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Beta-Lactam Versus Beta-Lactam/Macrolide Therapy in Pediatric Outpatient Pneumonia

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Summary.

Objective: The objective was to evaluate the comparative effectiveness of beta-lactam monotherapy and beta- lactam/macrolide combination therapy in the outpatient management of children with community-acquired pneumonia (CAP).

Methods: This retrospective cohort study included children, ages 1–18 years, with CAP diagnosed between January 1, 2008 and January 31, 2010 during outpatient management in the Geisinger Health System. The primary exposure was receipt of beta-lactam monotherapy or beta-lactam/macrolide combination therapy. The primary outcome was treatment failure, defined as a follow-up visit within 14 days of diagnosis resulting in a change in antibiotic therapy. Logistic regression within a propensity score- restricted cohort was used to estimate the likelihood of treatment failure.

Results: Of 717 children in the analytical cohort, 570 (79.4%) received beta-lactam monotherapy and 147 (20.1%) received combination therapy. Of those who received combination therapy 58.2% of children were under 6 years of age. Treatment failure occurred in 55 (7.7%) children, including in 8.1% of monotherapy recipients, and 6.1% of combination therapy recipients. Treatment failure rates were highest in children 6–18 years receiving monotherapy (12.9%) and lowest in children

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6–18 years receiving combination therapy (4.0%). Children 6–18 years of age who received combination therapy were less likely to fail treatment than those who received beta-lactam monotherapy (propensity-adjusted odds ratio, 0.51; 95% confidence interval, 0.28, 0.95).

Conclusion: Children 6–18 years of age who received beta- lactam/macrolide combination therapy for CAP in the outpatient setting had lower odds of treatment failure compared with those who received beta-lactam monotherapy

Keywords

pneumonia; child; pediatric; comparative effectiveness research; pneumonia bacterial; amoxicillin

INTRODUCTION

Community-acquired pneumonia (CAP) is a common and serious infection of childhood, with over 1.5 million children diagnosed in the outpatient setting each year.[1] A pathogen is identified in only a small minority of children. For this reason, affected children typically receive empirical antibiotic therapy based on their age and disease severity.[2]

In 2011, the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) jointly sponsored national guidelines for the management of children with CAP.[3] Beta-lactam antibiotic therapy (e.g., amoxicillin) is recommended for most children with CAP treated in the outpatient setting. While macrolides were recommended for the treatment of school-aged children and adolescents with atypical pathogens the role of beta- lactam/macrolide combination therapy in the outpatient setting was not addressed. Among hospitalized patients, macrolides were recommended in addition to beta-lactam therapy for children for whom *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* were clinically important “diagnostic considerations.” Additional guidelines in Europe support the use of amoxicillin in the majority of cases but have less strong evidence regarding combination therapy.[4,5] Despite these recommendations, there is a paucity of data regarding the comparative effectiveness of beta-lactam monotherapy and beta-lactam/macrolide combination therapy in children with CAP.[6] We sought to address this question of comparative effectiveness among children with CAP diagnosed in the ambulatory setting.

MATERIALS AND METHODS

Study Design and Data Source

This retrospective cohort study included patients from outpatient pediatric practices affiliated with the Geisinger Health System (GHS). The GHS provides primary care to a 31-county region in Central and Northeastern Pennsylvania. The primary care population of the GHS is similar to the regional resident population. The predominantly rural area is served by over 50 primary care clinics and 3 acute care hospitals. GHS uses EpicCare Electronic Health Records (EHR) (Epic Systems Corporation, Verona, WI) for all of their primary care and specialty clinic appointments, urgent care, and emergency department visits, and hospitalizations. This integrated EHR system allows for thorough data collection regarding initial and follow-up visits at any site (e.g., at their primary care clinic or the emergency department) within the GHS. This study was reviewed and approved by the Institutional

Review Boards at GHS, The Children's Hospital of Philadelphia, and Cincinnati Children's Hospital Medical Center with a waiver of informed consent.

Study Cohort

Children, ages 1–18 years, treated within the GHS network from January 1, 2008 to January 31, 2010 and had an initial diagnosis of CAP in the outpatient setting were eligible for this study. Subjects were eligible if they had a diagnosis of CAP using International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) diagnosis codes (480, 482.3, 482.8, 482.9, 483, and 486) *and* received beta-lactam antibiotics (i.e., penicillin, 2nd and 3rd generation cephalosporins), alone or in combination with macrolides (i.e., erythromycin, clarithromycin, azithromycin). The diagnosis of CAP was verified by EHR review and based on the presence of signs and symptoms of lower respiratory tract infection (e.g., cough, increased respiratory effort) and a physician diagnosis of CAP.

Children less than 1 year of age were excluded to minimize misclassification of a bacterial pneumonia diagnosis. While differentiating viral from bacterial infections is challenging, children less than one year of age experience a particularly high rate of viral respiratory infections (e.g., bronchiolitis), which would increase potential misclassification compared with older children.[3,7] Children with immunocompromising conditions (e.g., primary immune deficiency) or chronic medical conditions other than asthma (e.g., cystic fibrosis) that predispose them to severe or recurrent CAP were excluded using a previously reported classification method (n = 100).[8]

Study Definitions

Patients were considered to have asthma if they had an outpatient diagnosis code for asthma (ICD-9-CM codes 493–494) before the initial date of diagnosis for CAP or if they had received a prescription for inhaled corticosteroids. Albuterol and systemic corticosteroid (i.e., methylprednisone, dexamethasone, prednisone, or prednisolone) use were defined by prescriptions provided during the visit. Viral respiratory season was defined as November through March. Respiratory complaint was defined as a chief complaint that reflected a concern for respiratory illness (e.g., cough, difficulty breathing) rather than complaints with a broader range of potential causes (e.g., fever). Fever was defined as a temperature >38.5°C as measured during the office visit Only 1.8% of patients did not have a recorded temperature; however the remainder of their data was complete therefore they were included in the analysis.

Main Exposures

The primary exposure for this study was the receipt of empiric antibiotic therapy, classified as beta-lactam monotherapy or a beta-lactam plus a macrolide (i.e., combination therapy) prescribed at the time of CAP diagnosis. The antibiotic therapy received by individuals was independent of each other and was given according to standard practice.[9,10]

Outcome Measures

The primary outcome measure for this study was treatment failure, defined as a follow-up visit with an ICD-9 code for a respiratory-related diagnosis accompanied by a change in

antibiotic therapy in either the outpatient setting, in the emergency department, or as a hospital admission within 14 days of the initial diagnosis of CAP. Scheduled follow-up at specialty clinics were not considered treatment failures. We chose 14-day follow-up because among patients hospitalized with CAP, adverse events that occur beyond 14 days are typically not related to the initial episode of pneumonia.[11] To minimize potential misclassification of treatment failure, the analysis was repeated while limiting the time window for treatment failure to within 7 days of the initial CAP diagnosis. Adverse drug events, including medication-related side effects, were examined as a secondary outcome measure. These patients were identified by presence of a follow-up visit with a diagnosis code suggestive of drug intolerance (i.e., urticaria, dermatitis due to drugs, erythema multiforme, diarrhea, and candidiasis of the mouth, rash and other nonspecific skin eruptions).

Data Analysis

To evaluate comparability, the two treatment groups were compared in terms of the prevalence rates of binary pre-treatment patient characteristics. A propensity score was used to account for potential confounding by observed baseline covariates in the presence of a rare outcome, treatment failure. This approach was chosen because the number of covariates within our study was large relative to the small number of treatment failures, a situation in which multivariable modeling may create unreliable estimates.[12] The propensity score was estimated via a logistic regression model for the probability of being prescribed combination therapy given a set of baseline covariates. These covariates included age, respiratory complaint, receipt of albuterol, asthma status, receipt of systemic corticosteroids, fever, season of diagnosis, the presence of wheezing, crackles, or retractions at the time of diagnosis, and receipt of chest radiograph. Age was transformed to a quadratic variable in the propensity score model to achieve balance of the baseline covariates between treatment groups.. Interaction between wheezing and asthma was determined to be important a priori, and an interaction term was included in the final propensity score model. A final propensity score model was developed that could achieve balance between the treatment groups.[13]

Several methods of using the propensity score were evaluated: matching, stratification, use as a covariate, inverse-probability-of-treatment weighting. We chose the method of restricting the study cohort to those children who were within the middle 80% of the propensity score range. Eliminating those with the lowest 10% and highest 10% of propensity scores created a cohort of children that were the most similar in regards to the baseline characteristics included in the propensity score model while also including a large proportion of the original cohort for analysis. Matching on propensity score was not used because of the limited number of children who received combination therapy thereby eliminating a large number of children who received beta-lactam mono-therapy, a situation that can lead to loss of information and decreased precision in estimating the effect of antibiotic therapy on treatment failure.[14]

The primary analyses were conducted within the restricted cohort by using a logistic regression model to estimate the probability of treatment failure in children who received combination therapy when compared with children who received beta-lactam monotherapy

clustered by clinic. Asthma, an important confounder, was included a prior in the final model..[15] The decision to stratify the primary analysis by age group was also made a priori based on the likelihood of the pathogen causing CAP in the general population: children of ages 6 and older are more likely to be infected with an atypical bacterial pathogen, while those <6 years of age are more likely to be infected with *Streptococcus pneumoniae*.[3] Inclusions of other covariates and interactions in the logistic regression model were based on examinations of the data; e.g., a statistical test was performed for interaction between antibiotic therapy and wheezing because wheezing may modify the effect of therapy.

The primary analyses within the restricted cohort also included comparison of the two treatment groups on medication-related side effects and treatment failure without accounting for covariates using hypothesis tests using Fisher's exact procedure.

As an aide to interpretation of the results for the primary outcome, treatment failure at 14 days, auxiliary analyses were performed for treatment failure at 7 days. Statistical computations were performed using Stata version 11 (Stata Corporation, College Station, TX).

RESULTS

Study Cohort

In total, 915 children were included and of those, 717 children remained after restricting the cohort by propensity score. Within this cohort, the two treatment groups were similar on proportions of children with each patient characteristic (Table 1). The monotherapy group exhibited lower rates of rales, wheezing, and asthma, and higher rates for fever, pleural effusion, and infiltrates. Similar levels of comparability of the two treatment groups were observed within each of the two age categories (Table 2). The mean age was 5.8 years (interquartile range [IQR], 3–8 years). Of these, 570 (79.5%) received beta-lactam monotherapy and 147 (20.1%) received beta-lactam/macrolide combination therapy. Beta-lactam monotherapy was prescribed to 345 of 417 (82.7%) children <6 years and to 225 of 300 (75.0%) children ≥6.

Treatment Failure

Among the 717 children in the cohort, 248 (34.6%) patients had a respiratory-related follow-up visit within 14 days of their initial CAP diagnosis. Of these, 244 (98.3%) returned to an outpatient clinic, 1 (0.4%) returned to the emergency department and was discharged home, and 3 (1.2%) were hospitalized. Treatment failure occurred in 55 (7.7%) patients (Table 3). Among those <6 years, treatment failure occurred in 17 (4.9%) children receiving beta-lactam monotherapy and 6 (8.3%) receiving combination therapy. Among those ≥6 years of age, treatment failure occurred in 29 (12.9%) children receiving beta-lactam monotherapy and 3 (4.0%) receiving combination therapy. In the primary analysis, the final age- group-specific logistic regression models for treatment failure at 14 days, included therapy and asthma status. Therapy-by-wheezing interaction was not included in the final model (P = 0.29). Among children <6 years, differences in treatment failure between those who received combination therapy and those who received beta-lactam monotherapy were not statistically

significant (Table 4). Among those who were ≥6 years, children who received combination therapy had 49% lower odds of treatment failure compared with those who received beta-lactam monotherapy (Table 4).

We then restricted the definition of treatment failure to those returning for care within 7 days of the initial visit (Table 3). Among those <6 years of age, differences in treatment failures between those receiving beta-lactam monotherapy and those receiving combination therapy were not statistically significant (Table 4). The odds of treatment failure remained lower among children ≥6 years of age receiving combination therapy compared with those receiving beta-lactam monotherapy (Table 4).

Medication-Related Side Effects

Medication side effect-related visits occurred in 14 (1.9%) patients (Table 3). Side effect-related visits occurred in 11 (1.9%) patients receiving beta-lactam monotherapy and 3 (2.0%) patients receiving combination therapy; differences were not statistically significant when stratified by age (Table 3). The most commonly reported side effects were urticaria (n = 5), rash (n = 4), and diarrhea (n = 2).

DISCUSSION

In this multicenter outpatient study, 7.7% of children presenting with CAP experienced treatment failure within 14 days of diagnosis. Among children 6–18 years of age, those who received beta-lactam/macrolide combination therapy were less likely to experience treatment failure than those receiving beta-lactam monotherapy. Among children under 6 years of age, the test for association between antibiotic therapy and treatment failure was statistically inconclusive ($P = 0.0678$). Medication-related side effects were documented in the records of 1.9% of children treated for CAP.

The rate of treatment failure in this study is consistent with failure rates described in previous studies of children with CAP in the outpatient setting, which have ranged from 2.7% to 7.5%.[16–19] We noted 49% decreased odds of treatment failure in children 6–18 years of age who received beta- lactam/macrolide combination therapy compared with those who received beta-lactam mono-therapy. The benefit of combination therapy among the older children is consistent with a higher prevalence of *Mycoplasma pneumoniae* and other atypical organisms in this age group.[20,21] In contrast, children who are preschool-aged and younger have a much lower incidence of atypical pneumonia.[22–25] In one study that recruited both ambulatory and inpatient children, there was no statistical difference in failure rates among children younger than 5 years of age who received beta-lactam monotherapy compared to those who received levofloxacin, an antibiotic effective against both *S. pneumoniae* and atypical bacteria.[16] Among hospitalized children, school-aged children with CAP who received beta-lactam/macrolide combination therapy had a statistically significant decrease in their length of stay compared with those receiving beta-lactam monotherapy.[6] Our study found benefit of combination therapy among school-aged children in the outpatient setting.

Among children <6 years in this study, assessment of association between antibiotic regimen and treatment failure was inconclusive. Point and interval estimates for the odds ratio indicate that it is plausible that mono-therapy may be better than combination therapy. Children who are preschool-aged and younger have a low incidence of atypical pneumonia, and viral respiratory infections predominate.[22–25] We would not expect the addition of macrolide therapy to have a substantial impact on the incidence of treatment failure in this age group. These findings are consistent with other studies that failed to detect a difference in outcomes between preschool-aged children with CAP who received broad- spectrum antibiotics and those who received more narrow-spectrum of coverage.[6,16] While macrolide antibiotics also have anti-inflammatory properties,[26–28] our data suggest these properties may not have a large impact on the outcomes of young children with CAP.

There remains the question of how one might apply the findings of our study to clinical practice. Macrolides have sub-optimal activity against *S. pneumoniae* with rates of resistance exceeding 40% in some areas.[29] Drug-resistance to macrolides is associated with treatment failure in patients with infections caused by *S. pneumoniae*.[30–32] Thus, macrolides are not recommended as monotherapy for treatment of invasive pneumococcal infections such as pneumonia.[33] Furthermore, macrolide- resistance among *S. pneumoniae* isolates from those previously treated with macrolides raises concern that increasing macrolide use could dramatically worsen the problem of pneumococcal drug resistance.[34] In contrast, the role of antibiotics in the treatment of pneumonia caused by *M. pneumoniae* and other atypical bacteria remains controversial and the consequences of treatment failure in such infections appears minor.[35,36] While our data suggest a potentially important role for beta-lactam/macrolide combination therapy in the treatment of CAP, better delineation of sub-populations most likely to benefit from combination therapy is warranted before widespread adoption of this practice.

There were several limitations to our study. First, because we only reviewed the medical records of children with a diagnosis code suggesting pneumonia, children with CAP but without an ICD-9-CM code for pneumonia were not included in this study. Because this study excluded children with chronic comorbid conditions,[8] it is unlikely that otherwise healthy children with CAP were systematically excluded. Nevertheless, it is possible that children presenting with pneumonia were given diagnosis codes that were not captured by our coding algorithm (e.g., fever, cough), suggesting that the number of pneumonia cases within the GHS may have been greater than that represented in this study. However, expanding the algorithm to incorporate these codes would lead to the over-representation of children who were not suspected of having pneumonia. Within the Geisinger system, ICD-9-CM codes are assigned by the physician at the time of the visit, making it likely that these codes have a high positive predictive value for identifying patients with suspected pneumonia. Additionally, each pneumonia diagnosis was verified through chart review and children less than one year of age were excluded due to the high incidence of viral bronchiolitis in this younger age group.

The second limitation is that the results may be biased by unknown and unmeasured confounding factors.[37]

The propensity-score method used to account for confounding factors relies on the unverifiable assumption that all confounders were measured and included in the development of the propensity-score.

The third limitation is that the results may be biased by inadequate adjustment for a known confounder, illness severity at the time of presentation. We included markers of severity (e.g., receipt of systemic corticosteroids, retractions) in our propensity score model; however, it is possible that these did not fully adjust for illness severity. If antibiotic regimen was chosen based on illness severity, we would expect clinician to preferentially prescribe beta-lactam/macrolide combination therapy over beta-lactam monotherapy for children with more severe disease. This would bias our results toward greater odds of treatment failure among those receiving beta-lactam and macrolide combination therapy. Thus, among the older children, the benefit of combination therapy may be greater than that demonstrated in this study.

The fourth limitation concerns the degree of comparability between the two treatment groups. Restricting the analysis to patients within the middle 80% of the propensity score range achieved good but not perfect balance among some baseline covariates. For example, the monotherapy group exhibited slightly lower rates of wheezing and slightly higher rates of pleural effusion and infiltrates, raising the possibility of more severe disease in this group. However not all the patients received a chest radiograph, which make it difficult to determine a true imbalance in these characteristics. The fifth limitation is that there may be misclassification of the primary outcome. Treatment failure in pediatric CAP is inherently difficult to measure, as pneumonia-associated complications such as empyema are relatively uncommon in children initially treated in the outpatient setting, and challenging to define, as etiology is seldom identified. We used a previously established definition of treatment failure that included unplanned healthcare visits with a respiratory-related diagnosis code within 14 days of the CAP diagnosis during which an alternate antibiotic was prescribed with the rationale that this approach would identify patients with persistent symptoms attributable to CAP that the physician thought warranted additional antibiotic therapy.[16] Additionally, we repeated the analysis after restricting the time of follow-up visits to those occurring within 7 days of the index appointment in order to further minimize inclusion of follow-up visits that were unrelated to the initial CAP diagnosis; the results of this sub-analysis were similar to the results of our primary analysis.

The sixth limitation is that, not all antibiotic changes are equal and patients receiving beta-lactam/macrolide combination therapy may have had fewer opportunities to “fail” as providers would have fewer alternate treatment options. This limitation would underestimate the treatment failure rate in those receiving combination therapies, making the actual failure rate greater than that detected in this study. However, few patients required hospitalization therefore underestimation is unlikely to be clinically meaningful. Finally, we were only able to record antibiotic changes that were documented at a follow-up appointment. As we were unable to account for changes in therapy that may have occurred over the phone or otherwise outside of the clinic setting, it is possible that the rate of treatment failure may have been greater than that identified in this study. This non-differential misclassification would bias

our results to the null therefore suggesting a greater difference in treatment failure between treatment groups had this information been available for analysis.

In conclusion, children ≥6 years who received beta-lactam/macrolide combination therapy for CAP may be less likely to experience treatment failure compared with children six years of age and older receiving beta-lactam monotherapy.

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ABBREVIATIONS:

CAP	Community-acquired pneumonia
EHR	Electronic Health Record
GHS	Geisinger Health System
ICD-9-CM	International Classification of Diseases 9th revision, clinical modification
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
OR	Odds ratio
PIDS	Pediatric Infectious Diseases Society

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Key Points:

Children 6–18 years who received beta- lactam/macrolide combination therapy for outpatient community-acquired pneumonia had lower odds of treatment failure compared with those who received beta-lactam monotherapy. Children younger than 6 years did not benefit from receiving combination therapy.

TABLE 1—

Patient Characteristics By Treatment Category Within the Propensity-Score Cohort[a]

Variable	Restricted Cohort (n = 717)	Monotherapy (n = 570)	Combination (n = 147)	*P*-value
Age Category				
1 to < 6 years	417 (58.2)	345 (60.5)	72 (49.0)	0.01
6–18 years	300 (41.8)	225 (39.5)	75 (51.0)	
Respiratory Season	373 (52.0)	297 (52.0)	76 (51.7)	0.93
Respiratory Complaint	412 (57.5)	325 (57.0)	87 (59.2)	0.64
Albuterol	260 (36.3)	203 (35.6)	57 (38.8)	0.48
Systemic Corticosteroids	49 (6.8)	38 (6.7)	11 (7.5)	0.73
Rales	353 (49.2)	279 (49.0)	74 (50.3)	0.76
Wheezing	141 (19.7)	108 (19.0)	33 (22.5)	0.34
Retractions	4 (0.56)	4 (0.56)	0 (0)	0.31
Chest x-ray	333 (46.4)	264 (46.3)	69 (46.9)	0.89
Infiltrate	139 (41.7)	114 (43.2)	25 (36.2)	0.30
Pleural Effusion	8 (2.4)	8 (7)	0 (0)	0.32
Fever	61 (8.5)	53 (9.3)	8 (5.4)	0.14
Asthma	179 (25.0)	133 (23.3)	46 (31.3)	0.05

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TABLE 2—

Patient Characteristics by Treatment Category Stratified by Age Category[a]

Variable	Restricted Cohort	Monotherapy	Combination	*P*-value
Ages 1 to <6 years				
Respiratory Season	233 (55.9)	186 (53.9)	47 (65.3)	0.08
Respiratory Complaint	281 (67.4)	232 (67.3)	49 (68.1)	0.89
Albuterol	160 (38.4)	127 (36.8)	33 (45.8)	0.15
Systemic Corticosteroids	44 (10.6)	33 (9.6)	11 (15.3)	0.15
Rales	219 (52.5)	178 (51.6)	41 (56.9)	0.41
Wheezing	111 (26.6)	88 (25.5)	23 (31.9)	0.26
Retractions	2 (0.48)	2 (0.58)	0 (0)	0.52
Chest x-ray	190 (43.6)	163 (47.3)	27 (37.5)	0.13
Infiltrate	76 (40)	65 (39.9)	11 (40.7)	0.93
Pleural Effusion	3 (1.6)	3 (1.8)	0 (0)	0.29
Fever	31 (7.4)	28 (8.1)	3 (4.2)	0.25
Asthma	108 (25.9)	84 (24.4)	24 (33.3)	0.11
Ages 6–18 years				
Respiratory Season	140 (46.7)	111 (49.3)	29 (38.7)	0.11
Respiratory Complaint	131 (43.7)	93 (41.3)	38 (50.7)	0.16
Albuterol	100 (33.3)	76 (33.8)	32 (32.0)	0.78
Systemic Corticosteroids	5 (1.7)	5 (1.7)	0 (0)	0.19
Rales	134 (44.7)	101 (44.9)	33 (44.0)	0.89
Wheezing	30 (10.0)	20 (8.9)	10 (13.3)	0.27
Retractions	2 (0.67)	2 (0.89)	0 (0)	0.41
Chest x-ray	143 (47.7)	101 (44.9)	42 (56.0)	0.10
Infiltrate	63 (44.1)	49 (48.5)	14 (33.3)	0.10
Pleural Effusion	5 (1.7)	5 (2.2)	0 (0)	0.06
Fever	30 (10.0)	25 (11.1)	5 (6.7)	0.27
Asthma	71 (23.7)	49 (21.8)	22 (29.3)	0.18

TABLE 3—

Treatment Failure and Antibiotic Intolerance by Age Category[a]

	Restricted Cohort (n = 717)	Monotherapy (n = 570)	Combination Therapy (n = 147)	*P*-Value[b]
Treatment Failure, 14 Day				
Ages 1 to <6	23 (5.5)	17 (4.9)	6 (8.3)	0.25
Ages 6–18	32 (10.7)	29 (12.9)	3 (4.0)	0.03
Treatment Failure, 7 Day				
Ages 1 to <6	16 (4.4)	12 (4.0)	4 (6.8)	0.31
Ages 6–18	23 (11.5)	22 (11.5)	1 (1.6)	0.02
Medication Side- Effects				
Ages 1 to <6	8 (4.1)	6 (3.9)	2 (5.3)	0.30
Ages 6–18	6 (5.0)	5 (5.4)	1 (3.6)	0.38

[a]Values listed as number (percent).

[b]Fisher's exact test for each age group.

TABLE 4—

Logistic Regression Models for the Association of Empiric Antibiotic Therapy With Treatment Failure

	Odds ratio (95% confidence interval)	
14 Day Treatment Failure	1 to <6 years	6–18 years
Combination Therapy[a]	1.32 (0.82, 2.15)	0.53 (0.29, 0.98)
Combination Therapy[b]	1.34 (0.83, 2.18)	0.51 (0.28, 0.95)
	Odds ratio (95% confidence interval)	
7 Day Treatment Failure	1 to <6 years	6–18 years
Combination Therapy[a]	1.33 (0.74, 2.38)	0.35 (0.13, 0.96)
Combination Therapy[b]	1.33 (0.74, 2.39)	0.33 (0.12, 0.91)

[a]The final logistic regression model without adjustment for asthma status.

[b]The final logistic regression model included antibiotic therapy and asthma status.