Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia

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TITLE: Burden and Risk Factors for *Pseudomonas aeruginosa* Community-acquired Pneumonia: a Multinational Point Prevalence Study of Hospitalised Patients

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Take Home Message: *P. aeruginosa* is infrequent in CAP patients. Specific risk factors should be assessed when choosing antibiotics for CAP

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ABSTRACT

Pseudomonas aeruginosa is a challenging bacterium to treat due to its intrinsic antibiotic resistance to the most frequently used antibiotics in patients with community-acquired pneumonia (CAP). Data about the global burden and risk factors associated with *P. aeruginosa*-CAP are limited. We assessed the multinational burden and specific risk factors associated with *P. aeruginosa*-CAP.

We enrolled 3,193 patients in 54 countries with confirmed diagnosis of CAP that underwent microbiological testing at admission. Prevalence was calculated according to the identification of *P. aeruginosa*. Logistic regression analysis was used to identify risk factors for antibiotic-susceptible and antibiotic-resistant *P. aeruginosa*-CAP.

The prevalence of *P. aeruginosa* and antibiotic-resistant *P. aeruginosa*-CAP was 4.2% and 2.0%, respectively. The rate of *P. aeruginosa* CAP in patients with prior infection/colonization due to *P. aeruginosa* and at least one of the three independently associated chronic lung diseases [*i.e.*, tracheostomy, bronchiectasis and/or very severe COPD]) was 67%. In contrast, the rate of *P. aeruginosa* CAP was 2% in patients without prior *P. aeruginosa* infection/colonization and none of the selected chronic lung diseases.

The multinational prevalence of *P. aeruginosa*-CAP is low. The risk factors identified in this study may guide healthcare professionals in deciding empirical antibiotic coverage for CAP patients.

INTRODUCTION

Community acquired pneumonia (CAP) is a leading infectious cause of morbidity and mortality worldwide[1, 2]. Five to six billion people are diagnosed with CAP and more than 3.5 million people die annually secondary to CAP[1, 3]. Several viruses and bacteria cause CAP[4], but *Streptococcus pneumoniae* remains the most frequently identified bacterial pathogen in adults[5]. During the last few decades, the aetiology of CAP has been changing; antibiotic-resistant bacteria that were thought to be important only in hospital settings are now becoming more prevalent in community settings[6-8]. The evolution of this new pathogen ecology is threatening our capacity to treat patients with CAP[9-11].

Pseudomonas aeruginosa, a Gram-negative bacterium, intrinsically resistant to several groups of antibiotics, such as β-lactams[12], has been frequently reported in CAP patients with specific health care associated risk factors, such as residence in a nursing home and hospitalization during the past 90 days (*i.e.*, health care associated pneumonia, HCAP) [13-15]. Moreover, severe illnesses and poor clinical outcomes have been linked to *P. aeruginosa* infection in patients with CAP[15-17]. During recent years, *P. aeruginosa* circulating strains tend to have higher resistance patterns to anti-pseudomonal antibiotics, leading to infections that are challenging to treat[6].

The prevalence of CAP due to *P. aeruginosa* varies significantly between different patient groups and specific risk factors for *P. aeruginosa*-CAP are controversial[18, 19]. Currently available data about the prevalence of *P. aeruginosa*-CAP and its resistance patterns

are limited to single centre studies[15, 20] and studies with several methodological limitations[15, 21-23]. In a meta-analysis, *Chalmers et al.* reported data from 22 studies a prevalence ranging from 0 to 23% in different CAP populations and a pool prevalence of 8.6% for *P. aeruginosa* in patients with multidrug resistant risk factors and 4% in patients without risk factors[24]. All were single centre/region and majority were rated as poor methodological status[24]. As a result, the true prevalence of *P. aeruginosa*-CAP globally is unknown. Currently, the risk factors associated with *P. aeruginosa* infection recognised by Infectious Diseases Society of America/ American Thoracic Society (IDSA/ATS) guidelines for HCAP differ from those published in the CAP guidelines [13, 25]. Further, the global prevalence of multi-drug resistant (MDR) *P. aeruginosa* in CAP patients is unknown. Therefore, to close the gap regarding the global prevalence and the risk factors associated with *P. aeruginosa,* we designed a multinational, multicentre, worldwide study to determine the point prevalence of *P. aeruginosa*, its antibiotic resistance patterns, and the associated risk factors in hospitalised patients with CAP.

MATERIALS AND METHODS

Study Design

This is a multicentre, point-prevalence study of hospitalised patients with CAP in 222 hospitals in 54 countries. The coordinating institution for this project was the University of Texas Health San Antonio (UT Health) in San Antonio, Texas, USA. The UT Health Institutional Review Board approved the project to collect data and serve as a coordinating institution for the study (IRB# HSC20150184E). Study sites had to comply with local and national research regulations to participate in the study. Electronic invitations to participate were

sent to members of various medical professional societies representing physicians specializing in infectious diseases, pulmonary, critical care, and internal medicine. Additionally, first authors of previously published studies of MDR pathogens in CAP were sent individual invitations. This project received no funding. Subjects were enrolled on four randomly selected days in March, April, May, and June of 2015. Each site investigator selected the study days to participate in compliance with the IRB stipulations, and avoid potential patient de-identification[26]. Due to the observational nature of the study, patient consent was not required.

Study Subjects

Inclusion criteria

Patients ≥18 years of age hospitalised with CAP were eligible for the study. CAP had to be diagnosed per the current IDSA/ATS guidelines[13]: presence of new pulmonary infiltrates on thoracic imaging (chest radiograph, computed chest tomography, or lung ultrasound) during the initial 48 hours of hospitalization and ≥1 of the following conditions: 1) novel or increased cough with or without sputum production and/or purulent respiratory secretions; 2) fever (oral or rectal temperature ≥37.8 ° C) or hypothermia (oral or rectal temperature <36 ° C); 3) signs of systemic inflammation (abnormal white blood cell count [leucocytosis >10,000/cm^3, bandemia >10%, leukopenia <4,000/cm^3], procalcitonin levels above the local upper limit of normal, or increased C-reactive protein)[26].

Exclusion criteria

Patients were excluded from participating in the study if they had hospital-acquired pneumonia (HAP) or ventilator associated pneumonia (VAP)[25]. Patients without

microbiological testing from either blood, lower respiratory tract cultures, or sputum collected within 24 hours of hospital admission were also excluded.

Data collection

Data was collected and managed using REDCap™ (Research Electronic Data Capture), an electronic data capture tool hosted on the UT Heath San Antonio's server. REDCap™ is a protected web-based application designed to collect research data[27]. Confirmation of microbiological results and all electronic data entry had to be completed within 7 days of study enrolment.

Microbiological analysis

Diagnostic testing, such as blood cultures and respiratory collection; and clinical care decisions were decided by attending physicians, not per study protocol[26]. Local microbiological testing protocols were used to process blood and sputum samples collected within the first 24 hours of hospitalization. If available, data on pleural fluid, tracheobronchial aspirate, and bronchoalveolar lavage fluid were collected. Local testing executed by each hospital included respiratory and blood cultures, urinary antigen and drug susceptibility testing. Local quality control protocols for Minimum Inhibitory Concentration (MIC) breakpoints and Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards were followed according with local regulations and protocols[28, 29].

Study definitions

Patients that required invasive respiratory and/or vasopressor support (IRVS) during initial 24 hours of hospitalization were categorised as IRVS+[30]. *P. aeruginosa*-CAP was defined as any patient with a confirmed diagnosis of CAP in whom *P. aeruginosa* was isolated in any respiratory fluid, including pleural effusion, sputum and/or bronchoalveolar lavage, and/or in the blood. Drug-resistant *P. aeruginosa* was defined when the isolated pathogen was resistant to ≥1 antibiotic and MDR *P. aeruginosa* was defined by resistance to ≥3 of the evaluated antibiotics. Antibiotic resistance to the following anti-pseudomonal antibiotics were evaluated: piperacillin/tazobactam, cefepime, ceftazidime, amikacin, gentamicin, tobramycin, levofloxacin, ciprofloxacin, imipenem, meropenem, doripenem, colistin and polymyxin B.

Prior *P. aeruginosa* infection/colonization was defined as confirmed infection/colonization within the last year before the hospitalization, documented by the patient or available patient records. Chronic obstructive pulmonary disease (COPD) was defined according to FEV1/FVC ratio <0.7 and a compatible clinical history (including smoking history if relevant). Very severe COPD was defined as patients with COPD with evidence of very severe obstruction, determined by FEV1 <30% prior to hospital admission (see online supplement for the complete study dictionary). Site investigators were given these definitions in the study protocol manual and study dictionary prior to starting data collection[26].

Statistical analysis

The prevalence of *P. aeruginosa* as microbiological aetiology of CAP (*i.e., P. aeruginosa*-CAP) was calculated based on the counts of *P. aeruginosa* isolates divided by the study cohort (*i.e.,* CAP patients with microbiological test done), and is expressed as percentages.

Chi-squared tests were used to compare categorical variables, which were expressed as counts and percentages. Continuous variables are presented as medians with interquartile ranges (IQR) and nonparametric Mann-Whitney U test was used to compare them. To assess the relationship between CAP due to *P. aeruginosa* and 67 demographic, clinical, epidemiological, and treatment variables, stepwise logistic regression model was executed. P-value<0.05 was defined as statistically significant. Tableau desktop, professional edition for Mac, was used to generate prevalence maps. All statistical analyses were performed with IBM SPSS, Statistics for Mac, version 22.0, Armonk, NY: IBM Corp.

RESULTS

A total of 3,193 patients were recruited during four study days from 222 hospitals in 54 countries (1,877 [58.8%] males, median [IQR] age: 68 [54-80] years). The demographics, risk factors, comorbidities, severity of illness, and chronic treatments are reported in Table 1. Among the 6 continents, most patients were recruited from Europe (1,941 [60.8%]), followed by North America (484 [15.2%]), Asia (405 [12.7%]), South America (203 [6.4%]), Africa (128 [4.0%]) and Oceania (32 [1.0%]). Microbiological cultures were obtained from blood (2,211 [69.2%]), sputum (1,630 [51.0%]), and bronchoalveolar lavage (311 [9.7%]). At least one pathogen was identified in 1,173 patients (36.7%), Figure e1. Tables 2 and e1 display the prevalence of *P. aeruginosa*-CAP and antibiotic-resistant *P. aeruginosa*-CAP per continents and countries.

Prevalence of *Pseudomonas aeruginosa*-CAP

P. aeruginosa-CAP was identified in 133 (4.2%) patients, representing 11.3 % (133/1,173) of all patients that had a positive culture for bacterial pathogens. The continental

prevalence of *P. aeruginosa*-CAP was, 3.8% in Europe, 4.3% in North America, 5.2% in Asia, 4.9% in South America, 5.5% in Africa and 3.1% in Oceania, respectively (Figure 1). The prevalence of *P. aeruginosa*-CAP in each country, and a comparison between continents and countries is shown in Table 2 and e1. No statistically significant difference was found in the prevalence of *P. aeruginosa*-CAP among different continents. Croatia was the only country with statistically significant higher prevalence of *P. aeruginosa*-CAP (Table e1).

Prevalence of antibiotic-resistant *P. aeruginosa*-CAP

Antibiotic-resistant *P. aeruginosa*-CAP was identified in 64 (2.0%) patients, representing 5.4% (64/1,173) of all patients that had a positive culture. The continental prevalence of antibiotic-resistant *P. aeruginosa*-CAP was 1.6% in Europe, 2.5% in North America, 2.2% in Asia, 3.0% in South America, and 3.9% in Africa, respectively (Figure 1). There were no patients with antibiotic-resistant *P. aeruginosa*-CAP identified in Oceania. No statistically significant difference was found in the prevalence of antibiotic-resistant *P. aeruginosa*-CAP among different continents (Table 2).

Prevalence of multi-drug resistant *P. aeruginosa*-CAP

MDR *P. aeruginosa* was identified in 33 (1.0%) patients, representing 2.8% (33/1,173) of all patients that had a positive culture. The continental prevalence of MDR *P. aeruginosa*-CAP was 0.9% in Europe, 1.2% in North America, 0.5% in Asia, 2% in South America, and 2.3% in Africa, respectively. There were no patients with MDR *P. aeruginosa* identified in Oceania. No statistically significant difference was found in the prevalence of MDR *P. aeruginosa*-CAP

among different continents. No patients were infected with pan-drug resistant *P. aeruginosa (i.e.,* resistant to ≥ 3 groups of antibiotics and colistin) [31].

Risk factors

Patient demographics and risk factors were compared among *P. aeruginosa*-CAP and non-*P. aeruginosa* CAP (Table 1). The risk factors independently associated with *P. aeruginosa*-CAP in the multivariate analysis were prior pseudomonas infection/colonization (OR: 16.10 95% CI: 9.48, 27.35), prior tracheostomy (OR: 6.50, 95% CI: 2.61, 16.19), bronchiectasis (OR: 2.88, 95% CI: 1.65, 5.05), IRVS (OR: 2.33 95% CI: 1.44, 3.78) and very severe COPD (OR: 2.76 95% CI: 1.25, 6.06) (Table 3, Figure e2). Moreover, the risk factors associated with antibiotic-resistant *P.* aeruginosa-CAP were prior pseudomonas infection/colonization (OR: 17.29, 95% CI: 9.95, 33.42), tracheostomy (OR: 5.55, 95% CI: 1.73, 17.80) and IRVS (OR: 3.12, 95% CI: 1.63, 5.97). The risk factors found to be only statistically significant in the bivariate analysis were: COPD, coronary artery disease, inhaled corticosteroid use, indwelling catheter, and lower respiratory tract infection/ER visits/Hospitalisations/antibiotic treatments during the last 12 months (Table e3). Table 3 shows all the risk factors that had a statistically significant association with the different antibiotic resistance patterns (multivariate analyses are presented in Tables e2).

Figure 2 emphasizes the importance of the prevalence of *P. aeruginosa*-CAP, either one of the two main cluster of risk factors were tested among all the patients hospitalised with CAP or after stratifications based on the requirement of IRVS. Among all the patients with CAP, only 11% had risk factors (previously infected/colonization by pseudomonas and had chronic lung

diseases [*i.e.*, tracheostomy, bronchiectasis and/or very severe COPD]). The lack of these two sets of risk factors (*i.e.*, previously infected/colonization by pseudomonas and tracheostomy, bronchiectasis and/or very severe COPD based on FEV1) confirms that only 2-6% of patients might still be affected, independent of the need of IRVS. The sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios of these risk factors are presented in table e3.

DISCUSSION

This multinational point-prevalence study found a low prevalence of *P. aeruginosa* among hospitalised patients with CAP. Only 4.2%, 2.0% and 1.0% of hospitalised patients had CAP due to *P. aeruginosa*, antibiotic-resistant *P. aeruginosa*, or multidrug-resistant (MDR) *P. aeruginosa*, respectively. No patients were identified with pan-drug resistant *P. aeruginosa.* There was no statistically significant difference in prevalence rates between different continents. Croatia was the only country with statistically significant higher *P. aeruginosa*-CAP prevalence. Prior pseudomonas infection/colonization, tracheostomy, bronchiectasis, IRVS, and very severe COPD were independently associated with *P. aeruginosa*-CAP. Moreover, patients admitted with CAP with a past medical history of pseudomonas infection/colonization or chronic lung diseases (*i.e.*, tracheostomy, bronchiectasis and/or very severe COPD) had a higher risk of being infected with antibiotic-resistant *P. aeruginosa.*

Deciding empirical treatment for CAP patients has become challenging due to the emerging prevalence of drug-resistant bacteria, such as *P. aeruginosa*[6]. In a large retrospective study of culture positive patients in the United States, *Kollef et al.* reported a 19% prevalence of *P. aeruginosa* in hospitalised patients with CAP[15]. In a prospective cohort study in Europe,

Chalmers et al. reported a 0.7% prevalence of *P. aeruginosa* among all patients enrolled with CAP and 2.2% among those with positive cultures[32]. Recently, *Jain et al.* found *P. aeruginosa* in 0.4% of patients with CAP in a prospective cohort study in the United States and 1% among the patients with culture positive pneumonia[5]. We found the multinational point prevalence of *P. aeruginosa* as the causative pathogen of CAP was 4.2%, which corresponds to 11.3% of patients with positive culture pneumonia. Variations in the prevalence rates reported by different studies may be explained by differences in study design, especially the denominator used to calculate the prevalence rates[26]. However, these newly reported prevalence rates of *P. aeruginosa*–CAP are lower than prior reports[13-15], suggesting that only a small subgroup of patients may require empiric anti-pseudomonal antibiotic coverage.

The IDSA/ATS CAP guidelines recommend an antipseudomonal β-lactam antibiotic *plus* a fluoroquinolone or aminoglycoside in patients with risk factors for *P. aeruginosa*-CAP [13]. Dual antibiotic coverage has been recommended for HCAP, HAP, or VAP, where multidrug resistant pseudomonas is thought to be an important problem[25]. Our results challenge this approach, by showing that the worldwide prevalence of MDR *P. aeruginosa* in patients with CAP is very low (1% or 3% among culture positive pneumonia patients). Our results are consistent with the evidence from Spain by *Cilloniz et al.* who reported a prevalence of multidrug-resistant *P. aeruginosa* of 1.1% in a prospective cohort study of culture positive CAP patients[33]. Therefore, the recommended use of double antipseudomonal empirical coverage overestimates the actual rates of multidrug-resistant *P. aeruginosa* compared to what it is found in infections acquired in hospital settings, where the resistance rates seems to be higher than in patients coming from the community. However, it is suggested that patients critically ill with septic shock due to pneumonia should receive empiric double antipseudomonal coverage[25].

Several researchers have hypothesised that studies assessing the prevalence of pathogens responsible for CAP are difficult to generalize because these studies are conducted in different environments (*i.e.*, single hospital, regional, country or continent) with specific differences in healthcare delivery, including antibiotic availability and policies for antimicrobial use[19, 21, 23, 34]. In our study, we found that the prevalence of *P.* aeruginosa-CAP was not significantly different between participating centres representing different continents. In contrast, Croatia was the only country that had statistically significant higher *P. aeruginosa*-CAP prevalence. This study is novel by enrolling patients in a large number of centres representing more than 50 countries from all over the world to identify the prevalence of *P. aeruginosa* in CAP patients.

In general, many hospitalised patients receive initial empiric anti-pseudomonal coverage while waiting 48-72 hours for specific pathogen identification and antibiotic susceptibilities[1, 3].This practice has increased the use of broad-spectrum antibiotic agents and promoted antibiotic overuse with the risk of inducing antimicrobial resistance[11, 26]. Additionally, the delay between initial diagnosis and availability of antibiotic susceptibilities could negatively affect outcomes in patients with CAP due to inappropriate antibiotic coverage[13]. Therefore, initiation of empiric anti-pseudomonal coverage should be based on the likelihood that a pathogen circulates in the affected community and the presence of specific risk factors for *P.* aeruginosa-CAP[6, 13, 25]. In this regard, the risk factors listed in the IDSA/ATS pneumonia guidelines for *P. aeruginosa*-CAP are ICU admission, structural lung diseases, such as bronchiectasis, or COPD with multiple exacerbations[13]. Several risk factors have been reported for *P. aeruginosa*-CAP during the last few decades[6], but these previously reported risk factors (*e.g.*, heart failure, tube feeding[35], etc.) were statistically significant in the bivariate analysis of our study, but not in the multivariable analysis. In contrast, we found that prior

pseudomonas infection/colonization, prior tracheostomy, bronchiectasis, IRVS, and very severe COPD (FEV1 ≤30%) were independently associated with *P. aeruginosa*-CAP. These findings support the recommendation to consider these risk factors for empiric anti-pseudomonal antibiotics in patients with severe pulmonary diseases; but not in all patients with structural lung diseases. More importantly, patients with previous *P. aeruginosa* infection/colonization are at highest risk for *P. aeruginosa*-CAP and could benefit from empiric anti-pseudomonal antibiotic coverage, regardless of disease severity. Using these specific risk factors differs from the approach recommended by the IDSA/ATS guidelines and may help prevent overuse of anti-pseudomonal antibiotics in patients with CAP. More importantly antimicrobial stewardship programs that attempt to minimize the use of anti-pseudomonal coverage among patients without the specific pseudomonas risk factors may help prevent adverse events and overuse of unnecessary antimicrobial therapies.

This point prevalence study has some limitations. First, we were not able to determine clinical outcomes due to the study design. However, to determine prevalence rates and identify risk factors, point prevalence studies are ideal because they generate large sample sizes and gather generalizable data. Second, microbiological samples were not collected to do centralised antibiotic susceptibility testing due to the experimental design and feasibility. Nevertheless, laboratories at study sites were encouraged to follow the CLSI or EUCAST guidelines to determine antibiotic resistance[28, 29]. Third, microbiological diagnosis of patients with CAP could be confounded by other pathogens colonizing the respiratory tract; however, in our study we only reported pathogens with representative growth according to current clinical guidelines for CAP. Fourth, infections other than pneumonia are possible, but less likely to present in patients with clinical signs and symptoms and radiological confirmation of CAP. Fifth, quality

assessments were not performed because all data gathered were de-identifiable; however, all local investigators were instructed on how to enrol patients and how to use the data collection platform as described in the study protocol, data dictionary and the instructional video. Sixth, cystic fibrosis (CF) is a frequent cause of chronic *P. aeruginosa* colonization, although the majority of patients with CF might be included in the bronchiectasis group, CF was not directly recorded in our study. Finally, the empiric selection of antibiotics and diagnostic approach was performed according to the health care provider and it was not according to pre-specified criteria.

In conclusion, this multinational, point prevalence study found that the burden of *P. aeruginosa,* antibiotic-resistant *P. aeruginosa,* and multidrug-resistant *P. aeruginosa* as the etiologic pathogen of CAP is low (less than 5%). We identified five risk factors associated with *P. aeruginosa*-CAP: prior pseudomonas infection/colonization, tracheostomy, bronchiectasis, IRVS, and very severe COPD. These risk factors could serve to guide empiric anti-pseudomonal antibiotic treatment. Absence of these specific risk factors suggests that the empiric antibiotic treatment recommended for CAP patients will cover the most likely prevalent bacterial pathogens. Empiric anti-pseudomonal coverage should be reserved for a small subgroup of well-defined patients with a past medical history of pseudomonas infection/colonization and severe lung diseases (*i.e.,* prior tracheostomy, bronchiectasis and/or very severe COPD), regardless of disease severity. Importantly, not all patients with chronic pulmonary diseases would require empiric antipseudomonal coverage for CAP.

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TABLES

Table 1. Characteristics of patients with *Pseudomonas aeruginosa* community-acquired pneumonia (CAP) vs non-*P. aeruginosa*-CAP.

Variables	**CAP** **n=3,193** n (%)	***P. aeruginosa* CAP** **n= 133** n (%)	**No-*P. aeruginosa* CAP** **n= 3,060** n (%)	**p value**
Demographic characteristics, n (%)				
Age, median (IQR) years	68 (54, 80)	64.36 (52.5,78.5)	65.01 (54, 80)	0.748
Male	1,877 (58.8)	79 (59.4)	1,798 (58.8)	0.883
Underweight	150/2,055 (7.3)	9/89 (10.1)	141/1,966 (7.2)	0.297
Obesity	510 (16)	17 (12.8)	493 (16.1)	0.305
Respiratory past medical history, n (%)				
Active lung cancer	92 (2.9)	5 (3.8)	87 (2.8)	0.536
Asthma	234 (7.3)	8 (6)	226 (7.4)	0.553
Bronchiectasis	168 (5.3)	31 (23.3)	137 (4.5)	<0.001
Chronic aspiration	218 (6.8)	15 (11.3)	203 (6.6)	0.038
COPD	834 (26.1)	57 (42.9)	777 (25.4)	<0.001
Very severe COPD ($FEV_1 \leq 30\%$)	90 (2.8)	16 (12.0)	74 (2.4)	<0.001
Current/former smoker	1,114 (34.9)	46 (34.6)	1,068 (34.9)	0.940
Interstitial lung disease	91 (2.8)	6 (4.5)	85 (2.8)	0.240
Obstructive sleep apnoea	123 (3.9)	6 (4.5)	117 (3.8)	0.687
Oxygen therapy at home	208 (6.5)	26 (19.5)	182 (5.9)	<0.001
Lung transplantation	7 (0.2)	1 (0.8)	6 (0.2)	0.180
Tracheostomy	50 (1.6)	15 (11.3)	35 (1.1)	<0.001
Cardiovascular past medical history, n (%)				
Arrhythmia	455 (14.2)	20 (15)	435 (14.2)	0.791
Coronary artery disease	526 (16.5)	33 (24.8)	493 (16.1)	0.008
Heart failure	418 (13.1)	25 (18.8)	393 (12.8)	0.046
Hypertension	1,444 (45.2)	62 (46.6)	1,382 (45.2)	0.742
Stroke	250 (7.8)	13 (5.2)	237 (7.7)	0.394
Chronic medications, n (%)				
Inhaled corticosteroids use	544 (17)	48 (36.1)	496 (16.2)	<0.001

Proton pump inhibitor use	907 (28.4)	58 (6.4)	849 (27.7)	<0.001
Statins use	670 (21)	37 (27.8)	633 (20.7)	0.048
Steroids use	268 (8.4)	21 (15.8)	268 (8.4)	0.002
Chronic interventions, n (%)				
Enteric tube feeding	48 (1.5)	8 (6)	40 (1.3)	<0.001
Haemodialysis	51 (1.6)	4 (3)	47 (1.5)	0.185
Indwelling catheter	67 (2.1)	11 (8.3)	56 (1.8)	<0.001
Immunosuppressive conditions, n (%)				
Active solid tumour	245 (7.7)	11 (4.5)	234 (7.6)	0.791
AIDS	57 (1.8)	1 (0.8)	56 (1.8)	0.358
Aplastic anaemia	13 (0.4)	0 (0)	13 (0.4)	0.451
Asplenia	12 (0.4)	0 (0)	12 (0.4)	0.469
Biological drug use	35 (1.1)	3 (2.3)	32 (1)	0.190
Chemotherapy in the last 3 months	134 (4.2)	4 (3)	130 (4.2)	0.485
Haematological malignancy	150 (4.70)	3 (2.3)	147 (4.8)	0.174
HIV infection	107 (3.4)	3 (2.3)	104 (3.4)	0.473
Immunocompromised patients	623 (19.5)	28 (21.1)	595 (19.4)	0.647
Neutropenia	44 (1.4)	1 (0.8)	43 (1.4)	0.527
Other immunosuppressive condition	125 (3.9)	11 (8.3)	114 (3.7)	0.008
Other chronic medical conditions, n (%)				
Chronic renal failure	349 (10.9)	15 (11.3)	334 (10.9)	0.895
Dementia	333 (10.4)	14 (10.5)	319 (10.4)	0.970
Diabetes mellitus	681 (21.3)	28 (4.1)	653 (21.3)	0.937
Liver disease	129 (4)	4 (3)	125 (4.1)	0.537
Malnutrition	289 (9.1)	20 (15)	269 (8.8)	0.014
Mental illness	220 (0.726)	10 (7.5)	210 (6.9)	0.770
Prosthetic material	100 (3.1)	2 (1.5)	98 (3.2)	0.271
Recurrent skin infections	55 (1.7)	4 (3.0)	51 (1.7)	0.245
Other non-medical conditions, n (%)				
Bedridden	353 (11.1)	28 (21.1)	325 (92.1)	<0.001
Contact sport	5 (0.2)	0 (0)	5 (0.2)	0.641
Healthcare worker	44 (1.4)	4 (3)	40 (1.3)	0.100
Homeless	31 (1)	0 (0)	31 (1)	0.243
Injection of illicit drugs	37 (1.2)	1 (0.8)	36 (1.2)	0.654

Living in crowded conditions	671 (21)	24 (18)	647 (21.1)	0.391
Nursing home resident	258 (8.1)	18 (13.5)	240 (7.8)	0.018
Worker in livestock meat industry	29 (0.9)	0 (0)	29 (0.9)	0.259
Previous infections/colonization, n (%)				
Prior MRSA infection/colonization	81 (2.5)	10 (7.5)	71 (2.3)	<0.001
Prior ESBL-producing bacterial infection	54 (1.7)	5 (3.8)	49 (1.6)	0.059
Prior *Pseudomonas aeruginosa* infection/colonization	96 (3)	44 (33.1)	52 (1.7)	<0.001
Prior healthcare exposure, n (%)				
Antibiotic infusion at home during the last 12 months	140 (4.4)	12 (9)	128 (4.2)	0.008
Emergency room admission in the last 12 months	972 (30.4)	63 (47.4)	909 (29.7)	<0.001
Hospitalizations during the last 12 months	1026 (32.1)	70 (52.6)	956 (31.2)	<0.001
IV antibiotics during the last 12 months	812 (25.4)	64 (48.1)	748 (24.4)	<0.001
LRTI in the last 12months	928 (29.1)	66 (49.6)	862 (28.5)	<0.001
Oral antibiotics during the last 12 months	1219 (38.2)	77 (57.9)	1142 (37.3)	<0.001
Pneumonia severity, n (%)				
Invasive respiratory or vasopressor support (IRVS)	404 (12.7)	34 (25.6)	370 (12.1)	<0.001
ICU admission	599 (18.8)	43 (32.3)	556 (18.2)	<0.001
Non-invasive mechanical ventilation	334 (10.5)	15 (11.3)	319 (10.4)	0.753

CAP; Community-acquired pneumonia, MRSA; Methicillin resistant *Staphylococcus aureus*, COPD; Chronic obstructive pulmonary disease, FEV1; Forced expiratory volume during the first second, CAD; Coronary artery disease, ESBL; extended-spectrum beta-lactamases, LRTI; lower respiratory tract infections

Table 2. Prevalence of antibiotic-resistant *Pseudomonas aeruginosa*-Community-acquired pneumonia (CAP) and antibiotic-resistant *P. aeruginosa*-CAP in participating centres representing different continents.

	CAP patients n=3,193					
	Continent		**Rest of the world**		**OR (95% CI)**	**p value**
	%	**n**	**%**	**n**		
***Pseudomonas aeruginosa*-CAP**						
Global	4.2	133/3193	.	.	.	.
Africa	5.5	7/128	4.1	126/3065	1.34 (0.61, 2.95)	0.57
Asia	5.2	21/405	4.0	112/2788	1.30 (0.81, 2.10)	0.27
Europe	3.8	73/1941	4.8	60/1252	0.77 (0.54, 1.10)	0.15
North America	4.3	21/484	4.1	112/2,709	1.0 (0.65, 1.69)	0.83
Oceania	3.1	1/32	4.2	132/3161	0.74 (0.10, 5.46)	0.76
South America	4.9	10/203	4.1	123/2990	1.20 (0.62, 2.33)	0.57
Antibiotic resistant *Pseudomonas aeruginosa*-CAP						
Global	2	64/3193	.	.	.	.
Africa	3.9	5/128	1.9	59/3065	2.071 (0.817, 5.252)	0.125
Asia	2.2	9/405	2	55/2788	1.129 (0.554, 2.303)	0.738
Europe	1.6	32/1941	2.6	32/1252	0.639 (0.389, 1.049)	0.076
North America	2.5	12/484	1.9	52/2709	0.770 (0.408, 1.453)	0.420
Oceania	0	0/32	2	64/3161	.	0.416
South America	3	6/203	1.9	58/2990	1.540 (0.656, 3.612)	0.321
Multi-drug resistant *Pseudomonas aeruginosa*-CAP (≥3 antibiotics groups)						
Global	1.0	33/3193	.	.	.	.
Africa	2.3	3/128	1	30/3065	2.428 (0.731, 8.063)	0.135
Asia	0.5	2/405	1.1	31/2788	0.441 (0.105, 1.851)	0.250
Europe	0.9	18/1941	1.2	15/1252	0.772 (0.388, 1.537)	0.460
North America	1.2	6/484	1	27/2709	1.247 (0.512, 3.036)	0.626
Oceania	0	0/32	1	33/3161	.	0.561
South America	2	4/203	1	29/2990	2.052 (0.714, 5.895)	0.173
Carbapenem resistant *Pseudomonas aeruginosa*-CAP						
Global	1.1	34/3193	.	.	.	.
Africa	1.6	2/128	1.0	32/3065	1.504 (0.357, 6.348)	0.576
Asia	0.7	3/405	1.1	31/2788	0.664 (0.202, 2.181)	0.496
Europe	0.9	18/1941	1.3	16/1252	0.723 (0.367, 1.423)	0.346
North America	1.7	8/484	1.0	26/2709	1.734 (0.781, 3.854)	0.171
Oceania	0	0/32	1.1	34/3161	.	0.555
South America	1.5	3/203	1.0	31/2990	1.432 (0.434, 4.724)	0.554
Colistin resistant *Pseudomonas aeruginosa*-CAP						
Global	0.4	12/3193	.	.	.	.
Africa	0	0/128	0.4	12/3065	.	0.478
Asia	0.7	3/405	0.3	9/2788	2.304 (0.621, 8.547)	0.199
Europe	0.4	7/1941	0.4	5/1252	0.903 (0.286, 2.850)	0.861
North America	0	0/484	0.4	12/2709	.	0.142
Oceania	3.1	1/32	0.3	11/3161	9.238 (1.157, 73.754)	0.011
South America	0.5	1/203	0.4	11/2990	1.341 (0.172, 10.436)	0.779

Table 3. Multivariate analysis of risk factors for *Pseudomonas* aeruginosa-Community-acquired pneumonia (CAP), antibiotic resistant (AR) *P. aeruginosa*-CAP, multidrug-resistant (MDR) *P. aeruginosa*-CAP, and specific antibiotic resistance patterns.

	Prior *P. aeruginosa*	**IRVS**	**Tracheostomy**	**Bronchiectasis**	**COPD**	**Very severe COPD**
***P. aeruginosa*-CAP, n=133**	16.10 (9.48-27.35)	2.33 (1.44-3.78)	6.50 (2.61-16.19)	2.88 (1.65-5.05)	.	2.76 (1.25-6.06)
AR *P. aeruginosa*-CAP, n=64	17.29 (9.95-33.42)	3.12 (1.63-5.97)	5.55 (1.73-17.80)	.	.	.
Anti-pseudomonal cephalosporins, n=38	17.79 (7.32-43.22)	.	.	.	2.58 (1.07-6.19)	.
Piperacillin/ Tazobactam, n=30	9.72 (3.88-24.36)	4.14 (1.75-9.81)	.	3.33 (1.21-9.19)	.	.
Carbapenems, n=34	10.62 (4.26-26.45)	2.70 (1.14-6.34)	10.77 (3.09-37.52)	.	.	.
Aminoglycosides, n=31	17.32 (7.21-41.61)	3.02 (1.24-7.31)	.	.	.	.
Quinolones, n=50	17.35 (8.28-36.38)	2.84 (1.39-5.78)	4.35 (1.21-15.60)	.	.	.
MDR *P. aeruginosa*- CAP, n=33	12.34 (5.05-30.14)	3.42 (1.47-7.97)	.	.	2.69 (1.10-6.55)	.

IRVS, invasive respiratory or vasopressor support; MDR, multidrug resistant, COPD, chronic obstructive pulmonary disease.

FIGURE LEGENDS

Figure 1. Prevalence of *Pseudomonas aeruginosa*-Community-acquired pneumonia (CAP) and antibiotic-resistant *P. aeruginosa*-CAP by continents (Panel A and Panel B).

Figure 2. Prevalence of *Pseudomonas aeruginosa*-Community-acquired pneumonia (CAP) according to the relevant risk factors that include prior *Pseudomonas aeruginosa* (pPa) infection/colonization, grouped variables of severe lung diseases (LDz^3: tracheostomy, bronchiectasis and very severe COPD [*i.e.*, FEV1 <30%]) and stratified according to the need of invasive respiratory and/or vasopressor support (IRVS).