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MAJOR ARTICLE

Epidemiology and Outcomes of Community-Acquired *Escherichia coli* Pneumonia

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Background. *E. coli* is an under-recognized cause of bacterial community-acquired pneumonia (CAP). The objective of this study was to describe the epidemiology, risk factors, and outcomes of community-acquired *Escherichia coli* pneumonia in comparison with other gram-negative and pneumococcal pneumonias.

Methods. We conducted a large retrospective cohort study of adult patients admitted with pneumonia to 173 US hospitals included in the Premier Research database from July 2010 to June 2015. Patients were included if they had a principal diagnosis code for pneumonia or a principal diagnosis of respiratory failure or sepsis with a secondary diagnosis of pneumonia and had a positive blood or respiratory culture obtained on hospital day 1. The primary outcome was in-hospital case fatality. Secondary outcomes included intensive care unit admission, invasive mechanical ventilation, and use of vasopressors.

Results. Of 8680 patients with pneumonia and positive blood or respiratory cultures, 1029 (7.7%) had *E. coli* CAP. Patients with *E. coli* pneumonia were older and more likely to have a principal diagnosis of sepsis. Patients with *E. coli* pneumonia had significantly higher case fatality than patients with pneumococcal pneumonia (adjusted odds ratio, 1.55; 95% CI, 1.23–1.97), but it was not significantly different than other gram-negative pneumonias (adjusted odds ratio, 1.06; 95% CI, 0.85–1.32). Approximately 36% of the isolates were resistant to fluoroquinolones; 9.3% were resistant to ceftriaxone.

Conclusions. *E. coli* is an important cause of severe CAP; with mortality that was higher than pneumococcal pneumonia but similar to other gram-negative pneumonias. The rate of fluoroquinolone resistance was high, and empiric fluoroquinolones should be used with caution in these patients.

Keywords. bacterial; *E. coli*; epidemiology; gram-negative bacteria; pneumonia; respiratory tract infections.

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in the United States and worldwide [1, 2]. While *Streptococcus pneumoniae* (pneumococcus) and *Staphylococcus aureus* are the most common etiology of gram-positive bacterial CAP, pneumonias caused by gram-negative bacteria are increasingly being recognized as significant and virulent contributors [3].

Previous prospective and retrospective studies have reported that Enterobacteriaceae account for 3%–12% of CAP pathogens [3–5]. The Pneumonia Patient Outcome Research (PORT) study conducted more than 2 decades ago reported that *Escherichia coli* was the fourth most common causative pathogen and the second most common cause of "bacteremic" CAP [6]. A more recent study also implicated *E. coli* in ~5% of culture-positive CAP [7]. However, despite this prevalence, little attention has been paid to community-acquired *E. coli,* and few studies have described acute *E. coli* pneumonia in detail. Most previous studies have highlighted and emphasized the role of gram-negatives as the leading cause of hospital-acquired pneumonia, especially in ventilated patients [8–10]. With the increasing relevance of multidrug resistance among gram-negative bacteria in recent years, there is renewed interest in understanding the epidemiology, risk factors, and clinical outcomes of acute community-acquired pneumonia caused by gram-negative bacteria, including *E. coli*. It is not known whether risk factors, resistance patterns, or outcomes for patients with community-acquired *E. coli* pneumonia differ from those of other gram-negative bacterial pneumonias. The objective of this study was to describe the epidemiology, risk factors, and outcomes of community-acquired *E. coli* pneumonia in comparison with other gram-negative pneumonias and pneumococcal pneumonia using a national database of 173 US hospitals.

METHODS

Study Design

We conducted a multihospital retrospective cohort study of adult patients (aged ≥18 years) admitted with CAP to 173

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US hospitals included in the Premier Healthcare database (Premier Inc., Charlotte, NC, USA) from July 2010 to June 2015. Additional information about the database is provided in Supplementary Material 1a.

Patient Population and Study Definitions

We included adult patients hospitalized with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) principal diagnosis code of pneumonia or a principal diagnosis of respiratory failure or sepsis paired with a secondary diagnosis of pneumonia, as described previously [11–13]. Pneumonia was defined as bacterial CAP if it was a community-acquired (present on admission) infection, antibiotic treatment was initiated by hospital day 1 and continued for at least 3 consecutive days or until discharge, and a positive blood or respiratory culture was obtained on the first day of hospitalization. Additional study definitions are provided in Supplementary Material 1b. We excluded patients if they were transferred from another acute care facility, as initial severity, the timing of infection, and patient outcomes could not be evaluated. We also excluded patients with a hospital length of stay of ≤1 day and those who did not receive any antibiotics because the diagnosis of CAP may have been doubtful (Figure 1). Additional exclusion criteria are provided in Supplementary

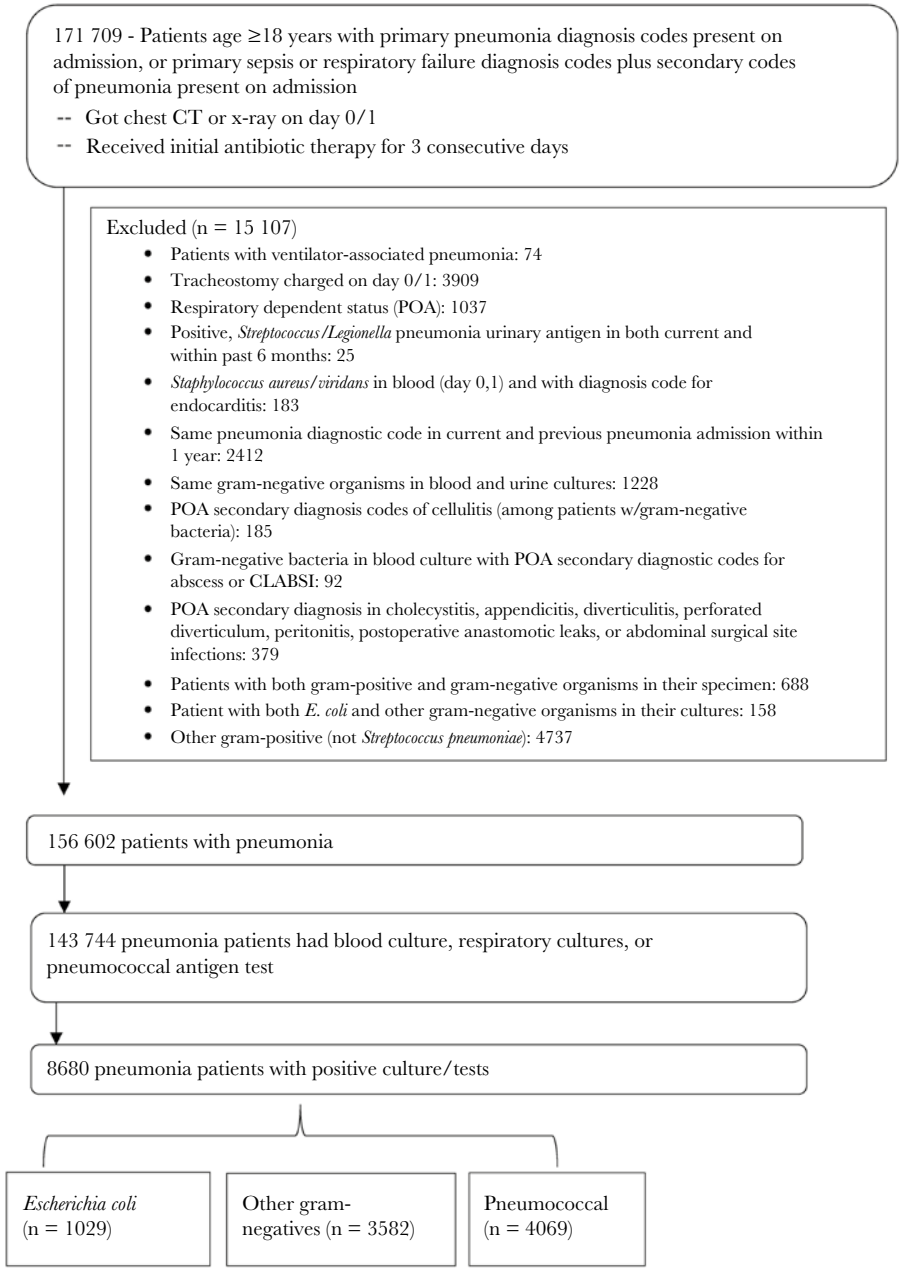

Figure 1. Patient selection flowchart. Abbreviations: CLABSI, central line bloodstream infection; CT, computed tomography; POA, present on admission.

Material 1c. Lastly, as we were only interested in comparing *E. coli* pneumonia with other gram-negative pneumonias and pneumococcal pneumonia, we excluded patients with other gram-positive pneumonias.

Baseline and Microbiological Variables

Patient-level factors included demographics and comorbid conditions. Comorbidities were defined using software provided by the Agency for Healthcare Research and Quality (Healthcare Cost and Utilization Project Comorbidity Software, version 3.1) based on the work of Elixhauser [14]. We also calculated combined comorbidity scores as described by Gagne et al. [15]. Indirect markers of disease severity were admission to an intensive care unit (ICU), invasive mechanical ventilation (IMV), and vasopressor use. We have previously demonstrated that these variables have excellent prognostic ability for inpatient mortality [12]. Hospital-level factors included regional geographic location, hospital bed size, teaching status, and urbanicity.

The Premier Healthcare database has pathogen susceptibility reports (performed locally) from each of the hospitals. The isolates were classified as susceptible (S) or resistant (R) to each of the antibiotics tested based on Clinical & Laboratory Standards Institute (CLSI) standards [16]. MDR *E. coli* was defined as any *E. coli* isolate that tested either intermediate (I) or resistant (R) to ≥1 agent in ≥3 antimicrobial classes [17]. Extended-spectrum β-lactamase (ESBL)–producing *E. coli* was defined as any isolate resistant to most beta-lactam antibiotics (with ≥1 nonsusceptible result [I or R] to cefotaxime, ceftriaxone, ceftazidime, cefepime) and the monobactam aztreonam [17]. The database does not contain antimicrobial minimal inhibitory concentration (MIC) data.

Outcomes

We compared *E. coli* pneumonia with other gram-negative pneumonias and pneumococcal pneumonia. Patients were followed until death or discharge from the hospital. The primary outcome was in-hospital case fatality. Secondary outcomes included ICU admission, IMV, and use of vasopressors. We also measured hospital length of stay (LOS) and cost of hospitalization.

Statistical Analysis

We compared patient demographics, clinical characteristics, and outcomes of patients with *E. coli* pneumonia with those of patients with pneumococcal pneumonia and other gram-negative pneumonias. We then compared outcomes using mixed-effects logistic regression for in-hospital mortality, admission to ICU, IMV, and vasopressor use, and we used gamma generalized linear regression for length of stay and cost. All models included hospital as a random effect and adjusted for demographic characteristics, insurance status, indicators of initial severity (ICU, IMV, and vasopressor), risk factors for resistant infections, and patient comorbidities. As our study sample size was sufficiently large, we decided a priori to include all covariates in our statistical models evaluating the outcomes. Odds ratios were used to report the results of logistic regressions and mean multipliers for gamma models, each with 95% CIs. Tests were 2-sided with a significance level of .05. Analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA).

RESULTS

Of the 171 709 patients with a diagnosis code for pneumonia, who had chest imaging and received antibiotics for 3 consecutive days, 15 107 patients were excluded, including 4737 patients with nonpneumococcal gram-positive pneumonia. Of the remaining 143 744 patients, 8680 had a positive blood, respiratory, or pneumococcal antigen test. Among these, 4069 patients had pneumococcal pneumonia and 4611 had gram-negative pneumonia. In patients with gram-negative pneumonias, the most common pathogens identified were *Pseudomonas aeruginosa* (n = 1342, 10%), *E. coli* (n = 1029, 7.7%), *Klebsiella pneumoniae* (n = 749, 5.6%), *Hemophilus influenzae* (n = 480, 3.6%), *Proteus mirabilis* (n = 250, 1.9%), and *Serratia marcescens* (n = 148, 1.1%). Our final 3 cohorts included 1029 (7.7%) patients with *E. coli* pneumonia, 4069 (30.3%) patients with pneumococcal pneumonia, and 3582 (26.7%) patients with other gram-negative pneumonias (Figure 1).

Patient Characteristics

Table 1 compares patient characteristics including demographics, principal diagnoses, associated comorbidities, and markers of severity of illness among the 3 cohorts. Compared with patients with pneumococcal pneumonia, patients with *E. coli* pneumonia were older (median age, 76 vs 64 years), had a higher comorbidity burden (combined comorbidity score, 4 vs 3; $P < .001$), and were more likely to have a principal diagnosis of sepsis (72% vs 60%). Compared with patients with other gram-negative pneumonias, patients with *E. coli* pneumonia were also older (median age, 76 vs 72 years) and more likely to have a principal diagnosis of sepsis (72% vs 47%). Among patients age ≥80 years, *E. coli* was the second most common cause of CAP, responsible for 17.9% of cases.

Initial Severity and Early Treatments

Table 2 compares the initial severity and tests performed including empiric antibiotic therapy among the 3 cohorts. Approximately 39% of patients with *E. coli* pneumonia received broad-spectrum empiric antibiotics covering MDR pathogens, compared with 44% of patients with other gram-negative pneumonias. Patients with *E. coli* CAP most commonly received empiric respiratory fluoroquinolones (42%) and third-generation cephalosporins (42%), followed by piperacillin-tazobactam

Table 1. Baseline Patient and Hospital Characteristics

Factor	Escherichia coli (n = 1029)	Other Gram-Negatives (n = 3582)	*P* Value[e]	Pneumococcal (n = 4069)	*P* Value[f]
Age, median [IQR], y	76.0 [64.0–85.0]	72.0 [62.0–81.0]	<.001[b]	64.0 [54.0–77.0]	<.001[b]
Age, No. (%)			<.001[c]		<.001[c]
18–49 y	50 (4.9)	330 (9.2)		688 (16.9)	
50–64 y	213 (20.7)	758 (21.2)		1376 (33.8)	
65–79 y	351 (34.1)	1413 (39.4)		1177 (28.9)	
≥80 y	415 (40.3)	1081 (30.2)		828 (20.3)	
Gender, No. (%)			<.001[c]		.27[c]
Female	494 (48.0)	1512 (42.2)		2032 (49.9)	
Male	535 (52.0)	2070 (57.8)		2037 (50.1)	
Race, No. (%)			.36[c]		.008[c]
White	766 (74.4)	2651 (74.0)		3075 (75.6)	
Black	120 (11.7)	455 (12.7)		565 (13.9)	
Hispanic	5 (0.49)	35 (0.98)		26 (0.64)	
Others	138 (13.4)	439 (12.3)		401 (9.9)	
Unknown	0 (0.0)	2 (0.06)		2 (0.05)	
Admission source, No. (%)			.17[c]		<.001[c]
Emergency room	911 (88.5)	3096 (86.4)		3757 (92.3)	
SNF/ICF	87 (8.5)	327 (9.1)		161 (4.0)	
Clinic	31 (3.0)	157 (4.4)		148 (3.6)	
Others	0 (0.0)	2 (0.06)		3 (0.07)	
Insurance payor, No. (%)			.63[c]		<.001[c]
Medicare	792 (77.0)	2727 (76.1)		2277 (56.0)	
Medicaid	82 (8.0)	338 (9.4)		482 (11.8)	
Managed care	77 (7.5)	264 (7.4)		643 (15.8)	
Commercial indemnity	30 (2.9)	89 (2.5)		179 (4.4)	
Others	48 (4.7)	164 (4.6)		488 (12.0)	
Principal diagnosis, No. (%)			<.001[c]		<.001[c]
Pneumonia	217 (21.1)	1322 (36.9)		1434 (35.2)	
Aspiration pneumonia	48 (4.7)	261 (7.3)		65 (1.6)	
Sepsis	739 (71.8)	1696 (47.3)		2431 (59.7)	
Respiratory failure	25 (2.4)	303 (8.5)		139 (3.4)	
Dialysis, No. (%)	57 (5.5)	185 (5.2)	.63[c]	131 (3.2)	<.001[c]
Immunosuppression, No. (%)[g]	217 (21.1)	789 (22.0)	.52[c]	754 (18.5)	.062[c]
Admission within last 6 mo, No. (%)	91 (8.8)	572 (16.0)	<.001[c]	182 (4.5)	<.001[c]
Patient comorbidities					
Combined comorbidity scores, median [IQR]	4.0 [2.0–6.0]	3.0 [2.0–6.0]	.100[b]	3.0 [1.00–5.0]	<.001[b]
Hypertension, No. (%)	720 (70.0)	2262 (63.1)	<.001[c]	2312 (56.8)	<.001[c]
Fluid and electrolyte disorders, No. (%)	644 (62.6)	1984 (55.4)	<.001[c]	2487 (61.1)	.39[c]
Chronic pulmonary disease, No. (%)	459 (44.6)	1963 (54.8)	<.001[c]	2051 (50.4)	<.001[c]
Anemia, No. (%)	380 (36.9)	1325 (37.0)	.97[c]	1282 (31.5)	<.001[c]
Diabetes, No. (%)	381 (37.0)	1 (33.4)	.031[c]	1 (27.7)	<.001[c]
Congestive heart failure, No. (%)	314 (30.5)	1 (28.7)	.25[c]	847 (20.8)	<.001[c]
Chronic kidney disease, No. (%)	218 (21.2)	671 (18.7)	.079[c]	554 (13.6)	<.001[c]
Coagulopthy, No. (%)	219 (21.3)	518 (14.5)	<.001[c]	543 (13.3)	<.001[c]
Weight loss, No. (%)	175 (17.0)	690 (19.3)	.10[c]	592 (14.5)	.049[c]
Other neurological disorders, No. (%)	166 (16.1)	660 (18.4)	.091[c]	411 (10.1)	<.001[c]
Hypothyroidism, No. (%)	182 (17.7)	568 (15.9)	.16[c]	522 (12.8)	<.001[c]
Dementia, No. (%)	158 (15.4)	396 (11.1)	<.001[c]	265 (6.5)	<.001[c]
Depression, No. (%)	119 (11.6)	466 (13.0)	.22[c]	559 (13.7)	.067[c]
Obesity, No. (%)	122 (11.9)	399 (11.1)	.52[c]	501 (12.3)	.69[c]
Valvular disease, No. (%)	109 (10.6)	324 (9.0)	.13[c]	318 (7.8)	.004[c]
Peripheral vascular disease, No. (%)	104 (10.1)	343 (9.6)	.61[c]	283 (7.0)	<.001[c]
Pressure ulcer, No. (%)	81 (7.9)	392 (10.9)	.004[c]	108 (2.7)	<.001[c]
Pulmonary circulation disease, No. (%)	88 (8.6)	304 (8.5)	.95[c]	296 (7.3)	.17[c]
Psychoses, No. (%)	76 (7.4)	197 (5.5)	.024[c]	230 (5.7)	.037[c]
Paralysis, No. (%)	54 (5.2)	308 (8.6)	<.001[c]	91 (2.2)	<.001[c]

Table 1. Continued

Factor	Escherichia coli (n = 1029)	Other Gram-Negatives (n = 3582)	*P* Value[e]	Pneumococcal (n = 4069)	*P* Value[f]
Metastatic cancer, No. (%)	59 (5.7)	222 (6.2)	.58[c]	126 (3.1)	<.001[c]
Liver disease, No. (%)	61 (5.9)	119 (3.3)	<.001[c]	215 (5.3)	.41[c]
Alcohol abuse, No. (%)	49 (4.8)	145 (4.0)	.31[c]	359 (8.8)	<.001[c]
Solid tumor without metastasis, No. (%)	50 (4.9)	186 (5.2)	.67[c]	123 (3.0)	.004[c]
Rheumatoid arthritis/collagen vascular disease, No. (%)	52 (5.1)	151 (4.2)	.25[c]	171 (4.2)	.23[c]
Drug abuse, No. (%)	25 (2.4)	102 (2.8)	.47[c]	281 (6.9)	<.001[c]
Lymphoma, No. (%)	14 (1.4)	96 (2.7)	.014[c]	108 (2.7)	.015[c]
Hospital characteristics					
Bed size, No. (%)			.84[c]		.013[c]
≤200 beds	210 (20.4)	710 (19.8)		917 (22.5)	
201–400 beds	474 (46.1)	1 (45.8)		1 (41.0)	
≥401 beds	345 (33.5)	1 (34.4)		1 (36.5)	
Urban/rural, No. (%)			.89[c]		.48[c]
Rural	133 (12.9)	469 (13.1)		493 (12.1)	
Urban	896 (87.1)	3 (86.9)		3 (87.9)	
Teaching hospital, No. (%)			.61[c]		.022[c]
No	631 (61.3)	2 (60.4)		2 (57.4)	
Yes	398 (38.7)	1 (39.6)		1 (42.6)	
Region, No. (%)			.053[c]		<.001[c]
Midwest	226 (22.0)	725 (20.2)		1 (26.4)	
Northeast	141 (13.7)	555 (15.5)		644 (15.8)	
South	464 (45.1)	1 (47.8)		1 (45.8)	
West	198 (19.2)	590 (16.5)		486 (11.9)	

Abbreviations: ANOVA, analysis of variance; HTN, hypertension; ICF, intermediate care facility; IQR, interquartile range; SNF, skilled nursing facility.

[a]By ANOVA.

[b]By Kruskal-Wallis test.

[c]By Pearson's chi-square test.

[d]By Fisher exact test.

[e]*Escherichia coli* vs other gram-negative organisms.

[f]*Escherichia coli* vs pneumococcal.

[g]Immunosuppression was defined as patients who had a diagnostic code for organ transplantation or AIDS or were receiving immunosuppressant drugs or corticosteroids (equivalent to ≥20 mg/d of prednisone) in the first 2 hospital days.

(34%) and macrolides (35%), similar to patients with other gram-negative pneumonias. Among patients with pneumococcal CAP, the most common empiric antibiotics were third-generation cephalosporins (54%), followed by macrolides (48%) and respiratory fluoroquinolones (44%).

Culture/Sensitivity and Resistance Patterns

Among the 1029 *E. coli* isolates, 69% were from blood cultures, 30% from respiratory cultures, and only 1% from both. Similar numbers for gram-negative CAP were 29%, 68%, and 3%, respectively. For pneumococcal CAP, blood and respiratory cultures were positive in 50% and 22% of cases, respectively, while 19% had a positive pneumococcal antigen test and 9% had >1 source of identification. Table 3 shows the antimicrobial resistance patterns of the isolates and compares them with 2 other gram-negative pathogens, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Approximately 89% of the patients with suspected *E. coli* pneumonia were treated initially with adequate antibiotics, compared with 65% for *Pseudominas aeruginosa* pneumonias and 91% for *Klebsiella pneumoniae* pneumonias. However, only 54% of *E. coli* isolates were resistant to ampicillin, 36% were resistant to fluoroquinolones, and 9% were resistant to ceftriaxone. In comparison, 31% of the *Pseudomonas* isolates and 10% of the *Klebsiella* isolates were resistant to fluoroquinolones. Among patients with *E. coli* pneumonia, those receiving adequate initial therapy had lower mortality than those who received inadequate initial therapy (13.6% vs 18.1%; $P = .12$), but the difference was not statistically significant.

Among patients with culture-positive *E. coli*, 958 were empirically treated with broad-spectrum antibiotics, including 427 patients who were started on a respiratory fluoroquinolone. Of these, 337 (79%) had an *E. coli* isolate that was sensitive to ceftriaxone. On hospital day 4, 162/337 (48%) patients were continued on respiratory fluoroquinolones, although 24 (15%) had a fluoroquinolone-resistant isolate. Also, by hospital day 4, 156 (46%) were switched to other antibiotics, and antibiotics were discontinued for the remaining 19 (6%) patients. Of the 156 patients who were switched to other antibiotics, 77 (49%) patients had a fluoroquinolone-resistant isolate. And of the 77

Table 2. Initial Illness Severity, Early Treatments, and Outcomes (Day 0/1)

Factor	*Escherichia coli* (n = 1)	Other Gram-Negative (n = 3)	*P* Value[e]	Pneumococcal (n = 4)	*P* Value[f]
Illness severity					
ICU admission, No. (%)	398 (38.7)	1 (43.1)	.011[c]	1 (36.1)	.13[c]
Vasopressors, No. (%)	189 (18.4)	634 (17.7)	.62[c]	511 (12.6)	<.001[c]
IMV, No. (%)	131 (12.7)	768 (21.4)	<.001[c]	501 (12.3)	.72[c]
NIV, No. (%)	77 (7.5)	416 (11.6)	<.001[c]	451 (11.1)	<.001[c]
Cultures/tests performed (day 0/1)					
Blood cultures, No. (%)	996 (96.8)	3 (94.2)	<.001[c]	3 (97.3)	.41[c]
Respiratory cultures, No. (%)	351 (34.1)	2 (73.5)	<.001[c]	1 (39.1)	.003[c]
Pneumococcal antigen, No. (%)	86 (8.4)	399 (11.1)	.010[c]	1 (30.1)	<.001[c]
Blood lactate, No. (%)	643 (62.5)	1 (54.2)	<.001[c]	2 (54.8)	<.001[c]
Arterial & venous blood gas, No. (%)	446 (43.3)	1 (51.8)	<.001[c]	1 (47.2)	.026[c]
Antibiotics administered by day 0/1					
Piperacillin/tazobactam, No. (%)	348 (33.8)	1 (32.2)	.33[c]	841 (20.7)	<.001[c]
Aminoglycosides, No. (%)	45 (4.4)	150 (4.2)	.79[c]	76 (1.9)	<.001[c]
Anti-MRSA agents, No. (%)	416 (40.4)	1 (47.8)	<.001[c]	1 (34.6)	<.001[c]
Antipseudomonal carbapenems, No. (%)	46 (4.5)	264 (7.4)	.001[c]	137 (3.4)	.089[c]
Third-generation cephalosporins, No. (%)	430 (41.8)	1 (34.5)	<.001[c]	2 (53.9)	<.001[c]
Antipseudomonal cephalosporins, No. (%)	93 (9.0)	525 (14.7)	<.001[c]	295 (7.2)	.053[c]
Respiratory fluoroquinolones, No. (%)	427 (41.5)	1 (36.5)	.003[c]	1 (44.5)	.087[c]
Antipseudomonal quinolones, No. (%)	419 (40.7)	1 (35.7)	.003[c]	1 (39.4)	.45[c]
Macrolides, No. (%)	364 (35.4)	1 (32.2)	.057[c]	1 (48.0)	<.001[c]
Empiric antibiotic therapy, No. (%)			<.001[c]		<.001[c]
Other antibiotics	168 (16.3)	687 (19.2)		417 (10.2)	
MDR-CAP	363 (35.3)	1 (40.5)		1 (26.8)	
CAP	498 (48.4)	1 (40.3)		2 (63.0)	
Hospital outcomes					
In-hospital case fatality, No. (%)	145 (14.1)	435 (12.1)	.097[c]	264 (6.5)	<.001[c]
ICU, No./total (%)	470 (45.7)	1 (49.6)	.028[c]	1 (41.9)	.029[c]
IMV, No./total (%)	222 (21.6)	1 (29.4)	<.001[c]	797 (19.6)	.15[c]
NIV, No./total (%)	182 (17.7)	762 (21.3)	.012[c]	779 (19.1)	.29[c]
Vasopressors, No./total (%)	282 (27.4)	928 (25.9)	.34[c]	816 (20.1)	<.001[c]
Length of stay, median [IQR], d	6.0 [4.0–10.0]	7.0 [4.0–11.0]	.098[b]	5.0 [4.0–9.0]	<.001[b]
Cost, median [IQR], $	11 598.8 [7096.6–21 330.2]	12 847.4 [7458.8–23 646.8]	.009[b]	9375.5 [5426.3–17 388.5]	<.001[b]

Day 0/1 refers to time in the emergency room or on hospital day 1. Costs are inflation-adjusted to 2015 annual costs by using the medical care component of the consumer price index. Respiratory fluoroquinolones included levofloxacin, gemifloxacin, and moxifloxacin, and antipseudomonal fluoroquinolones included levofloxacin and ciprofloxacin.

Abbreviations: ANOVA, analysis of variance; CAP, community acquired pneumonia; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; MDR, multidrug-resistant, NIV, noninvasive ventilation; SNF, skilled nursing facility.

[a]By ANOVA.

[b]By Kruskal-Wallis test.

[c]By Pearson's chi-square test.

[d]By Fisher exact test.

[e]*Escherichia coli* vs other gram-negative organisms.

[f]*Escherichia coli* vs pneumococcal.

Table 3. Resistance Patterns Comparing Among CAP Patients With *E. coli, P. aeruginosa,* and *K. pneumoniae*

	Escherichia coli (n = 1)		*Pseudomonas aeruginosa* (n = 1)		*Klebsiella pneumoniae* (n = 699)	
Factor	No.	Statistics	No.	Statistics	No.	Statistics
Resistant to ampicillin, No. (%)	995	540 (54.3)	NA		570	569 (99.8)
Resistant to piperacillin/tazobactam, No. (%)	773	34 (4.4)	1	106 (10.5)	532	33 (6.2)
Resistant to amoxicillin clavulanic acid, No. (%)	282	70 (24.8)	NA		237	27 (11.4)
Resistant to tetracycline, No. (%)	323	115 (35.6)	NA		248	45 (18.1)
Resistant to trimethoprim/sulfamethoxazole, No. (%)	977	330 (33.8)	NA		675	75 (11.1)
Resistant to aztreonam, No. (%)	453	50 (11.0)	462	137 (29.7)	329	30 (9.1)
Resistant to ceftriaxone, No. (%)	878	82 (9.3)	NA		561	48 (8.6)
Resistant to cefepime, No. (%)	628	61 (9.7)	1	196 (18.7)	427	40 (9.4)
Resistant to ceftazidime, No. (%)	460	54 (11.7)	858	125 (14.6)	309	29 (9.4)
Resistant to aminoglycosides, No. (%)	1	174 (17.0)	1	258 (20.1)	697	54 (7.7)
Resistant to carbapenem, No. (%)	847	2 (0.24)	1	178 (16.4)	566	11 (1.9)
Resistant to fluoroquinolone, No. (%)	1	365 (35.7)	1	391 (30.5)	696	70 (10.1)
MDR, No. (%)	1	74 (7.2)	1	199 (15.4)	697	42 (6.0)
ESBL, No. (%)	934	100 (10.7)	NA		630	57 (9.0)

n = the number of isolates for which susceptibility testing against that antibiotic was available; "statistics" = the number and percentage of the resistant isolates to that particular antibiotic; NA = not applicable, as the pathogen is intrinsically resistant to the antibiotic as per CLSI standards.

Abbreviations: CAP, community acquired pneumonia; CLSI, Clinical & Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.

patients with a fluoroquinolone-resistant, ceftriaxone-sensitive isolate, only 30 (39%) were switched to either ceftriaxone or cefepime.

Overall, ~7% of the *E. coli* isolates were MDR compared with 15% for *P. aeruginosa* and 6% for *K. pneumoniae*. ESBL-producing *E. coli* accounted for 11% of the isolates vs 9% of *K. pneumoniae*. Compared to CAP patients with ESBL-producing *E. coli*, patients with non-ESBL-producing *E. coli* were more likely to receive adequate empiric therapy (92% non-ESBL vs 63% ESBL *E. coli*; $P < .001$) and were less likely to die in the hospital (13% non-ESBL vs 24% ESBL *E. coli*; $P = .003$).

Outcomes

Table 4 shows the unadjusted outcomes by organism and the same outcomes adjusted for patient demographics, comorbidities, and severity of illness indicators. After adjustments, patients with *E. coli* pneumonia had statistically significantly higher in-hospital case fatality than patients with pneumococcal pneumonia (adjusted odds ratio [aOR], 1.55;

Table 4. Crude and Adjusted Comparisons of Patient Outcomes

		Odds Ratios/Mean Multipliers (95% CI)	
Outcome	Contrast	Unadjusted	Adjusted
In-hospital case fatality[a]	*E. coli* vs other gram-negatives	1.18 (0.96–1.44)	1.06 (0.85–1.32)
	E. coli vs pneumococcus	2.37 (1.91–2.95)	1.55 (1.23–1.97)
ICU[a]	*E. coli* vs other gram-negatives	0.81 (0.70–0.94)	0.79 (0.67–0.92)
	E. coli vs pneumococcus	1.20 (1.04–1.38)	1.12 (0.95–1.31)
IMV[a]	*E. coli* vs other gram-negatives	0.63 (0.53–0.75)	0.60 (0.5–0.72)
	E. coli vs pneumococcus	1.11 (0.93–1.32)	1.03 (0.85–1.25)
Vasopressor[a]	*E. coli* vs other gram-negatives	1.06 (0.91–1.25)	1.02 (0.85–1.21)
	E. coli vs pneumococcus	1.49 (1.27–1.75)	1.29 (1.07–1.54)
Cost[b]	*E. coli* vs other gram-negatives	0.95 (0.87–1.03)	0.95 (0.88–1.02)
	E. coli vs pneumococcus	1.14 (1.04–1.24)	1.07 (0.99–1.15)
Length of stay[b]	*E. coli* vs other gram-negatives	0.93 (0.87–0.98)	0.93 (0.89–0.98)
	E. coli vs pneumococcus	1.06 (1.00–1.13)	1.01 (0.96–1.07)

Cost is inflation-adjusted to 2015 annual costs by using the medical care component of the Consumer Price Index. Models were adjusted for age, gender, marital status, insurance status, dialysis, immunosuppression, hospital admission in the previous 6 months, admitted from SNF/ICF, combined comorbidity scores, hypertension, fluid and electrolyte disorders, chronic pulmonary disease, anemia, diabetes, congestive heart failure, chronic kidney disease, coagulopathy weight loss, other neurological disorders, hypothyroidism, dementia, depression, obesity, valvular disease, peripheral vascular disease, pressure, ulcer, pulmonary circulation disease, psychoses, paralysis, metastatic cancer, liver disease, alcohol disease, solid tumor w/out metastasis, rheumatoid arthritis/collagen, drug abuse, lymphoma, initial ICU, IMV, NIV, vasopressor use.

Abbreviations: ICF, intermediate care facility; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; SNF, skilled nursing facility.

[a]Odds ratio.

[b]Mean multiplier.

95% CI, 1.23–1.97), but the case fatality for patients with *E. coli* pneumonia was not significantly different than other gram-negative pneumonias (aOR, 1.06; 95% CI, 0.85–1.32). After adjustments, patients with *E. coli* pneumonias had less severe disease, as noted by significantly lower ICU admissions (aOR, 0.79; 95% CI, 0.67–0.92), lower IMV (aOR, 0.60; 95% CI, 0.5–0.72), and lower hospital length of stay (mean multiplier, 0.93; 95% CI, 0.89–0.98) in comparison with patients with other gram-negative pneumonias. However, ICU admission, IMV, length of stay, and hospitalization costs did not differ significantly between patients with *E. coli* pneumonia and pneumococcal pneumonias after adjustments.

DISCUSSION

In this large observational cohort of patients with community-acquired pneumonia at 173 US hospitals, we observed that *E. coli* accounted for ~8% of culture-positive bacterial CAP cases. *E. coli* pneumonia was common in older patients with multiple comorbidities and often associated with a principal diagnosis of sepsis. Compared with other gram-negative pneumonias, patients with *E. coli* pneumonias were less likely to be admitted to the ICU, were less likely to require IMV, and had shorter hospital length of stay. More than one-third of the *E. coli* isolates were resistant to fluoroquinolones, a commonly prescribed antibiotic to treat CAP, whereas resistance to ceftriaxone was uncommon. Overall, patients with *E. coli* pneumonia had higher case fatality than patients with pneumococcal pneumonia, but their case fatality was similar to other gram-negative pneumonias.

Multiple studies have described the microbial etiology of CAP. The Pneumonia PORT study, the first large, prospective study of pneumonia etiology and treatment, identified *E. coli* as the fourth most common cause of pneumonia [6]. Two decades later, Gadsby et al. used molecular testing to identify the etiology of pneumonia using respiratory samples and found *E. coli* to be present in 11.5% of all samples, making it the fifth most common pathogen identified [18]. All these studies have identified *E. coli* as a common cause of CAP. Our study generally confirms these findings in a larger and more recent multicenter US cohort. The fact that most of our results came from blood cultures in patients with no alternative source (eg, urine or abdominal infection) strengthens the case. It is not known whether physicians generally consider *E. coli* a cause of CAP. Our finding that, following culture results demonstrating *E. coli* sensitive to ceftriaxone, most physicians did not narrow the spectrum of antibiotic coverage suggests they may doubt that *E. coli* was the causative pathogen.

At least 4 studies have specifically evaluated the role of *E. coli* as an etiologic agent of CAP [19–22]. The reported prevalence of culture-positive *E. coli* pneumonia based on a few published studies evaluating culture-positive CAP ranges from 3.5% to 12% [4–6, 18, 21]. However, these studies focused on several hundred patients and were usually conducted at a single institution. Given what is known about the pathophysiology of bacterial pneumonia in general, taken together, the results of the aforementioned studies indicate that microaspiration in patients colonized with *E. coli* may cause pneumonia in these individuals in the community and is a process that is not exclusively health care associated [23, 24]. In the present study, *E. coli* accounted for ~8% of all culture-positive cases. Higher rates have been observed in elderly patients and those with severe pneumonia [19, 25].

With regard to disease severity in the present study, bacteremia was common in *E. coli* pneumonia, and nearly 40% of the patients needed ICU admission, 20% required respiratory support, and there was a 14% in-hospital case fatality rate. In the Pneumonia PORT study, among the 19 inpatients with *E. coli* pneumonia, associated bacteremia was reported in 48%, 84% had a pneumonia severity index category of 4–5, which conferred expected mortality as high as 27% at 30 days, and while the in-hospital case fatality was 0, the 90-day case fatality rate was 21% [6]. There is evidence to suggest that certain virulence factors such as alpha-hemolysin and cytotoxic necrotizing factor type–1 are often associated with bloodstream infection and sepsis due to *E. coli* [26]. Although expression of these virulence factors is more common in uropathogenic *E. coli*, other nonurosepsis strains are also capable of producing these factors [26]. In our study, we found that in-hospital case fatality was higher among patients with *E. coli* pneumonia than patients with pneumococcal pneumonia but similar to other gram-negative pneumonias, even after adjusting for baseline severity, treatments, and multiple comorbidities. However, in comparison to other gram-negative pneumonias, patients with *E. coli* pneumonia were significantly less likely to be admitted to the ICU, were less likely to be on IMV, and had shorter length of stay. The excess morbidity burden associated with gram-negative pneumonias suggests that overall gram-negative pathogens may be more virulent than other CAP pathogens, as has been suggested by a few previous studies [4, 27].

There is growing antimicrobial resistance among *E. coli* isolates in the past 2 decades, though these isolates are almost exclusively from urine [28–30]. In a large nation-wide US surveillance study from 1995 to 2003, ciprofloxacin resistance among uropathogenic *E. coli* ranged from 0.7% to 2.5% [31]. In contrast, a meta-analysis of studies published from 2004 to 2014 reported that the pooled rate of resistance to ciprofloxacin in patients with community-acquired uropathogenic *E. coli* was 27% (95% CI, 24%–31%) [32]. In our study, which reports on resistance in *E. coli* isolated from the respiratory tract and blood, we observed that more than one-third of the isolates were resistant to fluoroquinolones. The study period preceded the 2019 revision of the fluoroquinolone breakpoints for Enterobacteriaceae, so some isolates classified as susceptible may actually possess low-level fluoroquinolone resistance

or even be associated with an inability to achieve a favorable ratio of the 24-hour area under the concentration–time curve (AUC) to MIC ratio (AUC/MIC), which is associated with microbiological eradication. Taken together, the above indicate that we may have underestimated fluoroquinolone resistance. While fluoroquinolones are part of the recommended empiric therapy for CAP, there is growing evidence to suggest that caution should be exercised in patients with suspected gram-negative pneumonias including *E. coli*. Although fluoroquinolones are considered antipseudomonal drugs and can be used as part of a broad-spectrum approach to patients at risk for MDROs, our data suggest that ceftriaxone and other higher-generation cephalosporins might be a better choice for empiric treatment of patients at risk for gram-negative infections, especially patients over the age of 80, for whom *E. coli* was the second most commonly isolated organism. In our cohort, among patients with ceftriaxone-sensitive *E. coli* isolates that were resistant to fluoroquinolones, <40% were switched to ceftriaxone and other higher-generation cephalosporins.

Our study has several limitations. First, our definition of CAP was based on ICD-9 codes of pneumonia and a positive microbiological test result from either respiratory or blood cultures. As respiratory culture cannot distinguish true infection from colonization, it is impossible to correlate isolated pathogens like *E. coli,* which could colonize the respiratory tract, to pneumonia. This problem is not only confined to our study but is a practical dilemma in similar clinical situations. Also, relying on a definition of CAP that required positive blood/respiratory cultures likely inflated the proportion of overall CAP cases due to *E. coli,* because CAP cases due to other pathogens including viruses, atypical, and anaerobes were excluded. We also excluded patients with culture-negative CAP, and this may have also inflated the proportion of bacterial CAP cases in our cohort. The definition of pneumonia was based upon administrative claims data, which possibly misclassified cases and missed some cases altogether; however, these numbers are likely to be very small [33]. By excluding patients with diagnosis codes for urinary tract infection and gastrointestinal/intra-abdominal infection, we attempted to identify patients with primary pneumonia with no other explanation for having *E. coli* in their blood or respiratory secretions. We also excluded patients who had the presence of a second pathogen in respiratory or blood cultures or both to limit the sample strictly to *E. coli* CAP patients. To the extent that some of these patients may have also had *E. coli* pneumonia, we would have underestimated the prevalence.

In summary, it appears that *E. coli* is a relatively common cause of severe pneumonia. It is often severe and associated with higher case fatality than pneumococcal pneumonia but similar to other gram-negative pneumonias. Fluoroquinolone resistance was common, with a third of the isolates being resistant, whereas resistance to higher-generation cephalosporins was uncommon.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study qualified and was approved by the institutional review board at Cleveland Clinic for exemption of patient consent.

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