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Comparative Effectiveness of Beta-lactam vs. Macrolide monotherapy in Children with Pneumonia Diagnosed in the Outpatient Setting

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Abstract

Background—Most children diagnosed with community-acquired pneumonia (CAP) are treated in the outpatient setting. The objective of this study was to determine the comparative clinical effectiveness of beta-lactam monotherapy and macrolide monotherapy in this population.

Study Design—Children, 1–18 years old, with a clinical diagnosis of CAP at an outpatient practice affiliated (n=71) with Geisinger Health System during January 1, 2008 to January 31, 2010 were eligible. The primary exposure was receipt of beta-lactam or macrolide monotherapy. The primary outcome was treatment failure defined as change in antibiotic prescription within 14 days of the initial pneumonia diagnosis. Propensity scores were used to determine the likelihood of receiving macrolide monotherapy. Treatment groups were matched 1:1, based on propensity score, age group and asthma status. Multivariable conditional logistic regression models estimated the association between macrolide monotherapy and treatment failures.

Results—Of 1,999 children with CAP, 1,164 were matched. In the matched cohorts, 24% of children had asthma. Patients who received macrolide monotherapy had no statistical difference in treatment failure regardless of age when compared with patients who received beta-lactam monotherapy.

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Conclusion—Our findings suggest that children diagnosed with CAP in the outpatient setting and treated with beta-lactam or macrolide monotherapy have the same likelihood to fail treatment regardless of age.

Keywords

pneumonia; child; pediatric

INTRODUCTION

Community-acquired pneumonia (CAP) is a commonly diagnosed infection in children, and left untreated can result in substantial morbidity and mortality. Annually, as many as 1.5 million children in the United States are diagnosed with pneumonia in an outpatient setting.[1] There is great variability in the management of CAP as the etiology of the pneumonia is difficult to determine and rarely ascertained in clinical settings.[1] The most prevalent causes of pneumonia presented in the literature are viral pathogens in children less than five years old and typical and atypical bacterial pathogens in children five years and older.[2]

The intent of the 2011 guidelines published by the Pediatric Infectious Disease Society (PIDS) and Infectious Disease Society of America (IDSA) was to decrease variability in the management of children diagnosed with CAP. Therefore, this guideline does not recommend routine antibiotic therapy for preschool age children, as viral pathogens are largely responsible for clinical disease in this age group. However beta-lactam monotherapy (e.g. amoxicillin) is recommended as first line therapy when a bacterial pathogen is suspected and in school-aged children macrolide therapy should be considered when an atypical bacterium (e.g. *Mycoplasma pneumoniae*) is suspected as the causative agent.[3]

Few pediatric studies have compared beta-lactam monotherapy with macrolide monotherapy.[4, 5] While these studies found no statistically significant differences in clinical outcomes between children with CAP in these treatment groups, their inclusion of only hospitalized children precludes their generalizability to the outpatient setting where most cases of pneumonia are diagnosed and treated.

The objective of this study was to determine the comparative effectiveness of empiric beta-lactam and macrolide monotherapy in the outpatient management of children with CAP.

METHODS

STUDY DESIGN AND DATA SOURCE

This retrospective cohort study included children evaluated in outpatient 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. This predominantly rural area is served by 71 primary care clinics and 3 acute care hospitals. The 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 at initial

and follow-up visits from 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 SUBJECTS

Children, ages 1–18 years that were treated within the GHS network between January 1, 2008 and January 31, 2010 and had an initial clinical diagnosis of CAP in the outpatient setting were eligible for this study. A diagnosis of CAP was initially identified by International Classification of Diseases, 9th revision, clinical modification (ICD-9 CM) diagnosis codes for pneumonia (480, 482.3, 482.8, 482.9, 483, and 486) and verified by EHR review based on the presence of at least one sign or symptom of lower respiratory tract infection (e.g., cough, increased respiratory effort) and a physician documented diagnosis of CAP. An episode of pneumonia was defined as 14 days after the initial diagnosis. In our final analysis no patient had multiple episodes of pneumonia.

Children with immunocompromising conditions (e.g., primary immune deficiency) or chronic medical conditions other than asthma (e.g., cystic fibrosis) that predisposed them to severe or recurrent CAP were excluded (n=100, 3% of total cohort) using a previously reported classification method.[6] In addition, patients who did not receive antibiotics when initially diagnosed with pneumonia were excluded (n=375, 12%), as it is more likely that these patients were suspected of having a viral pneumonia, in which case antibiotics would have no effect on their outcome or if they did not receive beta-lactam or macrolide monotherapy (n=571, 18%). Children less than one year of age were excluded a priori to minimize misclassification of a bacterial pneumonia diagnosis, as these children experience a much higher rate of viral respiratory infections (e.g., bronchiolitis) that are difficult to distinguish clinically from bacterial pneumonia.[7, 8]

STUDY DEFINITIONS

Asthma, systemic corticosteroids, respiratory season, and respiratory complaint were used as covariates in the analysis. Patients were considered to have asthma or probable asthma if they had an outpatient diagnosis code of asthma (ICD-9-CM codes 493–494) at any visit before the initial date of diagnosis for CAP or if they received an inhaled corticosteroid at the time of diagnosis for CAP. Systemic corticosteroids were defined by receipt of methylprednisone, dexamethasone, prednisone, or prednisolone. Viral respiratory season was defined as November through March. Respiratory complaint was defined as a chief compliant 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).

TREATMENT MEASURES

The primary exposure of interest was electronic prescription of empiric antibiotic therapy, classified as beta-lactam monotherapy (e.g., penicillin or aminopenicillin (80% of cohort), 2nd or 3rd generation cephalosporins (20% of cohort)) or macrolide monotherapy (e.g., azithromycin, clarithromycin, erythromycin) at the time of CAP diagnosis.

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 either in the outpatient setting (in-person or via phone), in the emergency department, or as a hospital admission within 14 days of the initial diagnosis of CAP.[9] A follow-up of 14-days was chosen because previous work among patients initially treated as outpatients who were subsequently hospitalized with CAP demonstrated that adverse events occurring beyond 14 days are typically not related to the initial episode of pneumonia.[9] Follow-up at specialty clinics were not considered treatment failures as these were scheduled rather than emergent visits related to treatment failure.

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.

DATA ANALYSIS

Categorical variables were described using frequencies and proportions. Patient characteristics were compared across treatment groups using chi-square tests or Fisher's exact tests for categorical variables.

Propensity score analysis reduces the number of parameters needed in a multivariable model for adjustment when there are relatively few outcomes.[10] Propensity scores were therefore estimated as there are many variables that clinicians take into account when choosing antibiotics for CAP and relatively few treatment failures. In this study, the propensity score was derived from a logistic regression that estimated the conditional probability of being prescribed macrolide monotherapy given a set of covariates.[11] Patients were divided into those who were school-aged and older (6 years or greater), as these children are more likely to be infected with an atypical bacterial pathogen, and those who were preschool-aged and younger (less than 6 years), who are more likely to be infected with *Streptococcus pneumoniae*.[7] Variables used to develop the propensity scores included age, respiratory complaint, receipt of albuterol, asthma status, receipt of systemic corticosteroids, fever, respiratory season, wheezing, rales, and retractions present at initial diagnosis, and documentation of chest radiograph order. Interaction terms, age and wheeze, asthma and wheeze, and age and asthma, were tested in the propensity score. These interaction terms did not improve model fit as determined by a smaller Akaike Information Criterion (AIC) and were not statistically significant (p-value <0.05); therefore, they did not remain in the final propensity score model. The primary care clinic in which the patient received their initial diagnosis did not improve the statistical balance of between the treatment groups therefore primary care clinic was not included in the final model. The final propensity score model's calculated c statistic was 0.72, which represents adequate predictive accuracy.[12] Patients in each treatment group were matched 1:1 for the same probability of assignment, within one percentage point, exact asthma status and within age category.[13] Due to the paired data of the treatment groups within each age stratum, the Cochran-Mantel-Haenszel test was used to evaluate balance of the matching procedure.[14] The two treatment groups were considered to achieve statistical balance when the difference between the two groups for any given variable was 6% or less and the p-value was ≥ 0.05.

Conditional logistic regression analysis was performed to evaluate the odds of treatment failure associated with receipt of macrolide monotherapy compared with beta-lactam monotherapy in the matched cohort. Interaction between choice of antibiotic therapy and wheezing present at initial diagnosis was tested. This interaction term was not statistically significant with p-value determined a priori of < 0.05. An interaction term between age and antibiotic therapy was found to be statistically significant and therefore results are presented by age group and choice of antibiotic therapy. All statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute Inc, Cary, N.C.)

RESULTS

Study Population

Over the study period, we identified a total of 1,999 eligible children with CAP treated in the outpatient setting, most (68%) of whom received treatment at a primary care pediatric clinic. Of these, 703 (35%) received beta-lactam monotherapy and 1,296 (65%) received macrolide monotherapy. In the unmatched cohort, children receiving macrolide monotherapy were more likely to present with complain of respiratory symptoms, rales, wheezing, have a history of asthma and also were more likely to receive adjunct systemic corticosteroids (Table 1). After matching, 1,164 children remained in the cohort matched on age, asthma status and propensity score. Of these, 678 (58%) children were ages 1–5 and 486 (42%) were ages 6–18 years. Within this matched cohort, all covariates were equally balanced between those receiving beta-lactam monotherapy and those receiving macrolide monotherapy (Table 2).

Treatment Failure

Among the children in the matched cohort, treatment failure occurred in 42 (4%) patients within 7 days and an additional 12 (1%) patients within 14 days of their initial CAP diagnosis. Of these, 53 (98%) returned to an outpatient clinic and 1 (2%) was hospitalized. Treatment failure occurred in 33 (6%) children receiving beta-lactam monotherapy, 10 (30%) of whom were 6 years of age and younger and 21 (4%) receiving macrolide monotherapy of whom 9 (43%) were 6 years of age and younger. Among children younger than 6 years, there was no statistically significant difference in treatment failure within 14 days between those receiving beta-lactam monotherapy and those receiving macrolide monotherapy (Adjusted Odds Ratio (AOR): 0.90; 95% Confidence Interval: 0.37, 2.22)). Among those who were 6 years of age and older, children who received macrolide monotherapy had a non-statistically significant lower odds of treatment failure within 14 days compared with children 6 years of age and older who received beta-lactam monotherapy (AOR: 0.48; 95% CI: 0.22, 1.01).

We then restricted the definition of treatment failure to those returning for care within 7 days of the initial visit. There was no statistical association between treatment failures and receiving beta-lactam monotherapy or macrolide monotherapy.

DISCUSSION

In this multicenter outpatient study, 5% of children presenting with CAP experienced treatment failure within 14 days of diagnosis. The results of the study suggest that there may be an age effect in regards to choice of antibiotic therapy however this finding must be taken into context of the low rate of treatment failure in children <5 years of age. Although not statistically significant, children 6 to 18 years of age who received macrolide monotherapy were less likely to experience treatment failure than children of the same age who received beta-lactam monotherapy; however in children under 6 years of age, there was limited power to determine a statistical difference in treatment failure between the two treatment groups.

The finding of no statistical difference between beta-lactam and macrolide monotherapy among children in our population could be due to etiology of pneumonia. In a population estimate of children under 5 years in the United States, 86% of pneumonia episodes were due to respiratory syncytial virus or influenza, for which antibiotics of any kind would not be effective.[15] However, bacterial causes of pneumonia, such as *Streptococcus pneumoniae*, are responsible for a higher proportion of severe morbidity and mortality than viral causes. Since the etiology of the pneumonia is often unknown particularly in the outpatient setting, pediatricians may have a greater tendency to prescribe antibiotics in children with the thought being that prevention of severe morbidity or mortality from an untreated bacterial infection justifies overuse of antibiotics in patients who have a viral infection. In children older than 5 years, *Mycoplasma pneumonia* is more prevalent as a bacterial cause of pneumonia.[2]

Macrolide monotherapy is prescribed predominately to treat atypical bacteria. The higher proportion of macrolide monotherapy (65%) among school-aged children, 6 to 18 years of age, found in our study is consistent with the higher prevalence of atypical bacterial pneumonias (e.g. *Mycoplasma pneumoniae*) in this age group.[2] However, there are no individual clinical symptoms or signs that are sufficiently accurate to permit diagnosis of pneumonia caused by atypical vs. typical bacteria.[16] Therefore it is unclear whether our finding that macrolide monotherapy in this age group potentially leads to less treatment failure is due to the atypical pathogen coverage by macrolides vs. beta-lactam drugs, or uncontrolled bias that leads patients with more mild infections to receive macrolide treatment.

This study had several limitations. First, only children with an ICD-9 CM diagnosis code for pneumonia were included. Therefore it is possible that children with CAP but without an ICD-9-CM code for pneumonia were excluded. In this dataset, ICD-9-CM codes were 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 with complex chronic conditions were excluded to increase the likelihood of obtaining a cohort of otherwise healthy children with the exception of their CAP diagnosis.

Second, the propensity score was created based on the available variables that were assumed to be used for clinical decision making. H however, it is possible that additional factors, not accounted for in our propensity score, variables may have been used in exist for decision-making which led to unmeasured confounding, a limitation in any retrospective analysis that were not available through the electronic health record thereby not accounting for the difference between treatment groups. In addition, by matching on propensity score we inherently excluded any observation where a match could not be found. We optimized our matching scheme to include only subjects where beta-lactam or macrolide monotherapy was not absolutely indicated or contra-indicated so a suitable comparison subject was available to match.[10] In addition, the matching scheme minimizes differences between treatment groups by matching on severity of illness variables at presentation thereby allowing both treatment groups to have a similar severity of illness.

Finally, treatment failure may have been underestimated in this study. Patients who did not complete the original antibiotic prescription may have returned and received a different antibiotic prescription. We were only able to record antibiotic changes that were documented at a follow-up appointment or over the phone. If antibiotic changes occurred elsewhere in care this would lead to non-differential misclassification and may have biased our results to the null suggesting a greater difference in treatment failure between treatment groups than found. However it is highly unlikely that a patient diagnosed initially with pneumonia within the GHS would seek follow-up care outside of the 31-county region. A higher rate of treatment failure among children diagnosed with CAP in the outpatient setting may be needed to reach statistical significance however the magnitude of association found in our study suggests a reduced likelihood of treatment failure among school-aged children.

In conclusion, although the majority of children with CAP are treated in the outpatient setting there are relatively few studies addressing empiric therapy in this population. Our study findings add that among older children those who received beta-lactam monotherapy are comparable in likelihood of treatment failure as those children who received macrolide monotherapy. This may be due to the large proportion of children with a viral pneumonia being treated with antibiotics or a change in the prevalence of the pathogens causing CAP in the community.

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Table 1

Demographics in the **UNMATCHED** cohort of Patients

Variable Name	Total Cohort (n=1999)	Beta-lactam Monotherapy (703) n, (%)	Macrolide Monotherapy (1296), n (%)	P-Value
Age				
1–5 years		438 (62)	492 (38)	
6–18 years		265 (38)	804 (62)	<0.01
Clinical Signs & Symptoms				
Fever	146 (7)	79 (11)	67 (5)	<0.01
Respiratory Complaint	1236 (62)	396 (56)	840 (65)	<0.01
Rales	1081 (54)	327 (47)	754 (58)	<0.01
Wheezing	549 (27)	142 (20)	407 (31)	<0.01
Retractions	43 (2)	22(3)	21 (2)	0.03
History of Asthma	561 (28)	172 (24)	389 (30)	0.01
Receipt of Albuterol	836 (42)	260 (37)	576 (44)	<0.01
Receipt of Systemic Corticosteroids	253 (13)	62 (9)	191 (15)	<0.01
Respiratory Season	977 (49)	362 (51)	615 (47)	0.08
Chest Radiograph Performed	807 (40)	326 (46)	481 (37)	<0.01
Male Sex	900 (45)	369 (52)	730 (56)	0.10

Table 2

Demographics in the **MATCHED** cohort of Patients

Variable Name	Beta-lactam Monotherapy (n=582), n (%)	Macrolide Monotherapy (n=582), n (%)	P-Value
Age			
1–5 years	339 (58)	339 (58)	
6–18 years	243 (42)	243 (42)	>0.99
Clinical Signs & Symptoms			
Fever	43 (7)	45 (8)	0.82
Respiratory Complaint	346 (59)	378 (65)	0.05
Rales	288 (49)	258 (44)	0.08
Wheezing	125 (21)	116 (20)	0.52
Retractions	11 (2)	13 (2)	0.68
History of Asthma	141 (24)	141 (24)	>0.99
Receipt of Albuterol	212 (36)	193 (33)	0.24
Receipt of Systemic Corticosteroids	54 (9)	64 (11)	0.33
Respiratory Season	293 (50)	267 (46)	0.13
Chest Radiograph Performed	251 (43)	253 (43)	0.91
Male Sex	309 (53)	323 (56)	0.41