Antibiotic Choice and Clinical Outcomes in Ambulatory Children with Community-Acquired Pneumonia

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Objectives To describe antibiotic prescribing patterns in ambulatory children with community-acquired pneumonia and to assess the relationship between antibiotic selection and clinical outcomes.

Study design This was a retrospective cohort study of ambulatory Medicaid-enrolled children 0-18 years of age diagnosed with community-acquired pneumonia from 2010 to 2016. The exposure was antibiotic class: narrow-spectrum (aminopenicillins), broad-spectrum (amoxicillin/clavulanate and cephalosporins), macrolide monotherapy, macrolides with narrow-spectrum antibiotics, or macrolides with broad-spectrum antibiotics. The associations between antibiotic selection and the outcomes of subsequent hospitalization and development of severe pneumonia (chest drainage procedure, intensive care admission, mechanical ventilation) were assessed, controlling for measures of illness severity.

Results Among 252 177 outpatient pneumonia visits, macrolide monotherapy was used in 43.2%, narrow-spectrum antibiotics in 26.1%, and broad-spectrum antibiotics in 24.7%. A total of 1488 children (0.59%) were subsequently hospitalized and 117 (0.05%) developed severe pneumonia. Compared with children receiving narrow-spectrum antibiotics, the odds of subsequent hospitalization were higher in children receiving broad-spectrum antibiotics (aOR, 1.34; 95% CI, 1.17-1.52) and lower in children receiving macrolide monotherapy (aOR, 0.64; 95% CI, 0.55-0.73) and macrolides with narrow-spectrum antibiotics (aOR, 0.62; 95% CI, 0.39-0.97). Children receiving macrolide monotherapy had lower odds of developing severe pneumonia than children receiving narrow-spectrum antibiotics (aOR, 0.56; 95% CI, 0.33-0.93). However, the absolute risk difference was <0.5% for all analyses.

Conclusions Macrolides are the most commonly prescribed antibiotic for ambulatory children with community-acquired pneumonia. Subsequent hospitalization and severe pneumonia are rare. Future efforts should focus on reducing broad-spectrum and macrolide antibiotic prescribing. *(J Pediatr 2021;229:207-15)*.

The Infectious Diseases Society of America and the Pediatric Infectious Diseases Society national guidelines recommend narrow-spectrum antibiotics (high-dose amoxicillin) for children with presumed bacterial community-acquired pneumonia.[1] Macrolides are recommended in school-aged children and adolescents when atypical pathogens are suspected.[1] Before guideline publication, there was widespread use of macrolides and cephalosporins for community-acquired pneumonia in both the inpatient and ambulatory setting.[2,3] Although narrow-spectrum antibiotic use is increasing in the inpatient setting since publication of the 2011 guidelines, children with community-acquired pneumonia in the ambulatory setting are still most commonly treated with macrolides and cephalosporins.[4-6]

Despite high rates of broad-spectrum antibiotic use, children hospitalized with community-acquired pneumonia treated with parenteral narrow-spectrum antibiotics have equivalent hospital length of stay and rates of intensive care unit (ICU) transfer to children treated with parenteral cephalosporins.[7] Additionally, broad-spectrum antibiotic use in ambulatory children with acute upper respiratory infections has been associated with a higher rate of adverse events without any benefit in outcomes.[8] Observational data suggest that ambulatory children with community-acquired pneumonia who receive macrolides in combination

ED	Emergency department
ICD-9	*International Classification of Diseases, 9th edition*
ICD-10	*International Classification of Diseases, 10th edition*
ICU	Intensive care unit

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with beta-lactam antibiotics have lower odds of treatment failure than children receiving beta-lactam agents alone, but a number of clinical trials have failed to find a benefit to macrolides in children with community-acquired pneumonia.[9-12] Because the above studies were limited to hospitalized patients or single healthcare systems, there remains a relative paucity of data surrounding the association between antibiotic selection and clinical outcomes among children with community-acquired pneumonia managed in the ambulatory setting.

The primary objective of this study was to describe contemporary antibiotic selection patterns in ambulatory children with community-acquired pneumonia. The secondary objective was to assess the relationship between antibiotic selection and the clinical outcomes of hospitalization, severe pneumonia, and change in antibiotic therapy in children with community-acquired pneumonia managed in the ambulatory setting.

Methods

This was a retrospective cohort study using the IBM Watson Health MarketScan Medicaid database (IBM Corporation, Somers, New York), a proprietary Medicaid claims database from 11 deidentified, geographically diverse states that allows for longitudinal tracking of enrollees over time through a variety of healthcare settings. This study was determined to be exempt from human subjects research by the Institutional Review Board at the study institution.

Study Population

We included children 1-18 years of age with an outpatient claim from 2010 through 2016 with a diagnosis of community-acquired pneumonia. Eligible children were those discharged from the emergency department (ED) or outpatient clinics (primary, subspecialty, or urgent care) with a coded diagnosis of community-acquired pneumonia (*International Classification of Diseases, 9th edition* [ICD-9] and *International Classification of Diseases, 10th edition* [ICD-10]) discharge diagnosis codes (ICD-9: 481-483.8, 485-486; ICD-10: J13, J14, J15, J18).[13] To satisfy inclusion criteria, children had to have a prescription filled for an oral antibiotic within 1 calendar day after the index visit.

We excluded children who were not continuously enrolled in Medicaid for ≥1 year before and 30 days after the index visit. We also excluded children with complex chronic conditions predisposing to pneumonia (eg, cystic fibrosis, malignancy, sickle cell disease, technology dependence) according to a previously defined classification scheme.[14,15] Complex chronic conditions were ascertained using diagnosis codes assigned at the index visit or within the 1 year prior to the index visit. To identify children being evaluated for a new episode of community-acquired pneumonia, we excluded children hospitalized within the 30-day period preceding the index visit, and children who filled an antibiotic prescription within the 14 days prior to the index visit.

Patient Characteristics and Diagnostic Testing

We recorded patient age (1-4 years, 5-12 years, 13-18 years), sex, race and/or ethnicity (white, black, Hispanic, other), and visit setting (ED, or outpatient clinic, including urgent care clinics). Visits between December 1 and March 31 were classified as occurring during influenza season.[16] We defined asthma history as diagnosis code for asthma (ICD-9 493.x or ICD-10 J45.x) within 6 months before the index visit. We defined asthma codiagnosis at index visit by an ICD-9 or ICD-10 code for asthma at the index visit, plus an associated claim for a systemic corticosteroid. Each patient was also classified as to the presence and number of chronic condition indicators as defined by the Agency for Healthcare Research and Quality.[17] Chronic condition indicators represent a wide variety of chronic medical conditions such as asthma, diabetes, and mental illness. We recorded claims for medications administered, and used *Current Procedural Terminology* codes to characterize use of diagnostic tests.

Antibiotic Classifications

We reviewed claims for antibiotics filled within 1 day of the index visit, and classified antibiotic regimens into mutually exclusive groups: narrow-spectrum (aminopenicillins), broad-spectrum (amoxicillin/clavulanate, cephalosporins), macrolide monotherapy (azithromycin, erythromycin, clarithromycin), narrow-spectrum agents in combination with a macrolide, and broad-spectrum agents in combination with a macrolide. Children who had prescriptions filled for both a narrow-spectrum and a broad-spectrum antibiotic were classified in the broad-spectrum group. All other single antibiotics or combination regimens were classified as other antibiotics. Children who did not receive an oral antibiotic or who received only a urinary anti-infective (nitrofurantoin) were excluded from further analysis.

Outcome Measures

The outcome of hospitalization was defined as a claim for hospitalization for any reason occurring between 2 and 7 days after the index visit. We began the follow-up period at 2 days based on evidence that clinical changes before 2 days in acute upper respiratory tract infections are unlikely to be related to the initial antibiotic choice, and because we allowed up to 1 day after the index visit to determine the antibiotic selection.[8] The outcome of severe pneumonia was defined as ICU admission, a chest drainage procedure (defined by a *Current Procedural Terminology* code for thoracentesis [32554, 32555], thoracostomy [32035, 32036, 32551], video-assisted thoracoscopic surgery [32601-32609, 32650-32674], or thoracotomy [32096, 32097, 32098, 32100, 32124]), or death occurring between 2 and 7 days after the index visit. The outcome of change in antibiotic was defined as a new antibiotic claim occurring between 2 and 7 days after the index visit, regardless of antibiotic class.

Statistical Analyses

Antibiotic selection was described for the overall cohort and stratified by age group and visit setting. Bivariate

comparisons were made using the χ^2 and Wilcoxon rank-sum tests. Antibiotic selection was plotted by year and tested for temporal trends using the Cochran-Armitage test. Multivariable logistic regression was used to determine the odds of each outcome as a function of antibiotic class. In an attempt to control for baseline differences in patient severity that may have influenced antibiotic selection, we adjusted models for patient age, number of chronic condition indicators, hospitalization within the previous 6 months, site of visit (ED vs outpatient/urgent care), presentation during influenza season, asthma history, asthma codiagnosis at the index visit, intravenous antibiotic administration, and use of other medications (systemic corticosteroid, oseltamivir, albuterol). We also controlled for whether there was a claim for laboratory testing, chest radiography, or chest computed tomography scan. All variables used for adjustment in the multivariable models were chosen a priori based on previous research, biologic plausibility, and group consensus.[18-20] Children receiving antibiotics in the other category were excluded from the multivariable analysis.

Because macrolides appear to have a beneficial effect in children with asthma, and because children with asthma exacerbations are often infected with viral illnesses, we conducted a subanalysis excluding children with a codiagnosis of asthma at the index visit.[21-23]

Analyses were performed using SAS version 9.4 (SAS institute, Inc, Cary, North Carolina).

Results

Over the 7-year study period, 455 704 children were discharged from an ambulatory care setting with a diagnosis of community-acquired pneumonia. After exclusions, our final cohort consisted of 252 177 children, among whom 91 482 (36.3%) were treated in the ED and 160 695 (63.7%) were treated in an outpatient clinic (**Figure 1**; available at www.jpeds.com). The median patient age was 4 years (IQR, 2-7 years) (**Table I**). Overall, 57 565 children (22.8%) had a history of asthma and 34 104 (13.5%) had an asthma codiagnosis at the index visit. Although 45.1% of children presented during influenza season, oseltamivir was prescribed in only 0.8% of children. Chest radiography was performed in 55.5% of children.

Antibiotic Prescribing Patterns

Macrolide monotherapy was the most frequently used antibiotic regimen, used in 43.2% of the cohort. Narrow-spectrum antibiotics were prescribed to 26.1% of children and broad-spectrum antibiotics to 24.7% of children. Combination therapy consisting of a macrolide plus a narrow- or broad-spectrum antibiotic was prescribed in 11 719 children (4.6%) (**Figure 2**). Among children 1-4 years of age, 34.0% received narrow-spectrum antibiotics, 32.9% received macrolide monotherapy, and 28.8% received broad-spectrum antibiotics. Macrolide use increased with advancing age ($P < .001$). Across all age groups, children seen in outpatient clinics were more likely to receive broad-spectrum antibiotics and macrolide monotherapy, and less likely to receive narrow-spectrum antibiotics, than those seen in the ED ($P < .001$ for all comparisons).

Over the study period, we observed an increase in narrow-spectrum antibiotic prescribing (from 20.1% in 2010 to 31.8% in 2016), and a decrease in broad-spectrum antibiotic prescribing (28.8% to 21.2%) and macrolide monotherapy (45.8% to 40.5%) ($P < .001$ for all trends). In all age groups, narrow-spectrum prescribing increased, and broad-spectrum prescribing and macrolide monotherapy decreased, over the study period (**Figure 3**). The effect was most pronounced in children 1-4 years of age (18.2% increase in narrow-spectrum prescribing and 10.1% decrease in macrolide monotherapy) and least pronounced in children 13-18 years of age (2.6% increase in narrow-spectrum prescribing and 4.4% decrease in macrolide monotherapy).

Hospitalization after the Initial Pneumonia Visit

A total of 1488 children (0.69%) were hospitalized in the 2-7 days after the ambulatory pneumonia visit (**Table II**; available at www.jpeds.com). In each antibiotic class, <1% of children were hospitalized after the visit. Among children receiving narrow-spectrum antibiotics, 0.6% were hospitalized during follow-up. Compared with this group, the hospitalization rate was higher among children receiving broad-spectrum antibiotics (0.8% hospitalized; aOR for hospitalization, 1.34; 95% CI. 1.17-1.52) and among children receiving broad-spectrum antibiotics in combination with macrolides (1.0% hospitalized; aOR for hospitalization, 1.43; 95% CI, 1.10-1.86) (**Table III**). The hospitalization rate was lower in the macrolide monotherapy group (0.4% hospitalized; aOR for hospitalization, 0.64; 95% CI, 0.55-0.73) and in the group receiving macrolides in addition to narrow-spectrum therapy (0.4% hospitalized; aOR for hospitalization, 0.62; 95% CI, 0.39-0.97).

Development of Severe Pneumonia

A total of 117 children (0.05%) developed severe pneumonia after their pneumonia visit (**Table II**), including 107 children with hospitalization in an ICU and 25 with a chest drainage procedure. There were no deaths recorded in this sample. The incidence of severe pneumonia was ≤0.1% across antibiotic classes. Compared with children receiving narrow-spectrum antibiotic therapy, the odds of developing severe pneumonia were lower in children receiving macrolide monotherapy (aOR, 0.56; 95% CI, 0.33-0.93) (**Table III**), and the absolute risk difference was 0.1%.

Change in Antibiotic Therapy

A new antibiotic prescription was filled in 13 261 children (5.3%) within 2-7 days of the initial prescription filling (**Table II**). Among children receiving narrow-spectrum antibiotics, 4.4% underwent a change in antibiotic therapy during the follow-up period. Compared with this group, the incidence of antibiotic change was higher in the broad-spectrum group (5.1%; aOR, 1.15; 95% CI, 1.09-1.21)

Table I. Demographics of study cohort, stratified by antibiotic prescribing at initial visit*

		Initial antibiotic prescription					
Patient characteristics	Overall (n = 252 177)	Narrow (n = 65 872)	Narrow + macrolide (n = 4858)	Broad (n = 62 381)	Broad + macrolide (n = 6861)	Macrolide monotherapy (n = 108 917)	Other (n = 3288)
Age (y)	4 [2-7]	3 [2-5]	6 [3-9]	4 [2-6]	6 [3-9]	6 [3-9]	9 [4-16]
1-4	126 280 (50.1)	42 955 (65.2)	1792 (36.9)	36 326 (58.2)	2665 (38.8)	41 554 (38.2)	988 (30)
5-12	104 628 (41.5)	21 334 (32.4)	2586 (53.2)	22 890 (36.7)	3288 (47.9)	53 530 (49.1)	1000 (30.4)
13-18	21 269 (8.4)	1583 (2.4)	480 (9.9)	3165 (5.1)	908 (13.2)	13 833 (12.7)	1300 (39.5)
% Female	118 812 (47.1)	31 553 (47.9)	2338 (48.1)	29 332 (47)	3176 (46.3)	50 701 (46.6)	1712 (52.1)
Race/ethnicity							
White	128 108 (50.8)	27 939 (42.4)	2471 (50.9)	33 392 (53.5)	4099 (59.7)	58 380 (53.6)	1827 (55.6)
Black	71 468 (28.3)	23 001 (34.9)	1407 (29)	16 517 (26.5)	1529 (22.3)	28 182 (25.9)	832 (25.3)
Hispanic	23 719 (9.4)	6580 (10)	440 (9.1)	5720 (9.2)	521 (7.6)	10 166 (9.3)	292 (8.9)
Other	24 092 (9.6)	6565 (10)	416 (8.6)	5778 (9.3)	592 (8.6)	10 456 (9.6)	285 (8.7)
Missing	4790 (1.9)	1787 (2.7)	124 (2.6)	974 (1.6)	120 (1.7)	1733 (1.6)	52 (1.6)
Number of chronic condition indicator body systems							
0	97 183 (38.5)	27 061 (41.1)	1752 (36.1)	23 465 (37.6)	2369 (34.5)	41 555 (38.2)	981 (29.8)
1	91 197 (36.2)	23 509 (35.7)	1794 (36.9)	22 616 (36.3)	2503 (36.5)	39 612 (36.4)	1163 (35.4)
2	43 132 (17.1)	10 600 (16.1)	881 (18.1)	10 892 (17.5)	1276 (18.6)	18 779 (17.2)	704 (21.4)
≥3	20 665 (8.2)	4702 (7.1)	431 (8.9)	5408 (8.7)	713 (10.4)	8971 (8.2)	440 (13.4)
Asthma history†	57 565 (22.8)	14 638 (22.2)	1247 (25.7)	14 693 (23.6)	1817 (26.5)	24 362 (22.4)	808 (24.6)
Asthma codiagnosis at index visit‡	34 104 (13.5)	8927 (13.6)	798 (16.4)	8128 (13)	1104 (16.1)	14 756 (13.5)	391 (11.9)
Visited ED within the past year	119 969 (47.6)	34 797 (52.8)	2458 (50.6)	30 338 (48.6)	3358 (48.9)	47 399 (43.5)	1619 (49.2)
Hospitalized within the past year	14 004 (5.6)	4489 (6.8)	270 (5.6)	4072 (6.5)	442 (6.4)	4483 (4.1)	248 (7.5)
Site of visit							
ED	91 482 (36.3)	29 657 (45.0)	2135 (43.9)	20 750 (33.3)	2446 (35.7)	35 259 (32.4)	1235 (37.6)
Outpatient clinic	160 695 (63.7)	36 215 (55.0)	2723 (56.1)	41 631 (66.7)	4415 (64.3)	73 658 (67.6)	2053 (62.4)
Presentation during influenza season (Dec 1-Mar 31)	113 839 (45.1)	29 603 (44.9)	2068 (42.6)	29 454 (47.2)	3077 (44.8)	48 293 (44.3)	1344 (40.9)
Testing performed at index visit							
Blood gas analysis	192 (0.1)	50 (0.1)	11 (0.2)	46 (0.1)	18 (0.3)	56 (0.1)	11 (0.3)
White blood cell count	29 254 (11.6)	5625 (8.5)	768 (15.8)	9661 (15.5)	1556 (22.7)	10 913 (10)	731 (22.2)
Blood culture	19 805 (7.9)	4678 (7.1)	547 (11.3)	6584 (10.6)	1002 (14.6)	6530 (6)	464 (14.1)
Lactate	456 (0.2)	91 (0.1)	20 (0.4)	99 (0.2)	46 (0.7)	167 (0.2)	33 (1)
C-reactive protein	3642 (1.4)	851 (1.3)	120 (2.5)	1301 (2.1)	218 (3.2)	1073 (1)	79 (2.4)
Chest radiograph	139 936 (55.5)	39 550 (60)	3285 (67.6)	36 645 (58.7)	4796 (69.9)	53 689 (49.3)	1971 (59.9)
Chest computed tomography scan	61 (0)	3 (0)	2 (0)	15 (0)	3 (0)	31 (0)	7 (0.2)
Other medication use associated with visit							
Oseltamivir	1907 (0.8)	493 (0.7)	31 (0.6)	527 (0.8)	60 (0.9)	759 (0.7)	37 (1.1)
Albuterol	71 518 (28.4)	17 181 (26.1)	1511 (31.1)	18 047 (28.9)	2481 (36.2)	31 411 (28.8)	887 (27)
Systemic corticosteroid	48 868 (19.4)	10 727 (16.3)	1068 (22)	12 275 (19.7)	1886 (27.5)	22 208 (20.4)	704 (21.4)
Parenteral antibiotic	4038 (1.6)	696 (1.1)	129 (2.7)	1387 (2.2)	258 (3.8)	1493 (1.4)	75 (2.3)

Values are median [IQR] or number (%).
*All comparisons significant at $P < .001$ except oseltamivir use, which was significant at $P = .001$.
†Asthma history: ICD-9 or ICD-10 code for asthma within 6 months before the index visit.
‡Asthma codiagnosis: ICD-9 or ICD-10 code for asthma plus administration of a systemic corticosteroid.

(Table III). The incidence of antibiotic change was lower in children initially prescribed macrolides in addition to narrow-spectrum (0.4%; aOR, 0.47; 95% CI, 0.39-0.57) or broad-spectrum (2.4%; aOR, 0.48; 95% CI, 0.41-0.56) antibiotics. There was no significant difference in the incidence of antibiotic change between children receiving macrolide monotherapy and those receiving narrow-spectrum antibiotics (aOR, 0.97; 95% CI, 0.92-1.02).

Subanalysis in Children with Asthma Exacerbation

After excluding children with a codiagnosis of asthma, macrolide monotherapy was no longer associated with a decreased odds of severe pneumonia (aOR, 0.57; 95% CI, 0.32-1.03). Other associations did not materially differ from the main analysis.

Discussion

In this retrospective cohort study of >250 000 Medicaid-insured children, we found that a substantial portion of children treated for community-acquired pneumonia in the ambulatory setting received broad-spectrum antibiotics or macrolides. This pattern persists several years after publication of national guidelines emphasizing the use of narrow-spectrum aminopenicillins in children with nonsevere community-acquired pneumonia, although we did observe an increase in narrow-spectrum antibiotic use over the study period.[1] Very few children subsequently developed severe pneumonia or required hospitalization after their initial visit.

Our findings add to a growing body of literature demonstrating persistent use of macrolides and broad-spectrum

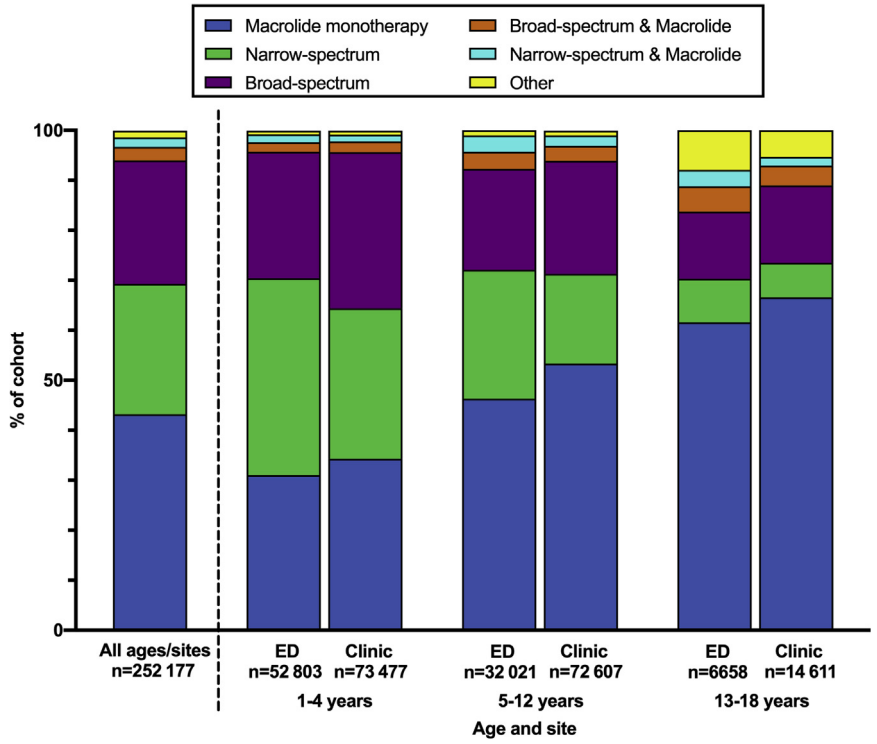

Figure 2. Antibiotic prescribing by site and age group. Clinic includes outpatient primary care, subspecialty, and urgent care clinics.

antibiotics in children with community-acquired pneumonia despite evidence-based guidelines recommending narrow-spectrum antibiotic therapy. Studies using nationally representative data from 2008 to 2015 found that children with community-acquired pneumonia treated in the ambulatory care setting received cephalosporins or macrolides at almost 70% of visits, without significant changes observed in antibiotic prescribing patterns over time. Azithromycin was the most commonly prescribed antibiotic in all settings and age groups.[5,6] Although we did observe an encouraging increase in narrow-spectrum antibiotic prescribing over time in our cohort, macrolides were still used in >40% of community-acquired pneumonia visits during the final year of our study period. Macrolides are intended to target atypical organisms such as *Mycoplasma pneumoniae*; however, the rate of macrolide use found in our cohort far exceeds the estimated point prevalence of atypical pathogens in pediatric community-acquired pneumonia of 8%-14%.[24-26]

Prescribing patterns in children <5 years of age bear special mention. Despite evidence that atypical pathogens are infrequent in this age group, only one-third of children <5 years of age in our cohort received amoxicillin and one-third received macrolides.[24] This finding is of particular concern given that the most common bacterial cause of community-acquired pneumonia in this age group is *S pneumoniae*.[1,24] *S pneumoniae* is highly sensitive to amoxicillin, but has high rates of resistance to macrolides and many oral cephalosporins.[1] We are encouraged by the temporal trends showing increased use of narrow-spectrum antibiotics and decreased use of broad-spectrum antibiotics and macrolides over the study period. However, the fact that one-quarter of children <5 years of age received macrolide monotherapy in the final year of the study period suggests that there remains room for improvement in prescribing habits in young children with community-acquired pneumonia.

Our study adds important data about short-term clinical outcomes of ambulatory children with community-acquired pneumonia based on antibiotic selection. We observed that children receiving broad-spectrum antibiotics, either with or without a macrolide, had higher odds of subsequent hospitalization within the follow-up period, although the absolute risk difference was small (0.5%). Additionally, children receiving broad-spectrum antibiotics alone had higher odds of a change in antibiotic therapy as compared with children receiving narrow-spectrum antibiotics. These findings may be due to a number of factors. First, although we controlled for a number of measures of severity, children receiving broad-spectrum antibiotics may have still had increased baseline severity as compared with children receiving narrow-spectrum antibiotics. Second, coverage may have been inadequate; although oral cephalosporins are considered broad-spectrum agents in our study, most second- and third-generation oral cephalosporins offer significantly inferior coverage of *S pneumoniae* as compared with narrow-spectrum aminopenicillins.[1] Third, children receiving broad-spectrum antibiotics may have had increased side effects leading to hospitalization or a change in antibiotic therapy. Our findings are

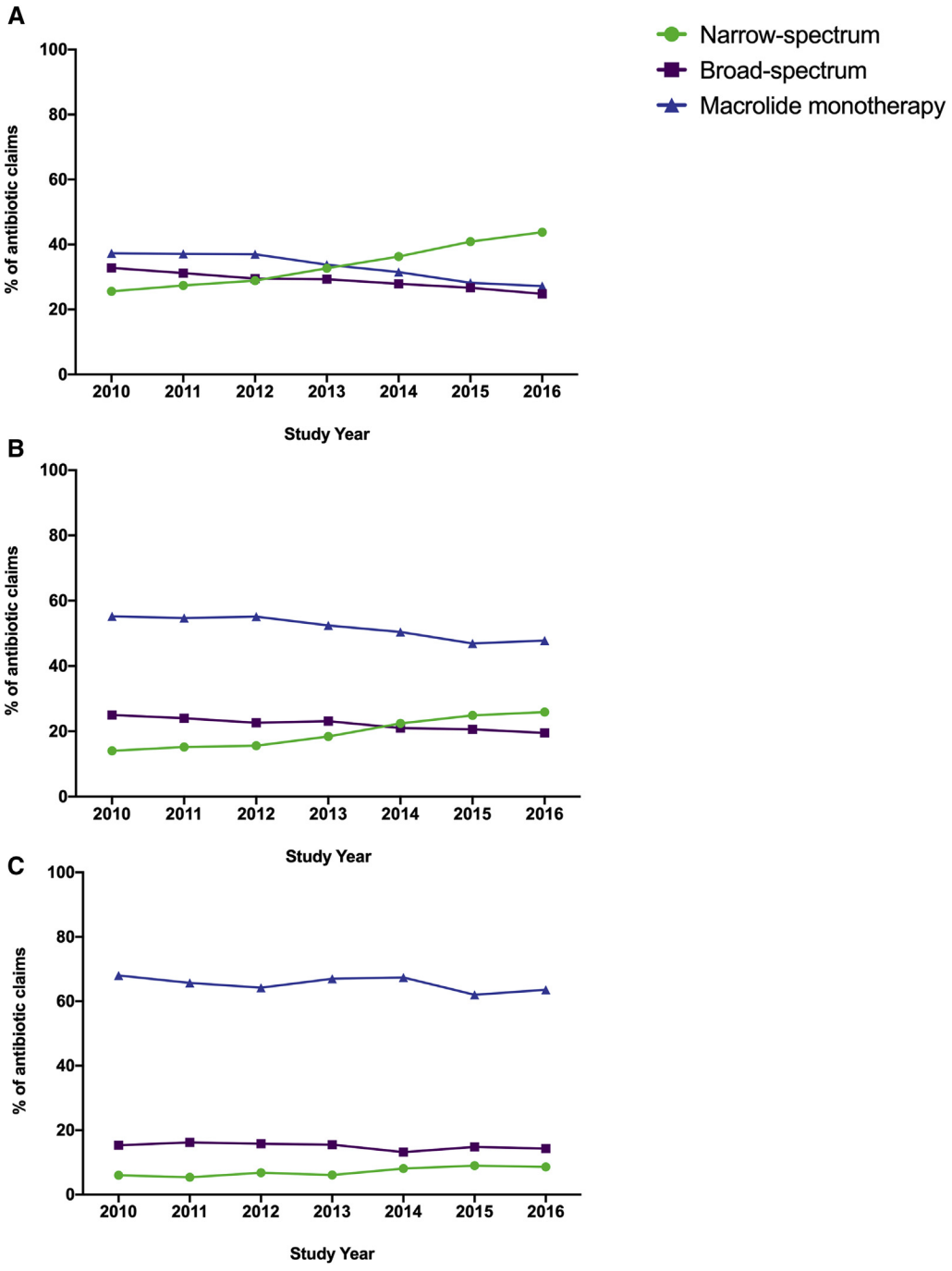

Figure 3. Changes in antibiotic claims for pediatric outpatient pneumonia over time by age group: **A,** 1-4 years, **B,** 5-12 years, and **C,** 13-18 years. All trends significant at the $P < .001$ level, except for broad-spectrum prescribing the 13-18 year age group ($P = .02$).

consistent with other studies showing no benefit to broad-spectrum antibiotics in pediatric community-acquired pneumonia.[7,8,27] One study of almost 14 000 children hospitalized with community-acquired pneumonia found no difference in length of stay, rates of ICU transfer, and rehospitalization rates between children receiving narrow-spectrum and broad-spectrum antibiotics.[7] Another study of >30 000 ambulatory children treated for acute upper respiratory tract infections observed no difference in the rates of treatment failure between children receiving narrow- and broad-spectrum antibiotics, but did find that children receiving broad-spectrum antibiotics had a significantly higher rate of adverse events.[8] Our findings provide further evidence that broad-spectrum antibiotics over no advantage to narrow-spectrum antibiotics in ambulatory children with community-acquired pneumonia.

Table III. aORs of pneumonia outcomes by antibiotic group*

Antibiotic groups	Hospitalization†	Severe pneumonia‡	Change in antibiotic therapy§
Narrow-spectrum	Referent	Referent	Referent
Narrow-spectrum + macrolide	0.62 (0.39-0.97)	0.39 (0.05-2.87)	0.47 (0.39-0.57)
Broad-spectrum	1.34 (1.17-1.52)	1.2 (0.76-1.91)	1.15 (1.09-1.21)
Broad-spectrum + macrolide	1.43 (1.1-1.86)	1.56 (0.64-3.77)	0.48 (0.41-0.56)
Macrolide monotherapy	0.64 (0.55-0.73)	0.56 (0.33-0.93)	0.97 (0.92-1.02)

Values are aOR (95% CI).
*Adjusted for patient age, number of chronic condition indicators, hospitalization within the previous 6 months, seen in ED (vs outpatient/urgent care), presentation during influenza season, asthma codiagnosis, intravenous antibiotic administration, blood gas analysis obtained, white blood cell count obtained, blood culture obtained, c-reactive protein obtained, lactate obtained, chest radiography obtained, chest computed tomography obtained, other medication given (oseltamivir, bronchodilator, corticosteroid).
†Hospitalization: hospital admission within 2-7 days after the index visit.
‡Severe pneumonia: ICU admission, pleural drainage procedure, or death within 2-7 days after the index visit.
§Change in antibiotic therapy: any new antibiotic prescription filled (regardless of class) within 2-7 days after the index visit.

As compared with children receiving narrow-spectrum antibiotics alone, children with additive macrolide therapy and those with macrolide monotherapy had decreased odds of subsequent hospitalization. Children receiving macrolide monotherapy also had decreased odds of severe pneumonia. There are a number of possible reasons for these findings. Again, despite our attempts to control for severity in our analysis, children receiving macrolides may have had less severe disease at presentation. Second, given that a large proportion of community-acquired pneumonia in children is viral in origin, our findings may be due to inherent antiviral and anti-inflammatory properties of macrolides.[1,24,28,29] This hypothesis is supported by the results of our subanalysis, which excluded children with a concurrent asthma exacerbations, many of which are triggered by respiratory viruses. In this subanalysis, macrolide monotherapy was no longer independently associated with a decreased odds of severe pneumonia. Third, the beneficial effect observed may be related to infection with atypical bacterial organisms, which would be more effectively treated with macrolides than with other antibiotic classes.

In a previous study comparing beta-lactam monotherapy with beta-lactam/macrolide combination therapy in the outpatient setting, the authors observed that among children 6-18 years of age, those receiving beta-lactam/macrolide combination therapy had significantly lower rates of treatment failure than children receiving beta-lactam monotherapy.[9] However, another study by the same group found no difference in outcomes among children treated with beta-lactam monotherapy vs macrolide monotherapy.[30] Multiple clinical trials have failed to show a benefit of macrolides over narrow-spectrum antibiotics for children with community-acquired pneumonia.[10-12] Observational data from adults demonstrated improved outcomes associated with macrolide use in patients with lower respiratory infections, but these findings have not been replicated in randomized trials.[31-34] We observed that children receiving macrolides in combination with narrow- or broad-spectrum antibiotic therapy had lower odds of a change in antibiotic therapy during the follow-up period. We speculate that clinicians may be reluctuant to modify antibiotic therapy for a child who is already taking 2 antibiotics, although we have no direct evidence to support this theory.

It is important to note that, although we observed small differences in the odds of hospitalization and severe pneumonia between antibiotic groups, the incidence of these outcomes was low across groups. For example, although children receiving macrolides either alone or in addition to narrow-spectrum antibiotics had lower odds of subsequent hospitalization than children receiving narrow-spectrum antibiotics alone, the absolute risk difference was 0.2% in each group. This means that clinicians would need to treat 500 children with a macrolide-containing regimen instead of narrow-spectrum therapy to prevent 1 additional hospitalization. Similarly, clinicians would need to treat 1000 children with macrolide monotherapy rather than narrow-spectrum antibiotics to prevent 1 case of severe pneumonia. Antibiotic overuse has well-documented risks, including increasing antibiotic resistance and side effects.[8,35-40] Taken in context, our findings do not support widespread use of macrolides in children with community-acquired pneumonia. However, the question of when to use macrolides in children with community-acquired pneumonia is a difficult one. National guidelines recommend the use of macrolides in school age children and teenagers with suspected atypical pneumonia.[1] Unfortunately, there are no reliable signs or symptoms that distinguish atypical pathogens from other etiologies, and real-time microbiologic testing for atypical pathogens is not widely performed; these limitations may push clinicians to empirically prescribe macrolides to a larger group of children than is indicated.[41] Future research may identify a subgroup of children more likely to benefit from macrolide therapy.

Our findings highlight the need for robust research and interventions aimed at understanding the reasons clinicians continue to prescribe broad-spectrum antibiotics and macrolides for children with community-acquired pneumonia. We observed that children treated in outpatient clinics were less likely to receive narrow-spectrum antibiotics than those cared for in the ED setting; we do not know the reason for this, but it is possible that EDs may be more likely to have access to standardized care pathways. Quality improvement initiatives have shown promise in increasing guideline-concordant antibiotic prescribing for children with community-acquired pneumonia, and their implementation should be considered in clinics and hospital systems that treat children.[42] Opportunities also exist for robust research aimed

at improving accurate, real-time pathogen identification. This could aid clinicians in selecting an appropriate antibiotic regimen in children with community-acquired pneumonia.

Our study has important limitations. First, our cohort included only children enrolled in Medicaid (estimated at 39% of children the US in 2017), and thus our findings may not be generalizable to all US children.[43] There may be differences in prescribing patterns, clinical care settings, or other social determinants of health between Medicaid and non-Medicaid populations. Additionally, the specific states included in the Truven database are undisclosed. However, our findings regarding prescribing patterns are strikingly similar to findings of other recent studies utilizing other data sources.[5,6] Second, the study used an administrative claims database, which limits our ability to adequately account for clinically relevant variables in our analysis. The reliance on diagnostic codes is an inherent limitation of administrative databases, because codes may be erroneously ascribed. We attempted to mitigate this issue by requiring a claim for an oral antibiotic prescription within 1 day of the index visit. Third, although our reliance on claims data is advantageous over studies that evaluate prescription writing alone, we were not able to verify that the children adhered to the antibiotics prescribed. Fourth, although we attempted to control for measures of severity in our multivariable analysis, we cannot rule out the possibility of residual confounding. Children treated with macrolides were more often seen in outpatient clinics than the ED and had a lower rate of chest radiography performed (**Table I**), suggesting that they may have had less severe disease than children receiving narrow-spectrum antibiotics. Although we controlled for these specific variables, we were unlikely to have controlled fully for severity of disease. Finally, very few children developed the outcome of severe pneumonia over the study period; thus, given the number of covariates in our multivariable model, the model may have been underpowered to detect statistically significant differences between antibiotic groups.

In summary, we found that broad-spectrum antibiotics and macrolides remain the most commonly used antibiotic for ambulatory children with community-acquired pneumonia, despite national guidelines emphasizing the use of narrow-spectrum aminopenicillins. Although children receiving macrolides as monotherapy or added to narrow-spectrum therapy had lower odds of subsequent hospitalization or development of severe pneumonia, these outcomes were rare regardless of antibiotic selection. Broad-spectrum antibiotic agents are not associated with improved clinical outcomes, and their use should be discouraged in children with community-acquired pneumonia treated in the outpatient setting. Future work should focus on real-time pathogen identification, increased understanding of the reasons why clinicians continue to prescribe inappropriately broad antibiotics to ambulatory children with community-acquired pneumonia, and increasing narrow-spectrum antibiotic therapy through educational campaigns and quality improvement initiatives. ■

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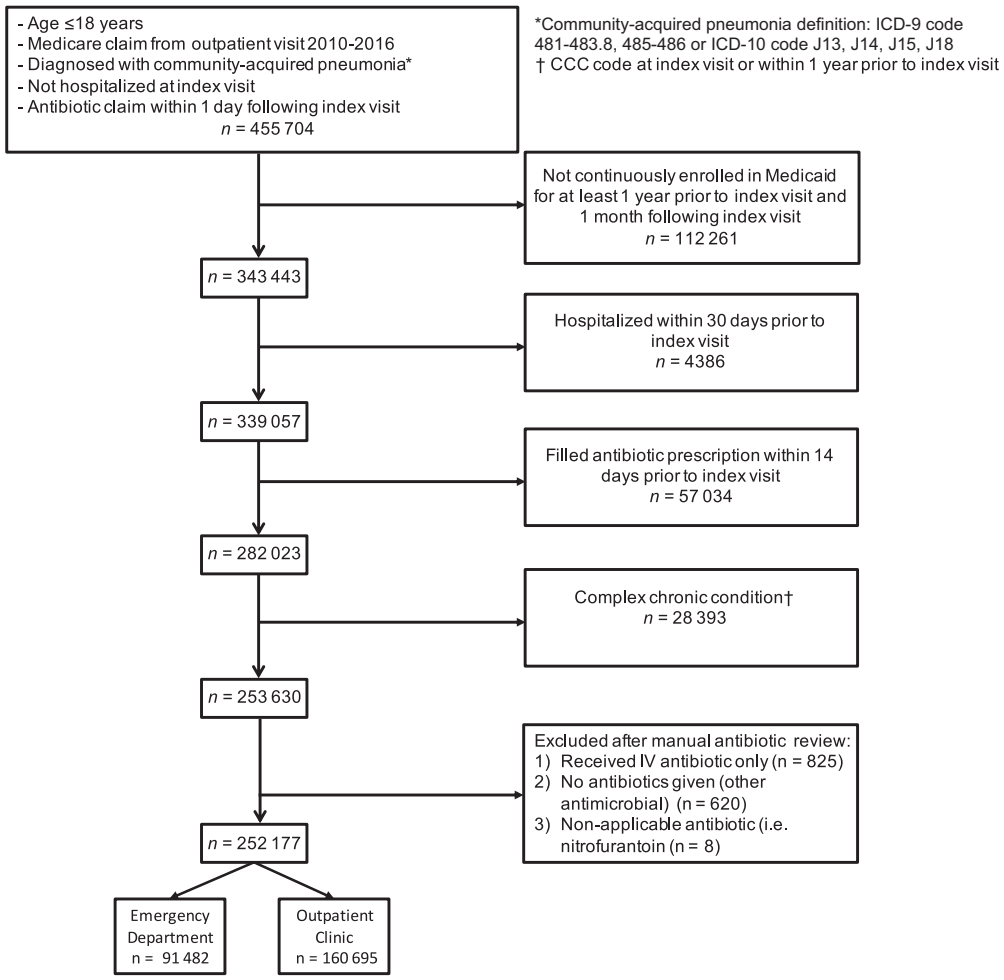

Figure 1. Patient selection. *IV*, intravenous.

Table II. Pneumonia outcomes by antibiotic group

Outcomes	Narrow-spectrum (n = 65 872)	Narrow-spectrum + macrolide (n = 4858)	Broad-spectrum (n = 62 381)	Broad-spectrum + macrolide (n = 6861)	Macrolide monotherapy (n = 108 917)	*P* value
Hospitalization*	428 (0.6)	20 (0.4)	526 (0.8)	67 (1)	402 (0.4)	<.001
Severe pneumonia†	35 (0.1)	1 (0)	40 (0.1)	6 (0.1)	28 (0)	<.001
Change in antibiotic therapy‡	2909 (4.4)	111 (2.3)	3204 (5.1)	162 (2.4)	4697 (4.3)	<.001

Values are number (%).
*Hospitalization: hospital admission within 2-7 days after the index visit.
†Severe pneumonia: ICU admission, pleural drainage procedure, or death within 2-7 days after the index visit.
‡Change in antibiotic therapy: any new antibiotic prescription filled (regardless of class) within 2-7 days after the index visit.