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Pediatrics 2012;129;e597; originally published online February 20, 2012;
DOI: 10.1542/peds.2011-1533

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KEY WORDS
clinical practice guideline, community-acquired pneumonia, pediatric

ABBREVIATIONS
3SLS—3-stage least squares regression analysis
ASP—antimicrobial stewardship program
CAP—community-acquired pneumonia
CPG—clinical practice guideline
CXR—chest radiograph
ICD-9-CM—International Classification of Diseases-Ninth Revision-Clinical Modification
IDSA—Infectious Diseases Society of America
VATS—video-assisted thoracoscopic surgery

Dr Newman collected all the data and participated in analysis and interpretation of the data and has been the primary writer of the manuscript; Ms Hedican, Mr Herigon, and Mr Williams participated in the analysis and interpretation of the data and provided critical intellectual content in the revision of the manuscript; Dr Williams and Dr Newland participated in the study design, analysis, and interpretation of the manuscript and provided critical intellectual content in the revision of the manuscript; and all authors approved the final version of the manuscript being submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1533

doi:10.1542/peds.2011-1533

Accepted for publication Nov 17, 2011

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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: Ms Hedican, Mr Herigon, and Dr Newland were supported by a grant from AHRQ (U18-HS10399).

WHAT'S KNOWN ON THIS SUBJECT: Community-acquired pneumonia (CAP) is a common pediatric illness caused by *Streptococcus pneumoniae*. New pediatric Infectious Diseases Society of America CAP guidelines are now available recommending ampicillin as empirical treatment of children hospitalized with uncomplicated CAP.

WHAT THIS STUDY ADDS: This study found that a CAP guideline led to an increase in the narrow-spectrum antibiotic ampicillin. Additionally, an increase in the use of amoxicillin at discharge was observed. Furthermore, change in therapy did not lead to increased adverse outcomes.

abstract

OBJECTIVES: We sought to describe the impact a clinical practice guideline (CPG) had on antibiotic management of children hospitalized with community-acquired pneumonia (CAP).

PATIENTS AND METHODS: We conducted a retrospective study of discharged patients from a children's hospital with an ICD-9-CM code for pneumonia (480–486). Eligible patients were admitted from July 8, 2007, through July 9, 2009, 12 months before and after the CAP CPG was introduced. Three-stage least squares regression analyses were performed to examine hypothesized simultaneous relationships, including the impact of our institution's antimicrobial stewardship program (ASP).

RESULTS: The final analysis included 1033 patients: 530 (51%) before the CPG (pre-CPG) and 503 (49%) after the CPG (post-CPG). Pre-CPG, ceftriaxone (72%) was the most commonly prescribed antibiotic, followed by ampicillin (13%). Post-CPG, the most common antibiotic was ampicillin (63%). The effect of the CPG was associated with a 34% increase in ampicillin use ($P < .001$). Discharge antibiotics also changed post-CPG, showing a significant increase in amoxicillin use ($P < .001$) and a significant decrease in cefdinir and amoxicillin/clavulanate ($P < .001$), with the combined effect of the CPG and ASP leading to 12% ($P < 0.001$) and 16% ($P < .001$) reduction, respectively. Overall, treatment failure was infrequent (1.5% vs 1%).

CONCLUSIONS: A CPG and ASP led to the increase in use of ampicillin for children hospitalized with CAP. In addition, less broad-spectrum discharge antibiotics were used. Patient adverse outcomes were low, indicating that ampicillin is appropriate first-line therapy for otherwise healthy children admitted with uncomplicated CAP. *Pediatrics* 2012;129:e597–e604

Community-acquired pneumonia (CAP) is a common pediatric illness, with estimates that ~2% of children have pneumonia annually.[1–3] Studies have identified *Streptococcus pneumoniae* as the most common bacterial pathogen in children.[4–8] The recently published pediatric CAP guideline recommends the use of ampicillin or ceftriaxone for children admitted with uncomplicated CAP.[9]

Generally, the need for broad-spectrum antibiotics to treat CAP is unnecessary. *S pneumoniae* resistance occurs by changing its penicillin-binding proteins, which can be overcome by high levels of ampicillin. The pharmacokinetics of ampicillin has demonstrated that high lung tissue levels can be attained, which will overcome this resistance.[10] In addition, unnecessary use of broad-spectrum antibiotics has been linked with the development of antibiotic resistance.[11]

At our institution, a clinical practice guideline (CPG) was developed and implemented for otherwise healthy children hospitalized with uncomplicated CAP. CPGs are implemented to standardize practice and improve the quality of care of patients. Adherence to guidelines has been shown to improve patient outcomes, including shorter hospitalizations and decreased morbidity and mortality.[12,13] In addition, our hospital implemented a prospective audit with feedback antimicrobial stewardship program (ASP) 4 months before initiation of the CPG. ASPs have been developed to minimize unnecessary antibiotic use.[14] Both CPGs and ASPs are recommended strategies by the Infectious Diseases Society of America (IDSA) to promote appropriate antimicrobial use.[15]

The primary goal of this CPG was to improve the antibiotic management of children hospitalized with uncomplicated CAP. Key recommendations included empirical treatment with ampicillin (200–300 mg/kg/day), utilization of amoxicillin (80–100 mg/kg/day) at time of discharge, and treatment duration of 5 to 7 days. This study describes the impact our CPG had on the antibiotic management of children hospitalized with uncomplicated CAP.

METHODS

Study Design and Participants

Medical records of patients discharged from Children's Mercy Hospital in Kansas City, Missouri, a tertiary referral hospital, were reviewed retrospectively. Patients who were hospitalized between July 8, 2007, and July 9, 2009, were eligible for inclusion if they had a principal or secondary discharge *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) code of 480 through 486 for pneumonia and received an antibiotic. Accuracy of diagnosis was not evaluated, but instead antibiotic utilization was reviewed based on provider diagnosis of pneumonia. Patients were excluded if they had any of the following characteristics: age <2 months, prematurity <36 weeks' gestation, diagnosed with pneumonia 3 days after admission, immunocompromise, or 1 of the following: congenital heart disease, chronic lung disease (except asthma), sickle cell disease, neurologic condition, or neuromuscular disorder. Patients admitted with an effusion on chest radiograph (CXR) requiring a diagnostic or therapeutic procedure including chest tube, thoracocentesis, or video-assisted thoracoscopic surgery (VATS) were excluded for complicated pneumonia. Patients admitted during the 12-month period from July 8, 2007, until the implementation of the CPG on July 9, 2008, were included in the pre-CPG analysis, while patients admitted during the 12-month period after introduction of the CPG were included in the post-CPG analysis. This study was approved by the institutional review board at Children's Mercy Hospital.

Failure Criteria

Patients included in the study were evaluated for potential treatment failure. A patient was considered to have experienced treatment failure if any of the following 3 situations occurred. First, if a patient was admitted and coverage was broadened after 48 hours of hospitalization based on provider's concern for clinical worsening, the treatment was considered a failure. For patients receiving ampicillin, the broadening to ceftriaxone and/or the addition of *Staphylococcus aureus* coverage (eg, clindamycin or vancomycin) was considered a treatment failure. And for patients receiving ceftriaxone, the addition of *S aureus* coverage was considered a treatment failure. The second situation was if a patient developed a complicated pneumonia after 48 hours of hospitalization as indicated by an effusion, on either CXR, chest ultrasound, or chest computed tomography, requiring a diagnostic or therapeutic procedure including chest tube, thoracocentesis, or VATS. The third situation was if a patient was discharged from the hospital and required readmission or change in antibiotic therapy within 30 days due to continued pneumonia symptoms or development of a complicated effusion/empyema. Finally, the records of included patients with uncomplicated CAP were cross-checked against a list of patients with *ICD-9-CM* codes for complicated pneumonia and effusion (510.0, 510.9, 511.0, 511.1, 511.9, and 513) to ensure no treatment failure was missed.

Data Collection

Charts were abstracted by a single investigator (RN) from the medical record into a standard spreadsheet. Data collected included patient's age and gender, past medical history, admission vital signs, history of fever, cough, upper respiratory infection symptoms,

current antibiotic use, physical examination findings, radiology and laboratory results, and antibiotic treatment choices. Vaccine status was not collected due to our inability to verify its accuracy.

Statistical Analysis

Data differences between the preintervention and postintervention groups were analyzed by using χ^2, t tests, or Wilcoxon rank sum tests. Analyses were performed by using SPSS Base 17.0 (SPSS, Inc, Chicago, IL).

To examine hypothesized simultaneous relationships among increases and decreases in medication use of empirical and discharge antibiotics, 3-stage least squares (3SLS) regressions were estimated by using Stata version 11.1 (Stata Corporation, College Station, TX). 3SLS can be used to estimate a system of structural equations in which a dependent variable in 1 equation can be simultaneously estimated to determine its effects as an endogenous or independent explanatory variable in a second equation.[16] Parameters of these regressions provide estimates of the relative effects of the exogenous or independent variables on the endogenous or dependent variables, specifically the effects of the CPG on the use of the antibiotic. Additionally, an ASP was started in March of 2008 and was included as an additional exogenous variable that could affect the antibiotic management for these children. All equations estimated are in the same form as the following:

$$perceftriaxone = \beta 0 + \beta 1 ceftriaxone + \beta 2 perampicillin + \varepsilon 1 \quad [1a]$$

$$perampicillin = \beta 3 + \beta 4 ampicillin + \beta 5 CPG + \beta 6 ASP + \varepsilon 2 \quad [1b]$$

3SLS was used to compare the effect of the CPG and ASP interventions on the percentage of inpatients empiric treated with ceftriaxone versus ampicillin. The equations simultaneously estimate a model in which 2 dependent (endogenous) variables (percentage of patients using ceftriaxone [perceftriaxone] and percentage of patients using ampicillin [perampicillin]) are hypothesized to be related to each other. In this model, the assumption is that an increase in the percentage of patients using ampicillin will be associated with a decrease in the percentage of patients using ceftriaxone after the implementation of the ASP and CPG. Exogenous (independent or explanatory) variables include number of patients receiving ceftriaxone, number of patients receiving ampicillin, ASP and CPG, 2 estimated constant terms, and error terms. In this equation and the others used, the number of patients receiving a medication is included to control for a possible "scale effect," in which the percentage use of a medication in a hospital by patients is likely to be greater when the number of patient visits is greater.

As noted, 2 other sets of equations were similarly estimated to examine relationships between percentage of patients discharged with amoxicillin or with amoxicillin/clavulanate and between percentage of patients discharged with amoxicillin or with cefdinir.

RESULTS

A total of 1903 charts were reviewed: 976 pre-CPG and 927 post-CPG. Of these, 870 (46%) patients were excluded for the following reasons: prematurity (n = 217, 25%), diagnosis other than CAP (n = 154, 18%), hematology/oncology diagnosis (n = 107, 12%), neurologic disorder/cerebral palsy (n = 97, 11%), chronic lung disease (n = 81, 9%), congenital heart disease (n = 58, 7%), age <2 months or >18 years (n = 49, 6%), genetic disorder/trisomy (n = 33, 4%), incomplete documentation (n = 25, 3%), chronic condition (n = 25, 3%), and other (n = 24, 2%). The remaining 1033 patients were included in the final analysis; 530 pre-CPG and 503 post-CPG.

Overall, patients were similar before and after CPG (Table 1). In both groups,

TABLE 1 Demographic Data and Clinical Characteristics of Children Admitted With Uncomplicated CAP Before and After the Implementation of a CPG

Characteristic	Pre-CPG (n = 530)	Post-CPG (n = 503)	P
Age, median (IQR), y	3.4 (1.6–6.1)	3.3 (1.5–6.2)	.96
Male gender, %	49	52	.38
History of asthma/RAD, %	26	31	.07
Previous pneumonia hospitalization, %	5	8	.07
Mean RR (SD)			
Patient age 2–12 mo	48 (13)	52 (13)	.08
Patient age 1–5 y	41 (13)	41 (12)	.75
Patient age 6–12 y	32 (12)	31 (8)	.51
Patient age 13–18 y	28 (13)	25 (6)	.29
Hypoxic on admission (O_2 saturation <92%), %	11	5	<.01
Admitted on supplemental O_2, %	25	24	.72
History of cough, %	87	87	.99
History of URI symptoms, %	51	49	.46
History of fever, %	88	89	.77
Antibiotic therapy before admission, %	43	34	<.01
Antibiotic treatment before admission (IQR), median d	3 (1–5)	3 (2–5)	.96
Accessory muscle use, %	31	29	.54
Abnormal auscultatory exam findings, %	79	83	.15
Abnormal admit CXR, %	94	96	.20
Admission CXR findings, %			
Focal parenchymal opacity	80	78	.31
Focal parenchymal opacity with effusion	9	11	.33
Blood culture obtained, %	56	54	.42
Median length of therapy, (IQR), d	10 (9-10)	10 (8-10)	.95

IQR, interquartile range; RAD, reactive airway disease; RR, respiratory rate; URI, upper respiratory infection.

the majority of children were aged 1 to 5 years (60% pre-CPG and 59% post-CPG). Additionally, no differences in percentage of fever, cough, and upper respiratory symptoms existed between the groups.

The use of antibiotics before admission was common. Pre-CPG, 225 (43%) children were treated with ceftriaxone (58, 11%), amoxicillin (56, 11%), azithromycin (43, 8%), amoxicillin/clavulanate (43, 8%), and cefdinir (28, 5%). Post-CPG, 173 (34%) children received amoxicillin (55, 11%), azithromycin (39, 8%), ceftriaxone (32, 6%), amoxicillin/clavulanate (24, 5%), and cefdinir (23, 5%).

A major goal of the CPG was to increase the use of ampicillin as the empiric antibiotic in healthy children with uncomplicated CAP. Before the CPG, 13% of patients empirically received ampicillin and 72% received ceftriaxone. In the year after the CPG, 63% empiric received ampicillin and 21% received ceftriaxone (Fig 1).

To determine if the ASP and CPG led to the change in empirical therapy, we evaluated monthly percentage antibiotic utilization in children with uncomplicated CAP (Fig 2). A 3SLS analysis demonstrated that the ASP ($P = .002$) and CPG ($P < .001$) were associated with significant increases in ampicillin use and a significant decrease in ceftriaxone ($P < .001$). The ASP was associated with a 20% increase in ampicillin use, while the inclusion of the CPG was associated with an additional combined increase of 34%. The 3SLS suggests that 47% of decreased ceftriaxone use was due to both the ASP and CPG ($P < .001$).

Not only did the ASP and CPG have a significant impact on the admission antibiotic, they also resulted in a significant change in discharge antibiotic choice. Implementation of the CPG resulted in a significant increase in amoxicillin use ($P < .001$) and a significant decrease in the use of cefdinir ($P < .001$) and amoxicillin/clavulanate ($P < .001$) (Fig 3). The 3SLS analysis of amoxicillin and cefdinir use demonstrated that the ASP resulted in a 22% increase in amoxicillin use ($P = .001$), while inclusion of the CPG increased amoxicillin use by an additional 29% ($P < .001$). The combined effects of the ASP and CPG were associated with a 12% reduction in the use of cefdinir ($P < .001$). Similar results were noted with amoxicillin and amoxicillin/clavulanate utilization. The ASP was associated with a 21% increase in amoxicillin use ($P < .001$), and the CPG led to an additional 28% increase ($P < .001$). The resultant amoxicillin/clavulanate reduction associated with the ASP and CPG was estimated to be 16% ($P < .001$).

Blood cultures were recommended by the CPG to be obtained in all hospitalized children. The number of blood cultures obtained before and after the CPG were similar (56% vs 54%, $P = .4$). Before the CPG, 24 (8%) blood cultures grew an organism with 10 (3%) considered a pathogen (9 *S pneumoniae* and 1 *Streptococcus pyogenes)*. After the CPG, 17 (6%) grew an organism with 13 (5%) considered a pathogen (12 *S pneumoniae* and 1 *S aureus*). Only 1 *S pneumoniae* isolate (post-CPG group) was penicillin resistant (minimal inhibition concentration [MIC] $>$ 8 μg/mL) and the lone *S aureus* isolate was methicillin susceptible.

The negative consequence of recommending treatment with ampicillin was evaluated by assessing the number of treatment failures. Overall, 8 (1.5%) pre-CPG patients and 5 (1%) post-CPG met failure criteria ($P = .28$). Of the 8 failures pre-CPG, 5 developed a complicated pneumonia, 2 were readmitted, and 1 required broadening of therapy for worsening clinical symptoms. Three were initially treated with ampicillin and 5 with ceftriaxone. After the guideline, 5 failures were identified: 4 required broadening of therapy for worsening clinical symptoms and 1 was readmitted. Among the post-CPG failed therapy patients, 4 were treated with ampicillin and 1 with ceftriaxone. No patients with positive blood cultures were identified as a treatment failure.

On admission, CXR with effusion in patients not requiring a drainage procedure occurred in 43 (9%) pre-CPG and 53 (11%) post-CPG children. In the pre-CPG review, 28 patients did not receive an antistaphylococcal antibiotic (eg, vancomycin, clindamycin, amoxicillin/clavulanate); 2 were treated with ampicillin as sole therapy and none met failure criteria. Post-CPG, 39 patients did not receive an antistaphylococcal

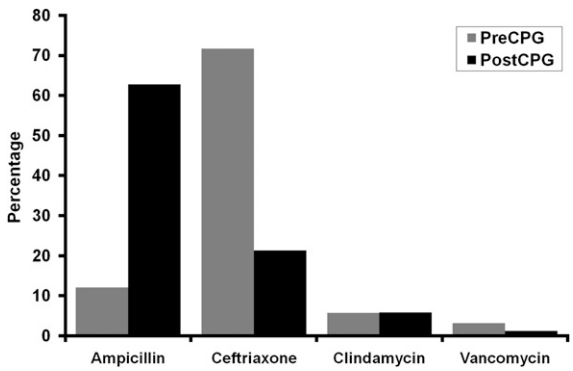

FIGURE 1
Percentage of total patients treated with the 4 most common empiric intravenous antibiotic choices in the pre- and post-CPG groups. Overall, a significant increase in ampicillin and a significant decrease in ceftriaxone were observed.

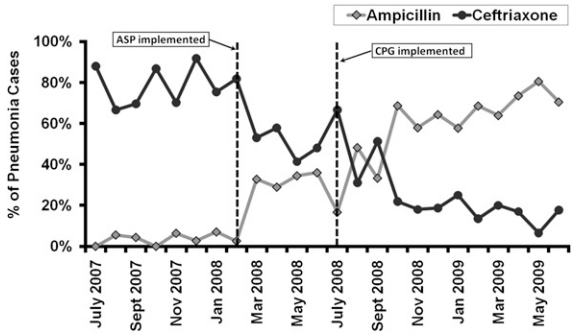

FIGURE 2

Monthly comparisons of the percentage of pneumonia cases empiric treated with ampicillin compared with ceftriaxone during the 24-month evaluation period. The ASP and CPG resulted in a significant increase in ampicillin use and a decrease in ceftriaxone use ($P < .001$).

antibiotic; 26 were treated with only ampicillin and 3 (12%) had failed therapy due to broadening of antibiotic coverage.

DISCUSSION

This is the first study in pediatrics to demonstrate a beneficial impact of a CPG on antibiotic use for healthy children hospitalized with uncomplicated CAP. Furthermore, this is the first study in pediatrics to analyze the impact of an ASP plus a CPG on the use of antibiotics for a common condition. The combined interventions of the ASP and CPG were associated with an increase in empiric prescribing of ampicillin with a subsequent decrease in ceftriaxone. Additionally, narrow-spectrum amoxicillin was prescribed more frequently on discharge than was broader-spectrum amoxicillin/clavulanate or cefdinir. These resultant changes did not lead to an increase in negative consequences.

The use of ampicillin as first-line therapy for CAP appears to be atypical among tertiary care children's hospitals. A study using the Pediatric Hospital Information Systems database observed only 5.5% of children with CAP received this antibiotic.[17] Recently, the Pediatric Infectious Diseases Society and IDSA published a guideline on the management of CAP in children recommending ampicillin in the setting where high-level penicillin resistance is lacking among invasive *S pneumoniae* isolates.[9] During the time after the implementation of the CPG, *S pneumoniae* resistance (minimal inhibition concentration >2 μg/mL) to penicillin at our hospital among invasive isolates was 24% (23 of 95). It is unclear from the guideline to know if this level of resistance is too high for the use of ampicillin. Our study results suggest that even at this level of *S pneumoniae* resistance, the narrow-spectrum agent ampicillin is appropriate in treating uncomplicated CAP in otherwise healthy children. Additionally, the IDSA guideline recommends therapy with a third-generation cephalosporin for patients who are not fully immunized. Our analysis occurred during the routine 7-valent pneumococcal vaccine era; with current routine use of 13-valent vaccine, the impact on invasive pneumococcal disease and the antibiotic resistance of non–PCV-13 serotypes must be monitored as the impact has yet to be determined.

In 2007, the IDSA published a guideline on the development of ASPs for which CPGs were listed as a supplemental strategy to improve the use of antimicrobial agents.[15] A unique aspect of this study was that a prospective-audit with feedback ASP was instituted 4 months prior to the implementation of the CPG. The analysis performed demonstrated the ASP's impact on both empiric and discharge antibiotic prescribing. Although it is not possible to statistically disentangle the effects of the ASP from those of the CPG alone, our findings indicate that while the ASP had an appreciable effect on antibiotic use, the combined effects of an ASP with the CPG had the greatest impact. This is similar to the bundle approaches used in the reduction of surgical site infections and central line–associated bloodstream infections.[18,19] In an era of increased antimicrobial resistance and decreased antimicrobial development, a bundled approach of ASP interventions is likely the best strategy in improving antibiotic utilization.

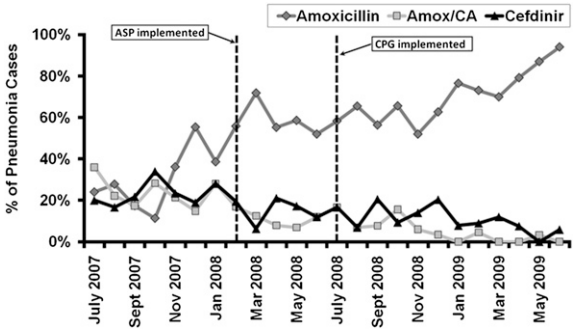

FIGURE 3

Monthly comparison of the percentage of pneumonia cases discharged on amoxicillin, amoxicillin/clavulanate, and cefdinir during the 24-month evaluation period. The ASP and CPG resulted in a significant increase in amoxicillin ($P = .001$) use. The combined ASP and CPG effect led to a reduction in cefdinir ($P < .001$) and amoxicillin/clavulanate use ($P < .001$).

Despite a provider's willingness to empiric treat with ampicillin, recommendations for length of therapy were not followed. A previously published guideline recommended that the length of therapy should be 7 to 10 days or possibly 14 days depending on the patient's response.[20] Importantly, the guideline states that this length was not based on any published clinical trials. Studies from the United States that evaluated antibiotics for the treatment of CAP in children have used 10 days as the standard length of therapy.[21–23] In children, 2 large randomized control trials demonstrated that 3 days of amoxicillin was as effective as 5 days in the treatment of childhood CAP.[24,25] US physicians may not follow conclusions from these studies because they originate from the developing world. Nonetheless, short-course therapy effectively treats CAP in adults[26] as well as many other infections including ventilator-associated pneumonia, hospital-acquired pneumonia, cystitis in adults, pharyngitis, acute otitis media, and cellulitis.[27–32] Because of this, we believe short-course therapy for CAP is still an important recommendation and further research is needed in children to demonstrate this is a safe and effective practice.

Our CPG recommends that blood cultures be obtained on all patients requiring admission. This recommendation was in part based on data identifying a positive blood culture rate up to 6.5% in uncomplicated CAP and up to 25% in complicated cases.[33] Results of our CPG analysis found that our providers did not follow this recommendation and obtained a similar number of blood cultures both before and after the CPG. Speculation for this low compliance is possibly secondary to the high number of patients treated with antibiotics before admission (43% and 34%), making the likelihood of a positive pretreated culture low. Overall, we found 4.9% of blood cultures grew a pathogen, while other studies identified even lower rates ranging from 1.2% to 2.7%.[34–37] Additionally, Shah and colleagues[38] recently found that children with uncomplicated CAP were at low risk for bacteremia. Although the positivity rates are low, the increase in the incidence of invasive disease caused by penicillin-resistant *S pneumoniae* makes this test potentially beneficial.[39,40]

CPGs are evidence-based documents intended to improve outcomes through the standardization of care. While many pediatric CPGs have been developed, only a few have published data on outcomes regarding the use of these guidelines.[41,42] A survey of pediatricians identified that for guidelines to be used, they need to be easy to follow, flexible, and practical, as well as have data demonstrating improved outcomes.[43] It is imperative that an evaluation tool is developed after the implementation of a guideline to determine if a guideline is being used and to assess its impact on the outcomes of interest. At our institution, an evaluation plan was established to determine if the guideline was being used and to ensure that negative consequences did not occur. As the data show, we have been successful in implementing this guideline without negative consequences, but we also have identified areas that we can target to improve care of these children.

One area where improvement can be made includes children who have CAP with effusions. Our retrospective review identified 9% to 11% of patients with a CXR interpretation of effusion. Our CPG has separate recommendations for patients with effusion, including addition of antimicrobial coverage for *S aureus*. We noted a treatment failure of 12% (3 of 26 patients) in the post-CPG group that were empiric treated with ampicillin. This is higher than our study's overall failure rate (1.3%) and highlights the need for *S aureus* coverage in these patients.[44]

Limitations are present in this study. First, this was a retrospective chart review, which prevented us from validating the accuracy of the bacterial pneumonia diagnosis. Second, ICD-9 codes were used to identify patients with suspected uncomplicated CAP. Because these codes include viral pneumonias, it is possible that some of these children did not truly have bacterial pneumonia. However, this study was less concerned with the correct diagnosis and more concerned that clinicians used the recommended antibiotic for the treatment of uncomplicated bacterial CAP. Finally, patients who experienced treatment failure and sought care at other institutions or had primary care physicians expand antimicrobial coverage for continued symptoms were not able to be captured in our analysis. We are the major inpatient admission center for our referral area, so missed patients are likely minimized.

CONCLUSIONS

This study demonstrated the impact that a prospective-audit with feedback ASP and CPG can have on the antibiotic management of children hospitalized with uncomplicated CAP. We showed that these interventions can increase the empirical use of ampicillin as well as amoxicillin for otherwise healthy hospitalized children with uncomplicated CAP without an increase in negative consequences. Because CAP is a common pediatric condition, the use of a narrow-spectrum agent is important in preventing the further development of antibiotic resistance. Second, although providers were willing to follow CPG recommendations for empirical antibiotic choices, other recommendations were not followed, including

length of therapy and obtaining blood cultures. Finally, CPGs should be continually monitored and evaluated to ensure successful implementation, utilization, and revisions when required.

ACKNOWLEDMENTS

We would like to acknowledge the members of the CAP CPG team at Children's Mercy Hospital. We would also like to acknowledge Christopher J. Harrison and Douglas Swanson for their help in providing susceptibility data on Children's Mercy Hospital's invasive *S pneumoniae* isolates.

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Pediatrics 2012;129;e597; originally published online February 20, 2012;
DOI: 10.1542/peds.2011-1533