

# Ceftriaxone resistance and adequacy of initial antibiotic therapy in community onset bacterial pneumonia

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## Abstract

Much remains unknown about the impact of initial antibiotic adequacy on mortality in community onset bacterial pneumonia (COBP). Therefore, we performed a study to determine how the adequacy of initial antibiotic therapy affects in-hospital mortality for patients with COBP.

We carried out a retrospective cohort study among the 11 BJC Healthcare community and academic hospitals in Missouri and Illinois. The electronic medical records for BJC Healthcare were queried to obtain a set of patient admissions with culture positive (respiratory or blood) COBP admitted from January 1, 2016 through December 31, 2019. Patients with COBP required an International Classification of Diseases (ICD)-10 diagnostic code for pneumonia, admission to the hospital through an emergency department, a chest radiograph with an infiltrate, an abnormal white blood cell count or temperature, an order for 1 or more new antibiotics, and a positive respiratory or blood culture. Antibiotic selection was deemed adequate if the patient had organisms susceptible to at least one of the antibiotics received according to in vitro testing using standard laboratory breakpoints.

Among 36,645 screened pneumonia admissions, 1843 met criteria for culture positive COBP. Eight hundred nineteen (44.4%) had ceftriaxone-resistant (CTX-R) organisms and 1024 had ceftriaxone-sensitive (CTX-S) organisms. The most common CTX-R pathogens were methicillin resistant *Staphylococcus aureus* (46.9%), *Pseudomonas* species (38.4%), and *Escherichia coli* (4.5%). On the day of admission 71% of all patients were given adequate antibiotic treatment (62.2% of CTX-R and 77.9% of CTX-S). Unnecessarily broad initial treatment was administered to 57.1% of CTX-S patients. In a logistic regression model accounting for comorbidities and severity of illness, inadequate therapy on the day of admission was associated with higher in-hospital mortality ( $P = .005$ ). Among CTX-S patients who were adequately treated, initial use of unnecessarily broad antibiotics was associated with increased in-hospital mortality ( $P = .003$ ).

Ceftriaxone resistance was common in this cohort of culture positive COBP patients. Inappropriate coverage on day of admission was associated with greater likelihood of in-hospital mortality.

**Abbreviations:** CAP = community acquired pneumonia, COBP = community onset bacterial pneumonia, CTX-R = ceftriaxone resistant, CTX-S = ceftriaxone sensitive, IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society, MDR = multidrug resistant, MRSA = methicillin resistant *Staphylococcus aureus*.

**Keywords:** adequate initial therapy, antibiotics, ceftriaxone resistance, community onset, pneumonia

## 1. Introduction

Community acquired pneumonia (CAP) remains a major cause of illness in the United States accounting for more than 1 million

hospitalizations annually.<sup>[1]</sup> Though a precise microbiologic etiology is not established in a majority of cases,<sup>[2-4]</sup> there has been a notable increase in the prevalence of multidrug resistant

Editor: Maya Saranathan.

This study was supported by the Mentors in Medicine Program, Division of Medical Education, Washington University School of Medicine.

Marin H. Kollef, MD takes responsibility for and is the guarantor of the content of the manuscript, including the data and analysis.

Dr. Kollef's efforts are supported by the Barnes-Jewish Hospital Foundation. The authors have no conflicts of interest to report.

Our data file can be accessed by emailing the corresponding author.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Van Besien RF, Hampton N, Micek ST, Kollef MH. Ceftriaxone resistance and adequacy of initial antibiotic therapy in community onset bacterial pneumonia. *Medicine* 2022;101:20(e29159).

Received: 9 June 2021 / Received in final form: 8 March 2022 / Accepted: 8 March 2022

<http://dx.doi.org/10.1097/MD.00000000000029159>

(MDR) bacteria in patients presenting from the community.<sup>[5]</sup> Exact figures for antibiotic resistance vary based on the population studied, ranging for 6% of CAP patients overall to 46.7% of patients admitted with proven bacterial pneumonia.<sup>[6,7]</sup>

Choosing empiric therapy for hospitalized patients with pneumonia arising outside of the hospital setting poses a challenge due to greater overall rates of infection with MDR pathogens. Clinicians need to treat for MDR organisms when present, yet overuse of broad spectrum antibiotics will escalate drug resistance. Furthermore, broad spectrum antibiotic use in CAP has been associated with greater mortality, thought to be driven in part by the increased incidence of *Clostridium difficile* infection complicating the treatment of CAP.<sup>[8]</sup> The rise of MDR organisms in CAP is reflected in current prescribing patterns for initial antibiotic therapy of CAP. For example, rates of vancomycin administration for CAP doubled between 2000 and 2009.<sup>[9]</sup> The 2019 combined Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines on CAP recognize this dilemma and recommend treatment with a beta-lactam (such as a third generation cephalosporin) as part of empiric therapy for hospitalized patients.<sup>[10]</sup> However, IDSA/ATS guidance on empiric treatment for MDR organisms such as methicillin resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* is less clear, with the authors recommending that clinicians take into account the severity of illness and “locally validated” risk factors.<sup>[10]</sup>

Inadequate antibiotic therapy for patients with sepsis and septic shock has been shown to be associated with excess mortality.<sup>[11–14]</sup> Similarly, patients with CAP due to antibiotic resistant bacteria have a greater risk of mortality when treated with inadequate initial antibiotics.<sup>[15]</sup> A study of 94 CAP patients found that individuals receiving initial antibiotics that were inconsistent with the IDSA/ATS guidelines fared worse.<sup>[16]</sup> Among bacteremic pneumonia patients, inadequate initial therapy was found to be common, particularly among those with ceftriaxone-resistant (CTX-R) organisms, and was associated with higher mortality.<sup>[17]</sup> In another study involving emergency department patients diagnosed and treated for CAP, 27.8% received inadequate antibiotics initially though no increase in mortality was found.<sup>[18]</sup> In a French study of CAP patients treated in an intensive care unit, adequate initial therapy was associated with better survival at 60 days.<sup>[19]</sup> More recently, Webb et al<sup>[20]</sup> found that inadequate initial therapy was associated with higher mortality in a subgroup analysis of their study of drug resistance in CAP. However, a majority of their cohort was culture negative limiting their sample size.

Much remains unknown about the impact of initial antibiotic adequacy on mortality in community onset bacterial pneumonia (COBP). The objective of our study is to describe the microbiology of COBP and to determine how adequacy of antibiotic therapy on the day of admission affects in-hospital mortality for culture positive cases.

## 2. Methods

### 2.1. Study design and setting

The electronic medical record system for BJC Healthcare was queried to perform a retrospective cohort study of patients diagnosed with pneumonia from January 1, 2016 through December 31, 2019. BJC Healthcare is one of the largest

healthcare systems in the United States containing 11 community hospitals in Missouri and Illinois as well as 2 academic hospitals affiliated with Washington University School of Medicine. Washington University and BJC Healthcare have a longstanding partnership to provide regional healthcare services. This study was approved by the Washington University Institutional Review Board (IRB ID# 201801189).

### 2.2. Participants

We applied the following criteria to select patients as having COBP: International Classification of Diseases (ICD)-10 diagnostic codes for pneumonia (A37.01, J13, J14, J15.x, J16.x, J18.x, J85.1), admission to the hospital through an emergency department, a chest radiograph with an infiltrate documented by board-certified radiologists, an abnormal white blood cell count ( $>11,000$  cells/ $\mu$ L or  $<4000$  cells/ $\mu$ L) or temperature, an order for 1 or more antibiotics (ordered within 24 hours of meeting the radiographic and clinical criteria), and a positive respiratory or blood culture. All criteria had to be met within the first 48 hours of hospital admission. To further support the diagnosis of pneumonia, a random subset of patients ( $\approx 5\%$ ,  $n=100$ ) had their chest radiographs reviewed by an investigator (MHK) blinded to group allocation to confirm the presence of new consolidations on the chest radiograph consistent with a diagnosis of pneumonia ( $>95\%$  of reviewed cases). Patients with cultures only growing organisms that were likely contaminants (including *Enterococcus*, *Candida*, as well as *Salmonella*, coagulase negative *Staphylococcus* or *Corynebacterium* isolated from blood) were eliminated from the analysis.

### 2.3. Variables of interest

Antibiotic adequacy for each patient was determined by comparing the set of antibiotics ordered to the susceptibilities of the organisms isolated from their blood and respiratory cultures. Antibiotic selection was deemed adequate if the patient had organisms susceptible to at least one of the antibiotics received (according to in vitro testing using standard laboratory breakpoints), while not having any organisms resistant to these drugs. In the unusual circumstance of a patient infected with multiple MDR organisms and receiving multiple antibiotics, adjudication of adequacy was determined by manual review. As not all isolates had susceptibility testing performed for all antibiotics ordered, several inferences were used to judge whether an antibiotic provided adequate coverage. Ciprofloxacin and levofloxacin were considered to be equivalent; linezolid and vancomycin were considered to be equivalent; ampicillin-sulbactam and amoxicillin-clavulanate were considered to be equivalent; organisms susceptible to ceftriaxone, methicillin, and cefotaxime were considered to be susceptible to carbapenems, piperacillin-tazobactam, and cefepime; MRSA was considered to be susceptible to vancomycin, linezolid, ceftaroline, and doxycycline; methicillin-susceptible *S aureus* was considered to be susceptible to carbapenems, ceftriaxone, cefepime, ceftaroline, piperacillin-tazobactam, doxycycline, vancomycin, linezolid, ceftazidim, nafcillin, oxacillin, ampicillin-sulbactam, and clindamycin.

Patients in our database were first screened against the definition of COBP. Then we examined their culture data for ceftriaxone resistance dividing the patients into 2 sub-groups: CTX-R and ceftriaxone sensitive (CTX-S). Subsequently,

patients were further divided into 5 cohorts based on antibiotic adequacy. The CTX-R group was divided into adequately and inadequately treated, while the CTX-S group was divided into inadequately treated, overtreated, and narrow spectrum. CTX-S patients were designated as being “overtreated” if they had an organism susceptible to ceftriaxone but received cefepime, meropenem, linezolid, vancomycin, ceftaroline, ceftazidime-avibactam, or ceftolozane-tazobactam. The “narrow spectrum” classification signifies that the patient received adequate coverage with ceftriaxone or a quinolone.

The primary outcome for the study was in-hospital mortality. Predictor variables of interest included age, gender, use of vasopressors on admission, admission to intensive care unit, as well as comorbidities as measured by the 5-year age adjusted Charlson Comorbidity Score.<sup>[21]</sup>

**2.4. Statistical analysis**

Data analysis was performed using R (version 3.5), including the dplyr package, as well as Microsoft Excel.<sup>[22,23]</sup> Categorical variables were compared using chi-squared testing and continuous variables between multiple groups were analyzed with ANOVA. An alpha of 0.05 was utilized for statistical significance. Two logistic regression analyses were prospectively planned to determine patient variables associated with increased in-hospital mortality. The first analysis was run on the entire cohort that included adequacy of antibiotic coverage as a variable. A second logistic regression was planned for the subgroup of patients with CTX-S organisms who were adequately treated to determine effect of overtreatment on mortality. All logistic regressions were binomial and performed using the generalized linear model function (glm) of R version 3.5. Goodness of fit testing was performed with the Hosmer-Lemeshow test. Testing for multicollinearity was performed by calculating the variance inflation factor. Sample size was a convenience sample based on the cohort for the study period.

**3. Results**

**3.1. Adequacy of initial antibiotic therapy lower in CTX-R bacteria**

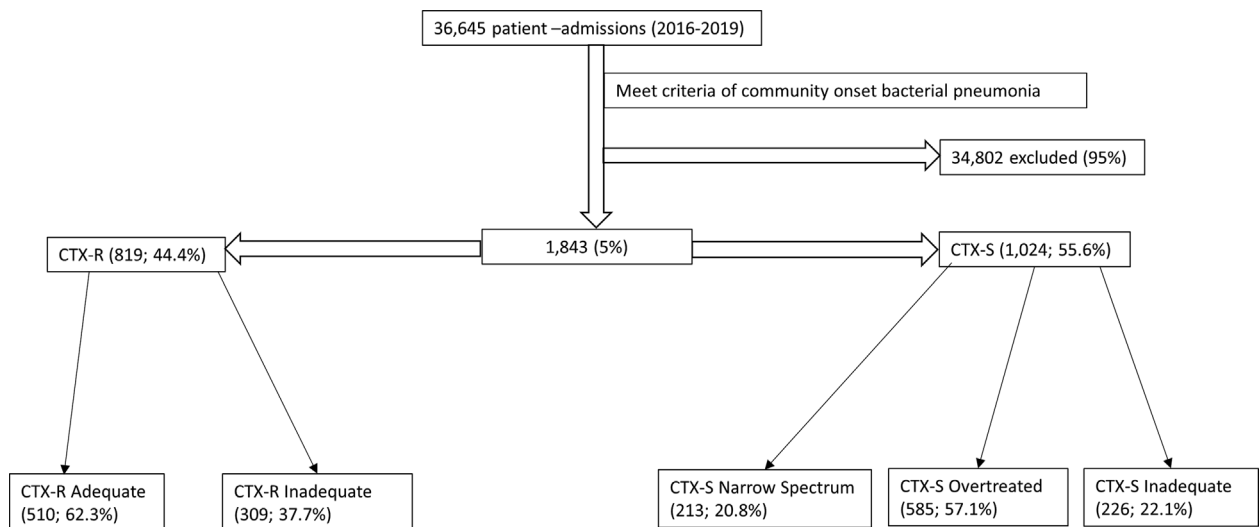
A total of 36,645 patient-admissions were screened, with 1843 meeting all of the criteria for COBP. Figure 1 shows a flowchart for cohort generation and division into the 5 subgroups based on antibiotic choices on the day of admission. Among patients with COBP 819 (44.4%) had CTX-R pathogens. Overall 1308 of the 1843 COBP patients (71%) were treated adequately, including 510/819 (62.3%) of CTX-R and 798/1024 (77.9%) of CTX-S patients. Baseline characteristics for the 5 subgroups are presented in Table 1.

**3.2. Nosocomial pathogens predominated the microbiology of CTX-R bacteria**

The most common pathogens infecting CTX-R patients were MRSA, *Pseudomonas* species, and *Escherichia coli* as shown in Table 2. The most common CTX-S organisms were methicillin sensitive *S aureus*, *Streptococcus pneumoniae*, and *E coli*. Most CTX-S patients were screened into the study by having positive blood cultures while most CTX-R patients had positive respiratory cultures.

**3.3. Broader spectrum initial antibiotic therapy prescribed in patients with CTX-R bacteria**

The distribution of CTX-R and CTX-S patients who received each of the most prescribed antibiotics on admission is shown in Figure 2. There were statistically significant differences in the administration rates of each of the 9 most prescribed antibiotics between the CTX-R and CTX-S groups with the exception of piperacillin-tazobactam. Antibiotic adequacy for both groups was also analyzed on the subsequent 3 days of admission (presumably susceptibility data would begin to become available



**Figure 1.** Flow-chart showing cohort generation based on antibiotics received on day of admission. There were 1843 patients meeting the study criteria for community-onset bacterial pneumonia. These patients were divided into ceftriaxone sensitive (CTX-S) and ceftriaxone resistant (CTX-R) cohorts. These cohorts were further divided into categories based on whether the initial antibiotic regimen was adequate or inadequate for those with CTX-R bacteria, and narrow spectrum, overtreated, and inadequate for those with CTX-S bacteria.

**Table 1**  
**Baseline characteristics.**

	CTX-R adequate* (N = 510)	CTX-R inadequate† (N = 309)	CTX-S narrow spectrum‡ (N = 213)	CTX-S overtreated§ (N = 585)	CTX-S inadequate¶ (N = 226)	P
Gender (M)	56.3%	52.4%	42.3%	53.2%	53.1%	.017
Age (yrs)	61.8 (19.0)	65.4 (17.1)	63.8 (16.1)	63.9 (16.8)	60.1 (16.1)	.002
Race (Caucasian)	67.3%	70.2%	75.6%	65.1%	59.1%	.003
Academic hospital	35.7%	27.8%	11.3%	32.5%	36.7%	<.001
On vasopressors	20.6%	10.7%	1.9%	22.9%	10.6%	<.001
Intensive care unit	45.5%	34.3%	12.2%	47.0%	37.6%	<.001
Charlson Comorbidity Score (5 yr age adjusted)	7.1 (3.7)	7.1 (3.6)	5.2 (3.4)	6.2 (3.6)	5.7 (3.7)	<.001

Results for age and Charlson Comorbidity reported as mean (standard deviation). Categorical variables compared by chi-squared testing and continuous variables compared with analysis of variance.

CTX-R = ceftriaxone resistant, CTX-S = ceftriaxone sensitive.

\* Ceftriaxone resistant organism adequately treated on day of admission.

† Ceftriaxone resistant organism inadequately treated on day of admission.

‡ Ceftriaxone sensitive organism without cefepime, meropenem, piperacillin-tazobactam, vancomycin, linezolid, ceftaroline, ceftolozane-tazobactam, and ceftazidime-avibactam treatment on day of admission.

§ Ceftriaxone sensitive organism treated with at least one of the above listed antibiotics on day of admission.

¶ Ceftriaxone sensitive organism inadequately treated on day of admission.

Antibiotics included in the analysis: ampicillin-sulbactam, azithromycin, aztreonam, ceftazidime-avibactam, ceftolozane-tazobactam, ceftriaxone, ciprofloxacin, clindamycin, doxycycline, ertapenem, gentamicin, levofloxacin, linezolid, meropenem, nafcillin, oxacillin, piperacillin-tazobactam, and vancomycin.

at approximately days 3–4), results of which are presented in Table 3. A majority (57.12%) of CTX-S patients were overtreated initially. Overtreatment peaked at day 2, while for both groups overall adequacy of therapy increased with each day of admission.

### 3.4. CTX-R bacteria associated with higher mortality

Mortality for the antibiotic treatment subgroups is shown in Table 4. CTX-R patients had higher in-hospital mortality compared with CTX-S patients (14.4% vs 10.2%,  $P = .007$ ). Logistic regression analyses for in-hospital mortality are displayed in Table 5. For the overall cohort of 1843 patients, antibiotic adequacy on admission was associated with decreased in-hospital mortality ( $P < .001$ ). For the subgroup of 798 CTX-S patients adequately treated, overtreatment was associated with increased in-hospital mortality ( $P = .003$ ).

## 4. Discussion

Ceftriaxone resistance was common in this cohort affecting 44.4% of patients with COBP. This is higher than some figures

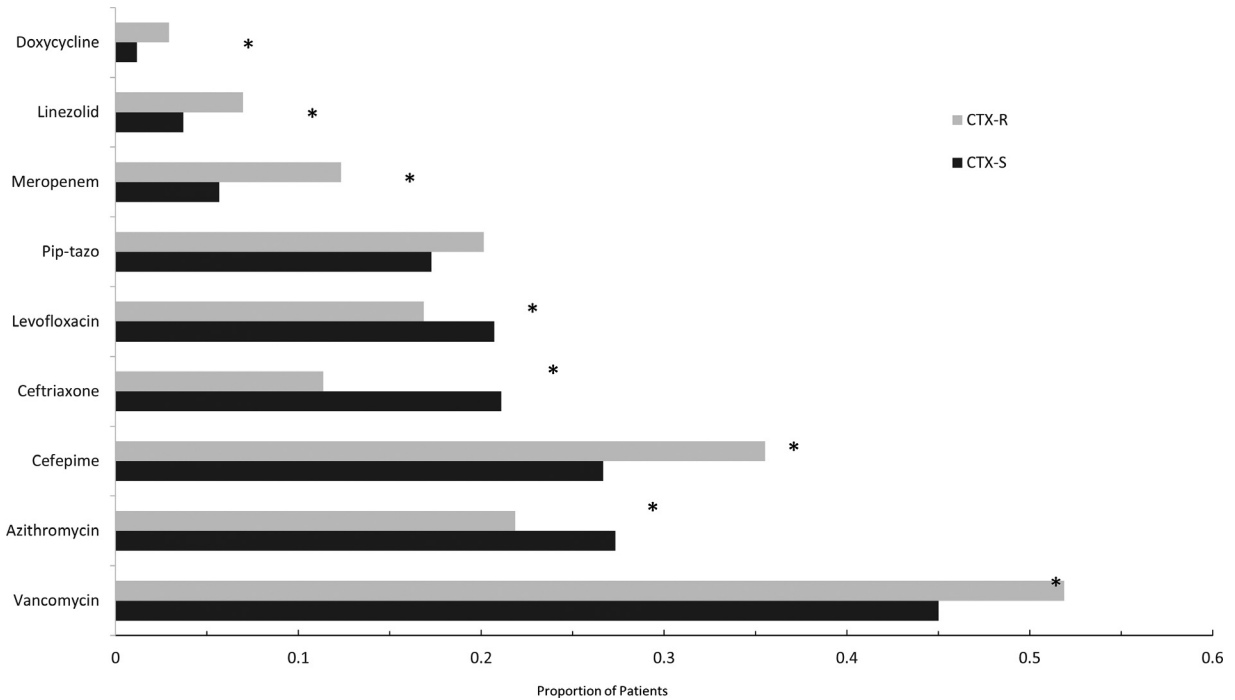
for drug resistant organisms previously found in studies of CAP, although it is important to recognize that our study is limited to patients with a positive culture and in a majority of pneumonia cases a positive culture is not obtained.<sup>[2–4,6,20]</sup> This value of 44.4% is similar to the 46.7% incidence of CTX-R organisms obtained by Shorr et al<sup>[7]</sup> in our institution in their study of culture positive pneumonia presenting through an academic hospital emergency department. Not surprisingly, MRSA and *Pseudomonas* were the predominant CTX-R organisms, though there was notable prevalence of ceftriaxone resistance among the enteric Gram negatives including *E coli*, *Klebsiella* species, and *Serratia* species. Our study also supports a higher mortality being associated with CTX-R organisms as shown in other studies of outpatient pneumonia.<sup>[24–26]</sup>

It should be noted that our study cohort represents a population with a high severity of illness, with 39.3% of patients admitted to an intensive care unit, which is greater than the number of patients requiring intensive care in the generalized CAP population.<sup>[2,10]</sup> One possible explanation is that our cohort contains only those patients with positive bacterial cultures, and blood and respiratory cultures are more commonly

**Table 2**  
**Microbiology of ceftriaxone-sensitive and ceftriaxone-resistant bacterial.**

Pathogen	Ceftriaxone-resistant		Ceftriaxone-sensitive	
	Blood cultures (n = 279)	Respiratory cultures (n = 584)	Blood cultures (n = 727)	Respiratory cultures (n = 361)
<i>Streptococcus pneumoniae</i>	0.7	0.2	27.9	39.0
<i>Staphylococcus aureus</i>	58.0	42.3	24.1	38.2
<i>Pseudomonas species</i>	20.0	47.8	–	–
<i>Acinetobacter species</i>	1.4	0.9	0.7	0.3
<i>Enterobacter species</i>	2.9	2.7	0.7	0.8
<i>Klebsiella species</i>	1.8	1.0	6.6	8.6
<i>Escherichia coli</i>	10.8	1.5	16	6.4
<i>Proteus species</i>	0.4	–	3.0	1.6
<i>Morganella morganii</i>	0.4	–	0.6	0.3
<i>Serratia species</i>	2.5	3.1	0.8	1.4
<i>Haemophilus influenza</i>	–	–	1.1	–
Other Streptococcal species	–	–	17.1	1.1
<i>Citrobacter species</i>	–	–	0.4	0.6
Other	1.1	0.3	1.1	1.7

Percent of patient admissions with at least 1 culture growing that organism (e.g., a patient with multiple blood cultures positive for the same pathogen during an admission is counted once).



**Figure 2.** Antibiotic choices on day of admission for ceftriaxone resistant (CTX-R; N=819) vs ceftriaxone sensitive (CTX-S; N=1024) patients. \*Signifies statistically significant difference ( $P < .05$ ).

**Table 3**

**(a) Adequacy of antibiotic coverage for CTX-S and CTX-R on first 4 days of admission. (b) Proportion of CTX-S patients who were overtreated on the first 4 days of admission.**

	Day 1	Day 2	Day 3	Day 4
<b>(a)</b>				
CTX-S adequate coverage	798/1024 (77.9%)	900/1024 (87.9%)	945/1024 (92.3%)	889/953 (93.4%)
CTX-R adequate coverage	509/819 (62.2%)	585/819 (71.4%)	825/819 (76.3%)	644/783 (82.4%)
<b>(b)</b>				
CTX-S overtreatment*	585/1024 (57.1%)	733/1024 (71.6%)	679/1024 (66.3%)	549/953 (57.7%)

CTX-R = ceftriaxone resistant, CTX-S = ceftriaxone sensitive.

\*Subset of CTX-S patients who had a ceftriaxone-sensitive organism and were treated with cefepime, meropenem, piperacillin-tazobactam, vancomycin, linezolid, ceftaroline, ceftolozane-tazobactam, or ceftazidime-avibactam on day of admission.

**Table 4**

**In-hospital mortality of each subgroup. Chi-squared testing used to calculate P value.**

	CTX-R adequate* (N = 510)	CTX-R inadequate† (N = 309)	CTX-S narrow spectrum‡ (N = 213)	CTX-S overtreated§ (N = 585)	CTX-S inadequate¶ (N = 226)	P
In-hospital mortality	72 (14.1%)	46 (14.9%)	5 (2.4%)	73 (12.5%)	27 (12.0%)	<.001

Chi-squared testing used to calculate P value.

CTX-R = ceftriaxone resistant, CTX-S = ceftriaxone sensitive.

\*Ceftriaxone resistant organism adequately treated on day of admission.

†Ceftriaxone resistant organism inadequately treated on day of admission.

‡Ceftriaxone sensitive organism treated without cefepime, meropenem, piperacillin-tazobactam, vancomycin, linezolid, ceftaroline, ceftolozane-tazobactam, or ceftazidime-avibactam on day of admission.

§Ceftriaxone sensitive organism treated with at least one of the above listed antibiotics on day of admission.

¶Ceftriaxone sensitive organism inadequately treated on day of admission.

**Table 5**  
**(a) Logistic regression analysis for in-hospital mortality for entire cohort of 1843 patient-admissions. (b) Logistic regression analysis for in-hospital mortality for the cohort of the 798 patients with CTX-S pathogens receiving adequate initial antibiotic treatment.**

<b>(a)</b>			
<b>Variable</b>	<b>Estimate</b>	<b>Standard error</b>	<b>P</b>
Academic medical center	0.009	0.168	.95
Gender (male)	0.103	0.15	.49
Age (yrs)	0.014	0.006	.02
Bacteremia	0.336	0.157	.03
Vasopressors day 1	0.727	0.184	<.001
ICU admission day 1	0.878	0.174	<.001
Charlson 5 yr (age adjusted) score	0.11	0.024	<.001
Adequate antibiotic coverage day 1	-0.471	0.167	<.001
<b>(b)</b>			
<b>Variable</b>	<b>Estimate</b>	<b>Standard error</b>	<b>P</b>
Academic medical center	-0.212	0.294	.47
Gender (male)	-0.021	0.249	.93
Age (yrs)	0.03	0.011	.004
Bacteremia	0.14	0.301	.63
Vasopressors day 1	0.489	0.305	.10
ICU admission day 1	0.617	0.293	.03
Charlson 5 yr (age adjusted) score	0.0608	0.042	.14
Overtreated	1.44	0.488	.003

(a) Testing for collinearity performed with by calculating the variance inflation factor ranging from 1.01 to 1.40 for these variables. Goodness of fit testing performed with Hosmer-Lemeshow test (chi squared 8.36 with df=8, *P*=.399).

(b) Variance inflation factor ranged from 1.01 to 1.39 for these variables. Goodness of fit testing performed with Hosmer-Lemeshow test (chi squared 11.61 with df=8, *P*=.166).  
 CTX-S=ceftriaxone sensitive.

obtained in those with severe illness, which is in keeping with the 2019 IDSA/ATS guidelines.<sup>[10]</sup>

As suggested by Figure 2, clinicians may have employed criteria such as presence of comorbidities and healthcare exposure to determine which patients harbor antibiotic resistant organisms, as CTX-R patients were more likely to receive empiric antibiotics to treat for resistant organisms (such as vancomycin, meropenem, and cefepime), while CTX-S patients were approximately twice as likely to receive empiric ceftriaxone. However, there was under treatment of CTX-R patients with only 62.15% receiving adequate treatment initially. Furthermore, a majority of CTX-S patients were overtreated on all days analyzed, peaking at 77% on day 2. Table 1 also suggests that clinicians are highly influenced by severity of illness (as assessed by intensive care unit admission and use of vasopressors) when deciding on the spectrum of antibiotics to administer. There were notable similarities in the CTX-R adequate group and the CTX-S overtreated group in terms of vasopressor use (20.6% vs 22.9%, *P*=0.35) and ICU admission (45.5% vs 47.0%, *P*=0.61). Thus, clinicians were likely treating patients in these 2 groups with broad spectrum antibiotics based on their disease severity. Additionally, we found underutilization of azithromycin overall in this population, with fewer than 30% of patients receiving it on day 1. According to the 2019 IDSA/ATS guidelines, atypical pathogen coverage should be given liberally to these patients.<sup>[10]</sup> The logistic regression analyses show that adequacy of therapy on the day of admission is inversely associated with in-hospital mortality. Furthermore, among the adequately treated CTX-S patients overtreatment

was associated with higher in-hospital mortality. Therefore, the initial antibiotic choice for COBP is of great importance. However, our findings should be weighed against other studies such as the Veterans Affairs study of Jones et al<sup>[27]</sup> finding that initial empiric MRSA coverage for pneumonia did not impact mortality in their population. Thus prevalence of local antibiotic resistance, along with disease severity and patient risk factors for infection with antibiotic resistant pathogens, are important factors to consider when making empiric treatment decisions for patients with CAP.<sup>[10]</sup>

The strengths of this study are that it involves a large, robust dataset across several hospitals (both community and academic) spanning 4 years. Furthermore, we systematically compared each individual's set of antibiotics to their unique culture susceptibilities for each of the first 4 days of admission. The major limitation is that this cohort is restricted to those who had positive bacterial cultures, thus affecting generalizability to the overall community onset pneumonia population in which a significant proportion are culture-negative have viral etiologies. Another limitation is that antibiotic adequacy was based on calendar day of administration as opposed to measuring time to antibiotic administration. Theoretically this could lead to a misclassification error if a patient was admitted late in the evening and received antibiotics shortly after midnight, as this would be counted as having inadequate initial therapy on day 1. However, we expect this effect to be limited overall, as day 2 data show significant coverage gaps as well. One would also expect this effect to be distributed equally to both CTX-R and CTX-S groups. Another limitation of our study is that clinicians at our institutions do not routinely employ scoring systems such as the CARMELI score or the DRIP score.<sup>[20,28]</sup> Lastly, our classification of patients coming in from the community as having COBP may be imprecise as it fails to differentiate individuals with healthcare exposure (e.g., recent hospitalization, residence in a nursing home, use of chronic dialysis) from those without such exposure. The most recent IDSA/ATS guidelines recommends against using the classification of healthcare-associated pneumonia as it may lead to greater unnecessary use of broad-spectrum antibiotics.<sup>[10]</sup> Therefore, we grouped all patients as having COBP regardless of whether or not they had some type of healthcare exposure prior to admission.

## 5. Conclusions

Treating infections in the 21st century is a balancing act between upholding antibiotic stewardship while ensuring adequate therapy to a population with an increasing prevalence of resistant organisms. This study shows that opportunities for improvement in the administration of initial therapy exist and potentially include enhanced stewardship practices, the use of rapid microbiologic diagnostics, and the use of machine learning/artificial intelligence derived algorithms to guide antibiotic decision making. Further research is needed to develop higher resolution tools to accurately predict which patients are likely to harbor resistant organisms including the broader use of molecular diagnostics and machine learning prediction instruments.<sup>[29-31]</sup>

## Author contributions

MHK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the

data analysis, including and especially any adverse effects. RFV, NH, STM, and MHK contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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