Patterns of antibiotic treatment failure in pediatric community-acquired bacterial pneumonia in the USA

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Abstract

Community-acquired bacterial pneumonia (CABP) is the leading global cause of pediatric mortality from infection[1,2]. Due to limited in-depth analyses of pediatric CABP antibiotic use and treatment failure[3], physicians face the ongoing challenge of choosing appropriate first-line treatment strategies empirically. Further, the rise in antibiotic resistant pathogens has significantly compromised treatment efficacy[3], creating an even bigger challenge for doctors to choose an effective antimicrobial therapy. Therefore, there is an urgent need to better understand specific indicators of pediatric CABP treatment failure to more accurately guide physician's treatment choices, and therefore increase the overall likelihood of success. In this study, we performed a retrospective analysis of pediatric patients with CABP using the Truven MarketScan® Commercial & Medicare Supplemental Databases to quantify factors associated with pediatric treatment failure. Our analysis revealed specific trends of treatment failure depending on the initial antibiotic class used for treatment, and the geographical region of each patient. Specifically, patients initially prescribed a beta-lactam drug were almost 2X more likely to fail compared to those initially prescribed a macrolide. More so, failure rates are region specific. These findings may have implications in informing more optimized treatment choices to improve the efficacy for pediatric CABP.

Methods

For the retrospective analysis, the final population consisted of 156,413 patients <18 years diagnosed with CABP (ICD-9-CM) during the enrollment window of June 2011 – May 2015. All patients were required to have met all inclusion criteria. These patients were treated with one of the following index drug classes: beta-lactam, macrolide, fluoroquinolone, or tetracycline monotherapy. United States regions were defined according to the U.S. census bureau.Treatment failure (Y/N) was defined as index drug refill, non-index drug fill, hospitalization, or emergency room visit 3-30 days post-index fill. Descriptive statistics were used to summarize demographics and treatment outcomes. Bayesian statistics were used to evaluate the impact of index drug on treatment failure.

To analyze the characteristics associated with treatment failure, we focused on three main criteria:

1. Initial drug index prescription

- Pediatric patients are almost two times more likely to receive a macrolide antibiotic compared to a beta-lactam drug when initially treated for CABP. The specific drug used within each class can be found in **Table 1**.
- Consistent with guidelines, Fluoroquinolones and tetracyclines make up a smaller percentage (0.6% and 0.3%, respectively).

Table 1: Clinical characteristics of pediatric patients treated for CABP

	Frequency†	Percent of Total	Percent of Therapeutic Class
Beta-lactam	**54,820**	**35.0%**	**100.0%**
amoxicillin	31,868	20.3%	58.1%
amoxicillin-clavulanate	22,935	14.6%	41.8%
ceftriaxone	17	0.0%	0.0%
Macrolide	**100,528**	**64.2%**	**100.0%**
azithromycin	97,017	61.9%	96.5%
clarithromycin	3,511	2.2%	3.5%
Fluoroquinolone	**867**	**0.6%**	**100.0%**
levofloxacin	612	0.4%	70.6%
moxifloxacin	49	0.0%	5.7%
ciprofloxacin	206	0.1%	23.8%
Tetracycline	**421**	**0.3%**	**100.0%**
doxycycline	421	0.3%	100.0%

† Mutually exclusive

2. Treatment failure

- 16.2% of pediatric CABP episodes resulted in treatment failure
- Patients who receive **treatment with a beta-lactam** (20.9%) were **significantly more likely** to fail compared to those who initially received a macrolide drug (13.7%) ($P < 0.001$) (**Figure 1**).
- Patients treated with a **macrolide** drug had the **lowest failure rate amongst** all drug classes

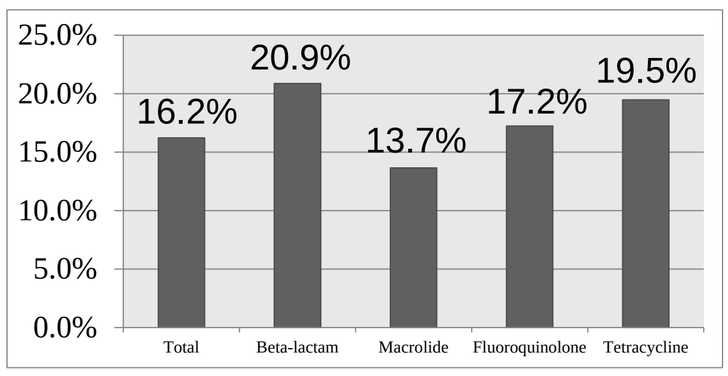


Figure 1. Composite treatment failure by drug index. The x-axis is the sub-group of patients initially treated with the given drug class, and the y-axis is the percentage of patients from the drug class who failed treatment.

- The most common evidence of treatment failure was due to a new antibiotic prescription fill (**Table 2**)
- Hospitalization and ER visits made up a minority of the failure rates

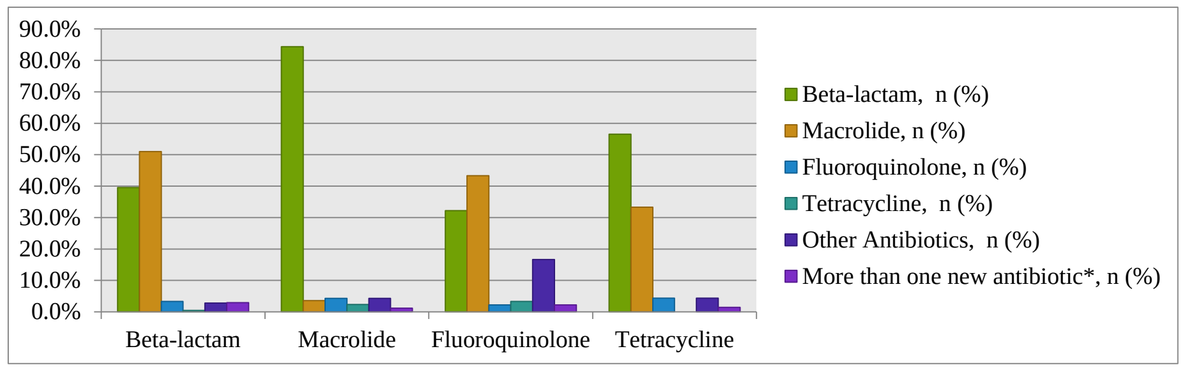
Table 2: Causes of treatment failure

	Beta-lactam	Macrolide	Fluoroquinolone	Tetracycline
Refill index antibiotic)	8.6%	18.5%	15.8%	14.6%
Only New Antibiotic Prescription)	86.4%	78.0%	78.9%	84.1%
CABP Hospitalization	2.3%	1.1%	1.8%	0.0%
CABP ER visit, n (%)	2.5%	1.8%	2.6%	1.2%

3. Refill antibiotic class of those that failed initial drug index

- A significant portion of patients who failed beta-lactam treatment were prescribed a second beta-lactam (39.5%, **Figure 2**).
- Patients who failed macrolide treatment were prescribed a second macrolide to a much lesser extent (3.9%, **10X less than for beta-lactams**)
- Beta-lactams were the most common antibiotic prescribed when a patient initially failed macrolide treatment (similar for macrolides).

Figure 2. New drug index of patients who failed due to new antibiotic fill. X-axis is the initial drug index group, and y-axis is the percentage of patients given the new fill, described in the legend and differentiated by color.



4. Treatment failure by region:

- The likelihood of treatment failure changes by region, depending on the initial index drug prescribed (**Figure 3**). For example, patients initially prescribed tetracycline are significantly more likely to fail if they reside in East South Central region (39.5%), compared to the mountain region (6.7%).
- Failure trends for beta-lactams and macrolides are region-specific (e.g. failure is greatest in East South Central region (22.5% for beta-lactams and 16.4% for macrolides).

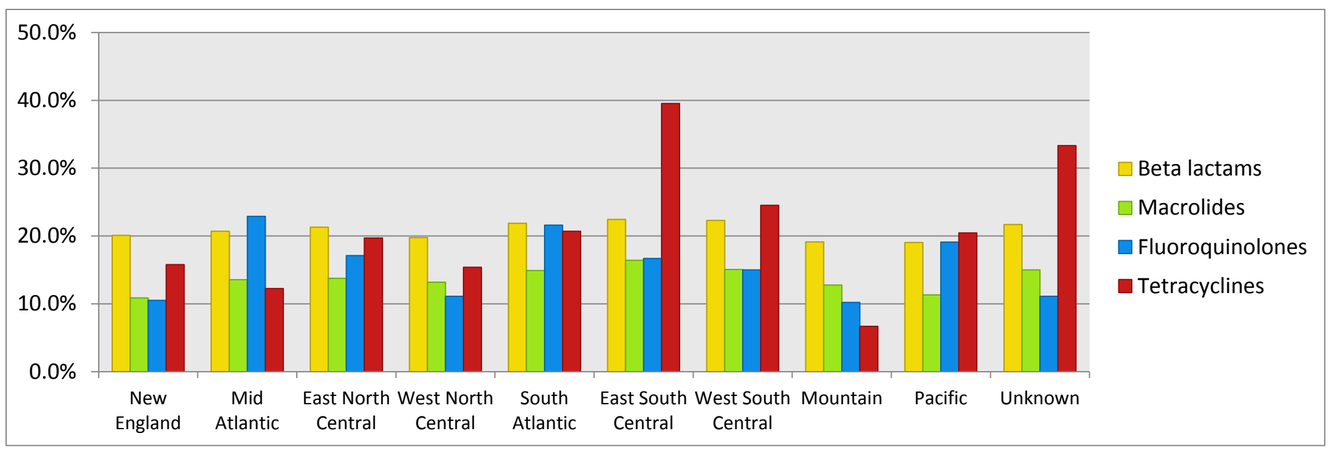


Figure 3. Composite treatment failure by region based on initial index drug. The x-axis is each United States census region, and the y-axis is the percentage of patients who failed treatment from the respective region for each initial index drug group (represented by colors, see legend).

Conclusions

Overall, beta-lactams and macrolides are the most common antibiotics used to treat pediatric patients with CABP. Several conclusions can be drawn based on trends in treatment failure:

- Patients treated with beta-lactams are significantly more likely to fail than those treated with macrolides.
- The majority of treatment failure is caused by new antibiotic prescription for all drug indices
- Failure is region specific, which suggests local factors affecting treatment outcome and warrants further study

Such analyses should help inform appropriate antibiotic choices to maximize treatment success.

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