.
Transferências de dados para países terceiros: Não há
Prazo de conservação: O código do titular deve ser destruído um mês após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 227/ 2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 04 de Abril de 2011

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