European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-020-03870-3

ORIGINAL ARTICLE

Bacterial etiology of community-acquired pneumonia in immunocompetent hospitalized patients and appropriateness of empirical treatment recommendations: an international point-prevalence study

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Received: 15 January 2020 / Accepted: 18 March 2020

Abstract

An accurate knowledge of the epidemiology of community-acquired pneumonia (CAP) is key for selecting appropriate antimicrobial treatments. Very few etiological studies assessed the appropriateness of empiric guideline recommendations at a multinational level. This study aims at the following: (i) describing the bacterial etiologic distribution of CAP and (ii) assessing the appropriateness of the empirical treatment recommendations by clinical practice guidelines (CPGs) for CAP in light of the bacterial pathogens diagnosed as causative agents of CAP. Secondary analysis of the GLIMP, a point-prevalence international study which enrolled adults hospitalized with CAP in 2015. The analysis was limited to immunocompetent patients tested for bacterial CAP agents within 24 h of admission. The CAP CPGs evaluated included the following: the 2007 and 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA), the European Respiratory Society (ERS), and selected country-specific CPGs. Among 2564 patients enrolled, 35.3% had an identifiable pathogen. *Streptococcus pneumoniae* (8.2%) was the most frequently identified pathogen, followed by *Pseudomonas aeruginosa* (4.1%) and *Klebsiella pneumoniae* (3.4%).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-020-03870-3) contains supplementary material, which is available to authorized users.

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Published online: 03 April 2020

CPGs appropriately recommend covering more than 90% of all the potential pathogens causing CAP, with the exception of patients enrolled from Germany, Pakistan, and Croatia. The 2019 ATS/IDSA CPGs appropriately recommend covering 93.6% of the cases compared with 90.3% of the ERS CPGs ($p < 0.01$). *S. pneumoniae* remains the most common pathogen in patients hospitalized with CAP. Multinational CPG recommendations for patients with CAP seem to appropriately cover the most common pathogens and should be strongly encouraged for the management of CAP patients.

Keywords Community-acquired pneumonia · Antimicrobial treatment · Guidelines · *Streptococcus pneumoniae*

Introduction

Community-acquired pneumonia (CAP) is a clinical and public health issue worldwide [1]. The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 estimated that lower respiratory infections affected approximately 471.8 million people and caused 2.6 million deaths in 2017 [2].

The selection of an appropriate empirical antimicrobial therapy is crucial for a successful outcome [3]. National and international CAP guidelines provide specific recommendations based on site of care (intensive vs. non-intensive care unit) and pathogen-related risk factors, including those for *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and influenza viruses. However, it is unclear if those recommendations provide adequate antimicrobial coverage.

The aim of the present study was to describe the bacterial etiology of CAP in adults hospitalized in different settings, as well as to assess the appropriateness of the empirical treatment recommendations issued by clinical practice guidelines (CPGs) in relation to the bacteria detected in CAP patients.

Materials and methods

Study design, setting, and participants

We performed a secondary analysis of the Global Initiative for MRSA Pneumonia (GLIMP) study, an international, multicenter, point-prevalence study [4]. GLIMP was conducted across 222 hospitals in 54 countries over 4 days, with 1 day per month randomly selected during March, April, May, and June 2015. All consecutive adults (≥ 18 years old) hospitalized for CAP at the participating centers were enrolled in the study. The following patients were excluded from the analysis: (i) immunosuppressed patients; (ii) patients not tested for bacterial agents of CAP within 24 h of admission; (iii) patients with a diagnosis of hospital-acquired or ventilator-associated pneumonia. Bacterial testing within 24 h of admission included the following: blood and respiratory cultures (e.g., sputum, pleural fluid, endotracheal aspirate, and bronchoalveolar lavage), pneumococcus urinary antigen, *Legionella* urinary antigen, serology for atypical pathogens, and lung biopsy. The GLIMP coordinating center was located at the University of Texas Health, San Antonio, in San Antonio, TX, USA. The coordinating center received expedited project approval by the institutional review board (number HSC20150184E). The review board waived the need for receipt of informed consent due to the nature of the study. A detailed description of the GLIMP organization and methodology was previously published [4].

Study outcomes

The primary outcome of this study was the assessment of the appropriateness of the empirical antimicrobial treatment recommendations for CAP issued by CPGs, with particular emphasis on the appropriateness of country-specific CPG recommendations (see definition below).

Study definitions

CAP was defined by the presence of pulmonary infiltrates on thoracic imaging (chest radiograph, computerized tomography, or ultrasound) during the first 48 h of hospitalization and ≥ 1 of the following criteria: new or increased cough with or without sputum production or with purulent respiratory secretions; fever (documented rectal or oral temperature ≥ 37.8 °C) or hypothermia (documented rectal or oral temperature < 36 °C); and evidence of systemic inflammation, such as abnormal white blood cell count (leukocytosis [> 10,000 cells/μL], leukopenia [< 4000 cells/μL], or bandemia [> 10%]) and increased C-reactive protein or procalcitonin concentrations above the local upper limit of normal. MRSA was defined according to the Clinical and Laboratory Standards Institute (CLSI) guidelines based on an oxacillin minimum inhibitory concentration ≥ 4 μg/mL. Immunosuppression was defined by the presence of at least one among the following conditions: (i) AIDS, defined either as human immunodeficiency virus infection with CD4+ lymphocyte count < 200/μL or by the occurrence of an AIDS-defining condition; (ii) aplastic anemia; (iii) asplenia; (iv) hematological cancer (e.g., lymphoma, acute or chronic leukemia, or multiple myeloma); (v) chemotherapy during the last 3 months; (vi) neutropenia (neutrophil count < 500/μL); (vii) administration of biological drugs (including trastuzumab and therapies for autoimmune diseases, e.g., anti-tumor necrosis

factor α, prescribed for ≥ 6 months before hospital admission); (viii) lung transplantation; (ix) chronic steroid use (> 10 mg/day of prednisone or equivalent prescribed for ≥ 3 months before hospital admission); (x) lung cancer either with neutropenia or treated with chemotherapy; (xi) other solid tumors either with neutropenia or treated with chemotherapy; (xii) other immunodeficiencies (including congenital/genetic immunodepression and immunosuppressive therapy administered for hematological cancers/solid organ transplantations other than lungs) [5].

The following CAP CPGs were evaluated: the 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines [6], the 2019 ATS/IDSA guidelines [7], the European Respiratory Society (ERS) guidelines [8], the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) guidelines [9], the Latin American Association of the Thorax (ALAT) guidelines [10], the Indian Chest Society and National College of Chest Physicians (ICS/NCCP) guidelines [11], the British Thoracic Society (BTS) guidelines [12], the guidelines issued by the German Respiratory Society, the Paul-Ehrlich-Society for Chemotherapy, the German Society for Infectious Diseases, the Competence Network CAPNETZ, the Austrian Respiratory Society, the Austrian Society for Infectious and Tropical Diseases and the Swiss Respiratory Society [13], the Pakistan Chest Society guidelines [14], the Portuguese Respiratory Society guidelines [15], and the Croatian guidelines [16] (Table 1).

The appropriateness of the recommendations issued by the CPGs was defined computing the concordance between the detected pathogens and the antibiotic(s) recommended by the CPGs. The therapy recommended by the CPGs relies on the clinical setting and the presence of risk factors for MRSA or *P. aeruginosa*. Treatment was deemed appropriate if effective against the diagnosed pathogen (Table 1).

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR). Categorical variables are summarized with absolute frequencies and percentages. Comparisons between groups were made with the chi-square or Fisher exact test, as appropriate. A two-sided p value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS Statistics, version 24, software (IBM, Armonk, NY, US).

Results

Among the 2564 patients (57.9% males; age, median, and IQR: 68; 53–80 years old) included in the analysis, 494 (19.3%) were admitted in an ICU. The following bacterial tests were performed in the study population: blood cultures (2110; 82.3%), sputum cultures (1886; 73.6%), other respiratory cultures (552; 21.5%), pneumococcal urinary antigen (894; 34.9%), *Legionella* urinary antigen (899; 35.1%), *Mycoplasma pneumoniae* serology (220; 8.6%), *Chlamydia pneumoniae* serology (202; 7.9%), *Legionella pneumophila* serology (175; 6.8%), and lung biopsy (7; 0.3%). At least one bacterial pathogen was identified as the causative agent of CAP in 906 (35.3%) patients. *Streptococcus pneumoniae* was the most prevalent pathogen, accounting for 211 (8.2%) cases. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the second and the third most prevalent pathogens, accounting for 105 (4.1%) and 87 (3.4%) cases, respectively. MRSA was responsible for 3.0% of CAP episodes globally, ranging from 1.2% of the cases in Portugal to 4.8% of the cases in USA and Argentina. After the stratification of non-ICU vs. ICU patients, *S. pneumoniae*, *P. aeruginosa*, and *K. pneumoniae* continued to be the most prevalent etiologies (Table 2). A significantly higher proportion of CAP cases was caused by MRSA in the ICU in comparison with those managed in the non-ICU setting (6.9% vs. 2.1%, p value < 0.01). Similarly, *P. aeruginosa* played a more relevant role in the ICU if compared with cases in the non-ICU setting (6.7% vs. 3.5%; p value < 0.01).

Guideline recommendations were appropriate to cover potential pathogens in approximately 90% of the cases, both in ICU and in non-ICU patients, with the only exception of Germany, Pakistan, and Croatia, where a slightly inferior bacterial coverage was reported (Table 3). When the performance of country-specific CPGs was analyzed, a similar or slightly inferior bacterial coverage compared with the 2007 ATS/IDSA, 2019 ATS/IDSA, and the ERS CPG recommendations was noted. Pakistan was the only country where nation-specific CPGs provided in the overall population and in the ICU population a higher empirical treatment coverage than the ATS/IDSA and ERS CPGs (Table 3).

The 2019 ATS/IDSA treatment recommendations appropriately covered a wider proportion of CAP cases than the ATS/IDSA 2007 and the ERS recommendations in the overall study population (93.6% vs. 92.2%, p value 0.04; 93.6% vs. 90.3%, p value < 0.01). Similar results were achieved when the non-ICU population (94.1% vs. 92.5%, p value 0.04; 94.1% vs. 90.5%, p value < 0.01) and the ICU population were evaluated (91.9% vs. 90.9%, p value 0.57; 91.9% vs. 89.5%, p value 0.19) (Table 3).

While MRSA CAP was diagnosed in 34/494 (6.9%) ICU cases, an anti MRSA empirical treatment was recommended by the 2007 and 2019 ATS/IDSA recommendations in 97/494 (19.6%) and 124/494 (25.1%) CAP ICU cases, respectively. Similarly, while *P. aeruginosa* CAP was diagnosed in 33/494 (6.7%) ICU patients, an anti *P. aeruginosa* empirical treatment was suggested by the 2007 ATS/IDSA, the 2019 ATS/IDSA, and the ERS recommendations in 163/494 (32.9%), in 118/494 (23.9%), and in 180/494 (36.4%) CAP ICU cases, respectively (Figs. 1 and 2).

Table 1 Main empirical treatment recommendations by national/international clinical practice guidelines for hospitalized CAP whether in the intensive care unit (ICU) or in non-ICU setting

CAP clinical practice guidelines	Non-ICU CAP empirical treatment recommendations	ICU CAP empirical treatment recommendations
ATS/IDSA guidelines 2007 [6]	FQ or β-lactam plus macrolide.	β-lactam plus either azithromycin or a respiratory FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ or antipseudomonal β-lactam plus aminoglycoside and azithromycin or antipseudomonal β-lactam plus aminoglycoside and FQ. If risk factors for community-acquired *Staphylococcus aureus*, add vancomycin or linezolid.
ATS/IDSA guidelines 2019 [7]	FQ or β-lactam plus macrolide. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ or a macrolide. If risk factors for community-acquired *Staphylococcus aureus*, add vancomycin or linezolid.	β-lactam plus either a macrolide or a respiratory FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ or a macrolide. If risk factors for community-acquired *Staphylococcus aureus*, add vancomycin or linezolid.
ERS guidelines [8]	β-lactam monotherapy or FQ or β-lactam plus macrolide.	Non-antipseudomonal cephalosporin III plus either macrolide or FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus either FQ or aminoglycoside and macrolide.
SEPAR guidelines [9]	FQ or β-lactam plus macrolide.	β-lactam plus either azithromycin or FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ. If risk factors for community-acquired methicillin-resistant *Staphylococcus aureus*, levofloxacin plus either vancomycin or linezolid.
ALAT guidelines [10]	FQ or β-lactam plus macrolide.	Non-antipseudomonal β-lactam plus FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ.
ICS/NCCP guidelines [11]	β-lactam plus macrolide. FQ only if β-lactam allergy and no risk for tuberculosis.	Non-antipseudomonal β-lactam plus macrolide. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus either macrolide or FQ. FQ can be used only if no risk factors for tuberculosis.
BTS guidelines [12]	β-lactam monotherapy or macrolide monotherapy, if low severity CAP. If moderate severity CAP, FQ or β-lactam plus macrolide.	β-lactam plus macrolide.
Germany guidelines [13]	FQ or β-lactam plus macrolide.	β-lactam plus macrolide. If influenza season, add oseltamivir. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus either FQ or aminoglycoside.
Pakistan Chest Society guidelines [14]	Macrolide monotherapy or FQ or β-lactam plus macrolide. If *Pseudomonas aeruginosa* risk factors, β-lactam plus either aminoglycoside or FQ or aminoglycoside and FQ.	β-lactam plus either FQ or macrolide. If *Pseudomonas aeruginosa* risk factors, β-lactam plus either aminoglycoside or FQ or aminoglycoside and FQ. If MRSA risk factors, add vancomycin or linezolid.
Portuguese Respiratory Society guidelines [15]	FQ or β-lactam plus macrolide or β-lactam plus doxycycline.	β-lactam plus either FQ or macrolide. If *Pseudomonas aeruginosa* risk factors, either β-lactam plus FQ or β-lactam plus aminoglycoside plus FQ or macrolide.
Croatian guidelines [16]	β-lactam monotherapy or β-lactam plus macrolide.	Either β-lactam plus macrolide or FQ. If *Pseudomonas aeruginosa* risk factors, antipseudomonal β-lactam plus FQ.

ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; *ERS*, European Respiratory Society; *SEPAR*, Spanish Society of Pneumology and Thoracic Surgery; *ALAT*, Latin American Association of the Thorax; *ICS/NCCP*, Indian Chest Society and National College of Chest Physicians; *BTS*, British Thoracic Society; *FQ*, fluoroquinolone; *β-lactam*, beta-lactam; *CAP*, community-acquired pneumonia

Discussion

The present study showed that bacterial pathogens were detected in 35.3% of CAP patients tested for bacteria, with *S. pneumoniae* identified in 8.2% of the cases. National and international CPGs recommended an appropriate empirical treatment in the vast majority (> 90%) of the patients hospitalized with CAP, with national CPGs providing a similar or slightly inferior bacterial coverage compared with the ATS/IDSA and ERS CPGs. The 2019 ATS/IDSA tended to perform better than the 2007 ATS/IDSA and the ERS CPGs, both in the non-ICU and in the ICU setting. In general, CPGs suggested anti MRSA and anti *P. aeruginosa* treatments more frequently than needed.

Table 2 Most frequently identified bacterial pathogens among immunocompetent patients diagnosed with CAP by country and by ICU admission status

Overall study population tested for bacteria ($n = 2564$)							
	1	2	3	4	5	Polymicrobial infections	Negative tests
Spain ($n = 481$)	*S. pneumoniae* 86 (17.9%)	*P. aeruginosa* 14 (2.9%)	MSSA 13 (2.7%)	*K. pneumoniae* 10 (2.1%)	*Legionella* 10 (2.1%)	29 (6.0%)	292 (60.7%)
USA ($n = 331$)	*S. pneumoniae* 16 (4.8%)	MRSA 16 (4.8%)	*P. aeruginosa* 15 (4.5%)	MSSA 9 (2.7%)	*K. pneumoniae* 6 (1.8%)	19 (5.7%)	237 (71.6%)
Italy ($n = 303$)	*S. pneumoniae* 21 (6.9%)	*P. aeruginosa* 11 (3.6%)	*M. pneumoniae* 10 (3.3%)	MRSA 10 (3.3%)	*K. pneumoniae* 8 (2.6%)	20 (6.6%)	184 (60.7%)
India ($n = 139$)	*K. pneumonia* 10 (7.2%)	*P. aeruginosa* 5 (3.6%)	*M. tuberculosis* 4 (2.9%)	*Acinetobacter* spp. 4 (2.9%)	*S. pneumoniae* 3 (2.2%)	4 (2.9%)	90 (64.7%)
Argentina ($n = 126$)	*S. pneumoniae* 8 (6.3%)	MRSA 6 (4.8)	MSSA 5 (4.0%)	*M. pneumoniae* 4 (3.2%)	*P. aeruginosa* 3 (2.4%)	2 (1.6%)	95 (75.4%)
UK ($n = 105$)	*S. pneumoniae* 6 (5.7%)	MRSA 4 (3.8%)	MSSA 4 (3.8%)	*H. influenzae* 3 (2.9%)	*P. aeruginosa* 3 (2.9%)	1 (1.0%)	74 (70.5%)
Pakistan ($n = 101$)	*P. aeruginosa* 8 (7.9%)	*H. influenzae* 5 (5.0%)	*S. pneumoniae* 4 (4.0%)	MRSA 4 (4.0%)	*Acinetobacter* spp. 3 (3.0%)	6 (5.9%)	75 (74.3%)
Germany ($n = 88$)	*S. pneumoniae* 6 (6.8%)	*E. coli* 6 (6.8%)	*P. aeruginosa* 5 (5.7%)	*K. pneumoniae* 4 (4.5%)	MRSA 3 (3.4%)	7 (8.0%)	51 (58.0%)
Portugal ($n = 81$)	*S. pneumoniae* 9 (11.1%)	MSSA 4 (4.9%)	*H. influenzae* 3 (3.7%)	MRSA 1 (1.2%)	*P. aeruginosa* 1 (1.2%)	1 (1.2%)	62 (76.5%)
Croatia ($n = 78$)	*P. aeruginosa* 10 (12.8%)	*K. pneumoniae* 8 (10.3%)	*Streptococcus* spp. 6 (7.7%)	*S. pneumoniae* 5 (6.4%)	MRSA 3 (3.8%)	3 (3.8%)	41 (52.6%)
Other countries ($n = 731$)	*S. pneumoniae* 47 (6.4%)	*K. pneumoniae* 36 (4.9%)	*P. aeruginosa* 30 (4.1%)	*H. influenzae* 27 (3.7%)	MSSA 24 (3.3%)	52 (7.1%)	457 (62.5%)
Total ($n = 2564$)	*S. pneumoniae* 211 (8.2%)	*P. aeruginosa* 105 (4.1%)	*K. pneumoniae* 87 (3.4%)	MRSA 78 (3.0%)	MSSA 70 (2.7%)	144 (5.6%)	1658 (64.7)
Non-ICU study population tested for bacteria ($n = 2070$)							
	1	2	3	4	5	Polymicrobial infections	Negative tests
Spain ($n = 424$)	*S. pneumoniae* 71 (16.7%)	*P. aeruginosa* 12 (2.8%)	*H. influenzae* 9 (2.1%)	*K. pneumoniae* 7 (1.7%)	MRSA 6 (1.4%)	17 (4.0%)	279 (65.8%)
USA ($n = 225$)	*S. pneumoniae* 10 (4.4%)	*P. aeruginosa* 9 (4.0%)	MRSA 6 (2.7%)	*Streptococcus* spp. 4 (1.8%)	*M. pneumoniae* 2 (0.9%)	6 (2.7%)	177 (78.7%)
Italy ($n = 275$)	*S. pneumoniae* 15 (5.5%)	MRSA 9 (3.3%)	*M. pneumoniae* 9 (3.3%)	*E. coli* 8 (2.9%)	*P. aeruginosa* 7 (2.5%)	15 (5.5%)	179 (75.1%)
India ($n = 78$)	*K. pneumoniae* 3 (3.8%)	*M. tuberculosis* 3 (3.8%)	*P. aeruginosa* 2 (2.6%)	*H. influenzae* 2 (2.6%)	*M. catarrhalis* 2 (2.6%)	1 (1.3%)	56 (71.8%)
Argentina ($n = 104$)	*S. pneumoniae* 7 (6.7%)	MRSA 4 (3.8%)	MSSA 4 (3.8%)	*M. pneumoniae* 3 (2.9%)	*P. aeruginosa* 1 (1.0%)	0 (0.0%)	81 (77.9%)
UK ($n = 96$)	*S. pneumoniae* 5 (5.2%)	MRSA 4 (4.2%)	*H. influenzae* 3 (3.1%)	*P. aeruginosa* 3 (3.1%)	*E. coli* 2 (2.1%)	0 (0.0%)	69 (71.9%)
Pakistan ($n = 87$)	*P. aeruginosa* 8 (9.2%)	*S. pneumoniae* 4 (4.6%)	*H. influenzae* 4 (4.6%)	MRSA 2 (2.3%)	*K. pneumoniae* 2 (2.3%)	5 (5.7%)	67 (77.0%)
Germany ($n = 55$)	*S. pneumoniae* 3 (5.5%)	*P. aeruginosa* 3 (5.5%)	*E. coli* 3 (5.5%)	MRSA 2 (3.6%)	MSSA 2 (3.6%)	3 (5.5%)	35 (63.6%)
Portugal ($n = 73$)	*S. pneumoniae* 9 (12.3%)	MSSA 4 (5.5%)	*H. influenzae* 3 (4.1%)	*P. aeruginosa* 1 (1.4%)	MRSA 1 (1.4%)	1 (1.4%)	54 (74.0%)
Croatia ($n = 73$)	*P. aeruginosa* 9 (12.3%)	*K. pneumoniae* 8 (11.0%)	*S. pneumoniae* 5 (6.8%)	*Streptococcus* spp. 5 (6.8%)	MRSA 3 (4.1%)	3 (4.1%)	39 (53.4%)
Other countries ($n = 580$)	*S. pneumoniae* 39 (6.7%)	*H. influenzae* 20 (3.4%)	*K. pneumoniae* 20 (3.4%)	MSSA 19 (3.3%)	*P. aeruginosa* 17 (2.9%)	33 (5.7%)	394 (67.9%)
Total ($n = 2070$)	*S. pneumoniae* 169 (8.2%)	*P. aeruginosa* 72 (3.5%)	*K. pneumoniae* 51 (2.5%)	MSSA 48 (2.3%)	*H. influenzae* 47 (2.3%)	84 (4.1%)	1430 (69.1%)
ICU study population tested for bacteria ($n = 494$)							
	1	2	3	4	5	Polymicrobial infections	Negative tests
Spain ($n = 57$)	*S. pneumoniae* 15 (26.3%)	MSSA 7 (12.3%)	*Legionella* 4 (7.0%)	*K. pneumoniae* 3 (5.3%)	*P. aeruginosa* 2 (3.5%)	12 (21.1%)	13 (22.8%)
USA ($n = 106$)	MRSA 10 (9.4%)	MSSA 7 (6.6%)	*P. aeruginosa* 6 (5.7%)	*S. pneumoniae* 6 (5.7%)	*K. pneumoniae* 4 (3.8%)	13 (12.3%)	60 (56.6%)
Italy ($n = 28$)	*S. pneumoniae* 6 (21.4%)	*P. aeruginosa* 4 (14.3%)	*Acinetobacter* spp. 3 (10.7%)	*H. influenzae* 2 (7.1%)	*K. pneumoniae* 2 (7.1%)	5 (17.9%)	5 (17.9%)
India ($n = 61$)	*K. pneumoniae* 7 (11.5%)	*Acinetobacter* spp. 4 (6.6%)	*P. aeruginosa* 3 (4.9%)	*S. pneumoniae* 2 (3.3%)	MRSA 1 (1.6%)	3 (4.9%)	34 (55.7%)
Argentina ($n = 22$)	*P. aeruginosa* 2 (9.1%)	MRSA 2 (9.1%)	*E. coli* 2 (9.1%)	*S. pneumoniae* 1 (4.5%)	*M. pneumoniae* 1 (4.5%)	2 (9.1%)	14 (63.6%)
UK ($n = 9$)	MSSA 2 (22.2%)	*S. pneumoniae* 1 (11.1%)	*S. pyogenes* 1 (11.1%)	Anaerobes 1 (11.1%)	–	1 (11.1%)	5 (55.6%)
Pakistan ($n = 14$)	MRSA 2 (14.3%)	*Acinetobacter* spp. 2 (14.3%)	*E. coli* 1 (7.1%)	*H. influenzae* 1 (7.1%)	*M. tuberculosis* 1 (7.1%)	1 (7.1%)	8 (57.1%)
Germany ($n = 33$)	*S. pneumoniae* 3 (9.1%)	*K. pneumoniae* 3 (9.1%)	*E. coli* 3 (9.1%)	*P. aeruginosa* 2 (6.1%)	*Legionella* 2 (6.1%)	4 (12.1%)	16 (48.5%)
Portugal ($n = 8$)	--	--	--	--	--	0 (0.0%)	8 (100.0%)
Croatia (n = 5)	*Enterobacter* spp. 1 (20.0%)	*P. aeruginosa* 1 (20.0%)	*Streptococcus* spp. 1 (20.0%)	--	--	0 (0.0%)	2 (40.0%)
Other countries ($n = 151$)	*K. pneumonia* 16 (10.6%)	MRSA 15 (9.9%)	*P. aeruginosa* 13 (8.6%)	*S. pneumoniae* 8 (5.3%)	*Acinetobacter* spp. 8 (5.3%)	19 (12.6%)	63 (41.7%)
Total ($n = 494$)	*S. pneumoniae* 42 (8.5%)	*K. pneumoniae* 36 (7.3%)	MRSA 34 (6.9%)	*P. aeruginosa* 33 (6.7%)	MSSA 22 (4.5%)	60 (12.1%)	228 (46.2%)

S. pneumoniae, *Streptococcus pneumoniae; P. aeruginosa*, *Pseudomonas aeruginosa*; MSSA, methicillin-sensitive *Staphylococcus aureus*; *K. pneumoniae*, *Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *M. tuberculosis*, *Mycobacterium tuberculosis*; *H. influenzae*, *Haemophilus influenzae*; *E. coli*, *Escherichia coli*; *M. catarrhalis*, *Moraxella catarrhalis*; *S. pyogenes*, *Streptococcus pyogenes*

Table 3 Appropriateness of guideline empirical treatment recommendations for CAP among immunocompetent patients by country and by ICU admission status

	Overall study population tested for bacteria ($n = 2564$)					Non-ICU study population tested for bacteria ($n = 2070$)	
	No. of cases	Country-specific guidelines	ATS/ID SA 2007 guidelines	ATS/ID SA 2019 guidelines	ERS guidelines	No. of cases	Country-specific guidelines
Spain	481	453 (94.2%)	455 (94.6%)	465 (96.7%)	448 (93.1%)	424	400 (94.3%)
USA	331	315 (95.2%)	306 (92.4%)	315 (95.2%)	299 (90.3%)	225	216 (91.6%)
Italy	303	--	273 (90.1%)	274 (90.4%)	259 (85.5%)	275	--
India	139	130 (93.5%)	131 (94.2%)	130 (93.5%)	129 (92.8%)	78	72 (92.3%)
Argentina	126	116 (92.1%)	116 (92.1%)	117 (92.9%)	113 (89.7%)	104	98 (94.2%)
UK	105	94 (89.5%)	98 (93.3%)	100 (95.2%)	98 (93.3%)	96	85 (88.5%)
Pakistan	101	89 (88.1%)	87 (86.1%)	88 (87.1%)	87 (86.1%)	87	76 (87.4%)
Germany	88	77 (87.5%)	78 (88.6%)	78 (88.6%)	77 (87.5%)	55	46 (83.6%)
Portugal	81	79 (97.5%)	79 (97.5%)	79 (97.5%)	79 (97.5%)	73	71 (97.3%)
Croatia	78	64 (82.1%)	65 (83.3%)	69 (88.5%)	64 (82.1%)	73	59 (80.8%)
Other countries	731	--	675 (92.3%)	686 (93.8%)	663 (90.7%)	580	--
Total	2564	--	2363 (92.2%)	2401 (93.6%)	2316 (90.3%)	2070	--

	Non-ICU study population tested for bacteria ($n = 2070$)			ICU study population tested for bacteria ($n = 494$)				
	ATS/ID SA 2007 guidelines	ATS/ID SA 2019 guidelines	ERS guidelines	No. of cases	Country-specific guidelines	ATS/ID SA 2007 guidelines	ATS/ID SA 2019 guidelines	ERS guidelines
Spain	400 (94.3%)	410 (96.7%)	394 (92.9%)	57	53 (92.9%)	55 (96.5%)	55 (96.5%)	54 (94.7%)
USA	208 (92.4%)	216 (96.0%)	206 (91.6%)	106	99 (93.4%)	98 (92.5%)	99 (93.4%)	26 (92.9%)
Italy	249 (90.5%)	249 (90.5%)	233 (84.7%)	28	--	24 (85.7%)	25 (89.3%)	26 (92.9%)
India	72 (92.3%)	73 (93.6%)	72 (92.3%)	61	58 (95.1%)	59 (96.7%)	57 (93.4%)	57 (93.4%)
Argentina	98 (94.2%)	99 (95.2%)	95 (91.3%)	22	18 (81.8%)	18 (81.8%)	18 (81.8%)	18 (81.8%)
UK	89 (92.7%)	91 (94.8%)	89 (92.7%)	9	9 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)
Pakistan	75 (86.2%)	76 (87.4%)	75 (86.2%)	14	13 (92.9%)	12 (85.7%)	12 (85.7%)	12 (85.7%)
Germany	46 (83.6%)	48 (87.3%)	46 (83.6%)	33	31 (93.9%)	32 (96.9%)	30 (90.9%)	31 (93.9%)
Portugal	71 (97.3%)	71 (97.3%)	71 (97.3%)	8	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)
Croatia	60 (82.2%)	64 (87.7%)	59 (80.8%)	5	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)
Other countries	546 (94.1%)	550 (94.8%)	534 (92.1%)	151	--	129 (85.4%)	136 (90.1%)	129 (85.4%)
Total	1914 (92.5%)	1947 (94.1%)	1874 (90.5%)	494	--	449 (90.9%)	454 (91.9%)	442 (89.5%)

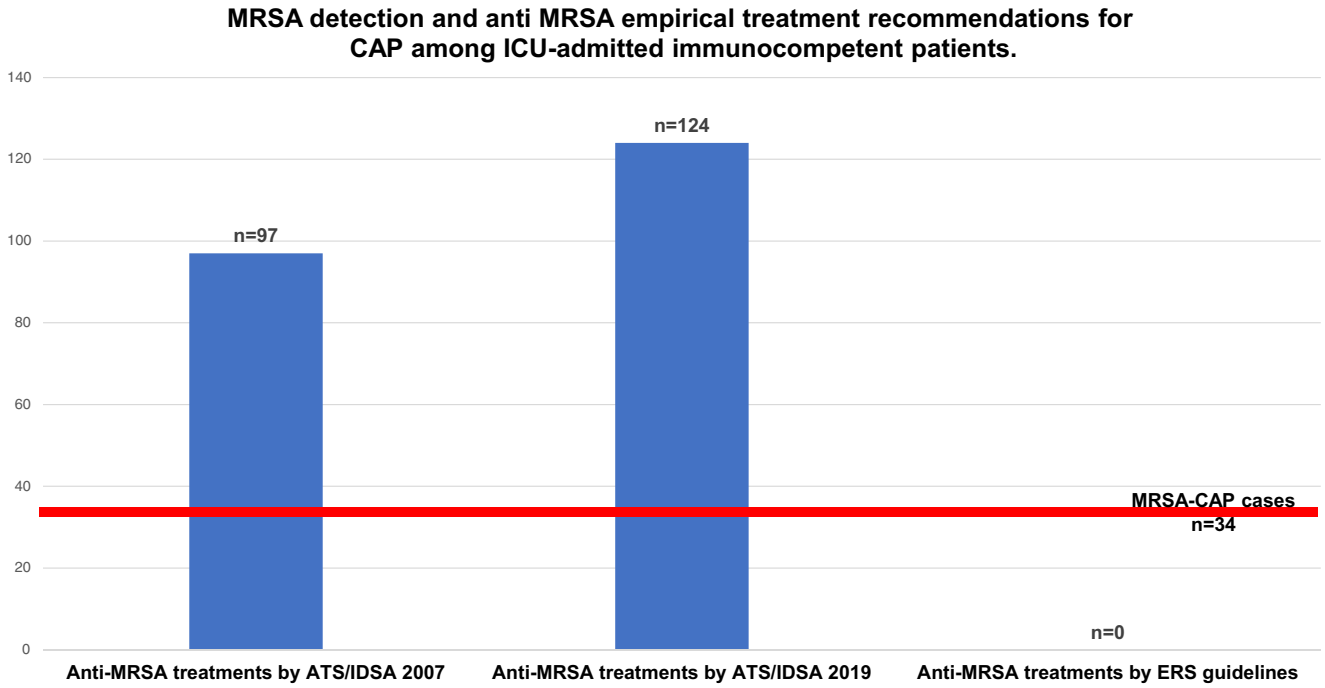

Fig. 1 MRSA detection and anti MRSA empirical treatment recommendations for CAP among ICU-admitted immunocompetent patients

The diagnostic yield of bacterial testing that we observed in hospitalized CAP (35.3% of the patients) is consistent with what is reported in other large studies, such as the EPIC study [17–20]. The EPIC study, which was a prospective, multicenter, population-based, active surveillance study conducted by the USA Centers for Disease Control and Prevention (CDC) between 2010 and 2012, enrolled 2259 adult patients hospitalized with CAP in the USA. The authors found a pathogen in only 37.7% of the cases [17–20]. On the contrary, in the Medicare administrative database, a pathogen was identified in 7.6% of the CAP cases [21]. When compared with previous studies, the novelty of the GLIMP approach lies in its point-prevalence design, international nature (222 centers in 54 countries in 6 continents), and the analysis of real-life

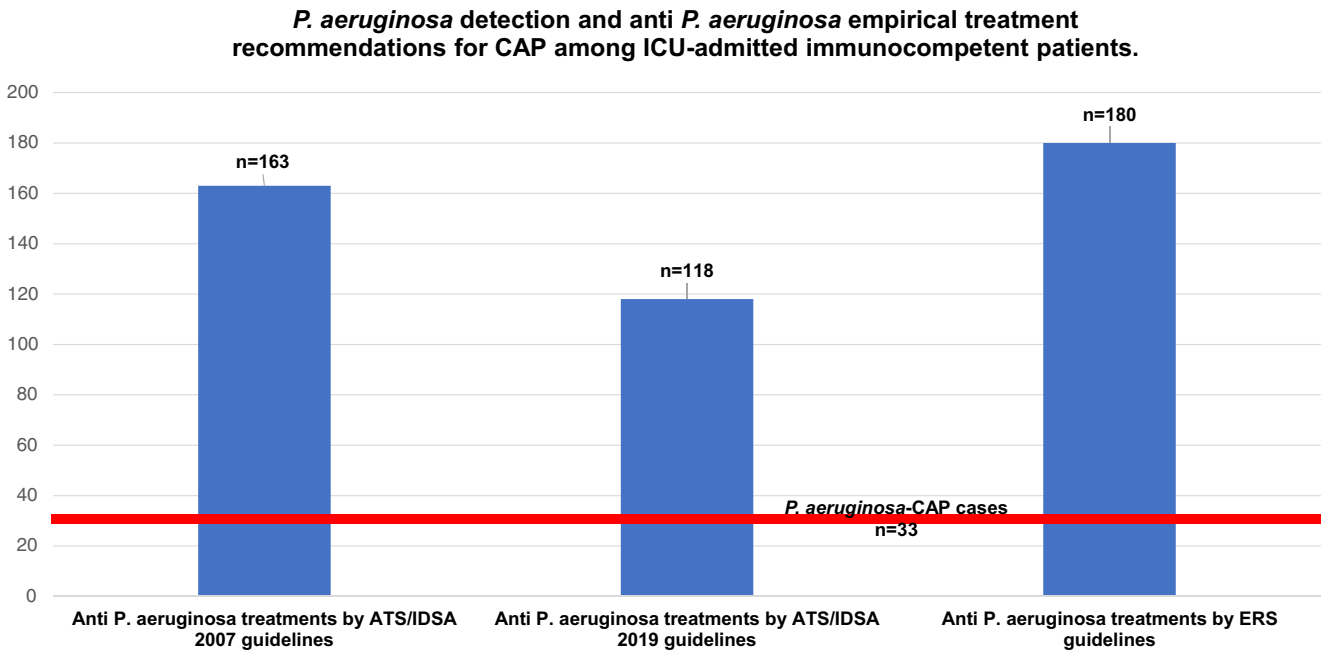

Fig. 2 *Pseudomonas aeruginosa* detection and anti *P. aeruginosa* empirical treatment recommendations for CAP among ICU-admitted immunocompetent patients

data. Furthermore, the GLIMP approach differs from the Medicare database for its primary rather than administrative data collection. Several other factors may also account for the different results reported by the GLIMP study and the Medicare database. The review of the Medicare database was published in 2011 but was performed in 2009, 6 years before the GLIMP study was performed: the microbiological progress may partially justify this difference. Second, the Medicare review findings may reflect the implementation of the 2007 ATS/IDSA CAP CPGs, which discouraged any microbiological studies in most cases, and the issue of cost in the USA health care system [22]. Third, GLIMP data were derived from clinical sites, which are mostly tertiary care centers, whereas Medicare data might have included both tertiary and non-tertiary health care centers. Despite the variability of study-related characteristics, the persistently low pathogen detection yield highlights the suboptimal understanding of the dynamics of CAP etiology and the weak evidence supporting recommendations for empirical antimicrobial treatment. Therefore, studies implementing innovative pathogen-discovery approaches are urgently needed [22].

Our findings confirmed a substantial variability of CAP etiology depending on the geographic region and the clinical setting. *S. pneumoniae* was the most prevalent etiology overall both in the non-ICU and ICU settings [18, 23–25]. However, *S. pneumoniae* prevalence ranged from 17.9% CAP cases in Spain to 2.2% CAP cases in India. This substantial variability in pneumococcal CAP cases may reflect the variability in pneumococcal vaccination rates and serotype circulation across regions [26, 27]. *Mycobacterium tuberculosis* was found to be an important agent of CAP, mainly in India and other Asian and African countries [28, 29].

MRSA was detected in 3.0% of CAP cases worldwide [4]. Our secondary analysis highlighted a high prevalence of *S. aureus* CAP cases in the USA, at the point that *S. aureus* CAP was more frequent than *S. pneumoniae* CAP in the USA (7.5% vs. 4.8% of the CAP cases in the overall population). The unusual etiologic distribution of CAP in the USA may result from an epidemiological shift due to the broad pneumococcal vaccination coverage in the USA [26, 27]. This shift in microbiology patterns may have important implications in the antibiotic treatment guideline recommendations. Among *S. aureus* CAP in the USA, MRSA accounted for more than half of the cases. Similarly, Moran and collaborators detected MRSA in 14 out of 627 (2.4%) of the patients hospitalized with CAP in the USA [30].

The significantly higher proportions of MRSA and *P. aeruginosa* CAP cases in the ICU compared with the non-ICU landscape suggests how clinical settings can influence the etiology of CAP. Frailty of patients harboring *P. aeruginosa* and severity of MRSA CAP may explain the higher frequency of *P. aeruginosa* and MRSA in the ICU [30–34]. These data strengthen the need for prompt microbiological testing in severe CAP cases, as those managed in the ICU. Furthermore, the not-infrequent occurrence of MRSA and *P. aeruginosa* CAP in the ICU calls for the selection of empirical antimicrobials based on the evaluation of pathogen-specific risk factors and for careful antimicrobial stewardship approaches in the ICU. Antimicrobial stewardship should allow a rapid de-escalation of unnecessary antimicrobial treatments once microbiological tests are available and also an appropriate antimicrobial treatment duration.

Our study documented the appropriateness of empirical treatment guideline recommendations in more than 90% of the CAP cases evaluated, both in the non-ICU and in the ICU setting, reinforcing the invitation to implement guideline recommendations when treating patients with CAP.

With the sole exception of the Pakistan Chest Society CPGs, country-specific CPGs were inferior to ATS/IDSA and ERS CPGs in the appropriateness of empirical treatment recommendations in the overall study population and also in the non-ICU and in the ICU settings. Of note, when applied to the UK CAP patients, BTS CPGs appropriately covered 89.5% of the CAP cases, while ATS/IDSA and ERS CPGs covered more than 93% of the cases. Similarly, the performance of ERS CPGs was inferior to the performance of the 2019 ATS/IDSA CPGs, even when applied to European countries, such as Spain, Italy, UK, Germany, and Croatia. The suboptimal performance of country-specific CPGs in the epidemiological settings where they were meant to be applied suggests the presence of pitfalls in these CPGs. We could speculate that the following factors may have contributed to the low performance of country-specific CPGs: (i) BTS CPGs allow β-lactam monotherapy and macrolide monotherapy in the non-ICU setting, leaving uncovered atypical agents of CAP and several Gram-negative pathogens, respectively; (ii) anti MRSA and anti *P. aeruginosa* empirical treatments are not suggested in the ICU by the BTS CPGs; (iii) Croatian CPGs favor β-lactam monotherapy in the non-ICU setting, leaving uncovered atypical agents of CAP; (iv) differences in the identification of *P. aeruginosa* risk factors. Similarly, the difference between the 2019 ATS/IDSA and the ERS CPGs may be associated with the more restrictive use of anti MRSA coverage based on the ERS CPGs and with the more selective anti *P. aeruginosa* treatment indications based on the 2019 ATS/IDSA CPGs. In addition, the ERS recommendations attempt to provide a single set of recommendations for a large number of countries, which differ for geographic distribution, ecology, and health care system (see Electronic Supplementary Materials).

The slightly better performance of the 2019 ATS/IDSA compared with the 2007 ATS/IDSA CPGs may result from the more attentive selection of *P. aeruginosa* and MRSA risk factors and should be carefully re-evaluated by future studies in the upcoming years.

Of note, we observed a significant difference between the frequency of anti MRSA treatments recommended by the 2007 and 2019 ATS/IDSA CPGs for ICU patients (97 and 124 empirical anti MRSA treatments recommended by the 2007 and 2019 ATS/IDSA CPGs, respectively) and the frequency of MRSA CAP diagnosed in the ICU (34 MRSA CAP). Similar results were found when anti *P. aeruginosa* treatment recommendations and *P. aeruginosa* CAP in ICU were evaluated. The high number of anti MRSA and anti *P. aeruginosa* empiric therapies recommended by the CPGs should prompt future studies to better define local risk factors for MRSA and *P. aeruginosa*, as suggested by the 2019 ATS/IDSA CPGs. More stringent recommendations may reduce the use of unnecessary therapies, leading to a decrease in the rate of drug-related adverse events and of antimicrobial resistance.

This study has several limitations. First, this is a secondary analysis of an observational point-prevalence study that cannot yield causal relationships. Second, the external validity of this study is hampered by geographic and temporal constrains. Specifically, data were mainly retrieved from tertiary care centers. Furthermore, the GLIMP study enrolled patients during the period March–June 2015, in order to cover the end of the winter season in the Northern Hemisphere and the start of the winter season in the Southern Hemisphere. Studies carried out during different seasons or the whole year may yield different results. Finally, the results of the GLIMP study are indicative of the testing efforts and the etiology of CAP in 2015 and cannot be generalized to any time period before or after the year 2015. Third, complete radiological and anamnestic information were not included in the original GLIMP dataset, hampering our ability to detect conditions at increased risk for anti MRSA coverage (e.g., necrotizing pneumonia and previous influenza).

In conclusion, *S. pneumoniae* is the most prevalent bacterial pathogen in patients hospitalized with CAP. CPGs seem to appropriately recommend to cover the most prevalent pathogens in different settings and should be strongly encouraged when managing patients with CAP. Future studies should promote innovative microbiological testing for CAP and should address the gap between the CPG recommendations and the antibiotic prescription for patients hospitalized with CAP.

Acknowledgments We would like to thank the European Respiratory Society, the World Federation of Societies of Intensive and Critical Care Medicine, the American College of Chest Physicians, the Asociación Latinoamericana de Tórax (ALAT), and the Sociedad Argentina de Infectología (SAI) for their support of this project. We would like to thank the following study contributors (GLIMP Collaborators) for their valuable collaboration: Argentina: Patricia Karina Aruj, Dept of Internal Medicine, University Hospital Alfredo Lanari, Buenos Aires, Argentina; Silvia Attorri, Hospital Luis Lago Maggiore, Mendoza, Argentina; Enrique Barimboim, Hospital Central de Mendoza, Argentina; Juan Pablo Caeiro and María I. Garzón, Hospital Privado Universitario, Córdoba, Argentina; Victor Hugo Cambursano, V.H. Dr Cazaux A. 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Data availability The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest MC, AS, GS, RM, ME, MG, PL, SRB, SB, RF, SPG, JMC, and MIR have no conflict of interest to declare. FB reports recent grants and personal fees from AstraZeneca, Bayer, Chiesi, Grifols, GSK, Guidotti, Insmed, Menarini, Novartis, Pfizer, and Zambon outside the present manuscript. AG reports recent grants and personal fees from Abbvie, Gilead, Janssen, MSD, Pfizer, ViiV, Menarini, and Angelini outside the present manuscript.

Ethical approval and informed consent The GLIMP coordinating center was located at the University of Texas Health, San Antonio, in San Antonio, TX, USA. The coordinating center received expedited project approval by the institutional review board (number HSC20150184E). The review board waived the need for receipt of informed consent due to the nature of the study. A detailed description of the GLIMP organization and methodology was previously published [4].

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