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ORIGINAL RESEARCH

Macrolide Therapy and Outcomes in a Multicenter Cohort of Children Hospitalized with *Mycoplasma pneumoniae* Pneumonia

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BACKGROUND: *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia in childhood. Few studies have addressed the association of antimicrobial treatment and outcomes.

OBJECTIVE: To determine whether macrolide therapy is associated with improved outcomes among children hospitalized with *M. pneumoniae* pneumonia.

DESIGN: Multicenter retrospective cohort study.

SETTING: Thirty-six children's hospitals which contribute data to the Pediatric Health Information System.

PATIENTS: Children 6-18 years of age discharged with a diagnosis of *M. pneumoniae* pneumonia.

MAIN EXPOSURE: Initial macrolide therapy.

MAIN OUTCOME MEASURES: Length of stay (LOS), all-cause readmissions, and asthma-related hospitalizations.

RESULTS: Empiric macrolide therapy was administered to 405 (58.7%) of 690 patients. The median LOS was 3 days (interquartile range, 2-6 days). Eight (1.2 %) patients were readmitted within 28 days, and 160 (23.2%) were readmitted within 15 months of index discharge. Ninety-five (13.7%) patients were hospitalized for asthma within 15 months of index discharge. Empiric macrolide therapy was associated with a 32% shorter overall LOS (adjusted beta-coefficient, −0.38; 95% confidence interval [CI]: −0.59 to −0.17). Macrolide therapy was not associated with all-cause readmission at 28 days (adjusted odds ratio, 1.12; 95% CI: 0.22-5.78) or 15 months (adjusted odds ratio, 1.00; 95% CI: 0.59-1.70) or with asthma-related hospitalizations at 15 months (adjusted odds ratio, 0.85; 95% CI: 0.36-1.97).

CONCLUSION: In this large multicenter study of children hospitalized with *M. pneumoniae* pneumonia, empiric macrolide therapy was associated with a shorter hospital LOS. Macrolide therapy was not associated with 28-day or 15-month hospital readmission. *Journal of Hospital Medicine* 2012;7:311–317 © 2012 Society of Hospital Medicine

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia (CAP), among school-age children and adolescents.[1–4] Though pneumonia caused by *M. pneumoniae* is typically self-limited, severe illness may occur.[5] *M. pneumoniae* has also been implicated in airway inflammation, which may lead to the onset and development of chronic pulmonary disease.[6–10] Few studies have directly addressed appropriate treatment strategies for *M. pneumoniae* pneumonia,[11] and, despite its high prevalence and potential for causing severe complications, treatment recommendations remain inconsistent.

The efficacy of macrolide therapy in particular for *M. pneumoniae* remains unclear. In vitro susceptibility studies have shown bacteriostatic activity of erythromycin, clarithromycin, and azithromycin against *M. pneumoniae*.[12–18] Additionally, several small retrospective studies have shown that among children with atypical CAP (including *M. pneumoniae* pneumonia), those treated with macrolides were less likely to have persistence or progression of signs and symptoms after 3 days of therapy.[19,20] Lu et al[21] found a shorter duration of fever among macrolide recipients compared with non-recipients. In adults, Shames et al[22] found a shorter duration of fever and hospitalization among erythromycin recipients compared with controls. Other randomized controlled trials have also addressed the use of macrolides in treatment of *M. pneumoniae*, but the ability to draw meaningful conclusions is limited by small samples sizes and by lack of details about the number of patients with *M. pneumoniae*.[11]

In addition to their antimicrobial effect, macrolides also have anti-inflammatory properties.[23–27] The importance of these anti-inflammatory properties is supported by studies showing clinical cure in patients treated with macrolides despite persistence of *M. pneumoniae* organisms,[28–31] clinical improvement despite the administration of doses that provide tissue levels below the minimum inhibitory concentration of

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the organism,[32–34] and clinical cure in patients with macrolide-resistant *M. pneumoniae*.[18,35]

The objectives of the current study were to examine the impact of macrolide therapy on the length of stay (LOS) and short- and longer-term readmissions, including longer-term asthma-related readmissions, in children hospitalized with *M. pneumoniae* pneumonia.

METHODS

Data Source

Data for this retrospective cohort study were obtained from the Pediatric Health Information System (PHIS), which contains administrative data from 38 freestanding children's hospitals. Data quality and reliability are assured through a joint effort by the Child Health Corporation of America (Shawnee Mission, KS) and PHIS-participating hospitals as described previously.[36,37] Encrypted medical record numbers allow for tracking of individual patients across hospitalizations. This study was reviewed and approved by the Committees for the Protection of Human Subjects at The Children's Hospital of Philadelphia (Philadelphia, PA).

Patients

Children 6-18 years of age with CAP were eligible if they were discharged from a participating hospital between January 1, 2006 and December 31, 2008. Subjects were included if they received antibiotic therapy on the first day of hospitalization and if they satisfied one of the following International Classification of Diseases, 9th revision (ICD-9) discharge diagnosis code criteria: 1) Principal diagnosis of *M. pneumoniae* pneumonia (483.0); 2) Principal diagnosis of a pneumonia-related symptom (eg, fever, cough) (780.6 or 786.00-786.52 [except 786.1]) and a secondary diagnosis of *M. pneumoniae* pneumonia; or 3) Principal diagnosis of pneumonia (481-483.8 [except 483.0], 485-486) and a secondary diagnosis of Mycoplasma (041.81).

Children younger than 6 years of age were excluded due to the low prevalence of *M. pneumoniae* infection.[2,38] Patients with comorbid conditions predisposing to severe or recurrent pneumonia (eg, cystic fibrosis, malignancy) were excluded using a previously reported classification scheme.[39] In addition, we excluded patient data from 2 hospitals due to incomplete reporting of discharge information; thus data from 36 hospitals were included in this study.

Validation of Discharge Diagnosis Codes for *Mycoplasma pneumoniae*

To assess for misclassification of the diagnosis of *M. pneumoniae*, we reviewed records of a randomly selected subset of subjects from The Children's Hospital of Philadelphia; 14 of 15 patients had signs of lower respiratory tract infection in conjunction with a positive *M. pneumoniae* polymerase chain reaction test from nasopharyngeal washings to confirm the diagnosis of *M. pneumoniae* pneumonia. Hence, the positive predictive value of our algorithm for diagnosing *M. pneumoniae* pneumonia was 93.3%.

Study Definitions

We identified children with asthma in 2 ways. Asthma-related hospitalizations were identified by an ICD-9 code for asthma (493.0-493.92) in any discharge diagnosis field during any hospitalization in the 24 months prior to the current hospitalization. Baseline controller medications were identified by receipt of inhaled corticosteroids (eg, fluticasone) or leukotriene receptor antagonists on the first day of hospitalization.

Systemic corticosteroids (either oral or intravenous) included dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone. Measures of disease severity included admission to the intensive care unit within 48 hours of hospitalization, and administration of vancomycin or clindamycin, vasoactive infusions (epinephrine, norepinephrine, dopamine, and dobutamine), and invasive (endotracheal intubation) and noninvasive (continuous positive airway pressure) mechanical ventilation within 24 hours of hospitalization, as previously described.[40,41] Viral respiratory season was defined as October through March.

Measured Outcomes

The primary outcomes of interest were hospital LOS and all-cause readmission within 28 days and 15 months after index discharge. We examined readmissions for asthma 15 months after index discharge as a secondary outcome measure because of the potential role for *M. pneumoniae* infection in long-term lung dysfunction, including asthma.[42] The 15-month time frame was selected based on longitudinal data available in PHIS for the entire study cohort.

Measured Exposures

The main exposure was early initiation of macrolide therapy, defined as receipt of erythromycin, clarithromycin, or azithromycin on the first day of hospitalization.

Data Analysis

Continuous variables were described using median and interquartile range (IQR) or range values, and compared using the Wilcoxon rank-sum test. Categorical variables were described using counts and frequencies, and compared using the chi-square test. Multivariable linear (for LOS) and logistic (for readmission) regression analyses were performed to assess the independent association of macrolide therapy with the primary outcomes. Because the LOS data had a skewed distribution, our analyses were performed using logarithmically transformed LOS values as the dependent variable. The resulting beta-coefficients were transformed to reflect the percent difference in

LOS between subjects receiving and not receiving macrolide therapy.

Building of the multivariable models began with the inclusion of macrolide therapy. Variables associated with primary outcomes on univariate analysis ($P < 0.20$) were also considered for inclusion as potential confounders.[43] These variables were included in the final multivariable model if they remained significant after adjusting for other factors, or if their inclusion in the model resulted in a 15% or greater change in the effect size of the primary association of interest (ie, macrolide therapy).[44] Because corticosteroids also have anti-inflammatory properties, we assessed for interactions with macrolide therapy. There was no interaction between macrolide and systemic corticosteroid therapy ($P = 0.26$, Likelihood ratio test), therefore our primary model adjusted for systemic corticosteroids.

Despite adjusting for systemic corticosteroid therapy in our primary analysis, residual confounding by indication for corticosteroid therapy might exist. We therefore repeated the analysis after stratifying by receipt or non-receipt of systemic corticosteroid therapy. Because the benefit of macrolides in preventing long-term dysfunction may be limited to those without a prior diagnosis of asthma, we repeated the analysis of readmissions within 15 months of index discharge (any readmission and asthma-related readmissions) while limiting the cohort to those without evidence of asthma (ie, no prior asthma-related hospitalizations and no chronic asthma medications). Because children with underlying conditions or circumstances that would predispose to prolonged hospitalizations may have been included, despite our restriction of the cohort to those without an identified chronic complex condition, we also repeated the analysis while limiting the cohort to those with a LOS $\leq$7 days. Finally, all analyses were clustered on hospital using the robust standard errors of Huber and White to account for the correlation of exposures and outcomes among children within centers.

Data were analyzed using Stata version 11 (Stata Corporation, College Station, TX). Statistical significance was determined a priori as a two-tailed P value <0.05.

RESULTS

Patient Characteristics

During the study, 690 children ages 6 to 18 years met inclusion criteria. Characteristics of these patients are shown in Table 1. The median age was 10 years (IQR, 7-13 years). Ten patients (1.4%) also had a concomitant discharge diagnosis of pneumococcal pneumonia, while 19 patients (2.7%) had a concomitant discharge diagnosis of viral pneumonia; 1 of these patients had discharge diagnoses of both viral and pneumococcal pneumonia.

TABLE 1. Demographic Information and Processes of Care for Children With a Discharge Diagnosis of *Mycoplasma pneumoniae* Pneumonia

Variable	All Subjects	Empiric Macrolide Therapy		*P*
		Yes	No	
Demographics				
Male sex	356 (51.6)	200 (49.4)	156 (54.7)	0.166
Race				
Black	135 (19.6)	81 (20.0)	54 (19.0)	0.506
White	484 (70.1)	287 (70.9)	197 (69.1)	
Other	62 (9.0)	31 (7.7)	31 (10.9)	
Missing	9 (1.3)	6 (1.5)	3 (1.1)	
Presentation during viral respiratory season	420 (60.9)	242 (59.8)	178 (62.5)	
Prior asthma hospitalization	41 (5.9)	31 (7.7)	10 (3.5)	0.023
Intensive care unit admission	127 (18.4)	74 (18.3)	53 (18.6)	0.914
Laboratory tests and procedures				
Additional radiologic imaging*	24 (3.5)	13 (3.2)	11 (3.9)	0.646
Arterial blood gas	116 (17.3)	72 (18.5)	44 (15.6)	0.316
Complete blood count	433 (64.4)	249 (64.0)	184 (65.0)	0.788
Blood culture	280 (41.7)	167 (42.9)	113 (39.9)	0.436
Mechanical ventilation	16 (2.3)	5 (1.2)	11 (3.86)	0.024
Medications				
Chronic asthma medication	116 (16.8)	72 (17.8)	44 (15.4)	0.419
Beta-agonist therapy	328 (47.5)	215 (53.1)	113 (39.7)	0.001
Vasoactive infusions	22 (3.2)	13 (3.2)	9 (3.2)	0.969
Systemic corticosteroids	252 (36.5)	191 (47.2)	61 (21.4)	<0.001
Clindamycin or vancomycin	86 (12.5)	24 (5.9)	62 (21.8)	<0.001

NOTE: Values listed as number (percent).
* Includes chest computed tomography or ultrasound.

Macrolide therapy was administered to 405 (58.7%) patients. Systemic corticosteroid therapy was administered to 252 (36.5%) patients. Overall, 191 (27.7%) of the 690 patients received both macrolides and systemic corticosteroids empirically, while 224 (32.5%) received neither; 61 (8.8%) received corticosteroids but not macrolides, while 214 (31.0%) received macrolides but not corticosteroids. Asthma hospitalization within the 24 months prior to admission was more common among those receiving macrolides (N = 60/405, 14.8%) than among those not receiving macrolides (N = 30/285, 10.5%) ($P = 0.023$). Macrolide recipients also more commonly received concomitant systemic corticosteroids (N = 191/405, 47.2%) than macrolide non-recipients (N = 61/285, 21.4%) ($P < 0.001$) and more commonly received beta-agonist therapy (N = 215/405, 53.1%) than macrolide non-recipients (N = 113/285, 39.7%) ($P = 0.001$).

Length of Stay

The overall median LOS was 3 days (IQR, 2-6 days); the median LOS was 3 days (IQR, 2-5 days) for empiric macrolide recipients and 4 days (IQR, 2-9 days) for non-recipients ($P < 0.001$). Overall, 22.9% (N = 158) of children had an LOS $\geq$7 days and 8.8% (N = 61) of children had an LOS $\geq$14 days. The LOS was $\geq$7 days for 15.3% (N = 62) of macrolide recipients and 33.7% (N = 96) of non-recipients. LOS was

TABLE 2. Adjusted Association of Empiric Macrolide Therapy With Outcomes

	Association of Empiric Macrolide Therapy With Outcomes*
Length of stay (days)	
Adjusted beta-coefficient (95 % CI)	−0.38 (−0.59 to −0.17)
Adjusted percent change (95% CI)	−32% (−45% to −15%)
P value	0.001
Any readmission within 28 days	
Adjusted odds ratio (95% CI)	1.12 (0.22 to 5.78)
P value	0.890
Any readmission within 15 mo	
Adjusted odds ratio (95% CI)	1.00 (0.59 to 1.70)
P value	0.991
Asthma hospitalization within 15 mo	
Adjusted odds ratio (95% CI)	1.09 (0.54 to 2.17)
P value	0.820

*All models adjusted for age, prior asthma hospitalization, intensive care unit admission, chronic asthma medications, albuterol, systemic corticosteroid therapy, and vancomcyin or clindamycin.
Abbreviation: CI, confidence interval.

TABLE 3. Multivariable Analysis of the Association Between Empiric Macrolide Therapy and Outcomes, Stratified by Receipt or Non-Receipt of Systemic Corticosteroid Therapy

	Concomitant Systemic Corticosteroid Therapy*	
	Yes	No
Length of stay		
Adjusted beta-coefficient (95% CI)	−0.40 (−0.74 to −0.07)	−0.37 (−0.58 to −0.16)
Adjusted percent change (95% CI)	−33% (−52% to −7%)	−31% (−44% to −15%)
P value	0.020	0.001
Readmission within 28 days		
Adjusted odds ratio (95% CI)	1.09 (0.05 to 26.7)	1.50 (0.21 to 10.8)
P value	0.960	0.687
Readmission within 15 mo		
Adjusted odds ratio (95% CI)	1.57 (0.65 to 3.82)	0.81 (0.45 to 1.46)
P value	0.32	0.49
Asthma hospitalization within 15 mo		
Adjusted odds ratio (95% CI)	1.51 (0.58 to 3.93)	0.85 (0.36 to 1.97)
P value	0.395	0.700

*All models adjusted for age, prior asthma hospitalization, intensive care unit admission, chronic asthma medications, albuterol, and vancomcyin or clindamycin.
Abbreviation: CI, confidence interval.

≥7 days for 17.5% (N = 44) of systemic steroid recipients and 26% (N = 114) of non-recipients. In unadjusted analysis, macrolide therapy (beta-coefficient, −0.49; 95% confidence interval [CI]: −0.72 to −0.25; $P < 0.001$) and systemic corticosteroid administration (beta-coefficient, −0.26; CI: −0.37 to −0.14; $P < 0.001$) were associated with shorter hospital LOS (Appendix 1).

In multivariable analysis, macrolide therapy remained associated with a shorter LOS (Table 2; Appendix 2). Systemic corticosteroid administration was associated with a 23% shorter LOS (adjusted beta-coefficient, −0.26; 95% CI: −0.39 to −0.14; $P < 0.001$). In contrast, previous hospitalization for asthma was associated with a 31% longer LOS (adjusted beta-coefficient, 0.27; 95% CI: 0.09-0.045; $P = 0.004$). Receipt of beta-agonist therapy or chronic asthma medications were not associated with significant differences in LOS. In analysis stratified by receipt or non-receipt of concomitant systemic corticosteroid therapy, empiric macrolide therapy remained associated with a significantly shorter LOS in both systemic corticosteroid recipients and non-recipient (Table 4). When the cohort was restricted to subjects with a LOS ≤7 days, macrolide therapy remained significantly associated with a shorter LOS (adjusted percent change, −20%; 95% CI: −32% to −5%; $P = 0.015$).

Readmission

Overall, 8 children (1.2%) were readmitted for pneumonia-associated conditions within 28 days of index discharge. Readmission occurred in 1.2% of macrolide recipients and 1.1% of non-recipients ($P = 0.83$) (Table 4). In unadjusted analysis, neither macrolide therapy (odds ratio [OR], 1.18; 95% CI: 0.25-5.45; $P = 0.84$) nor systemic corticosteroid administration (OR, 1.04; 95% CI: 0.27-4.10; $P = 0.95$) was associated with 28-day readmission (Appendix 3). In multivariable analysis, empiric macrolide therapy was not associated with 28-day readmission in the overall cohort (Table 2; Appendix 4)), or when the analysis was stratified by receipt or non-receipt of concomitant systemic corticosteroid therapy (Table 3).

Overall, 160 children (23.2%) were readmitted within 15 months of index discharge; 95 were readmitted for asthma during this time (Table 3). Overall readmission occurred in 23.7% of macrolide recipients and 22.5% of macrolide non-recipients ($P = 0.702$). Asthma readmission occurred in 15.1% of macrolide recipients and 11.9% of macrolide non-recipients ($P = 0.240$). In unadjusted analysis, empiric macrolide therapy was not significantly associated with any readmission within 15 months (OR, 1.07; 95% CI: 0.69-1.68; $P = 0.759$) or with asthma-related readmission within 15 months (OR, 1.31; 95% CI: 0.73- 2.36; $P = 0.369$). In multivariable analysis, neither any readmission nor asthma readmission within 15 months was associated with empiric macrolide therapy overall (Table 2) or when stratified by receipt or non-receipt of concomitant systemic corticosteroid therapy (Table 3).

The analyses for readmissions within 15 months of index discharge were repeated while limiting the cohort to those without prior asthma hospitalizations or chronic asthma medications. In this subset of patients, readmissions for any reason occurred in 55 (18.6%) of 295 macrolide recipients and 50 (22.0%) of 227 non-recipients. The difference was not statistically significant in multivariable analysis (adjusted odds ratio, 0.79; 95% CI: 0.41-1.51; $P = 0.47$). Readmissions for asthma occurred in 30 (10.2%) of 295 macrolide recipients and 26 (11.5%) of 227 non-recipients; this difference was also not significant in multivariable analysis (adjusted odds ratio, 0.83; 95%

TABLE 4. Readmissions Following Index Hospital Discharge Stratified by Receipt of Empiric Macrolide Therapy

	Empiric Macrolide Therapy N/Total (%)	
Readmission	Yes	No
Any readmission within 28 days		
Overall	5/405 (1.2)	3/285 (1.1)
Systemic corticosteroid therapy	2/186 (1.1)	1/66 (1.5)
No systemic corticosteroid therapy	3/177 (1.7)	2/261 (0.8)
Any readmission within 15 mo		
Overall	96/405 (23.7)	64/285 (22.5)
Systemic corticosteroid therapy	52/186 (28.0)	17/66 (25.8)
No systemic corticosteroid therapy	32/177 (18.1)	59/261 (22.6)
Asthma hospitalization within 15 mo		
Overall	61/405 (15.1)	34/285 (11.9)
Systemic corticosteroid therapy	39/186 (21.0)	13/66 (19.7)
No systemic corticosteroid therapy	14/177 (7.9)	29/261 (11.1)

CI: 0.36-1.93; $P = 0.83$). The magnitude of the estimate of effect for 28-day and 15-month readmissions, and 15-month asthma hospitalizations, was similar to the primary analysis when the cohort was restricted to subjects with a LOS $\leq$7 days.

DISCUSSION

This multicenter study examined the role of macrolide therapy in children hospitalized with *M. pneumoniae* pneumonia. Empiric macrolide therapy was associated with an approximately 30% shorter hospital LOS and, in stratified analysis, remained associated with a significantly shorter hospital LOS in both systemic corticosteroid recipients and non-recipients. Empiric macrolide therapy was not associated with short- or longer-term hospital readmission.

Previous small randomized trials have been inconclusive regarding the potential benefit of macrolide therapy in *M. pneumoniae* pneumonia.[11] Our study, which demonstrated a shorter LOS among macrolides recipients compared with non-recipients, has several advantages over prior studies including a substantively larger sample size and multicenter design. Animal models support our observations regarding the potential beneficial antimicrobial role of macrolides. *M. pneumoniae* concentrations in bronchoalveolar lavage specimens were significantly lower among experimentally infected mice treated with clarithromycin, a macolide-class antibiotic, compared with either placebo or dexamethasone.[45] Combination therapy with clarithromycin and dexamethasone reduced histopathologic inflammation to a greater degree than dexamethasone alone.[45]

While the relative importance of the antimicrobial and anti-inflammatory properties of macrolides is not known, observational studies of children infected with macrolide-resistant *M. pneumoniae* suggest that the antimicrobial properties of macrolides may provide disproportionate clinical benefit. The duration of fever in macrolide recipients with macrolide-resistant *M. pneumoniae* (median duration, 9 days) reported by Suzuki et al[46] was significantly longer than those with macrolide-susceptible infections (median duration, 5 days), and similar to the duration of fever in patients with *M. pneumoniae* infection treated with placebo (median duration, 8 days) reported by Kingston et al.[47] Additionally, macrolide therapy was associated with significant improvements in lung function in patients with asthma and concomitant *M. pneumoniae* infection, but not in patients with asthma without documented *M. pneumoniae* infection.[9] As corticosteroids also have anti-inflammatory properties, we expect that any anti-inflammatory benefit of macrolide therapy would be mitigated by the concomitant administration of corticosteroids. The shorter LOS associated with empiric macrolide therapy in our study was comparable among corticosteroid recipients and non-recipients.

Atypical bacterial pathogens, including *M. pneumoniae*, are associated with diffuse lower airway inflammation[6,48] and airway hyperresponsiveness,[6] and have been implicated as a cause of acute asthma exacerbations.[7,49–54] Among patients with previously diagnosed asthma, acute *M. pneumoniae* infection was identified in up to 20% of those having acute exacerbations.[7,54] Macrolide therapy has a beneficial effect on lung function and airway hyperresponsiveness in adults with asthma.[9,55] Among mice infected with *M. pneumoniae*, 3 days of macrolide therapy resulted in a significant reduction in airway hyperresponsiveness compared with placebo or dexamethasone; however, after 6 days of therapy, there was no significant difference in airway hyperresponsiveness between those receiving macrolides, dexamethasone, or placebo, suggesting that the benefit of macrolides on airway hyperresponsiveness may be brief. Our findings of a shorter LOS but no difference in readmissions at 28 days or longer, for macrolide recipients compared with non-recipients, support the limited benefit of macrolide therapy beyond the initial reduction in bacterial load seen in the first few days of therapy.

M. pneumoniae infection has also been implicated as a cause of chronic pulmonary disease, including asthma.[6–10] In the mouse model, peribronchial and perivascular mononuclear infiltrates, increased airway methacholine reactivity, and increased airway obstruction were observed 530 days after *M. pneumoniae* inoculation.[6] *M. pneumoniae* has been identified in 26 (50%) of 51 children experiencing their first asthma attack,[7] and 23 (42%) of 55 adults with chronic, stable asthma.[9] Nevertheless, results of other studies addressing the issue are inconsistent, and the role of *M. pneumoniae* in the development of asthma remains unclear.[56] In order to investigate the impact of macrolide therapy on the development of chronic pulmonary disease requiring hospitalization, we examined the readmission rates in the 15 months following index discharge. The proportion of children hospitalized

with asthma following the hospitalization for *M. pneumoniae* pneumonia was higher for both macrolide recipients and non-recipients compared with the 24-months prior to infection. These results support a possible role for *M. pneumoniae* in chronic pulmonary disease. However, macrolide therapy was not associated with long-term overall hospital readmission or long-term asthma readmission, either in the entire cohort or in the subset of patients without prior asthma hospitalizations or medications.

This study had several limitations. First, because the identification of children with *M. pneumoniae* pneumonia relied on ICD-9 discharge diagnosis codes, it is possible that there was misclassification of disease. We minimized the inclusion of children without *M. pneumoniae* by including only children who received antibiotic therapy on the first day of hospitalization and by excluding patients younger than 6 years of age, a group at relatively low-risk for *M. pneumoniae* infection. Further, our algorithm for identification of *M. pneumoniae* pneumonia was validated through review of the medical records at 1 institution and was found to have a high positive predictive value. However, the positive predictive value of these ICD-9 codes may vary across institutions. Additionally, the sensitivity of ICD-9 codes for identifying children with *M. pneumoniae* pneumonia is not known. Also, not all children with pneumonia undergo testing for *M. pneumoniae*, and different tests have varying sensitivity and specificity.[57,58] Thus, some children with *M. pneumoniae* pneumonia were not diagnosed and so were not included in our study. It is not known how inclusion of these children would affect our results.

Second, the antibiotic information used in this study was limited to empiric antibiotic therapy. It is possible that some patients received macrolide therapy before admission. It is also likely that identification of *M. pneumoniae* during the hospitalization prompted the addition or substitution of macrolide therapy for some patients. If this therapy was initiated beyond the first day of hospitalization, these children would be classified as macrolide non-recipients. Since macrolide administration was associated with a shorter hospital LOS, such misclassification would bias our results towards finding no difference in LOS between macrolide recipients and non-recipients. It is therefore possible that the benefit of macrolide therapy is even greater than found in our study.

Third, there may be unmeasured confounding or residual confounding by indication for adjunct corticosteroid therapy related to clinical presentation. We expect that corticosteroid recipients would be sicker than non-recipients. We included variables associated with a greater severity of illness (such as intensive care unit admission) in the multivariable analysis. Additionally, the shorter LOS among macrolide recipients remained when the analysis was stratified by receipt or non-receipt of systemic corticosteroid therapy.

Fourth, we were only able to record readmissions occurring at the same hospital as the index admission; any readmission presenting to a different hospital following their index admission did not appear in our records, and was therefore not counted. It is thus possible that the true number of readmissions is higher than that represented here. Finally, despite the large number of patients included in this study, the number of short-term readmissions was relatively small. Thus, we may have been underpowered to detect small but significant differences in short-term readmission rates.

In conclusion, macrolide therapy was associated with shorter hospital LOS, but not with short-term or longer-term readmission in children presenting with *M. pneumoniae* pneumonia.

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