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Prevalence and Risk Factors for *Enterobacteriaceae* in Patients Hospitalized with Community-Acquired Pneumonia

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Summary at a Glance

Hospitalized adults with community acquired pneumonia have low prevalence of *Enterobacteriacea* (6%) and multidrug-resistant *Enterobacteriacea* (1.2%), respectively. Specific risk factors, such as prior extended-spectrum beta-lactamase infection and being underweight, should raise the clinical suspicion for *Enterobacteriace* and multidrug-resistant *Enterobacteriace* in patients hospitalized with CAP.

ABBREVIATION LIST

CAP: Community-acquired pneumonia

EB: *Enterobacteriaceae*

MDR-EB: Multidrug-resistant *Enterobacteriaceae*

COPD: Chronic obstructive pulmonary disease

VAP: Ventilator associated pneumonia

HAP: Hospital-acquired pneumonia

BAL: Bronchoalveolar lavage

CLSI: Clinical Laboratory Standards Institute

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2 **- Data curation**	Lead	MIR, DV, SA,NJS
	Equal	LFR
	Supporting	PF, PJM, RGW, AR, OS, FS, IML, FM, MJ, MS
3 **-Formal analysis**	Lead	MIR, DV, SA,NJS
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4 **- Funding acquisition**	Lead	NA
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5 **- Investigation**	Lead	MIR, DV, SA, NJS, LFR, PF, PJM, RGW, AR, OS, FS, IML, FM, MJ, MS
	Equal	GLIMP investigators
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6 **- Methodology**	Lead	MIR, SA, DV
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7 **- Project administration**	Lead	MIR, SA, DV
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14 **- Writing – review & editing**	Lead	MIR, SA, DV
	Equal	NA
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ABSTRACT

Background and objective: *Enterobacteriaceae* (EB) spp. family is known to include potentially multidrug-resistant microorganisms, and remains as an important cause of community-acquired pneumonia (CAP) associated with high mortality. The aim of this study was to determine the prevalence and specific risk factors associated with EB and multidrug-resistant EB in a cohort of hospitalized adults with CAP.

Methods: We performed a multinational, point-prevalence study of adult patients hospitalized with CAP. Multidrug-resistant EB was defined when ≥3 antimicrobial classes were identified as non-susceptible. Risk factors assessment was also performed for patients with EB and multidrug-resistant EB infection.

Results: Of 3,193 patients enrolled with CAP, 197 (6%) had a positive culture with EB. Fifty one percent (n=100) of EB were resistant to at least one antibiotic and 19% (n=38) had multidrug-resistant EB. The most commonly EB identified were *Klebsiella pneumoniae* (n=111, 56%) and *Escherichia coli* (n=56, 28%). The risk factors that were independently associated with EB -CAP were male gender, severe CAP, underweight (BMI<18.5), and prior extended-spectrum beta-lactamase infection. Additionally, prior extended-spectrum beta-lactamase infection, being underweight, cardiovascular diseases and hospitalization in the last 12 months were independently associated with multidrug-resistant EB CAP.

Conclusion: This study of adults hospitalized with CAP found a prevalence of EB of 6% and multidrug-resistant EB of 1.2%, respectively. The presence of specific risk factors, such as prior extended-spectrum beta-lactamase infection and being underweight, should raise the clinical suspicion for EB and multidrug-resistant EB in patients hospitalized with CAP.

Key words: Community-acquired pneumonia, *Enterobacteriaceae*, multidrug-resistance, prevalence, risk factors.

Short title: *Enterobacteriaceae* in pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) is a leading infectious cause of death worldwide, and is a costly illness due to its mortality and long-term morbidity.[1-3] Current Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines recommend the use of a respiratory fluoroquinolone as monotherapy or a β-lactam antibiotic (usually third-generation cephalosporin) *plus* a macrolide as initial therapy for outpatient and non-intensive care unit (ICU) inpatient treatment of CAP.[4,5] However, after these guidelines were published 10 years ago, an alarming increase in antimicrobial resistance to these first-line antibiotics has emerged in the common bacterial pathogens known to cause CAP.[6,7]

Streptococcus pneumoniae remains as the most common bacterial pathogen identified in patients with CAP.[8,9] However, several pathogens thought to be confined to hospital settings have been isolated more frequently in patients with CAP.[9,10] Of these pathogens, gram-negative rods (GNR), such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., and the *Enterobacteriaceae* spp. family, have become important causes of lower respiratory tract infections.[11,12] More importantly, these gram-negative bacteria are often drug-resistant microorganisms associated with high mortality and have been linked to infections in chronically-ill, healthcare-exposed and immunocompromised patients.[12,13]

Few studies have assessed the prevalence of the *Enterobacteriaceae* spp. (EB) family (*Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Proteus* spp.,

Serratia spp.) in CAP patients.[14] Thus, limited data are available regarding the risk factors associated with enteric GNRs, especially resistant *Enterobacteriaceae* spp. pathogens. The aim of the present study was to determine the prevalence and specific risk factors associated with EB and multidrug-resistant (MDR) EB infection in CAP patients using a large international cohort of adults hospitalized with CAP.

METHODS

Study design and setting

This was a multinational (54 countries), multicenter (222 participating hospitals), point-prevalence study of adult patients (>18 years of age) hospitalized with CAP. The University of Texas Health San Antonio was the coordinating center and received approval by the Institutional Review Board (IRB# HSC20150184E) to administer the study. All centers that participated in the study complied with local, regional, and/or national research regulations. An international research oversight committee was established in October 2014 to oversee all aspects of developing and executing the study protocol (SA, LFR, PF and MIR).[15]

Electronic invitations were sent to members of different professional societies worldwide from internal and emergency medicine, infectious diseases, critical care and pulmonary medicine. Invitations were also sent to multiple authors of publications of

MDR pathogens in CAP. Site investigators voluntarily agreed to participate, and no funding was provided. Study participants were diagnosed and treated per local standards of care, including microbiological assessment and treatment decisions, without any feedback from the study oversight committee or predetermined protocols. We enrolled participants on four days randomly selected by each site investigator during the months of March, April, May, and June 2015; to assure patient de-identification.[15]

Inclusion criteria

We included hospitalized adult patients ≥18 years of age with diagnosis of CAP defined by IDSA/ATS CAP guidelines.[4] Briefly, CAP was confirmed by the presence of pulmonary infiltrates <48 hours of admission by chest imaging (chest radiography, lung ultrasound or computed tomography) and the presence of ≥1 of the following signs and symptoms: 1) a new or augmentation of the cough reflex with or without sputum production and/or purulent respiratory secretions; 2) fever (documented by rectal or oral temperature ≥37.8 °C) or hypothermia (<36^{o}C by rectal or oral temperature); 3) evidence of systemic inflammation, such as leukocytosis (>10,000/cm^3), leukopenia (< 4,000/cm^3), bandemia (>10%), increased C-reactive protein or procalcitonin levels.

Exclusion criteria

We excluded patients with nosocomial pneumonia, such as hospital-acquired and/or ventilator-associated pneumonia, as defined by current clinical guidelines.[16] Patients for whom site investigators did not report blood, sputum, or lower respiratory tract cultures obtained within 24 hours of hospital admission were also excluded due to our inability to identify the etiological pathogen.[15]

Data collection

We used the validated data capture tool (REDCap™, Research Electronic Data Capture) hosted at UT Health San Antonio server to collect and manage study data.[17] After study enrolment, we allowed participating sites 7 days to complete electronic data entry and confirm microbiological results. All data were anonymized before being transmitted to the coordinating center.

Microbiological analysis

Microbiological testing and processing were conducted according to local standard protocols for sputum, urine, and blood during the first 24 hours of hospitalization. Additionally, data on pleural fluid, tracheobronchial aspirate, and bronchoalveolar lavage fluid, were collected if they were available. Each laboratory complied with local quality control protocols or those of the Clinical and Laboratory Standards Institute.[18,19]

Gram-negative bacilli pathogens belonging to the family of *Enterobacteriaceae* spp. included *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Proteus* spp., and *Serratia* spp. Antibiotic resistance was assessed by testing resistance against major classes of antimicrobial agents (*e.g.*, beta-lactams, carbapenems, aminoglycosides, fluoroquinolones, cephalosporins, etc.) according to current clinical practice guidelines.[18,20]

Study definitions

Multidrug-resistant *Enterobacteriaceae* spp. (MDR-EB) was defined as resistance to ≥3 antimicrobial classes known to be active against these pathogens,[20] when obtained from blood, or respiratory sources, such as: sputum, bronchoalveolar lavage, or pleural fluid.

Chronic lung diseases were defined as the group of conditions that include asthma, bronchiectasis, COPD, chronic aspiration, tracheostomy present at the time of admission and long term oxygen therapy.

Severe CAP was defined as patients with a CAP diagnoses that required admission to the intensive care unit, and/or invasive or non-invasive mechanical ventilation, or required vasopressors/inotropes in the first 24 hours of hospital admission. All study definitions were provided to local investigators prior to the starting data collection.

Statistical analysis

The EB and MDR-EB prevalence were calculated using EB and MDR-EB isolates as the numerator, and total number of enrolled patients as the denominator, respectively (Figure 1). Using the Chi-squared test we compared categorical variables, expressed as counts (percentages), between the study groups. We performed regressions analyses to compare prevalence among the participating sites, representing different continents and countries. We assessed in a logistic regression analysis the relationship between the two dependent variables (EB and MDR-EB CAP) with the variables that showed a p value <0.05 in the bivariate analysis. Odds ratios (OR) with 95% confidence interval (CI) were used to present regression analysis results. Statistical significance of the results was defined as p-value <0.05. Statistical analyses were performed with IBM SPSS, Statistics for Mac, version 22.0, Armonk, NY: IBM Corp.

RESULTS

A total of 3,702 patients were enrolled in the study and 509 of them were excluded due to the lack of microbiological information. 3,193 patients with signs and symptoms consistent with CAP in whom at least one microbiological culture was obtained within the first 24 hours of hospital admission were enrolled in the study. In 1,173 patients, at least one pathogen was identified in the culture samples, and they were considered the culture-positive cohort (Figure 1).

Enterobacteriaceae prevalence and geographical distribution

EB were identified in 197 (6%) of 3,193 patients enrolled in the study (Figure 2, Panel A, Table S1 in the Supplementary Information). Among the 197 patients with EB pneumonia, 190 were monomicrobial EB and 7 were polymicrobial (combinations of two EBs) (Figure 2, panel C). Of the EB identified, the most frequently isolated pathogens were *K. pneumoniae* (n=111; 56%), *E. coli* (n=56; 28%), *Enterobacter* spp. (n=25; 13%), *Proteus* spp. (n=8; 4%), and *Serratia* spp. (n=4; 2%) (Figure 3, panel A). The prevalence of EB among the 6 continents was highest in Africa (n=23, 18%) (Table 1). The countries that showed the highest prevalence of EB above 10% were: Colombia, Nigeria, Moldova, Croatia, Egypt and Germany compared to other participating countries (Table S1 in the Supplementary Information).

Antibiotic-resistance patterns

From the 197 EB identified, 97 (49%) were sensitive to the antibiotics tested, 62 (31%) were resistant to one or two antimicrobials and 38 (19%) were classified as MDR-EB (Figure 3, panel B). EB showed resistance to fluoroquinolones (n=61; 31%), piperacillin-tazobactam (n=60; 30%), cephalosporins (n=56; 28%), aminoglycosides (n=27; 14%) and carbapenems (n=16; 8%) (Figure 3, panel E).

Multidrug-resistant *Enterobacteriaceae* prevalence and geographical distribution

Among the isolated EB, 19% (n=38) were confirmed to be MDR-EB with a prevalence rate of 1.2% (Figure 2, panel D). In addition, the continent with the highest prevalence of MDR-EB was Africa (n=8, 6.3%) (Table 1). The countries with the highest prevalence of MDR-EB above 5% were: Nigeria (7.7.%), Colombia (7.4%) and Moldova (6.5%) (Table S1 in the Supplementary Information).

Risk factors for *Enterobacteriaceae*

In the univariate analysis, several variables were associated with EB CAP (Table 1; Table S2 in the Supplementary Information). In the multivariate logistic regression

analysis, we found that the risk factors that were independently associated with EB-CAP were prior extended-spectrum beta-lactamase (ESBL) infection (OR: 4.04; 95%CI: 2.04-8.01, p<0.01), being underweight (OR: 2.25, 95%CI: 1.31-3.86, p<0.01), severe CAP (OR: 2.41, 95%CI: 1.79-3.25, p<0.01) and male gender (OR: 1.48, 95%CI: 1.08-2.02, p=0.01) (Table 2). In culture-positive CAP patients, risk factors independently associated were prior ESBL infection (OR: 3.71, 95%CI: 1.65-8.35, p<0.01), being underweight (OR: 2.02, 95%CI: 1.13-3.63, p=0.02), and severe CAP (OR: 1.78, 95%CI: 1.30-2.45, p<0.01)(Table 2).

Risk factors for multidrug-resistant *Enterobacteriaceae*

Prior ESBL infection (OR: 8.50, 95%CI: 3.12-23.16, p<0.01), being underweight (OR: 2.76, 95%CI: 1.07-7.12, p=0.04), cardiovascular diseases (OR 0.44; 95%CI: 0.22-0.90, p=0.02) and hospitalization in the last 12 months (OR: 2.67, 95%CI: 1.18-6.03, p=0.02) were the risk factors independently associated with MDR-EB CAP (Table 2). The risk factors independently associated with MDR-EB enrolled in the culture-positive cohort were prior ESBL infection (OR: 5.60, 95%CI: 1.86-16.80, p<0.01), cardiovascular diseases (OR 0.43; 95%CI: 0.21-0.91, p=0.03), and hospitalization in the last 12 months (OR: 2.36, 95%CI: 1.17-4.78, p=0.02) (Table 2).

DISCUSSION

This multinational study showed that patients with community-acquired pneumonia have a 6% prevalence of *Enterobacteriaceae* as an etiological pathogen. The prevalence among the 6 continents enrolled were variable, ranging from 4-18% for EB CAP and 0.6-6.3% for MDR-EB CAP, with the highest prevalence rates found in Africa. Prior ESBL infection and being underweight were independently associated with both EB and MDR-EB in patients with CAP.

The overall prevalence rates of EB and MDR-EB CAP identified in this study were higher (6% and 1%, respectively) compared to the 1-3% prevalence rate of EB CAP (excluding *Pseudomonas aeruginosa* and *Acinetobacter* spp.) reported in three observational studies from Spain,[21-23] and in one from Germany.[24] Moreover, in patients with culture positive results, the denominator drives a higher prevalence of EB and MDR-EB in CAP patients, resulting in 17% and 3%, in contrast to ~2-6% (only for EB-CAP) reported in the previously mentioned studies.[21-24] It is important to mention that participation for this study was voluntary and it could have certainly account for some countries and continents contributing to a higher number of patients enrolled. We hypothesized that regional variability between patients' characteristics, healthcare systems in developed and developing countries, risk factors, and antibiotic resistance patterns, might have played a role in the differences observed. Therefore, these data

suggest that identifying the common pathogens that cause CAP is necessary to appreciate the frequency of these pathogens at any given time, which can guide antimicrobial treatment strategies.

The EB pathogens isolated in our study are consistent with previous reports that found *K. pneumoniae* and *E. coli* to be the most commonly isolated EB in CAP.[21,24,25] *Enterobacter spp*., *Proteus spp*., and *Serratia spp*. were less commonly identified in patients hospitalized with CAP among the 54 participating countries in our study. Current guideline-recommended empiric antibiotic therapy that include a third-generation cephalosporin and a macrolide or monotherapy with a respiratory fluoroquinolone[4] for patients with CAP would not cover 30% of isolated EB due to in-vitro resistance at presentation. More than half of the EB isolated pathogens showed resistance to ≥1 of the tested antibiotics and one third of the EB demonstrated to be MDR. These numbers should raise awareness of the emerging antimicrobial resistance to bacterial pathogens, particularly in CAP patients.

A major finding of the present study is that prior ESBL infection and being underweight were both independent risk factors for EB and MDR-EB CAP. Few studies have evaluated the risk factors associated with EB CAP, and these studies often included *P. aeruginosa* and *Acinetobacter* spp., as EB.[21,22,24,26] Underweight has been associated with the development of CAP, but not specifically with EB or MDR-EB. A detailed systematic review that evaluated the risk factors associated with CAP found that poor

nutritional status that in different studies is related to hypoalbuminemia, hypoproteinemia, malnourishment, malnutrition, or a low nutritional score was a strong predictor of CAP [27]. However, in contrast Cilloniz C. et al. presented a comprehensive review of the topic and did not mentioned low body mass index or underweight associated with any of potential MDR pathogens including EB [28]. Despite this, prior investigations showed that CAP due to EB tends to be associated with exposure to the healthcare system, such as previous antibiotic use, current use of corticosteroids, prior hospital admission, probable aspiration, severe CAP, and comorbidities of the cardiovascular, cerebrovascular, and pulmonary systems.[21,22,26] Our assessment of individual risk factors identified that the prior evidence of *P. aeruginosa* infection and at least one of three lung diseases (i.e. tracheostomy present on admission, bronchiectasis and very severe COPD [Forced expiratory volume in one second less than 30%]) were independently associated with *P. aeruginosa* CAP.[29] Therefore, our data suggest that there is no significant overlap among the risk factors associated with *P. aeruginosa* CAP and the ones associated with EB CAP, respectively. The EB risk factors suggested in our study may assist clinicians to further individualize the selection of antibiotics by limiting the unnecessary coverage for *P. aeruginosa* in certain patients with CAP.

This is one of the first international studies involving more than 50 countries around the world that systematically evaluated the prevalence and risk factors for EB and MDR-EB in CAP patients, and should be considered one of its main strengths. This

point-prevalence study carries some limitations inherent to the study design, such as the inability to follow patients over time and track the outcomes beyond the period of observation. In addition, due to the nature of the study, we were not allowed to report identifiable data and therefore, it was not possible to return to the individual patient medical records to confirm that each variable was entered appropriately. We relied on the honesty and the accountability of each one of the site investigators to follow the ethical rules defined by the individual study centers. Additionally, we attempted to standardize the methodology through the training videos, data abstraction form and data dictionary, as well as microbiological standard testing according to international standards. This study does not attempt to generalize other epidemiological reports or outbreaks in centers not participating in this study and from sources other than CAP. In addition, MDR EB could represent an important source of hospital-acquired infections not evaluated in our study. Microbiologic genetic testing was not performed, as it is not available in resource-limited countries included in this study. Finally, there is a possibility that a small proportion of patients (n=13 [6.6.%]) with prior ESBL infection may represent a relapse or recurrence infection with the same microorganism. However, the data obtained in this point-prevalence study did not include the source of prior ESBL infection, the resolution of the prior disease and/or the time from prior infection to current EB CAP event.

In conclusion, the prevalence of EB- and MDR-EB as etiological pathogens of CAP is 6% worldwide. Despite the alarming rise of MDR-EB, most of the guideline-

recommended empiric antibiotic regimens would still cover the pathogens most frequently causing CAP. Selection of empiric antibiotic therapy for patients with CAP should consider the prevalence of antibiotic-resistant pathogens in the community and identify certain risk factors that may change the probability of MDR-EB CAP. Future studies should explore how these variables influence the use of empiric antibiotics in different communities around the world.

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Disclosure statement:

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Author contributions:

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FIGURE LEGENDS

Figure 1. Study flow diagram

Figure 2: Panel A: Prevalence of *Enterobacteriaceae* (EB) among patients with CAP (microbiologically-tested cohort). Panel B: Prevalence of EB in culture-positive CAP. Panel C: Percentage of monomicrobial and polymicrobial EB CAP. Panel D: Prevalence of MDR-EB among in the microbiologically-tested cohort. Panel E: Prevalence of MDR-EB in culture-positive CAP. Panel F: Prevalence of resistant and multidrug-resistant EB.

Figure 3: Panel A: Types of *Enterobacteriaceae* (EB) among total EB isolated (n=197). Panel B: Antibiotic susceptibility among isolated EB. Panel C: Percentage of resistance and multidrug-resistance among EB that showed to be resistant to at least one antibiotic (n=100). Panel D: Number of bacteria by type that showed resistance to each one of the five antibiotics tested. Panel E: Antibiotic-resistance profile among isolated EB.

Table 1. Characteristics of all patients with community-acquired pneumonia (CAP) (n=3,193) due to *Enterobacteriaceae* (EB) and multidrug-resistant (MDR)-EB in comparison to the rest of the population (including continents) with CAP.

	NON-EB CAP n=2,996	**EB CAP n=197**	**p-value**	**NON MDR-EB CAP n=3,155**	**MDR-EB CAP n=38**	**p-value**
Demographic characteristics						
Age, median (IQR) years	68 (54-80)	66 (54-78)	0.68	68 (54-80)	66 (47-76)	0.17
Male gender, n (%)	1,744 (58.2)	133 (67.5)	0.01	1,855 (58.8)	22 (57.9)	0.91
Underweight, n (%)	132 (4.4)	18 (9.1)	<0.01	144 (7.1)	6 (20.7)	0.04
Alcoholism	250 (8.3)	17 (8.6)	0.89	266 (8.4)	1 (2.6)	0.20
Current/former smoker, n (%)	1,043 (34.8)	71 (36)	0.73	1,099 (34.8)	15 (39.5)	0.55
Bedridden, n (%)	322 (10.7)	31(15.7)	0.03	345 (10.9)	8 (21.1)	0.04
Nursing home resident, n (%)	238 (7.9)	20 (10.2)	0.27	252 (8.0)	6 (15.8)	0.08
Chronic medical comorbidities						
Chronic lung diseases						
Active lung cancer, n (%)	86 (2.9)	6 (3.0)	0.89	91 (2.9)	1 (2.6)	0.92

Asthma, n (%)	225 (7.5)	9 (4.6)	0.13	234 (7.4)	0 (0.0)	0.81
Bronchiectasis, n (%)	153 (5.1)	15 (7.6)	0.13	161 (5.1)	7 (18.4)	<0.01
Chronic aspiration, n (%)	191 (6.4)	27 (13.7)	<0.01	210 (6.7)	8 (21.1)	<0.01
COPD, n (%)	775 (25.9)	59 (29.9)	0.21	823 (26.1)	11 (28.9)	0.69
FEV_1 ≤30%, n (%)	82 (2.7)	8 (4.1)	0.28	88 (2.8)	2 (5.3)	0.36
Oxygen therapy at home, n (%)	187 (6.2)	21 (10.7)	0.02	202 (6.4)	6 (15.8)	0.02
Tracheostomy, n (%)	38 (1.3)	12 (6.1)	<0.01	47 (1.5)	3 (7.9)	<0.01
Cardiovascular diseases						
Coronary artery disease, n (%)	487 (16.3)	39 (19.8)	0.19	524 (16.6)	2 (5.3)	0.06
Heart failure, n (%)	383 (12.8)	35 (17.8)	0.04	412 (13.1)	6 (15.8)	0.62
Hypertension, n (%)	1,370(45.7)	74 (37.6)	0.03	1,435 (45.5)	9 (23.7)	<0.01
Other comorbid conditions						
Diabetes mellitus, n (%)	637 (21.3)	44 (22.3)	0.72	674 (21.4)	7 (18.4)	0.66
Enteral tube feeding, n (%)	39 (1.3)	9 (4.6)	<0.01	44 (1.4)	4 (10.5)	<0.01
Liver disease, n (%)	121 (4)	8 (4.1)	0.99	125 (4)	4 (10.5)	0.04
Cirrhosis, n (%)	59 (2)	5(2.5)	0.58	62 (2)	2 (5.3)	0.15
Chronic renal failure, n (%)	329 (11)	20 (10.2)	0.72	344 (10.9)	5 (13.2)	0.66
Stroke, n (%)	231 (7.7)	19 (9.6)	0.33	245 (7.8)	5 (13.2)	0.22
Active solid tumor, n (%)	227 (7.6)	18 (9.1)	0.43	243 (7.7)	2 (5.3)	0.57
Immunocompromised patients, n (%)	550 (18.4)	37 (18.8)	0.88	578 (18.3)	9 (23.7)	0.40
Previous infections/colonization						
Prior ESBL-producing bacterial infection, n (%)	41 (1.4)	13 (6.6)	<0.01	48 (1.5)	6 (15.8)	<0.01

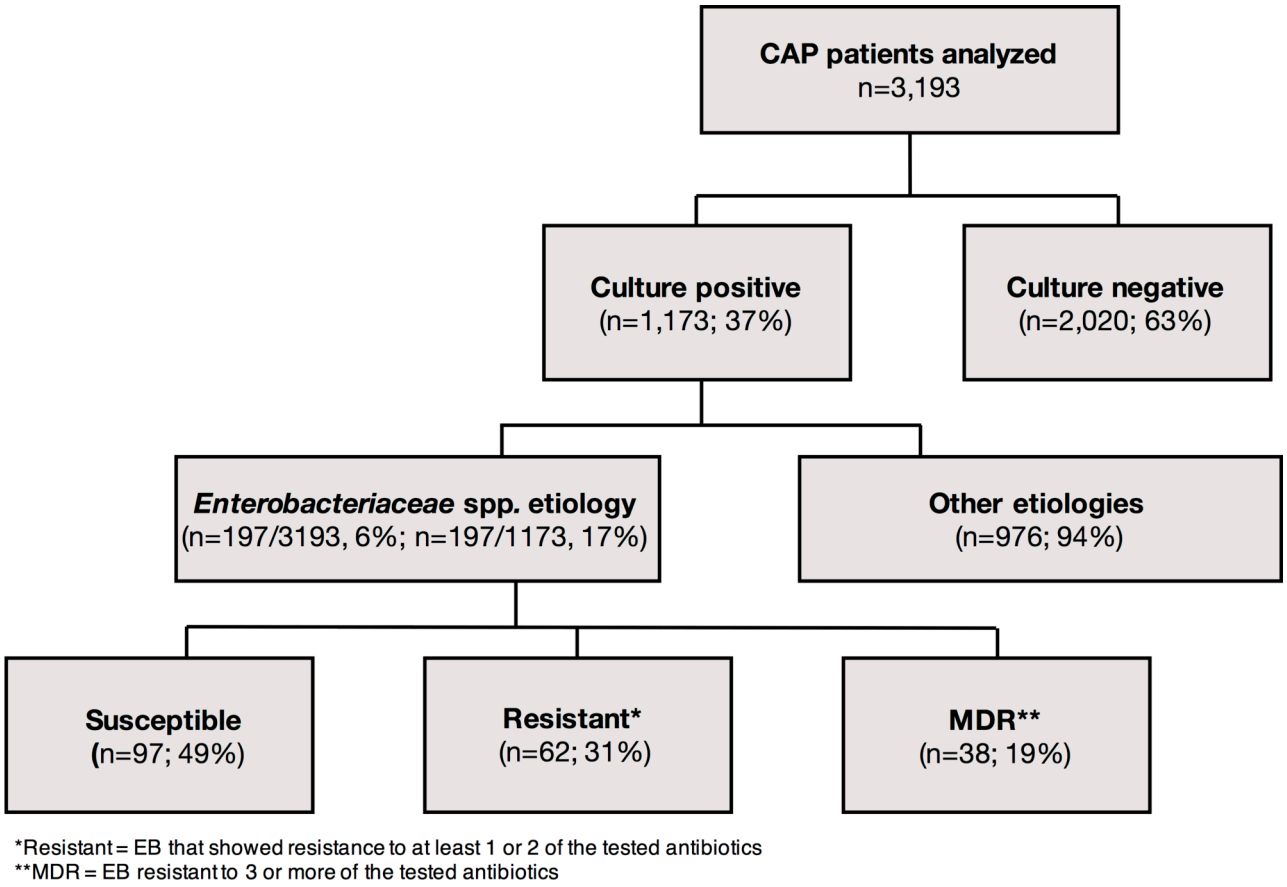
Prior healthcare exposure						
Hospitalization during the last 12 months, n (%)	950 (31.7)	76 (38.6)	0.04	1,004 (31.8)	22 (57.9)	<0.01
IV antibiotics during the last 12 months, n (%)	747 (24.9)	65 (33.0)	0.01	796 (25.2)	16 (42.1)	0.02
Severity of illness						
Severe CAP, n (%)	866 (28.9)	99 (50.3)	<0.01	950 (30.1)	15 (39.5)	0.21
Continents						
Europe (n=1.941)	1837 (94.6)	104 (5.4)	0.02	1923 (99.1)	18 (0.9)	0.1
North America (n=484)	463 (95.7)	21 (4.3)	0.08	481 (99.4)	3 (0.6)	0.26
Asia (n=405)	376 (92.8)	29 (7.2)	0.38	400 (98.8)	5 (1.2)	0.81
South America (n=203)	186 (91.6)	17 (8.4)	0.18	200 (98.5)	3 (1.5)	0.73
Africa (n=128)	105 (82.0)	23 (18)	<0.01	120 (93.8)	8 (6.3)	<0.01
Oceania (n=32)	29 (90.6)	3 (9.4)	0.45	31 (96.9)	1 (3.1)	0.32

CAP = community-acquired pneumonia; EB = *Enterobacteriaceae* spp.; NON-EB = Non-*Enterobacteriaceae*; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in 1 second; ESBL = extended-spectrum beta-lactamase; IV = intravenous

Risk factors	CAP				Culture-positive CAP			
	EB (n=197/3193)		MDR-EB (n=38/3193)		EB (n=197/1173)		MDR-EB (n=38/1173)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (male)	1.48 (1.08-2.02)	0.01			1.37 (0.99-1.92)	0.06		
Underweight	2.25 (1.31-3.86)	<0.01	2.76 (1.07-7.12)	0.04	2.02 (1.13-3.63)	0.02	2.29 (0.85-6.12)	0.10
Chronic lung diseases*	1.20 (0.88-1.63)	0.24	1.36 (0.68-2.73)	0.38	1.19 (0.86-1.64)	0.30	1.27 (0.62-2.58)	0.51
Enteral tube feeding	1.78 (0.78-4.08)	0.17	3.50 (1.02-12.02)	0.05	1.76 (0.68-4.58)	0.25	3.17 (0.86-11.76)	0.08
Bedridden status	1.11 (0.72-1.72)	0.62	1.32 (0.56-3.10)	0.53	1.19 (0.74-1.90)	0.48		
Prior ESBL infection	4.04 (2.04-8.01)	<0.01	8.50 (3.12-23.16)	<0.01	3.71 (1.65-8.35)	<0.01	5.60 (1.86-16.80)	<0.01
Hospitalization during last 12 months	1.13 (0.77-1.68)	0.53	2.67 (1.18-6.03)	0.02			2.36 (1.17-4.78)	0.02
IV antibiotics during last 12 months	1.07 (0.71-1.62)	0.76	0.75 (0.32-1.77)	0.52				
Severe CAP	2.41 (1.79-3.25)	<0.01			1.78 (1.30-2.45)	<0.01		
Chronic liver disease			2.67 (1.01-7.11)	0.05				
Cardiovascular diseases**	0.84 (0.62-1.13)	0.25	0.44 (0.22-0.90)	0.02	1.00 (0.73-1.39)	0.98	0.43 (0.21-0.91)	0.03
Chronic renal failure							1.75 (0.62-4.91)	0.29

CAP = Community-acquired pneumonia; EB = *Enterobacteriaceae* spp.; MDR = Multidrug-resistant; ESBL = Extended-spectrum beta-lactamase; IV= intravenous
*Chronic lung diseases include asthma, bronchiectasis, COPD, chronic aspiration, tracheostomy present at the time of admission and long term oxygen therapy. ** Cardiovascular diseases included coronary artery disease, hypertension and heart failure.

Table 2. Multivariate regression analysis among CAP and culture-positive CAP patients demonstrating the risk factors independently associated with *Enterobacteriaceae* (EB) and multidrug-resistant (MDR) EB community-acquired pneumonia.



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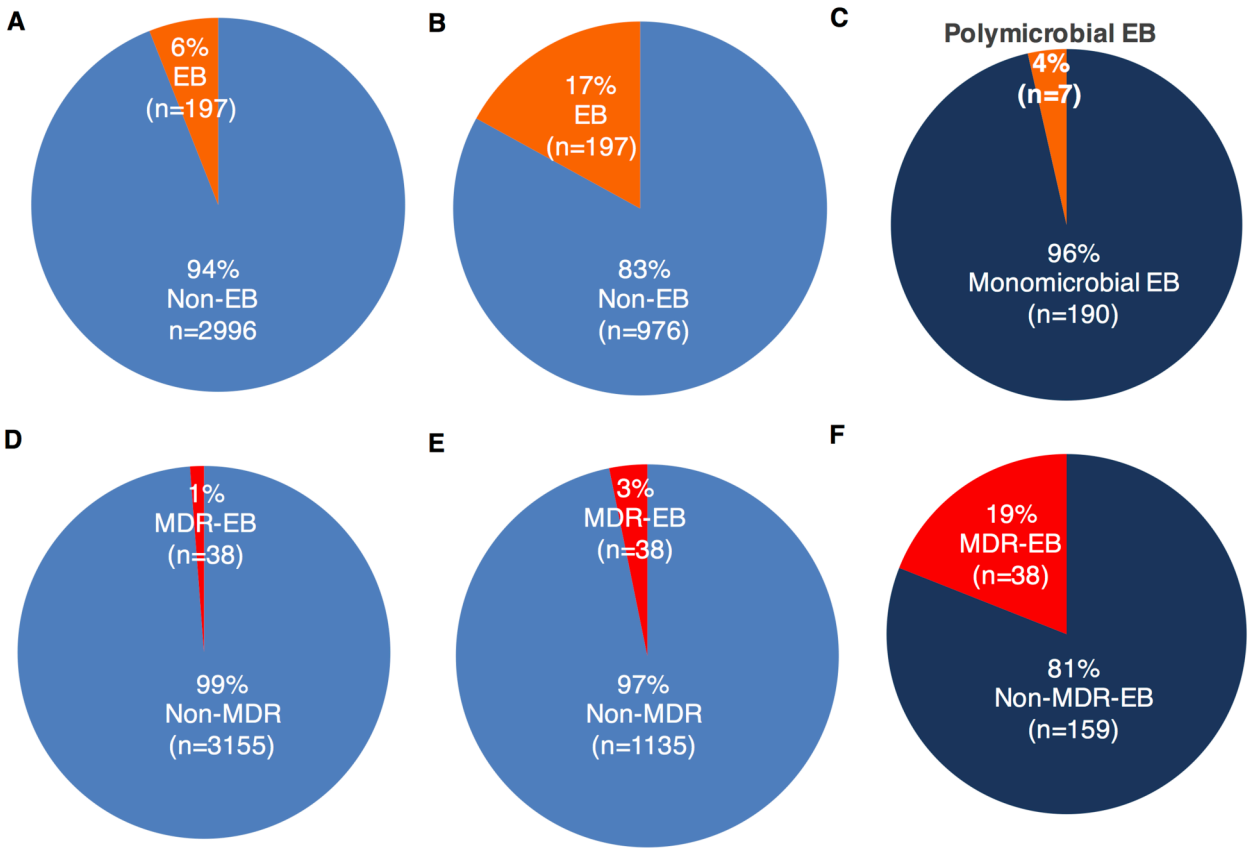

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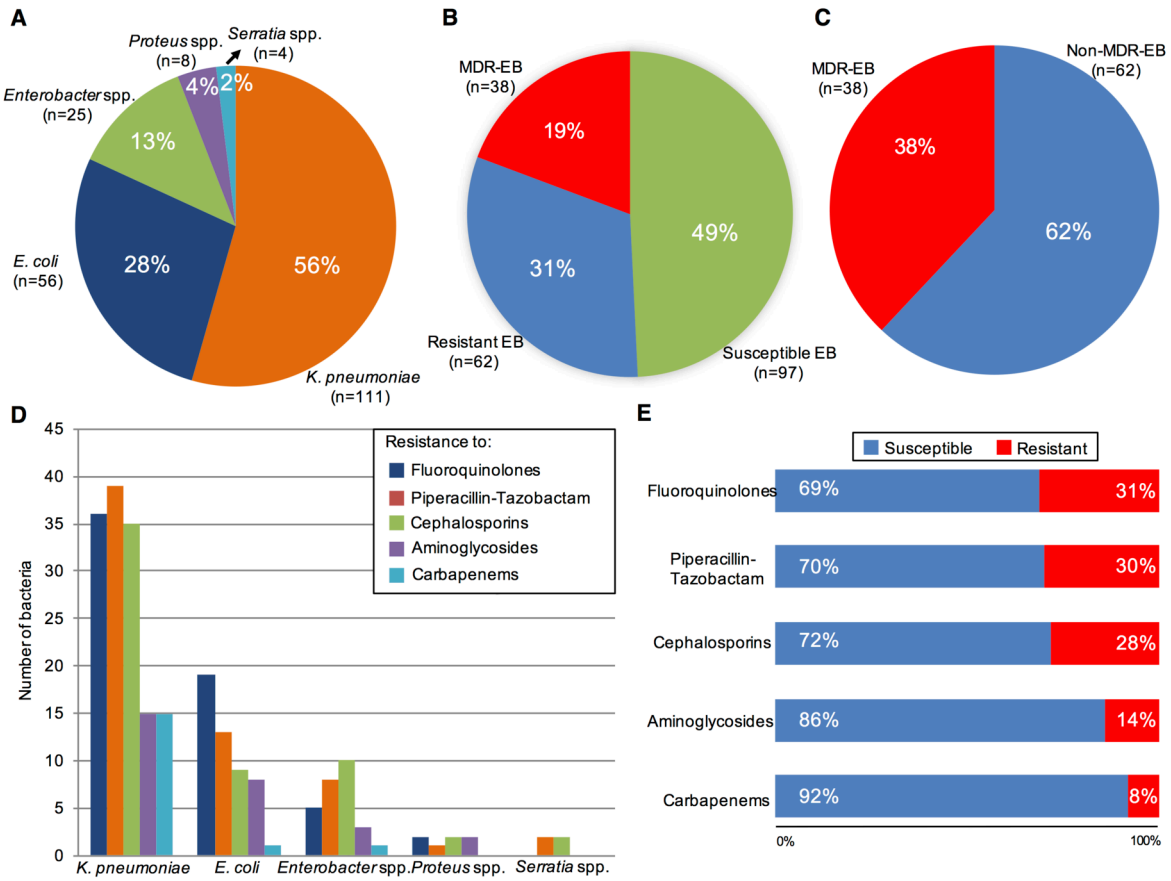

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