Variability in Antibiotic Prescribing for Community-Acquired Pneumonia

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abstract

BACKGROUND AND OBJECTIVES: Published guidelines recommend amoxicillin for most children with community-acquired pneumonia (CAP), yet macrolides and broad-spectrum antibiotics are more commonly prescribed. We aimed to determine the patient and clinician characteristics associated with the prescription of amoxicillin versus macrolide or broad-spectrum antibiotics for CAP.

METHODS: Retrospective cohort study in an outpatient pediatric primary care network from July 1, 2009 to June 30, 2013. Patients prescribed amoxicillin, macrolides, or a broad-spectrum antibiotic (amoxicillin–clavulanic acid, cephalosporin, or fluoroquinolone) for CAP were included. Multivariable logistic regression models were implemented to identify predictors of antibiotic choice for CAP based on patient- and clinician-level characteristics, controlling for practice.

RESULTS: Of 10 414 children, 4239 (40.7%) received amoxicillin, 4430 (42.5%) received macrolides and 1745 (16.8%) received broad-spectrum antibiotics. The factors associated with an increased odds of receipt of macrolides compared with amoxicillin included patient age ≥5 years (adjusted odds ratio [aOR]: 6.18; 95% confidence interval [CI]: 5.53–6.91), previous antibiotic receipt (aOR: 1.79; 95% CI: 1.56–2.04), and private insurance (aOR: 1.47; 95% CI: 1.28–1.70). The predicted probability of a child being prescribed a macrolide ranged significantly between 0.22 and 0.83 across clinics. The nonclinical characteristics associated with an increased odds of receipt of broad-spectrum antibiotics compared with amoxicillin included suburban practice (aOR: 7.50; 95% CI: 4.16–13.55) and private insurance (aOR: 1.42; 95% CI: 1.18–1.71).

CONCLUSIONS: Antibiotic choice for CAP varied widely across practices. Factors unlikely related to the microbiologic etiology of CAP were significant drivers of antibiotic choice. Understanding drivers of off-guideline prescribing can inform targeted antimicrobial stewardship initiatives.

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DOI: 10.1542/peds.2016-2331

WHAT'S KNOWN ON THIS SUBJECT: Community-acquired pneumonia is commonly treated by outpatient pediatricians. Although management guidelines for community-acquired pneumonia have been published, many children receive off-guideline therapy. The drivers of this variability in prescribing are unknown.

WHAT THIS STUDY ADDS: Analysis of >10 000 encounters for community-acquired pneumonia demonstrated that both clinical (fever, age) and nonclinical characteristics (insurance status and practice location) were associated with antibiotic choice. Understanding nonclinical drivers of off-guideline prescribing can inform targeted antimicrobial stewardship initiatives.

To cite: Handy LK, Bryan M, Gerber JS, et al. Variability in Antibiotic Prescribing for Community-Acquired Pneumonia. *Pediatrics.* 2017;139(4):e20162331

Community-acquired pneumonia (CAP) is a common and serious infection in children. An estimated 1.2 million children are diagnosed as having pneumonia in the primary care setting annually in the United States.[1] Evidenced-based clinical practice guidelines for the management of CAP in infants and children were developed by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America in 2011 with the goal of decreasing morbidity and mortality in otherwise healthy children and increasing appropriate antibiotic use.[2] Despite these guidelines, there is significant variability in antibiotic prescribing practices in pediatric primary care settings,[3] including both the choice to use antibiotics at all and, if antibiotics are chosen, the specific agent selected.[4,5]

Current recommendations specify amoxicillin, a β-lactam antibiotic, as first-line therapy for most children with CAP in the outpatient setting because it provides excellent coverage for *Streptococcus pneumoniae*.[2] Despite these guidelines, macrolide antibiotics are the most commonly prescribed class of antibiotics for outpatient CAP of any etiology, raising concern that children are receiving inappropriate treatment, because studies report that >25% of *S. pneumoniae* isolates are resistant to macrolides.[1,6–9] The factors that influence macrolide and other broad-spectrum antibiotic prescribing for typical pneumonia, however, are unknown. Macrolides are only recommended for treatment of older children suspected to have atypical pneumonia due to less-common organisms, such as *Mycoplasma pneumoniae*.[2] Furthermore, broad-spectrum antibiotics, such as amoxicillin-clauvulanic acid and cephalosporins, have no advantage over amoxicillin for treatment of *S. pneumoniae* and put children at risk for adverse events, such as *Clostridium difficile* infection, while contributing to the global problem of antibiotic resistance.[10,11]

Although antibiotic prescribing practices may be associated with a clinical diagnosis of pneumococcal CAP versus CAP caused by atypical pathogens, clinicians cannot reliably make this distinction on signs and symptoms alone.[12,13] Instead, recent work suggests that variation in antibiotic prescribing might be influenced by nonclinical patient and clinician characteristics including geographic location, insurance status, patient race, and practice affiliation; however, the predictors of antibiotic prescribing for CAP are incompletely understood.[6,14–18] Identifying the drivers of off-guideline prescribing will likely help target interventions to optimize appropriate antibiotic use.[19] Therefore, we conducted a retrospective cohort study of children diagnosed as having CAP to examine and compare factors associated with antibiotic prescribing for CAP in one of the largest pediatric primary care networks in the United States.

METHODS

Data Source

This study was conducted in a network of 31 primary care pediatric practices, all of which participate in a practice-based research network and share a common electronic health record (EHR) system. Practices span urban, suburban, and rural settings throughout Pennsylvania and New Jersey, serving a diverse patient population of >200 000 children. Five practices include trainees. Data were abstracted from the EHR system (EpicCare, Epic Systems, Inc, St. Louis, MO) that contains detailed patient-level data from clinical encounters, telephone calls, follow-up visits, hospitalizations and associated prescriptions, and laboratory and radiologic information. This study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia.

Study Population

Study subjects included children aged 3 months to 18 years with a primary care encounter between July 1, 2009 and June 30, 2013, resulting in an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for pneumonia and an antibiotic prescription (detailed below). Children were required to have 1 documented well visit during the study period or the year before enrollment. Patients were excluded if they had a complex chronic condition[20]; allergy to penicillin, a cephalosporin, or a macrolide antibiotic documented in the medical record; multiple antibiotic prescriptions; an emergency department visit for pneumonia in the previous 2 weeks; incomplete data for exposures of interest; or if they were from a practice with <50 pneumonia cases during the study period. Children with multiple antibiotic prescriptions were excluded to limit inclusion of patients with >1 active infection.

Definition of CAP

Pneumonia was defined by using a previously validated algorithm: a primary ICD-9-CM diagnosis of pneumonia (480–483 and 485–486) or a primary ICD-9-CM diagnosis of a pneumonia symptom, such as fever or cough (780.6, 786.0, 786.2–786.5, 786.7) with a secondary ICD-9-CM diagnosis of pneumonia, empyema (510), or pleurisy (511.0–1 and 511.9).[1,3,21,22] The majority of cases identified by this algorithm that were not associated with an antibiotic prescription represented follow-up visits from previous encounters, and, therefore, all cases lacking an antibiotic prescription were excluded rather than considered as cases managed without antibiotics.

Data Collection

Patient-level data extracted from the EHR system included patient demographics, allergies, and a diagnosis of pneumonia in the previous 3 months, and visit-level data included chief complaint, vital signs, visit level of service, previous visit to the pediatrician in the preceding 2 weeks with primary associated ICD-9-CM code, immunization status, secondary diagnoses, and diagnostic tests and results. Clinical presentation exposure variables included demographics of age, sex, race, and insurance type and clinical variables of fever at the time of the office visit, respiratory examination, history of asthma, immunization status, ordering of a chest radiograph, number of sick visits in previous year, and previous antibiotic exposure.[23,24] All charts documenting a hospitalization, an emergency department visit, return visits to the pediatrician with a change in antibiotics, or a telephone call within 2 weeks were manually reviewed for data accuracy. Additional covariates related to the provider were the clinic site and setting (urban versus suburban) and the provider's years in practice since board certification, with a provider with >10 years since certification considered to be experienced.[6,14,15] Each provider's years in practice were calculated by using data from the American Board of Pediatrics.

Outcomes

The primary outcome, antibiotic prescription, was categorized as narrow-spectrum (penicillin or amoxicillin), macrolide (azithromycin, erythromycin, and clarithromycin), or broad-spectrum (amoxicillin–clavulanic acid, cephalosporin, or fluoroquinolone). Trimethoprim-sulfamethoxazole, clindamycin, tetracyclines, and linezolid were not included because they are infrequently used for CAP in patients without antibiotic allergies.

Additional Definitions

Asthma was defined as patient receipt of oral or inhaled corticosteroids, a secondary diagnosis of asthma by ICD-9-CM code, or the inclusion of asthma on the problem list at the time of the visit. Fever was defined as a temperature of ≥38.3°C at the time of the visit. Respiratory examination results were considered abnormal if breath sounds were described as asymmetric, decreased, diminished, wet, or tubular, or if rales, rhonchi, crackles, coarse breath sounds, or wheeze were noted.

Statistical Analysis

Descriptive counts and percentiles were provided for patients prescribed amoxicillin versus macrolides versus broad-spectrum antibiotics among the total sample as well as within key covariate subgroups. Univariate logistic regression was conducted between the outcome of antibiotic prescription and each candidate variable, including sex, age, race, insurance type, history of asthma, fever, sick visits per year, abnormal respiratory examination results, chest radiograph ordered, antibiotics in previous 3 months, provider's years in practice, and suburban versus urban location. We constructed multivariate logistic regression models for the odds of prescription of amoxicillin versus a macrolide and the odds of prescription of amoxicillin versus a broad-spectrum antibiotic against the identified collection of exposure variables. Independent models were maintained to evaluate the choice of prescribing amoxicillin versus azithromycin, representing a clinician's diagnosis of likely *S. pneumoniae* versus atypical pneumonia. The model evaluating the prescription of amoxicillin versus a broad-spectrum antibiotic should represent a clinician's diagnosis of *S. pneumoniae* versus a more resistant *S. pneumoniae* or an alternate typical pathogen (*Haemophilus influenzae, Moraxella catarrhalis*). Statistically significant exposures were considered for inclusion in a multivariate model if they were significantly associated with at least 1 of the outcomes, as were variables that were a priori hypothesized as significant, including patient age, race, asthma history, and respiratory examination. The collection of variables included in each multivariate model was forced to be the same to allow for comparison of covariate effects across the 2 models. The practice site was entered in the model as a confounder because prescribing within a single practice was likely to be correlated. Two practices that merged during the study period were analyzed as a single practice. Predicted probabilities of prescription of macrolides or broad-spectrum antibiotics were generated based on the final models with the suburban/urban indicator removed to explore practice-level variation.

RESULTS

Of the 13 974 children diagnosed as having CAP, 10 414 children treated by 196 physicians met inclusion/exclusion criteria (Fig 1). The majority (60%) of children were >5 years of age, 14.2% were African American, 17.9% were covered by public insurance, and 91.5% of patients received care in a suburban practice. Overall, 40.1% of children received amoxicillin, 42.5% received macrolides, 16.8% received broad-spectrum antibiotics, and 22.4% had been exposed to antibiotics in the previous 3 months (Table 1). In the broad-spectrum antibiotic group, the majority of children (77.5%) received amoxicillin–clavulanic acid, whereas 22.2% received a cephalosporin

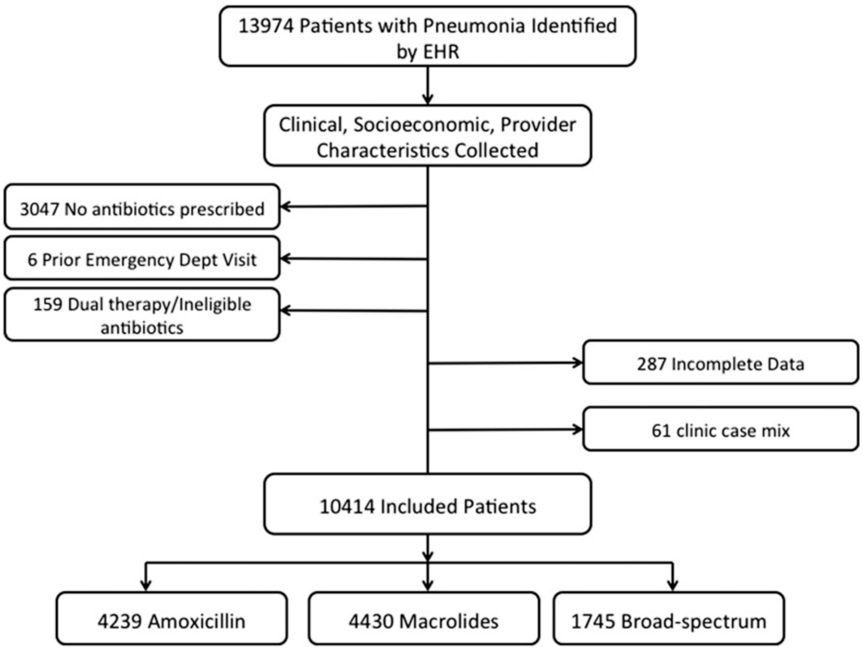

FIGURE 1
Networkwide cases of CAP resulting in antibiotic prescriptions of interest.

and only 6 children received a fluoroquinolone.

Overall, 8669 patients were treated with either amoxicillin or macrolides. The results of univariate logistic regression to determine variables for inclusion in the multivariate model are reflected in Table 2. In the multivariate logistic regression model for prescription of macrolides versus amoxicillin, the factors associated with increased odds of prescription of macrolides included age ≥5 years (adjusted odds ratio [aOR]: 6.18; 95% confidence interval [CI]: 5.53–6.91), private insurance (aOR: 1.47; 95% CI: 1.28–1.70), history of asthma (aOR: 1.15; 95% CI: 1.04–1.28), and previous antibiotic exposure (aOR: 1.79; 95% CI: 1.56–2.04), whereas abnormal examination results (aOR: 0.80; 95% CI: 0.66–0.97) and the presence of fever (aOR: 0.44; 95% CI: 0.37–0.53) were associated with decreased odds of macrolide prescription (Table 3). The predicted probability of macrolide prescribing ranged from 0.22 to 0.83 across the clinical sites after adjusting for other factors associated with antibiotic choice (Fig 2).

Of the 5984 patients treated with either amoxicillin or broad-spectrum antibiotics, the factors associated with the greatest increased odds of prescription of broad-spectrum antibiotics included suburban practice (aOR: 7.50; 95% CI: 4.16–13.55) and previous antibiotic exposure (aOR: 3.31; 95% CI: 2.83–3.86). Patient age of ≥5 years (aOR: 1.27; 95% CI: 1.10–1.46) had only a modest effect on the odds of broad-spectrum antibiotic receipt. The predicted probability of broad-spectrum prescribing ranged from 0.02 to 0.81 across the clinical sites after adjusting for other factors associated with antibiotic choice (Fig 3). Adjusting for trends over time did not influence either model.

DISCUSSION

Antibiotic choice for CAP varied widely across a large, diverse primary care network, and differences in prescribing practices were not

TABLE 1 Prescription Counts and Percentages Within Demographic and Clinical Subgroups

	Total Cohort, *n* (% of Total Sample)	Amoxicillin Monotherapy, *n* (% Within Each Covariate Group)	Macrolide Monotherapy, *n* (% Within Each Covariate Group)	Broad-Spectrum Therapy, *n* (% Within Each Covariate Group)
Patient count	10414	4239 (40.7)	4430 (42.5)	1745 (16.8)
Male sex	5319 (51.1)	2131 (50.3)	2291 (51.7)	897 (51.4)
Age ≥5 y	6214 (60.0)	1824 (43.0)	3559 (80.3)	831 (47.6)
African American race	1485 (14.2)	880 (20.8)	448 (10.1)	157 (9.0)
Hispanic ethnicity	631 (6.1)	297 (7.0)	221 (5.0)	113 (6.5)
Public insurance	1859 (17.9)	1036 (24.4)	565 (12.8)	258 (14.8)
Suburban practice	9531 (91.5)	3666 (86.5)	4162 (94.0)	1703 (97.6)
Experienced provider	8070 (77.5)	3314 (78.2)	3308 (74.7)	1448 (83.0)
Asthma	3966 (38.1)	1588 (37.5)	1667 (37.6)	711 (40.7)
PCV UTD	7934 (76.2)	3721 (87.8)	2773 (62.6)	1440 (82.5)
Fever ≥38.3°C at visit	1030 (9.9)	531 (12.5)	254 (5.7)	245 (14.0)
Abnormal respiratory exam	9660 (92.8)	3937 (92.9)	4108 (92.7)	1615 (92.6)
Chest radiograph ordered	929 (8.9)	390 (9.2)	304 (6.9)	235 (13.5)
>3 Sick visits	3445 (33.1)	1432 (33.8)	1242 (28.0)	771 (44.2)
Antibiotic exposure	2339 (22.4)	715 (16.9)	941 (21.2)	683 (39.1)

PCV UTD, pneumococcal conjugate vaccinations up to date.

TABLE 2 Estimated Odds Ratios From Univariate Logistic Regression for Receipt of Either Macrolide or Broad-Spectrum Antibiotic Compared With Amoxicillin

	Odds Ratio, Macrolide Versus Amoxicillin (95% CI)	Odds Ratio, Broad-Spectrum Versus Amoxicillin (95% CI)
Male sex	1.06 (0.97–1.15)	1.05 (0.94–1.17)
Age ≥5 y	5.41 (4.9–5.95)[a]	1.20 (1.08–1.25)[a]
Private insurance	2.21 (1.98–2.48)[a]	1.86 (1.61–2.16)[a]
Race	0.43 (0.38–0.49)[a]	0.38 (0.32–0.45)[a]
Experienced provider	0.83 (0.75–0.91)[a]	1.36 (1.18–1.57)[a]
Asthma	1.01 (0.92–1.10)	1.15 (1.02–1.29)[a]
Fever ≥38.3°C at visit	0.42 (0.36–0.50)[a]	1.14 (0.96–1.34)
>3 Sick visits per year	0.76 (0.70–0.83)[a]	1.55 (1.38–1.73)[a]
Chest radiograph obtained	0.73 (0.62–0.85)[a]	1.53 (1.29–1.82)[a]
Abnormal respiratory exam	0.98 (0.83–1.15)	0.95 (0.77–1.18)
Suburban practice	2.43 (2.08–2.82)[a]	6.34 (4.61–8.71)[a]
Previous antibiotic exposure	1.33 (1.19–1.48)[a]	3.17 (2.80–3.59)[a]

[a] Variables were found to be significant in univariate analysis and were candidates for the multivariate model.

TABLE 3 Estimated Odds Ratios From Multivariate Logistic Regression for Receipt of Either Macrolide or Broad-Spectrum Antibiotic Compared With Amoxicillin

	aOR, Macrolide Versus Amoxicillin (95% CI)	aOR, Broad-Spectrum Versus Amoxicillin (95% CI)
Male sex	1.01 (0.92–1.12)	0.98 (0.86–1.12)
Age ≥5 y	6.18 (5.53–6.91)[a]	1.27 (1.10–1.46)[a]
Private insurance	1.47 (1.28–1.70)[a]	1.42 (1.18–1.71)[a]
Race	0.83 (0.71–0.99)[a]	0.90 (0.71–1.13)
Experienced provider	0.75 (0.65–0.85)[a]	1.23 (1.02–1.48)[a]
Asthma	1.15 (1.04–1.28)[a]	1.12 (0.98–1.29)
Fever ≥38.3°C at visit	0.44 (0.37–0.53)[a]	1.18 (0.97–1.43)
>3 Sick visits per year	0.94 (0.83–1.06)	1.12 (0.97–1.31)
Chest radiograph ordered	0.93 (0.76–1.13)	1.79 (1.43–2.25)[a]
Abnormal respiratory exam	0.80 (0.66–0.97)[a]	0.93 (0.72–1.20)
Suburban practice	0.83 (0.52–1.32)	7.50 (4.16–13.55)[a]
Previous antibiotic exposure	1.79 (1.56–2.04)[a]	3.31 (2.83–3.86)[a]

[a] Variables were found to be significant in multivariate analysis.

entirely driven by the clinical factors that should predict antibiotic choice. Despite current guidelines recommending amoxicillin for most children with CAP, the majority were prescribed macrolides. Although age and previous antibiotic use were appropriate drivers of prescribing patterns, sociodemographic factors, including insurance status and practice location, that should not be correlated with bacterial etiology were also associated with antibiotic choice.

This study confirms previous work from large administrative databases documenting prescribing patterns at variance with known bacterial epidemiology and begins to explain this discordance through more granular data that can identify key clinical-, demographic-, and clinician-level variables.[6,16] Although the bacterial etiology of CAP is changing with the introduction of pneumococcal vaccines, *S. pneumoniae* remains the leading cause of bacterial CAP, and guidelines strongly recommend targeting this organism.[2] Less guidance is provided on when to prescribe macrolides, which have inferior pneumococcal activity compared with amoxicillin.[2,7,25–27] Currently, it is not possible to determine how many patients in our study had atypical pneumonia because testing for respiratory pathogens is not routinely performed in the outpatient setting. A recent study of hospitalized children with CAP reported that 19% of school-aged children and 3% of children <5 years are infected by *Mycoplasma pneumoniae*, suggesting that many practices in the current study might be overprescribing macrolides.[28]

The decision to prescribe macrolide or broad-spectrum antibiotics can be partially explained by clinical factors. Patient age and absence of fever are appropriate clinical characteristics to consider when determining if a child has pneumococcal pneumonia versus atypical pneumonia. However, the decision to prescribe a broad-spectrum antibiotic instead of amoxicillin was not affected by patient age, suggesting that providers were likely no longer considering atypical pneumonia, but rather were deciding on therapy for typical pathogens. The association of broad-spectrum antibiotic prescribing with previous antibiotic use likely reflects the concern for a resistant organism. A larger percentage of children in the broad-spectrum group also had a chest radiograph performed, suggesting that the patients prescribed broad-spectrum antibiotics may have been sicker.

Although clinical factors seemed to influence decision-making, nonclinical drivers of prescribing remained. Practice setting was a strong predictor of antibiotic prescribing. Although previous work has looked at regional differences,[15] this study highlights differences between practices contained within a single health system. On the basis of our predictive model, for 10 average children with CAP, macrolides would have been prescribed to 2 of these children in 1 practice and 8 similar children in another practice.

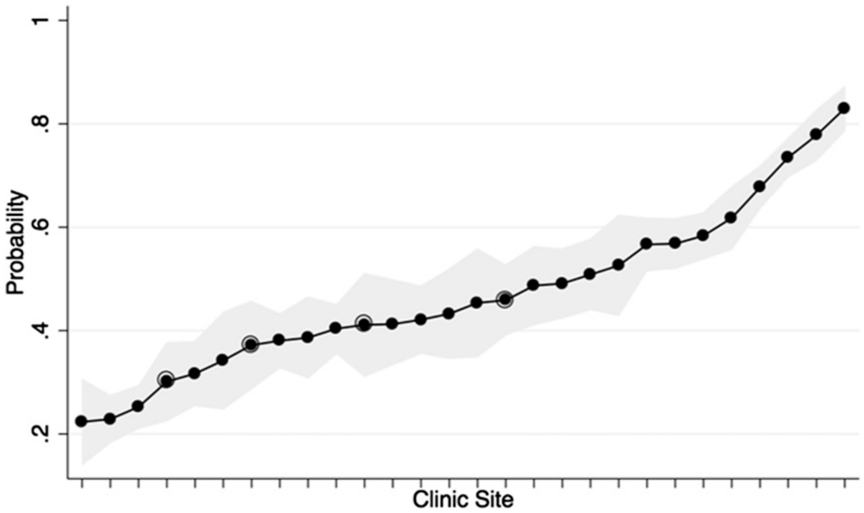

FIGURE 2
Predicted probability of macrolide prescribing. Clinics are ordered by their predicted probability of prescription of a macrolide (lowest to highest). Urban clinics are circled. Predicted probabilities were generated based on the multivariate logistic regression model with clinic type (urban or suburban) removed from the model.

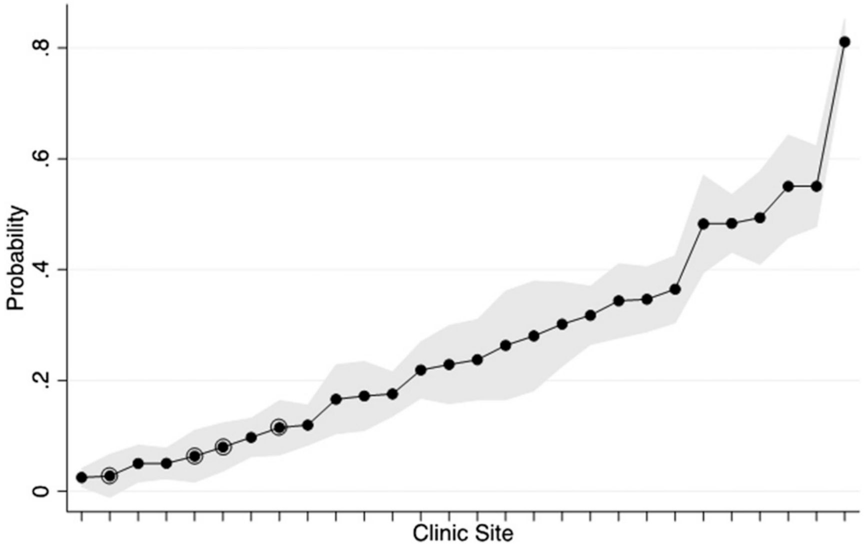

FIGURE 3
Predicted probability of broad-spectrum prescribing. Clinics are ordered by their predicted probability of prescription of a broad-spectrum antibiotic (lowest to highest). Urban clinics are circled. Predicted probabilities were generated based on the multivariate logistic regression model with clinic type (urban or suburban) removed from the model.

The effect of the practice setting is additionally highlighted by the markedly increased odds (7.50) of receipt of a broad-spectrum antibiotic compared with amoxicillin by seeing a pediatrician in one of the suburban practices compared with an urban practice. In this practice network, 4 of the 5 urban practices are considered academic with pediatric residents, and 2 of these practices merged during the study period. All 5 have medical students. The academic setting may be the major driver of differences between these practice locations, because teaching sites may be more likely to follow guidelines, and requires additional study. Alternatively, the practice variation seen in the urban environment may reflect unmeasured covariates related to patient individualities. However, there may be additional characteristics that influence practice variation, including clinic size, a provider's average time with each patient, the tendency to follow-up with patients with a visit or phone call, and the baseline knowledge of each physician, which also were not measured. In both models, the association of private insurance with receipt of macrolides or broad-spectrum antibiotics confirms the findings of previous studies.[6] Providers may make different treatment decisions because of consideration of medication cost, influence from the parents of a privately insured patient during the visit, or unconscious biases about family preference.[29] These factors may also vary across individual clinics, contributing to the across-practice variation we observed. Although race has been identified as a significant predictor of prescription patterns in previous work, it was not a major driver in our study population.[14,17,18] Efforts to increase guideline-adherent prescribing, such as provider education and decision-support tools, should address these nonclinical drivers of prescribing patterns, including physician preferences, prescribing norms within a practice, and parental drivers of prescribing practices.

Our study has limitations. This is a retrospective cohort study and, therefore, unmeasured confounding may be present that affects the choice of treatment prescribed. Because the study population included only healthy children with outpatient CAP, these data might not be generalizable to other children with pneumonia, such as those requiring hospitalization or with complex chronic conditions.[2] Only data that could be queried electronically were collected and analyzed, so we could not account for additional factors that may not be well documented, such as parental requests for antibiotics, any undocumented physical examination findings that might have influenced antibiotic selection, or internal use of order sets or clinical pathways. The definition of CAP was based on clinical diagnoses and could not be confirmed with radiologic or microbiologic data. However, microbiologic data are generally not available to practitioners when making diagnosis and treatment decisions, reflecting the real-world setting in which practitioners work, and our intent was to measure predictors of antibiotic choice in children with presumed pneumonia. Encounters for patients who were treated at a hospital emergency department or inpatient unit outside of the study hospital network could not be identified and, thus, an antibiotic choice might have been attributed to a clinician when it was previously selected by a different physician. However, chart review of 3577 patients identified only 3% of patients who were previously diagnosed as having CAP by a different health care provider.

CONCLUSIONS

Antibiotic choice for CAP varied widely across pediatric practices and was heavily influenced by nonclinical factors unrelated to microbial etiology. Understanding the role of demographic, practice, and socioeconomic determinants of prescribing will allow for the design of effective outpatient antimicrobial stewardship programs to improve the management of CAP and other common pediatric infections.

ABBREVIATIONS

aOR: adjusted odds ratio
CAP: community-acquired pneumonia
CI: confidence interval
EHR: electronic health record
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Accepted for publication Dec 21, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Handy was supported by NIH grant T32-AI096345 and NIAID grant L40-AI-107932, and a pilot grant from the Center for Pediatric Clinical Effectiveness at the Children's Hospital of Philadelphia. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-0027.

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Pediatrics 2017;139;
DOI: 10.1542/peds.2016-2331 originally published online March 7, 2017;