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MAJOR ARTICLE

Antibiotic Use and Outcomes in Young Children Hospitalized With Uncomplicated Community-Acquired Pneumonia

Meghan E. Hofto, Nichole Samuy, and Robert F. Pass

Department of Pediatrics, Division of Hospital Medicine, University of Alabama at Birmingham and Children's of Alabama, Birmingham, Alabama, USA

Background. We aimed to compare children aged 36 months or younger hospitalized with uncomplicated community-acquired pneumonia (CAP) who are not treated with antibiotics to those treated with antibiotics in terms of clinical features and outcome measures.

Methods. Administrative data and medical record review were used to identify patients from 3 to 36 months of age hospitalized from 2011 to 2019 with uncomplicated CAP. Patients were considered treated if they received antibiotics for >2 inpatient days and/or at discharge, and not treated if they received ≤2 inpatient days and no antibiotics at discharge. Untreated patients were compared to treated patients based on demographic features, clinical and laboratory results, and outcomes of interest, including illness severity, length of stay, and 30-day hospital readmissions.

Results. Three hundred twenty-two CAP cases were included; 266 (83%) received antibiotics for >48 hours and/or at discharge. Fifty-six patients received ≤2 inpatient days of antibiotics and no antibiotics at discharge; the majority received no inpatient antibiotics. There were no differences between the 2 groups in illness severity, length of stay, or hospital readmissions. The proportion of patients treated with antibiotics decreased from 88% (2011–2013) to 66% during the most recent years studied (2017–2019).

Conclusions. There was no difference in outcome of uncomplicated CAP in previously healthy children <36 months of age between those treated and not treated with antibiotics. Additional tools are needed to facilitate identification of viral CAP in young children and decrease unnecessary antibiotic use.

Keywords. antibiotic stewardship; community-acquired pneumonia; guidelines; viral respiratory infection.

Although it is generally accepted that viruses cause the majority of community-acquired pneumonia (CAP) in young children, narrow-spectrum antibiotics (typically penicillin, amoxicillin, or amoxicillin/clavulanate) are recommended for all children hospitalized with uncomplicated CAP by multiple guidelines promulgated by subspecialty societies and health service systems [1–5]. While monitoring adherence to guideline recommendations for use of narrow-spectrum antibiotics for children hospitalized with CAP, we noted that some patients did not receive antibiotic treatment. The purpose of this study was to determine the proportion of children aged 3 months to 3 years hospitalized with CAP who did not receive a treatment course of antibiotics and determine if there were differences in clinical outcome related to treatment.

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Correspondence: Meghan Hofto, MD, MPH, Children's of Alabama, 1600 Seventh Ave S, Suite 108, Birmingham, AL 35233, USA (mhofto@uabmc.edu).

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METHODS

Study Design

This was a retrospective observational study of children with uncomplicated CAP hospitalized between September 2011 and December 2019 at a single, freestanding, urban children's hospital in Birmingham, Alabama, with 380 beds and >15 000 admissions per year. The exposure of interest was a treatment course of antibiotics for CAP. The outcomes of interest were illness severity (indicated by requirement for intensive care), length of hospital stay, and readmission after discharge. This study used the definition of CAP ("signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside of the hospital") included in the Infectious Diseases Society of America/Pediatric Infectious Diseases Society guideline [3]. The Institutional Review Board of the University of Alabama at Birmingham approved this study. As this study only involved de-identified data, patient consent was not obtained.

Study Population

Children admitted with an *International Classification of Diseases, Ninth Revision* (*ICD-9*) or an *International Classification of Diseases, Tenth Revision* (*ICD-10*) discharge diagnosis code for pneumonia (480–487.0 or J12.0–J18.9, respectively) were

identified for possible inclusion. The target population was children 3–36 months of age without underlying comorbidities that increase the risk of bacterial pneumonia or cause acute respiratory symptoms independent of infection. Patients with chronic lung disease (other than asthma), immunodeficiency, admission for status asthmaticus, or prior admission within 1 month of the index hospitalization were excluded. Patients with a clinical diagnosis of aspiration pneumonia or prior history of aspiration in the medical record were also excluded. Patients were excluded if they had complicated CAP ("parapneumonic effusions, multilobar disease, abscesses or cavities, necrotizing pneumonia, empyema, pneumothorax, or bronchopleural fistula") per the guideline [3], or received treatment with antibiotics for a concomitant infection other than CAP.

Administrative data, including age, sex, race/ethnicity, length of stay, and discharge diagnosis codes, were obtained from the local institution. We reviewed medical records in order to confirm that patients met the guideline definition of CAP and to collect data on antimicrobial use before, during, and after hospitalization, clinical findings, and laboratory and microbiology results, as well as illness severity and hospital readmissions. Radiographic results were evaluated based on the radiologist read of the image and categorized as "focal opacity" if "pneumonia," "cannot exclude pneumonia," or "focal opacity" were mentioned, or "viral versus atelectasis" if there was a mention of presumed viral process or atelectasis. There was overlap between the 2 categories, as some reports mentioned "likely viral process or atelectasis but cannot rule out developing pneumonia."

The "treated with antibiotics group" (TAG) was defined as the patients treated inpatient for >2 days (48 hours) with antibiotics or discharged home with a prescription for an antibiotic, and the "no antibiotics group" (NAG) was defined as the group treated inpatient for ≤2 days and discharged home on no antibiotics. We defined these groups prior to initiation of this study, and selected the criteria because we thought they would accurately reflect a clinical decision to treat for possible bacterial infection (TAG) or not to treat (NAG). The possibility of overlap between the 2 groups in antibiotic use was recognized.

Statistical Analysis

Statistical analysis was performed using commercially available software (SAS version 9.4, SAS Institute, Cary, North Carolina). Central tendency was expressed as median and interquartile range (IQR). Proportions were compared using Fisher exact test and χ^2 test. Continuous variables were analyzed using Wilcoxon rank-sum test. *P* values < .05 were considered significant.

RESULTS

Identification of the Study Population

Administrative data identified 2313 patients aged 3 months to 19 years with possible CAP based on a discharge diagnosis code. Review of diagnosis and procedure codes excluded 997 (43%), leaving 1316 cases. Medical record review excluded an additional 338. Figure 1 details the reasons for exclusion. Of the remaining 978 patients, 444 patients were aged 3–36 months; 15 were excluded because they received antibiotics for another indication (14 for acute otitis media, 1 for urinary tract infection), and 107 were excluded due to complicated CAP. All complicated pneumonias were either present on admission or developed in patients already on antibiotics. Patients with bronchiolitis were included only if they had a diagnosis code for pneumonia.

Demographic and Clinical Characteristics of the Study Population

Of the 322 patients with uncomplicated CAP in the final study population, 266 (83%) were treated with or discharged home on antibiotics. Table 1 shows demographic and clinical characteristics comparing the TAG patients to the NAG patients. Patients were fairly evenly distributed in age from 3 to 12 months (91/322 [28%]), 13 to 24 months (127/322 [39%]), and 25 to 36 months (104/322 [32%]), but the NAG patients were statistically older (median age, 25 months vs 17 months; *P* = .003) than the TAG patients. There were no statistically significant differences in sex, race, or ethnicity between the groups. Fever, hypoxemia at time of admission, and vomiting were present at similar rates, with a similar maximum preadmission temperature recorded. The proportion of patients with a code for bronchiolitis was similar between the 2 groups: 17% (n = 9) in NAG vs 19% (n = 49) in TAG (*P* = .7). The TAG patients were more likely to have received antibiotics prior to admission (outpatient or emergency department) (236/266 [89%]) and on admission (263/266 [99%]) than the NAG patients (37/56 [66%], prior and 24/56 [43%], on admission) (*P* < .001 for both comparisons).

Outcome measures were similar between the 2 groups (Table 1). Similar proportions of patients in both groups required care in the intensive care unit (ICU) during hospitalization, and all but 2 of these patients (both in TAG) were initially admitted to the ICU. There were no statistically significant differences between TAG and the NAG in either median hospital length of stay or 30-day readmissions. Both readmissions in NAG were due to new viral illnesses after complete recovery from the index hospitalization. Of the 13 TAG readmissions, 7 were due to persistent or worsening symptoms, and 6 were due to new illness after complete recovery from the index hospitalization.

Radiologic and Laboratory Findings

The majority (311/322 [97%]) of patients had radiographic imaging during hospitalization. The NAG patients were more likely to have a radiologist read of viral process or atelectasis (50/51 [98%]) than the TAG patients (178/260 [68%]) (*P* < .001). The TAG patients were more likely to have a read suggesting possible bacterial pneumonia than the NAG patients (182/260 [70%] vs 8/51 [16%]; *P* < .001). Some radiograph reports mentioned both viral airway disease and pneumonia or focal opacity; this occurred more frequently in TAG (100/260 [38%] than in NAG (7/51 [14%]; *P* = .01).

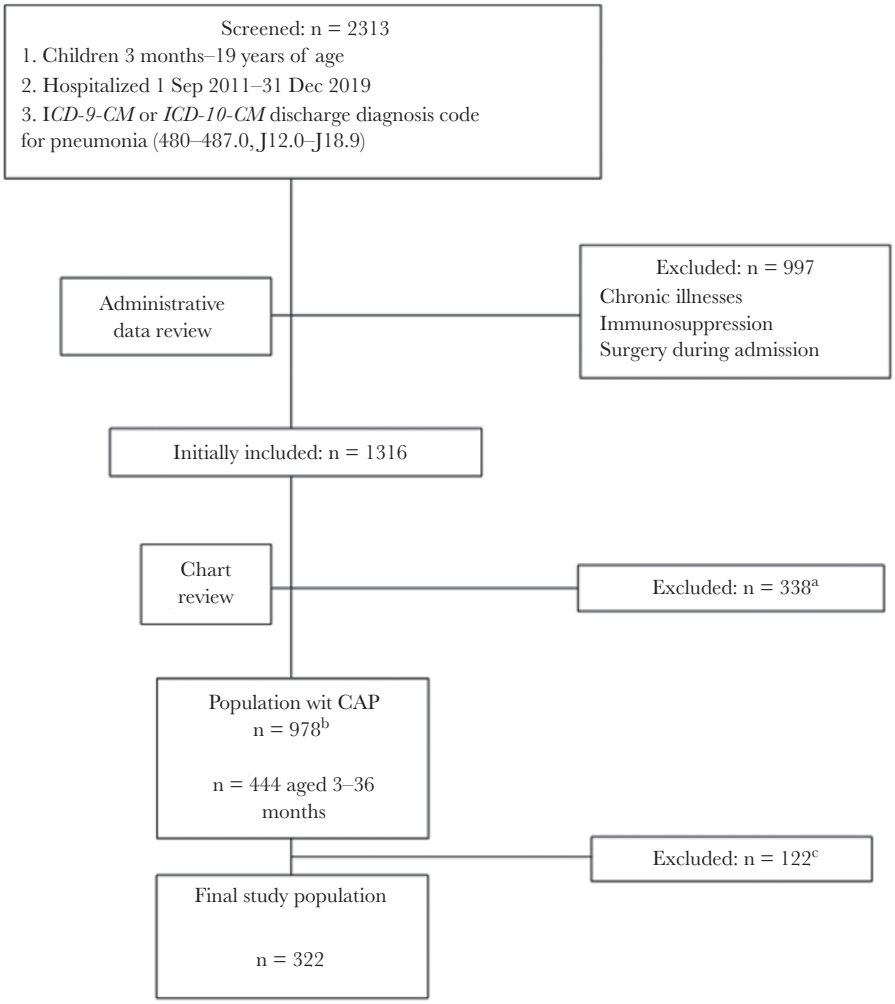

Figure 1. Accrual of the study population. [a]Exclusions: chronic lung disease (n = 104), immunosuppression (n = 35), not community-acquired pneumonia (CAP) (n = 78), readmission (n = 93), postsurgical complication (n = 28). [b]CAP according to guideline definition and inclusion and exclusion criteria for this study. [c]Excluded for antibiotics given for indication other than CAP (n = 15) or complicated CAP (n = 107). Abbreviations: CAP, community-acquired pneumonia; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification*.

The median white blood cell count ($\times 10^9$/L) was 12.0 (IQR, 8.7–19.0) for TAG and 10.7 (IQR, 7.8–14.1) for NAG, a difference that was not statistically significant. Fifty-five percent of the TAG patients and 58% of the NAG patients had blood cultures obtained. All blood cultures were negative.

Viral testing was more common in NAG (39/56 [70%]) vs TAG (152/266 [57%]) (P = .01; Table 2). Forty-eight percent (73/152) of the TAG patients were positive for at least 1 virus compared with 67% (26/39) of the NAG patients (P = .001). A higher proportion of NAG patients had both a radiographic finding of viral process and a positive viral test (23/50 [46%] for NAG vs 65/260 [25%] for TAG; P = .003). For both groups, respiratory syncytial viruses (RSVs) were the most commonly detected, followed by influenza viruses. Seven patients (5 in TAG and 2 in NAG) had 2 viruses detected. Of the 73 TAG patients positive for a virus, there were no significant differences from other TAG patients in maximum preadmission temperature, age, chest radiograph findings, or hypoxemia. The virus-positive TAG patients were more likely to be treated in the ICU than other TAG patients (8/73 [11%] vs 3/193 [2%]; P = .002).

Antibiotic Exposure in the TAG and the NAG Groups

We examined the data for possible overlap in antibiotic exposure between TAG and NAG. Among the TAG patients, 257 of 266 (97%) were discharged from the hospital with an antibiotic prescription. Seven of the 9 not discharged on antibiotics completed ≥6 days of treatment prior to discharge, and the other 2 patients had 3 or 4 inpatient days of treatment plus prehospital treatment. In contrast, no NAG patients were prescribed antibiotics at discharge; 32 of them received no inpatient antibiotics. Among the 24 NAG patients who received ≤2 days of inpatient antibiotics, 11 received ≤1 day of inpatient antibiotics and ≤1 dose of antibiotics prior to hospitalization. Five NAG patients received a single dose of antibiotics prior to admission

Table 1. Characteristics of Patients With Community-Acquired Pneumonia Categorized by Presence or Absence of Antibiotic Treatment

Characteristic	Treated With Antibiotics (n = 266)	Not Treated With Antibiotics (n = 56)	*P* Value
Sex, female	124 (47)	20 (36)	.1
Race/ethnicity			
African American	112 (42)	16 (29)	.07
White, non-Hispanic	119 (45)	32 (57)	.1
White, Hispanic	31 (12)	8 (14)	.7
Other	4 (1)	0	
Age, mo, median (IQR)	17 (11–26)	25 (16–31)	.003
Fever prior to admission	232 (87)	45 (80)	.2
Maximum temperature[a], °C, median (IQR)	39.4 (38.9–40)	39.4 (38.4–39.8)	.4
Hypoxemia	108 (41)	24 (43)	.8
Vomiting	130 (49)	25 (45)	.6
Antibiotic use			
Prior to admission[b]	236 (89)	37 (66)	<.001
After admission	263 (99)[c]	24 (43)	<.001
Intensive care unit admission	11 (4)	2 (4)	1
Length of stay, d, median (IQR)	2 (1–3)	1.5 (1–3)	.3
Inpatient readmissions, 30 d	13 (5)	2 (4)	1

Data are presented as No. (%) unless otherwise indicated.

[a]Based on parental report or emergency department record.

[b]Includes antibiotics prescribed prior to and given in the emergency department.

[c]Three patients hospitalized <24 hours did not receive antibiotics during hospitalization, but were prescribed antibiotics at discharge.

and had antibiotics discontinued on hospital day 2. Among the remaining 8 NAG patients, only 2 received 2 inpatient days of antibiotics and had >4 total days of antibiotics prior to hospitalization. We cannot exclude the possibility that treating physicians concluded that those 2 NAG patients were thought to be fully treated, but both were diagnosed with viral pneumonia in the medical record when antibiotics were discontinued.

Trends in Antibiotic Use and Viral Testing

There were no significant differences in antibiotic use at discharge by quarter of the year; 85% of those discharged in quarters 2 and 3 (local spring and summer) and 81% discharged in quarters 1 and 4 (local respiratory virus season) were prescribed antibiotics at discharge. Antibiotic use significantly declined in recent years. The TAG group contained 88% (134/152) of patients from 2011–2013, 86% (83/96) of patients from 2014–2016, and only 66% (49/74) of patients from 2017–2019 ($P < .001$). There was no significant difference in viral testing over time; 60% (91/152) of patients from 2011–2013, 52% (50/96) of patients from 2014–2016, and 68% (50/74) of patients from 2017–2019 had viral testing performed ($P = .12$).

DISCUSSION

In this study of 322 healthy children, aged 3–36 months, hospitalized with uncomplicated CAP, 56 did not receive a treatment course of antibiotics. While there were differences in

Table 2. Virus Detection, Including Multiplex Viral Polymerase Chain Reaction and Rapid Testing for Influenza and Respiratory Syncytial Virus, by Group

Virus	Treated With Antibiotics (n = 266)	Not Treated With Antibiotics (n = 56)	*P* Value
Tested for virus	152 (57)	39 (70)	.01
Positive	73 (48)	26 (67)	.001
Negative	79 (30)	13 (23)	
Not obtained	114 (43)	17 (30)	
RSV only	30 (41)	12 (46)	
Influenza only	15 (19)	5 (19)	
hMPV only	10 (14)	3 (10)	
Rhinovirus/enterovirus only	3 (4)	1 (4)	
Parainfluenza only	4 (5)	3 (10)	
Adenovirus only	4 (5)	2 (7)	
Two of above viruses	5 (7)[a]	2 (7)[b]	

Data are presented as No. (%) unless otherwise indicated. Aside from proportions tested for virus and with a positive test for virus, there were no statistically significant differences between groups.

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

[a]Three RSV plus other and 2 rhinovirus/enterovirus plus other.

[b]One RSV plus influenza and 1 RSV plus adenovirus.

the radiographic findings and age, there were no differences between patients who were treated with antibiotics and those who were not in either sex, race, ethnicity, or clinical features (fever, vomiting, hypoxemia). There were also no differences in disease severity (ICU stay), length of hospital stay, or readmissions between treated and untreated patients. No patient from the NAG group required readmission for antibiotic treatment. We found that physicians were increasingly willing to overlook guideline recommendations for treating all hospitalized children with CAP with antibiotics. The proportion of patients treated with antibiotics decreased from 88% in 2011–2013, to 66% during the most recent years studied (2017–2019). This finding suggests that it is possible to identify patients <3 years of age hospitalized with uncomplicated CAP who do not require antibiotic treatment.

Factors that appear to have influenced physician decision making regarding the need for antibiotics include antibiotic treatment prior to hospitalization, chest radiograph interpretation, and respiratory virus testing results. A focal finding on chest radiograph and antibiotics started on admission were more common in patients who received a treatment course of antibiotics. Mention of viral process or atelectasis and a positive result on viral testing were associated with a diagnosis of viral pneumonia and no antibiotic treatment. There were no statistically significant differences in antibiotic use by detected virus. There were no active efforts at the study hospital to encourage decreased use of antibiotics for hospitalized children with uncomplicated CAP, and viral testing during that time did not change significantly to affect provider behavior. However, it is possible that growing awareness of studies that report that respiratory viruses cause the majority of pneumonias in young children influenced physician management.

Multiple studies in recent years provide evidence that CAP in this age group is predominantly caused by viruses [6–10]. A 2010 study reported rates of polymerase chain reaction detection of respiratory viruses in 90% of children <3 years of age hospitalized with pneumonia and 52% in a control group [10]. A study conducted in hospitals in 3 US cities using molecular methods reported detection of respiratory viruses and bacteria in 66% and 17%, respectively, of 2222 children with CAP; the preponderance of viruses was more striking in younger children [7]. Detection of respiratory viruses other than rhinovirus occurred in <3% of a control group. A 2017 publication from the same research group focused on viruses and reported respiratory virus detection in 69% of children hospitalized with CAP and 24% of asymptomatic controls [9]. A study from Sweden that compared viral detection rates in children with CAP and controls reported significantly higher rates of infection with influenza, human metapneumovirus (hMPV), and RSV in cases [8]. Similar results were reported in a study from Australia with strikingly increased rates of infection in cases compared with controls for RSV, hMPV, influenza viruses, and adenovirus [6]. Two recent studies in the outpatient setting that compared outcomes for children with CAP according to antibiotic treatment found little or no evidence that antibiotics were beneficial. A 2019 randomized, placebo-controlled clinical trial of "fast-breathing pneumonia" in HIV-uninfected children 2–59 months of age in Africa found that pneumonia resolved in 93% of placebo recipients and 96% of amoxicillin recipients by day 4. There was not a significant difference between groups in overall treatment failure rate up to 14 days [11]. A retrospective, single-institution, emergency department–based study that examined outcomes of CAP in children 3 months to 18 years of age found no difference in treatment failure rates comparing antibiotic treated with untreated patients [12]. Based on these and other reports, the evidence that viruses cause the vast majority of uncomplicated CAP cases in young children is persuasive [13].

Bronchiolitis has clinical features similar to pneumonia. The current study only included bronchiolitis patients who had a diagnosis code for pneumonia. Chest radiographs were obtained in almost every patient in the current study, and misinterpretation of atelectasis as a focus of bacterial infection on chest radiograph could be driving antibiotic use. The American Academy of Pediatrics guideline on bronchiolitis recommends avoiding chest radiographs; decreasing imaging in bronchiolitis could decrease misdiagnosis of bacterial pneumonia and unnecessary antibiotic use [14].

Studies of CAP in children and adults report that measuring serum levels of C-reactive protein and/or procalcitonin may assist in distinguishing bacterial from viral respiratory infections [15, 16]. Wider use of these tests in young children hospitalized with pneumonia may possibly lead to a decrease in unnecessary use of antibiotics. However, neither of these tests were used consistently in the study population, and routine use of these tests has not been endorsed by guidelines. Improved means of identifying children with CAP who do not require antibiotic treatment will have a significant impact on antibiotic stewardship and preventing harm. In a study of hospitalized children treated with antibiotics, adverse events were reported in 21%, and two-thirds of those required further medical intervention [17]. Younger children in particular are at higher risk for antibiotic-associated adverse events [18].

It is important to recognize that the current study was limited to previously healthy inpatients with uncomplicated CAP between 3 and 36 months of age, without recent hospitalizations, chronic lung disease, or immune impairment due to disease or medications. Results should not be used to inform treatment of pneumonia patients who do not meet those criteria. A strength of this study is that we reviewed medical records to confirm that included patients met the guideline definition of CAP and to collect clinical data. We acknowledge limitations of this study, including the possibility that differences in disease severity not documented in the medical record influenced treatment decisions and are a source of bias. The study was conducted at a

single site and is unable to assess hospital-based or regional differences in antibiotic prescribing practices for CAP. This was a retrospective study; a prospective, protocol-driven study would be able to collect more clinical and laboratory findings and study physician decision making.

CONCLUSIONS

Most pneumonia in children <3 years of age is due to viral infection, and recent studies have challenged the idea that antibiotics are necessary in younger patients with CAP. Based on the current study, it appears that a substantial proportion of previously healthy children <3 years of age hospitalized with uncomplicated CAP will do well without antibiotic treatment. This conclusion is also relevant for the outpatient setting where most young children with CAP are managed. Better tools for identifying those who require antibiotics will make it possible to achieve a significant advance in antibiotic stewardship.

Notes

Author contributions. M. E. H. conceptualized and designed the study and the data collection instrument, assembled and analyzed data, drafted the initial manuscript, and approved the final manuscript. R. F. P. conceptualized and designed the study and data collection instrument, contributed to data analysis, and prepared and approved the final manuscript. N. S. designed the data collection instrument, contributed to data collection and analysis, and prepared and approved the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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