

Bacterial Treatment Failure in Adults With Community-Acquired Bacterial Pneumonia: An Analysis of a Large US Claims Database

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ABSTRACT

- Community-acquired bacterial pneumonia (CABP) is a leading cause of hospitalization and death worldwide.
- Approximately 20% of patients are estimated to have experienced at least 1 treatment failure with commonly used antibiotics, suggesting the need for better treatment options for CABP.^{1,2}
- Reports of the burden of treatment failure obtained from literature are mostly restricted to failures leading to a hospitalization.³
- In 2013, the Centers for Disease Control listed CABP caused by *Streptococcus pneumoniae* (*S. pneumoniae*) as a serious threat, based on findings that 30% of severe *S. pneumoniae* cases were resistant to clinically relevant antibiotics.⁴
- Despite increasing rates of antibiotic resistance, evidence on the effect of this growing resistance on treatment failure with common CABP antibiotic therapies is not well documented.⁵
- The objective of this study was to compute failure rates of common antibiotic treatments used to treat CABP in adults.

METHODS

Study Design

- Retrospective claims analysis using the Truven Health MarketScan[®] Commercial and Medicare Supplemental Databases for July 1, 2010 through June 30, 2015 (study period).

Study Population

- Patients aged 18 and over, with an outpatient diagnosis of CABP (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 481.x, 482.x, 485.x, 486, 487.0) in the primary position, between June 30, 2011 and May 30, 2015 (enrollment period), and a prescription fill within 3 days of the first CABP medical claim for the following antibiotic monotherapies:
 - Beta-lactam: amoxicillin, amoxicillin-clavulanate, ceftriaxone
 - Macrolide: azithromycin, clarithromycin
 - Fluoroquinolone: levofloxacin, moxifloxacin, ciprofloxacin
 - Tetracycline: doxycycline
- The prescription fill date was considered the index date.
- Continuous enrollment in non-HMO medical and pharmacy coverage in the 12 months prior to the first CABP claim through 30 days following the index date, unless there is evidence of patient death prior to the 30 days.
- No medical claim with a primary diagnosis of CABP (inpatient or outpatient) AND no prescription fills for any antibiotic in the 30 days prior to the first outpatient CABP claim in the enrollment period, AND no hospitalization for any reason within 2 days of the index date.

Study Cohorts

- Antibiotic drug class: beta-lactam, macrolide, fluoroquinolone, tetracycline.
- Antibiotic agent: amoxicillin, amoxicillin-clavulanate, ceftriaxone, azithromycin, clarithromycin, levofloxacin, moxifloxacin, ciprofloxacin, doxycycline.

Covariates

- Demographic characteristics: age, gender, health plan type, geographic area of residence, and index year, measured on the index date.
- Clinical characteristics: Deyo-Charlson Comorbidity Index (DCCI), individual DCCI conditions, asthma, arrhythmias, and receipt of pneumococcal vaccine, measured in the 12-month baseline period, and CABP diagnosis.

Outcomes

- Composite treatment failure: The first of any one of the following in the 30 days after the index date:
 - Refill for the index agent after exhaustion of days' supply, as recorded on prescription claim
 - Antibiotic fill other than the index agent dispensed >1 day after the index date and not restricted to the antibiotics of interest
 - Emergency room (ER) visit with a CABP diagnosis ≥3 days and <30 days after the index fill
 - Hospitalization with a CABP diagnosis ≥3 days and <30 days after the index fill
- Reason for treatment failure: Binary indicators for each of the 4 events comprising composite failures.
- Death: Evaluated within 30 days of the index using claims-based proxy.

Statistical Analysis

- Categorical measures are presented as frequencies and percentages, and continuous measures as means and standard deviations (SD).
- Multinomial logistic regression was used to obtain adjusted rates of composite treatment failure and the reason for failure, controlling for demographic and pre-index clinical characteristics, and index drug class or agent. Odds ratios (OR) and 95% confidence intervals are presented for select significant predictors of composite treatment failure.

RESULTS

Study Population

- A total of 257,165 adult CABP patients met the inclusion criteria of the study.
- Patients were most likely to be prescribed macrolides (43.6%) and fluoroquinolones (44.4%) (Table 1). Azithromycin (39.5% overall) and levofloxacin (36.6% overall) were the most commonly prescribed antibiotics among the 9 agents evaluated (Table 1).
- Due to low counts, a post hoc decision was made to exclude patients prescribed ceftriaxone or ciprofloxacin as their first (index) antibiotic.
- All analyses were conducted using the remaining 251,947 adult patients with CABP.

Patient Characteristics

- The average age of a study patient was 52.2 ± 17.4 years and 47.7% were male.
- Pneumonia, organism unspecified (ICD-9-CM 486.XX) was the most common diagnosis (84.5%) (Table 2).
- The average DCCI score was 0.88 ± 1.53 (range 0–32), and most patients (59.7%) did not have claims noting any DCCI condition. The most common DCCI conditions were chronic obstructive pulmonary disease (COPD) (18.1%) and diabetes (11.5%).

Treatment Failure

- A total of 55,741 patients (22.1%) failed their index antibiotic therapy (Table 3).
- The treatment failure rate among those aged 18 to 64 years was 21.2%, and 25.7% for those 65 years and older.
- More than 70% of initial treatment failures resulted in a new antibiotic fill; second-line agents were most likely to be either fluoroquinolones (31.0%) or beta-lactams (30.7%).
- Failure resulting in CABP hospitalization occurred in 5.4%, and an ER visit in 3.3% of failures. Rates of hospitalization and ER visits failures were highest in the fluoroquinolone group.
- Patients receiving beta-lactams as their index therapy were at a significantly higher likelihood of failing index therapy (P<0.0001).
- Patients initiated on fluoroquinolones were more likely to refill their index drug, and consequently less likely to fill a prescription for a different drug class as second-line therapy (P<0.0001).
- Increasing age, more distant index year, and pre-index DCCI, were among the significant predictors of treatment failure (Figure 1a).
 - Due to multicollinearity, DCCI and the individual comorbidity indicators could not be included in the same model. A second logistic model was evaluated and demonstrated that pre-index metastatic cancer, hemiplegia or paraplegia, rheumatologic disease, and COPD were also among the significant predictors of composite treatment failure (Figure 1b).
- The adjusted risk of treatment failure was highest in the beta-lactam group (25.7%), followed by macrolide group (22.9%). Patients initiated on fluoroquinolones were the least likely to fail index treatment (20.8%) (Figure 2).

30-Day Mortality

- The overall 30-day post-index mortality rate was 7.6%; 6.5% for those aged 18 to 64 years and 11.6% among those ≥65 years of age.
- Those with treatment failure experienced a significantly greater mortality rate than those without (18.1% vs 4.6%, P<0.001).
- Nearly one-quarter of CABP patients (24.3%) aged 65 years and older with treatment failure had evidence of death within 30 days of antibiotic initiation.

LIMITATIONS

- Study uses claims data captured for the purpose of provider reimbursement, and not for research.
- The diagnosis code recorded for the majority of CABP patients was "Pneumonia, organism unspecified," therefore patients with viral pneumonia may be included.
- Antibiotic prescriptions are assumed to be for the treatment of CABP.

RESULTS (continued)

Table 1. Distribution of Index Drug

Index Drug	Frequency	Total (%)	Therapeutic Class (%)
TOTAL	257,165	100.0%	—
Beta-lactam	16,749	6.5%	100.0%
Amoxicillin	2,622	1.0%	15.7%
Amoxicillin-Clavulanate	13,904	5.4%	83.0%
Ceftriaxone	223	0.1%	1.3%
Macrolide	112,054	43.6%	100.0%
Azithromycin	101,492	39.5%	90.6%
Clarithromycin	10,562	4.1%	9.4%
Fluoroquinolone	114,174	44.4%	100.0%
Levofloxacin	95,019	36.9%	83.2%
Moxifloxacin	14,160	5.5%	12.4%
Ciprofloxacin	4,995	1.9%	4.4%
Tetracycline	14,188	5.5%	100.0%
Doxycycline	14,188	5.5%	100.0%

Note: Patients receiving ceftriaxone and ciprofloxacin were excluded from treatment failure analyses due to low counts.

Table 2. Clinical Characteristics of Study Population

Clinical and Disease Characteristics	Total (N=251,947)
Index Year, n (%)	
2011	32,033 (12.7%)
2012	80,358 (31.9%)
2013	59,041 (23.4%)
2014	55,398 (22.0%)
2015	25,207 (10.0%)
DCCI, Mean (SD)	0.88 (1.53)
DCCI, n (%)	
0	150,354 (59.7%)
1	49,989 (19.8%)
2	23,540 (9.3%)
3+	28,064 (11.1%)
Individual Charlson Comorbidity Index Comorbidities, n (%)	
Myocardial Infarction	4,141 (1.6%)
Congestive Heart Failure	11,975 (4.8%)
Peripheral Vascular Disease	12,687 (5.0%)
Cerebrovascular Disease	13,434 (5.3%)
Dementia	2,744 (1.1%)
Chronic Pulmonary Disease	45,698 (18.1%)
Rheumatologic Disease	6,521 (2.6%)
Peptic Ulcer Disease	1,761 (0.7%)
Mild Liver Disease	7,458 (3.0%)
Diabetes	28,856 (11.5%)
Diabetes With Chronic Complications	8,754 (3.5%)
Hemiplegia or Paraplegia	1,207 (0.5%)
Renal Disease	8,857 (3.5%)
Chronic Kidney Disease	6,763 (2.7%)
End-stage Renal Disease	1,006 (0.4%)
Cancer	14,571 (5.8%)
Moderate or Severe Liver Disease	411 (0.2%)
Metastatic Cancer	2,426 (1.0%)
AIDS	995 (0.2%)
Other Comorbidities, n (%)	
Asthma	22,611 (9.0%)
Arrhythmias	22,163 (8.8%)
481 (pneumococcal pneumonia)	3,645 (1.4%)
482.x (other bacterial pneumonia)	16,369 (6.5%)
485.x (bronchopneumonia organism unspecified)	12,843 (5.1%)
486 (pneumonia organism unspecified)	213,012 (84.5%)
487.0 (influenza with pneumonia)	2,494 (1.0%)
Multiple CABP Diagnoses	3,584 (1.4%)

KEY: AIDS – acquired immune deficiency syndrome; CABP – community-acquired bacterial pneumonia; DCCI – Deyo-Charlson Comorbidity Index; SD – standard deviation.

Table 3. Unadjusted Treatment Failure by Index Drug Class

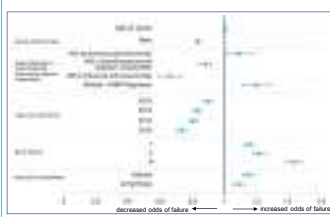
Index Failure Type	Index Drug Class ^a				
	All Patients N=251,947	Beta-lactam N=16,726	Macrolide N=112,054	Fluoroquinolone N=109,179	Tetracycline N=14,188
Composite Treatment Failure, n (%)	55,741 (22.1%)	4,289 (26.0%)	24,650 (22.0%)	23,562 (21.6%)	3,240 (22.8%)
Refill Index Antibiotic, n (%)	11,493 (20.6%)	561 (13.1%)	4,896 (19.9%)	5,708 (24.2%)	328 (10.1%)
Only New Antibiotic Prescription, n (%)	39,099 (70.1%)	3,385 (78.9%)	18,105 (73.4%)	14,991 (63.6%)	2,618 (80.8%)
New Agent Drug Class					
Beta-lactam	12,017 (30.7%)	456 (13.5%)	6,167 (34.1%)	4,716 (31.5%)	678 (25.9%)
Macrolide	8,011 (20.5%)	1,189 (35.1%)	679 (3.8%)	5,454 (36.4%)	689 (26.3%)
Fluoroquinolone	12,129 (31.0%)	1,264 (37.3%)	8,536 (47.1%)	1,296 (8.6%)	1,033 (39.5%)
Tetracycline	3,369 (8.6%)	226 (6.7%)	1,545 (8.5%)	1,585 (10.6%)	13 (0.5%)
Other Antibiotics	2,598 (6.6%)	190 (5.6%)	998 (5.5%)	1,259 (8.4%)	151 (5.8%)
More than 1 new antibiotic ^b	975 (2.5%)	60 (1.8%)	180 (1.0%)	681 (4.5%)	54 (2.1%)
Hospitalization, n (%)	3,016 (5.4%)	222 (5.2%)	803 (3.3%)	1,826 (7.7%)	165 (5.1%)
Emergency Room visit, n (%)	1,835 (3.3%)	111 (2.6%)	688 (2.8%)	924 (3.9%)	112 (3.5%)

^a Comparisons between drug classes were statistically significant (P<0.0001) for composite treatment failure and all individual failure types.

^b A total of 298 patients (0.5%) with treatment failures were defined by having both a refill of their index antibiotic and a fill for a new agent on the same day.

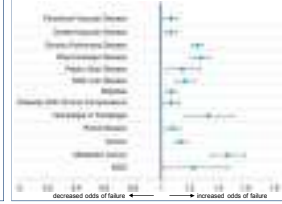
^c On the same date.

Figure 1a. Select Significant Predictors of Composite Treatment Failure (OR, 95% CI)



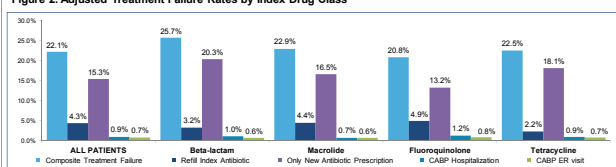
KEY: CABP – community-acquired bacterial pneumonia; CI – confidence interval; DCCI – Deyo-Charlson Comorbidity Index; OR – odds ratio.

Figure 1b. Deyo-Charlson Comorbidity Index Predictors of Composite Treatment Failure (OR, 95% CI)



KEY: AIDS – acquired immune deficiency syndrome; CI – confidence interval; OR – odds ratio.

Figure 2. Adjusted Treatment Failure Rates by Index Drug Class



KEY: CABP – community-acquired bacterial pneumonia; ER – emergency room.
Note: The denominator for the calculation of treatment failure rates is the total sample of the study aged 18 years and older. Adjusted treatment failure was estimated using logistic regression models, while controlling for demographics, clinical characteristics, and CABP diagnosis.

CONCLUSIONS

- In this population of CABP patients with employer-sponsored insurance, more than 1 in 5 patients aged 18 years and older, and approximately 1 in 4 aged 65 and older treated with 1 of the 7 antibiotics evaluated failed their initial antibiotic therapy.
- 30-day mortality was 4 times greater among treatment failures than non-treatment failures, and 1 in 4 patients 65 years and older failing treatment had evidence of death within 30 days after antibiotic initiation.
- There remains a significant unmet need in treating CABP in patients aged 18 years and older.