

Antibiotic Use and Outcomes in Children in the Emergency Department With Suspected Pneumonia

Matthew J. Lipshaw, MD,^a Michelle Eckerle, MD, MPH,^{ab} Todd A. Florin, MD, MSCE,^c Eric J. Crotty, MD,^{bd} Jessi Lipscomb, BS,^e Judd Jacobs, BS,^e Mantosh S. Rattan, MD,^{bd} Richard M. Ruddy, MD,^{ab} Samir S. Shah, MD, MSCE,^{bfg} Lilliam Ambroggio, PhD, MPH^h

abstract

BACKGROUND AND OBJECTIVES: Antibiotic therapy is often prescribed for suspected community-acquired pneumonia (CAP) in children despite a lack of knowledge of causative pathogen. Our objective in this study was to investigate the association between antibiotic prescription and treatment failure in children with suspected CAP who are discharged from the hospital emergency department (ED).

METHODS: We performed a prospective cohort study of children (ages 3 months–18 years) who were discharged from the ED with suspected CAP. The primary exposure was antibiotic receipt or prescription. The primary outcome was treatment failure (ie, hospitalization after being discharged from the ED, return visit with antibiotic initiation or change, or antibiotic change within 7–15 days from the ED visit). The secondary outcomes included parent-reported quality-of-life measures. Propensity score matching was used to limit potential bias attributable to treatment selection between children who did and did not receive an antibiotic prescription.

RESULTS: Of 337 eligible children, 294 were matched on the basis of propensity score. There was no statistical difference in treatment failure between children who received antibiotics and those who did not (odds ratio 1.0; 95% confidence interval 0.45–2.2). There was no difference in the proportion of children with return visits with hospitalization (3.4% with antibiotics versus 3.4% without), initiation and/or change of antibiotics (4.8% vs 6.1%), or parent-reported quality-of-life measures.

CONCLUSIONS: Among children with suspected CAP, the outcomes were not statistically different between those who did and did not receive an antibiotic prescription.



Divisions of ^aEmergency Medicine, ^dRadiology, ^eBiostatistics and Epidemiology, ^fHospital Medicine, and ^gInfectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ^bDepartment of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio; ^cDepartment of Pediatrics, Feinberg School of Medicine, Northwestern University and Division of Emergency Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; and ^hDepartment of Pediatrics, University of Colorado Denver and Sections of Emergency Medicine and Hospital Medicine, Children's Hospital Colorado, Denver, Colorado

Dr Lipshaw conceptualized and designed the study, drafted the initial manuscript, conducted the initial analyses, contributed to the interpretation of the results, and reviewed and revised the manuscript; Drs Eckerle, Shah, and Ruddy conceptualized and designed the study, contributed to the interpretation of the results, and reviewed and revised the manuscript; Dr Florin conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, collected data, contributed to the interpretation of the results, and reviewed and revised the manuscript; Drs Crotty and Rattan conceptualized and designed the study, collected data, and reviewed and revised the manuscript; Mr Jacobs and Ms Lipscomb coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content; (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Antibiotics are often prescribed for pediatric pneumonia in ambulatory children despite the high prevalence of viral etiology. Studies in the developing world have shown low rates of treatment failure in children with community-acquired pneumonia treated with a placebo.

WHAT THIS STUDY ADDS: In this propensity score–matched analysis of a prospectively enrolled ambulatory cohort evaluated for pneumonia and discharged from the emergency department, antibiotic treatment was not associated with lower treatment failure rates or improved quality-of-life outcomes after discharge.

To cite: Lipshaw MJ, Eckerle M, Florin TA, et al. Antibiotic Use and Outcomes in Children in the Emergency Department With Suspected Pneumonia. *Pediatrics*. 2020;145(4):e20193138

Community-acquired pneumonia (CAP) is a common pediatric infection.¹ Although typically diagnosed by chest radiographs (CXR) or examination findings, no true gold standard for the diagnosis of CAP exists.² National guidelines strongly recommend foregoing CXR to confirm pneumonia in children with suspected CAP who are being managed as outpatients. Instead, the use of clinical suspicion and physical examination findings are recommended. However, traditional clinical signs and symptoms of CAP have limited diagnostic accuracy and interrater reliability.³⁻⁵

The lack of practical tools to differentiate bacterial from viral causes of CAP makes treatment decisions challenging. No clinical, radiologic, or laboratory features are reliable for differentiating bacterial and viral pneumonia.⁶⁻⁸ Despite the high prevalence of viral infection in children with CAP, antibiotic treatment is common.⁹⁻¹² In the Centers for Disease Control and Prevention Etiology of Pneumonia in the Community cohort, only 15% of hospitalized children with radiographic pneumonia had a detectable bacterial etiology; however, 88% received antibiotics.¹³ In addition, the most common bacteria identified was *Mycoplasma pneumoniae*, yet CAP caused by this organism has not been definitively shown to improve with antibiotic treatment.¹⁴

Viruses cause the majority of CAP in children; however, most studies of pneumonia etiology have occurred in hospitalized patients.¹³ The prevalence of bacterial etiology is lower in children with CAP not requiring hospitalization, and thus, empirical antibiotics in this population may be unnecessary.^{15,16} Although a large randomized controlled trial of amoxicillin versus a placebo for children with nonsevere pneumonia in a low-resource African

country revealed that 93% of children given a placebo did not experience treatment failure, this has not been fully evaluated in outpatients in high-resource settings.¹⁷ Unnecessary treatment leads to unnecessary medication side effects, adverse drug events, and increasing antibiotic resistance.^{18,19}

Our objectives in this study were to (1) determine the association between antibiotic prescription and treatment failure in children with suspected CAP who were discharged from the emergency department (ED) and (2) determine the association between antibiotic prescription and parent-reported quality-of-life (QoL) measures.

METHODS

Study Design

This was a planned secondary analysis from a prospective cohort study of children with suspected CAP presenting to a tertiary-care pediatric ED.^{20,21} Study approval was obtained from our institutional review board. Informed consent was obtained from all legal guardians of subjects at the time of study enrollment, and assent was obtained from all children ≥ 11 years of age.

Study Population

Children 3 months to 18 years of age with signs and symptoms of lower respiratory tract infection for whom a CXR was obtained for clinical suspicion of pneumonia were eligible for enrollment. Signs and symptoms of lower respiratory tract infection were defined as one or more of the following: cough, sputum production, chest pain, dyspnea, tachypnea, or abnormal lung physical examination findings.^{20,22} Children were excluded if they had been hospitalized in the previous 14 days, had a history of aspiration pneumonia, or had chronic complex conditions (eg, immunodeficiency, chronic corticosteroid use, heart disease,

neuromuscular disease, chronic lung disease, sickle cell disease, or cystic fibrosis); children with asthma were included.²³

For this study, our analytic data set excluded children who were hospitalized at enrollment. In addition, because antibiotic exposure was the primary exposure, children on antibiotics at the time of their ED visit were also excluded (Fig 1).

Study Procedure

Clinicians completed a standardized case report form after the CXR was ordered.²⁰ Clinicians included pediatric emergency medicine attending physicians and fellows, pediatricians, and nurse practitioners. In addition, historical information was collected by parents and recorded on a separate case report form by research coordinators. Data collected from the clinician included physical examination findings, perceived severity of illness, and planned disposition.^{20,21}

Exposure Measurements

The primary exposure was administration of antibiotics and/or receipt of an antibiotic prescription during the ED visit. Exposure measurement was abstracted from the electronic health record and reviewed for accuracy by 2 investigators (T.A.F. and L.A.).

Parents reported age, sex, race, history of previous episode of wheeze, history of previous episode of pneumonia or pneumonia hospitalization, prematurity, receipt of recommended vaccines based on age, and receipt of the current season's influenza vaccine. Parents were asked about the presence and duration of specific symptoms related to their child's current illness. These symptoms included total days of current illness, days of fever, maximum temperature,

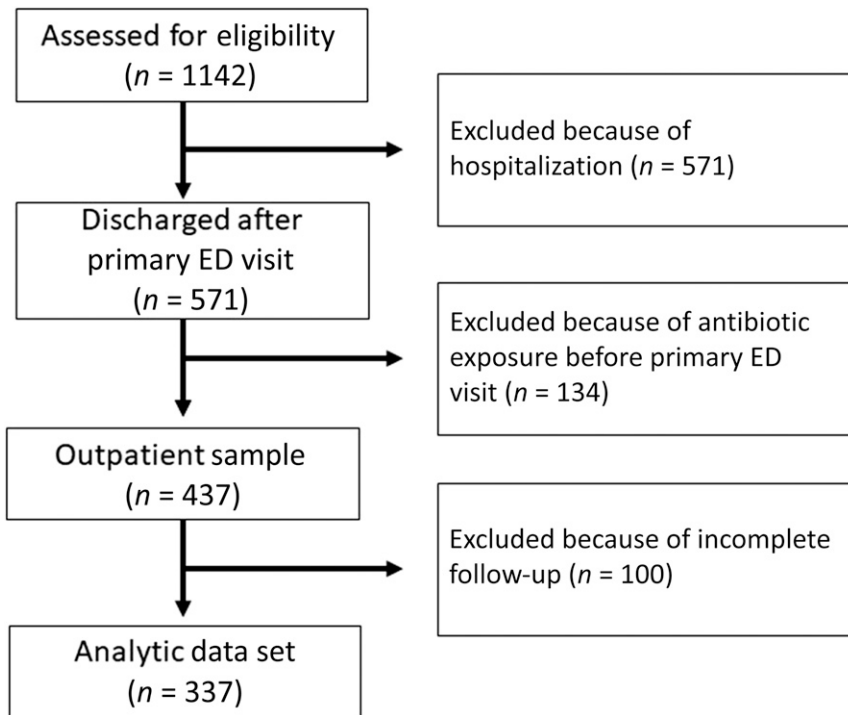


FIGURE 1
Flow diagram of study enrollment.

cough, difficulty breathing, apnea, wheezing, noisy breathing, rapid breathing, difficulty eating, decreased oral intake, lack of oral intake for >12 hours, congestion and/or rhinorrhea, vomiting, diarrhea, chest pain, abdominal pain, and lethargy.

During their physical examination of the patient, clinicians documented on a standardized case form the patient's general appearance (ie, well, mildly ill, moderately ill, or severely ill), impression of overall illness severity (mild, moderate, or severe), behavior (ie, playing, appropriate; quiet, appropriate; sleeping, easily arousable; sleeping, not easily arousable; fussy, consolable; or irritable), oxygen saturation percentage at the time of physical examination, skin color, capillary refill time, grunting, head bobbing, retractions, and presence of and focality of wheeze, decreased breath sounds, crackles, and rhonchi. Historical and physical examination

findings on the case report form were selected by literature review and expert consensus as previously described.²⁰ All CXRs and the corresponding radiology reports from the on-call radiologist were manually reviewed (T.A.F) and confirmed if the radiologist's impression of the ED CXR was consistent with pneumonia or not.

Outcome Measurements

The primary outcome was treatment failure, defined as having at least one of the following: (1) a return visit with hospitalization for pneumonia within 30 days of discharge, (2) return visit with a change in antibiotics within 30 days of discharge, and (3) parental report of change in antibiotics by a physician at any time between ED discharge and the follow-up phone call, which occurred 7 to 15 days after an ED visit. This primary outcome was chosen because of its clinical significance and is consistent with

definitions of antibiotic effectiveness used by other studies and adult guidelines.²⁴⁻²⁸ Time periods of follow-up were chosen to capture any potential event within 30 days while minimizing the risk of recall bias, acknowledging that most revisits were most likely to occur in the first week after ED discharge.²⁹

The secondary outcomes included ED revisits occurring 30 days after enrollment identified by medical record review. In addition, parents reported QoL measures 7 to 15 days after being discharged from the ED. QoL measures included days until return to normal activity, presence and length of symptoms (eg, fever), and information regarding scheduled or unscheduled medical care (ie, from their primary care physician, revisit to the ED, or subsequent hospitalizations).

Data Analysis

Categorical variables were described by using counts and percentages and compared between groups (ie, those who received antibiotics and those who did not) with the χ^2 test. Maximum temperature was normally distributed and was described by using mean and SD. For this variable, Student's *t* test was used to compare groups. All other continuous and discrete variables were described by using median and interquartile range (IQR) because of nonnormal distributions. The Kruskal-Wallis test compared continuous nonnormally distributed variables among groups.

Because of the large number of clinical confounders associated with the decision to prescribe antibiotics, propensity scores were generated to estimate the probability of receiving antibiotic prescription (ie, the primary exposure) in the ED for each observation.³⁰ Variables in the propensity score were chosen on the basis of clinical significance and included age, sex, history of

pneumonia, history of fever, general appearance, and days of illness. In addition, the presence of wheeze, decreased breath sounds, and crackles and the clinician's impression of disease severity were included on the basis of statistical significance ($P < .05$) in the propensity score model. Although race has been associated with antibiotic prescribing, race was well balanced before and after propensity score matching and not included in the model.³¹ Previous studies have reported that antibiotic prescribing is not statistically impacted by the radiologist's impression from the CXR.^{21,32} Therefore, ED CXR results were not included in determining the propensity score. A 1:1 nearest-neighbor matching without replacement based on propensity score was executed by using the MatchIt package in the R statistical program.³³ Patients with propensity scores outside of the region of common support were discarded before matching.³³ To assess covariate balance after matching, standardized mean differences were compared. The standardized mean differences were assessed graphically by using a Love plot (Supplemental Fig 2).³⁴ After matching, all covariates that had an absolute mean difference of <0.25 were determined to be balanced.^{35,36}

The first model was a logistic regression model to determine the association of prescribing antibiotics and treatment failure in the matched cohort. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). For count variable outcomes, which included QoL measures in days, Poisson regression was performed to assess the association of prescribing antibiotics and the outcomes. The results for these models are presented as risk ratios (RRs) and 95% CIs. A second logistic regression model was developed and adjusted for CXR impression in the matched

TABLE 1 Baseline Characteristics of Unmatched Sample

	Not Treated With or Prescribed Antibiotics	Treated With or Prescribed Antibiotics	<i>P</i>
<i>N</i>	169	168	—
Demographics			
Age, y, median (IQR)	3.3 (1.3–8.5)	3.8 (2.1–7.3)	.43
Male sex, <i>n</i> (%)	72 (42.6)	77 (45.8)	.63
Past medical history, <i>n</i> (%)			
Wheezing	56 (33.1)	49 (29.2)	.43
Pneumonia	29 (17.2)	35 (20.8)	.27
Receipt of seasonal influenza vaccine	83 (50.6)	79 (47.6)	.66
Parent-reported symptoms			
Days of current illness, median (IQR)	4 (2–7)	5 (3–7)	.054
Fever, <i>n</i> (%)	136 (80.5)	153 (91.1)	<.01
Cough, <i>n</i> (%)	155 (91.7)	162 (96.4)	.11
Difficulty breathing, <i>n</i> (%)	132 (78.1)	121 (72.0)	.24
Wheezing, <i>n</i> (%)	110 (65.1)	83 (49.4)	<.01
Difficulty eating, <i>n</i> (%)	47 (27.8)	54 (32.1)	.45
Congestion and/or rhinorrhea, <i>n</i> (%)	151 (89.3)	129 (76.8)	<.01
Vomiting, <i>n</i> (%)	68 (40.2)	84 (50.0)	.091
Diarrhea, <i>n</i> (%)	29 (17.2)	28 (16.7)	.99
Clinician examination and assessment, <i>n</i> (%)			
General appearance			.19
Well	84 (52.5)	80 (49.4)	
Mildly ill	72 (45.0)	71 (43.8)	
Moderately ill	4 (2.5)	11 (6.8)	
Wheeze	51 (31.9)	30 (18.5)	<.01
Crackles	33 (20.6)	60 (37.3)	<.01
Focal crackles	21 (63.6)	49 (81.7)	.094
Retractions	46 (28.7)	41 (25.3)	.57
Rhonchi	51 (31.9)	46 (28.4)	.58
Focal rhonchi	9 (17.6)	15 (32.6)	.14
Decreased breath sounds	27 (16.9)	46 (28.4)	.02
Focal decreased breath sounds	10 (37.0)	40 (87.0)	<.01
CXR consistent with PNA	1 (0.6)	68 (52.3)	<.01
Unilateral positive CXR results	7 (4.1)	89 (53.0)	<.01

PNA, pneumonia; —, not applicable.

cohort. All statistical analyses were performed by using the R statistical software (version 3.5.0).

RESULTS

Study Population

Of 1142 children in the parent study, 337 met the inclusion criteria for this study and 49.9% received antibiotics (Fig 1). The median age was 3.4 years (IQR: 1.5–7.3). There were no statistical differences in demographic factors such as age, sex, race, history of prematurity, or immunization status between children who did and

did not receive antibiotic prescription at the initial ED visit. Children who received antibiotics or an antibiotic prescription in the ED were more likely to have fever, crackles, and decreased breath sounds (including focally decreased breath sounds) and be characterized by the clinician as having moderate disease; they were also less likely to have wheeze or nasal congestion (on history or examination; Table 1).

After matching by propensity scores, 294 (87%) remained in the final analysis, and covariates were appropriately balanced

(Supplemental Table 4, Supplemental Fig 2).

Treatment Failure

In the matched cohort, 26 (8.8%) children experienced treatment failure. There was no statistical difference between groups in treatment failure. Additionally, there was no statistical difference in the individual components of treatment failure: return visits with hospital admission (3.4% with antibiotics versus 3.4% without; $P = .99$), return visits with change in antibiotics (2% vs 0.6%; $P = .67$), or initiation or change in antibiotics in the 2 weeks after discharge (4.8% vs 6.1%; $P = .61$). Both models with and without adjustment for CXR impression demonstrated no statistical difference in treatment failure between the 2 groups (OR 1.0 [95% CI 0.45–2.2] and OR 0.66 [95% CI 0.19–2.3], respectively; Table 2).

Parent-Reported QoL Measures

Children who received antibiotics or an antibiotic prescription had an increased risk of being kept from usual activity for more days (RR 1.3; 95% CI 1.1–1.5); this was not

statistically significant after adjustment for CXR impression (RR 1.1; 95% CI 0.94–1.4; Table 2). There were no statistical differences between groups for any other parent-reported symptoms after discharge. Symptoms typically associated with antibiotic side effects such as diarrhea (17.0% with antibiotics versus 20.4% without), vomiting (15.0% vs 8.2%), and abdominal pain (15.0% vs 12.9%) were not statistically different between children who received antibiotics and those who did not. In addition, time to resolution for the parent-reported symptoms was not statistically different (Table 3).

DISCUSSION

In this prospective study of children with suspected CAP managed as outpatients, no association was found between receipt of antibiotic prescription and treatment failure regardless of whether CXR impression was considered in the model. In addition, antibiotic prescription was not associated with a difference in QoL measures or parent-reported symptoms after discharge.

The children in our study may have been more likely to have a viral rather than bacterial pathogen causing infection. A recent cohort of hospitalized children at 3 US hospitals underwent blood and nasopharyngeal polymerase chain reaction testing for bacteria and viruses, of whom 15% had a bacterial pathogen identified and 73% had a viral pathogen identified.¹³ The relatively low rate of detectable bacterial infection in pediatric pneumonia has been replicated in 2 studies of hospitalized children in Japan (49.6%) and the United Kingdom (30%).^{37,38} In addition, our cohort was relatively young (median age of 3.4 years), and viruses tend to predominate in younger children.^{13,37} Although true rates of bacterial infection may be higher because bacteria are more difficult to detect than viruses, this would have likely led our results to be farther from the null because we would have expected improved outcomes in children who received antibiotics.

Although there have been no trials of antibiotics versus a placebo for nonsevere pneumonia in high-

TABLE 2 Clinical Outcomes of Propensity Score–Matched Cohort

	Not Treated With or Prescribed Antibiotics, n (%)	Treated With or Prescribed Antibiotics, n (%)	P^a	Model 1, ^a OR (95% CI)	Model 2, ^b OR (95% CI)
<i>N</i>	147	147	—	—	—
Clinical outcomes, n (%)					
Treatment failure	13 (8.8)	13 (8.8)	.99	1.0 (0.45–2.2)	0.66 (0.19–2.3)
Admission within 30 d	5 (3.4)	5 (3.4)	.99	1.1 (0.23–5.7)	0.4 (0.03–4.7)
ED revisit within 30 d	13 (8.8)	12 (8.2)	.99	0.92 (0.40–2.1)	0.81 (0.23–2.8)
Parent-reported outcomes					
Diagnosis of pneumonia since discharge, n (%)	1 (0.7)	0 (0.0)	.99	NA	NA
Medical care sought since discharge, n (%)	54 (36.7)	65 (44.2)	.24	1.4 (0.86–2.2)	1.1 (0.59–2.1)
Type of medical care sought since discharge, n (%)			.52		
Unscheduled visit	11 (20.4)	10 (15.4)		—	—
Scheduled follow-up	33 (61.1)	49 (75.4)		—	—
Follow-up because of worsening or not improving	6 (11.1)	4 (6.2)		—	—
Routine visit	2 (3.7)	1 (1.5)		—	—
Telephone follow-up	2 (3.7)	1 (1.5)		—	—
Unscheduled visit or visit because of worsening, n (%)	17 (11.6)	14 (9.5)	.22	0.60 (0.26–1.4)	0.51 (0.15–1.8)
Addition or change of antibiotic at any follow-up, n (%)	7 (4.8)	9 (6.1)	.61	1.3 (0.47–3.6)	0.44 (0.071–2.7)
Days child kept from usual activity, median (IQR)	2 (0–3)	2 (1–4)	<.01	1.3 (1.1–1.5)	1.1 (0.94–1.4) ^c
Days of parental missed work, median (IQR)	0 (0–1)	0 (0–2)	.4	1.3 (1.0–1.6)	1.2 (0.88–1.6) ^c

NA, not available; —, not applicable.

^a Propensity score–matched cohort.

^b Propensity score–matched cohort; model additionally adjusted for the presence of radiographic pneumonia.

^c Rate ratio.

TABLE 3 Symptoms After ED Discharge Based on Phone Follow-up

	Not Treated With or Prescribed Antibiotics	Treated With or Prescribed Antibiotics	P ^a	OR (95% CI)	OR (95% CI), Adjusted ^b
<i>N</i>	147	147	—	—	—
Parental report of symptoms since discharge					
Presence of fever, <i>n</i> (%)	56 (38.1)	62 (42.2)	.552	1.2 (0.74–1.9)	1.2 (0.65–2.2)
Days of fever, median (IQR)	2 (1–3.25)	2 (1–3)	.82	0.94 (0.75–1.2) ^c	1.0 (0.73–1.4) ^c
Days of cough, median (IQR)	7 (3–7)	7 (4–7)	.97	1.0 (0.91–1.1) ^c	1.0 (0.91–1.2) ^c
Cough compared with discharge, <i>n</i> (%)			.43		
Worse	4 (3.7)	3 (2.4)		—	—
About the same	29 (26.9)	25 (20.2)		—	—
Better	49 (45.4)	69 (55.6)		—	—
All better	26 (24.1)	27 (21.8)		—	—
Presence of difficulty breathing, <i>n</i> (%)	49 (33.3)	38 (25.9)	.20	0.70 (0.42–1.2)	0.56 (0.27–1.1)
Presence of wheezing, <i>n</i> (%)	53 (36.1)	42 (28.6)	.21	0.71 (0.43–1.2)	0.80 (0.41–1.5)
Presence of rapid breathing, <i>n</i> (%)	37 (25.2)	40 (27.2)	.79	1.1 (0.66–1.9)	1.3 (0.33–1.7)
Presence of runny nose, <i>n</i> (%)	103 (70.1)	95 (64.6)	.38	0.78 (0.48–1.3)	1.4 (0.71–2.9)
Presence of vomiting, <i>n</i> (%)	23 (15.6)	22 (15.0)	.99	0.95 (0.50–1.8)	1.1 (0.46–2.5)
Presence of diarrhea, <i>n</i> (%)	30 (20.4)	25 (17.0)	.55	0.80 (0.44–1.4)	1.1 (0.53–2.4)
Presence of abdominal pain, <i>n</i> (%)	19 (12.9)	22 (15.0)	.736	1.2 (0.61–2.3)	1.4 (0.58–3.2)

—, not applicable.

^a Unadjusted after propensity score matching.

^b Adjusted for the presence of radiographic pneumonia.

^c Rate ratio.

resource settings, Ginsburg et al¹⁷ performed a randomized, placebo-controlled trial of amoxicillin for the treatment of World Health Organization–defined nonsevere fast-breathing pneumonia in Malawi. Treatment failure occurred in 4% of children given amoxicillin and 7% of children given a placebo.¹⁷ The placebo was statistically inferior to amoxicillin, although the low rates of treatment failure in each group and the high number needed to treat (*n* = 33) to prevent 1 case of treatment failure highlight the need to weigh risks as well as benefits of antibiotic treatment. The low rates of treatment failure are consistent with our results; however, the lack of antibiotic efficacy in our study is potentially attributable to our smaller sample size. Their study location, a malaria-endemic region, and the World Health Organization’s definition of pneumonia make it difficult to translate those results to high-resource settings.

Greenberg et al³⁹ conducted a randomized controlled trial in Israel comparing 3, 5, and 10 days of

amoxicillin for the treatment of pneumonia and found high rates (40%) of treatment failure in the children treated for only 3 days compared with 0% in the 10-day group. Their study inclusion criteria required a CXR with alveolar pneumonia, a temperature >38.5°C, and a white blood cell count of >15 000, which likely selected children with bacterial pneumonia. In addition, our cohort was composed of children with clinically suspected CAP of any etiology as opposed to alveolar radiographic pneumonia. Given that the Infectious Diseases Society of America guideline cautions against the routine use of CXR in outpatients and that most outpatient settings do not have readily available CXR, our results are more applicable to children with clinically suspected CAP rather than the population assessed by Greenberg et al.^{3,39}

Lipsett et al⁴⁰ prospectively enrolled children with suspected CAP, and negative CXR results revealed that children observed off of antibiotics had only a 1.2% rate of subsequent pneumonia diagnoses or clinical

worsening. Our study results support the finding that subsequent clinical deteriorations of children with suspected CAP managed as outpatients are rare. In addition, our rates of treatment failure were similar to previously described rates in children treated in the outpatient setting.^{28,41}

Antibiotic-associated diarrhea is a common complication of oral antibiotics in children, occurring in ~11% of children exposed to antibiotics and lasting a mean of 4 days.⁴² We did not find a difference in either the incidence of diarrhea in our population based on antibiotic exposure or length of symptoms of diarrhea based on parental report.

Although we found no statistical differences in the outcomes examined in those who did and did not receive antibiotics, it is not clear if there are specific circumstances in which antibiotics must be prescribed or may safely be withheld. Although newer biomarkers such as procalcitonin have been shown to correspond to detection of bacteria in hospitalized children with CAP, there have been no

biomarkers demonstrated to be useful in children treated as outpatients, nor have clinical decision rules been derived or validated to help determine which children may benefit from antibiotics.⁴³

This study has several limitations. The study was designed to assess outcomes in children suspected of pneumonia, with or without radiographic confirmation, because the most recent Infectious Diseases Society of America guidelines do not recommend radiographs in this cohort for the purpose of making treatment decisions. Although 20% had radiographic pneumonia on CXR, nearly all of these were in the group prescribed antibiotics. Although we were able to match on the basis of clinical signs and symptoms, the unequal distribution of radiographic pneumonia between the groups may have led to residual confounding by indication. We examined the influence of radiographic findings in the final multivariate model, and it showed similar results. We did not use antibiotic type in our analysis; however, because only 3.9% of children in our sample were prescribed a macrolide, antibiotic type is unlikely to have been a major confounder. In addition, the possibility of a type II error must be considered. We were limited in our

sample size because of the convenience sample of our study; therefore, our study was not powered to detect a small treatment effect but was powered to detect a medium or large effect of antibiotics on the development of treatment failure. A proportion (23%) of our cohort was lost to phone follow-up. Seventy-five percent of the patients lost to follow-up were in the group not treated with antibiotics, which may have led us to overestimate the rate of treatment failure in this group. Because our hospital is the pediatric referral center for a wide catchment area and admits 99.6% of local pediatric pneumonia cases, it is unlikely that we missed any potential hospitalizations.⁴⁴ In addition, we cannot be sure that parent-reported changes in antibiotics were respiratory related.

There is evidence that the microbiology of CAP differs between younger and older children because *Mycoplasma pneumoniae* is more prevalent in children >5 years old.¹³ However, rates of treatment failure did not vary significantly between children <5 years old (7%) and children ≥5 years old (12%; $P = .2$). Although age was included in the propensity score model and was well balanced between groups, we were unable to perform an age-stratified

analysis to determine an age effect on outcomes based on limited sample size. Viral diagnostic testing may influence antibiotic prescribing; however, it was infrequently obtained with few positive clinical viral test results ($n = 5$; <2%) in our sample.

CONCLUSIONS

We found that in a cohort of children with suspected CAP discharged from the hospital ED, receipt of antibiotics or an antibiotic prescription did not lead to statistical differences in treatment failure or parent-reported adverse effects or QoL measures. Our results suggest that opportunities exist to safely manage more children with suspected CAP treated as outpatients without antibiotics.

ABBREVIATIONS

CAP: community-acquired pneumonia
CI: confidence interval
CXR: chest radiograph
ED: emergency department
IQR: interquartile range
OR: odds ratio
QoL: quality of life
RR: risk ratio

Dr Ambroggio conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, collected data, assisted in statistical analysis, contributed to the interpretation of the results, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: <https://doi.org/10.1542/peds.2019-3138>

Accepted for publication Jan 9, 2020

Address correspondence to Matthew J. Lipshaw, MD, Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, ML 2008, Cincinnati, OH 45229. E-mail: matthew.lipshaw@cchmc.org

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

Copyright © 2020 by the American Academy of Pediatrics

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

FUNDING: Supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grants 1K23 AI121325-01 [Dr Florin] and K01 AI125413-01A1 [Dr Ambroggio]) and a pediatric research grant from The Gerber Foundation (Dr Florin). The funders had no role in the design or conduct of the study or the collection, management, analysis, or interpretation of the data. 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.

REFERENCES

- Haq IJ, Battersby AC, Eastham K, McKean M. Community acquired pneumonia in children. *BMJ*. 2017;356:j686
- Lynch T, Bialy L, Kellner JD, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. *PLoS One*. 2010;5(8):e11989
- Bradley JS, Byington CL, Shah SS, et al; Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25–e76
- Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. *Lancet Infect Dis*. 2015;15(4):439–450
- Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia?: the rational clinical examination systematic review. *JAMA*. 2017;318(5):462–471
- Nohynek H, Valkeila E, Leinonen M, et al. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory tract infections in children. *Pediatr Infect Dis J*. 1995;14:7
- Don M, Valent F, Korppi M, Canciani M. Differentiation of bacterial and viral community-acquired pneumonia in children. *Pediatr Int*. 2009;51(1):91–96
- Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. *Pediatr Radiol*. 1988;18(6):453–454
- Gotta V, Baumann P, Ritz N, et al; ProPAED Study Group. Drivers of antibiotic prescribing in children and adolescents with febrile lower respiratory tract infections. *PLoS One*. 2017;12(9):e0185197
- Handy LK, Bryan M, Gerber JS, Zaoutis T, Feemster KA. Variability in antibiotic prescribing for community-acquired pneumonia. *Pediatrics*. 2017;139(4):139
- Kronman MP, Hersh AL, Feng R, Huang YS, Lee GE, Shah SS. Ambulatory visit rates and antibiotic prescribing for children with pneumonia, 1994-2007. *Pediatrics*. 2011;127(3):411–418
- Florin TA, Byczkowski T, Gerber JS, Ruddy R, Kuppermann N. Diagnostic testing and antibiotic use in young children with community-acquired pneumonia in the United States, 2008-2015. *J Pediatric Infect Dis Soc*. 2019; piz026
- Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835–845
- Biondi E, McCulloh R, Alverson B, Klein A, Dixon A, Ralston S. Treatment of mycoplasma pneumonia: a systematic review. *Pediatrics*. 2014;133(6):1081–1090
- Garber MD, Quinonez RA. Chest radiograph for childhood pneumonia: good, but not good enough. *Pediatrics*. 2018;142(3):e20182025
- Rudan I, O'Brien KL, Nair H, et al; Child Health Epidemiology Reference Group (CHERG). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health*. 2013;3(1):10401
- Ginsburg AS, Mvalo T, Nkwopara E, et al. Placebo vs amoxicillin for nonsevere fast-breathing pneumonia in Malawian children aged 2 to 59 months: a double-blind, randomized clinical noninferiority trial. *JAMA Pediatr*. 2019;173(1):21–28
- Lovegrove MC, Geller AI, Fleming-Dutra KE, et al. US emergency department visits for adverse drug events from antibiotics in children, 2011-2015. *J Pediatric Infect Dis Soc*. 2019;8(5):384–391
- Michaelidis CI, Fine MJ, Lin CJ, et al. The hidden societal cost of antibiotic resistance per antibiotic prescribed in the United States: an exploratory analysis. *BMC Infect Dis*. 2016;16(1):655
- Florin TA, Ambroggio L, Brokamp C, et al. Reliability of examination findings in suspected community-acquired pneumonia. *Pediatrics*. 2017;140(3):140
- Lipshaw MJ, Florin TA, Krueger S, et al. Factors associated with antibiotic prescribing and outcomes for pediatric pneumonia in the emergency department [published online ahead of print July 8, 2019]. *Pediatr Emerg Care*. doi:10.1097/PEC.0000000000001892
- Jain S, Self WH, Wunderink RG, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415–427
- Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr*. 2014;14:199
- Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. *JAMA*. 2017;318(23):2325–2336
- Menendez R, Torres A. Treatment failure in community-acquired pneumonia. *Chest*. 2007;132(4):1348–1355
- Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72
- Genné D, Kaiser L, Kinge TN, Lew D. Community-acquired pneumonia: causes of treatment failure in patients enrolled in clinical trials. *Clin Microbiol Infect*. 2003;9(9):949–954
- Ambroggio L, Test M, Metlay JP, et al. Comparative effectiveness of beta-lactam versus macrolide monotherapy in children with pneumonia diagnosed in the outpatient setting. *Pediatr Infect Dis J*. 2015;34(8):839–842
- Ambroggio L, Herman H, Fain E, Huang G, Florin TA. Clinical risk factors for

- revisits for children with community-acquired pneumonia. *Hosp Pediatr*. 2018;8(11):718–723
30. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55
 31. Kornblith AE, Fahimi J, Kanzaria HK, Wang RC. Predictors for under-prescribing antibiotics in children with respiratory infections requiring antibiotics. *Am J Emerg Med*. 2018; 36(2):218–225
 32. Nelson KA, Morrow C, Wingerter SL, Bachur RG, Neuman MI. Impact of chest radiography on antibiotic treatment for children with suspected pneumonia. *Pediatr Emerg Care*. 2016;32(8):514–519
 33. Ho DE, Imai K, King G, et al. Match it: nonparametric preprocessing for parametric causal interference. *J Stat Softw*. 2011;42:28
 34. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107
 35. Stuart EA, Cole SR, Bradshaw CP, Leaf PJ. The use of propensity scores to assess the generalizability of results from randomized trials. *J R Stat Soc Ser A Stat Soc*. 2001;174(2):369–386
 36. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25(1):1–21
 37. Hamano-Hasegawa K, Morozumi M, Nakayama E, et al; Acute Respiratory Diseases Study Group. Comprehensive detection of causative pathogens using real-time PCR to diagnose pediatric community-acquired pneumonia. *J Infect Chemother*. 2008;14(6):424–432
 38. Elemraïd MA, Sails AD, Eltringham GJ, et al; North East of England Paediatric Respiratory Infection Study Group. Aetiology of paediatric pneumonia after the introduction of pneumococcal conjugate vaccine. *Eur Respir J*. 2013; 42(6):1595–1603
 39. Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. *Pediatr Infect Dis J*. 2014;33(2):136–142
 40. Lipsett SC, Monuteaux MC, Bachur RG, Finn N, Neuman MI. Negative chest radiography and risk of pneumonia. *Pediatrics*. 2018;142(3):142
 41. Ambroggio L, Test M, Metlay JP, et al. Beta-lactam versus beta-lactam/macrolide therapy in pediatric outpatient pneumonia. *Pediatr Pulmonol*. 2016;51(5):541–548
 42. Turck D, Bernet JP, Marx J, et al. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr*. 2003; 37(1):22–26
 43. Stockmann C, Ampofo K, Killpack J, et al. Procalcitonin accurately identifies hospitalized children with low risk of bacterial community-acquired pneumonia. *J Pediatric Infect Dis Soc*. 2018;7(1):46–53
 44. Beck AF, Florin TA, Campanella S, Shah SS. Geographic variation in hospitalization for lower respiratory tract infections across one county. *JAMA Pediatr*. 2015;169(9):846–854