

Effectiveness of Antimicrobial Guidelines for Community-Acquired Pneumonia in Children

abstract

OBJECTIVE: To assess the effectiveness of guidelines and education on empirical therapy for community-acquired pneumonia.

METHODS: Administrative records for children with a primary diagnosis of pneumonia from January 2007 to September 2009 were reviewed. Antimicrobial use was measured monthly over 3 periods: (1) before creation of an antimicrobial stewardship task force (ASTF), (2) after ASTF formation but before release of guidelines for antimicrobial use, and (3) after guideline release. Antimicrobial use over time was assessed by using quasi-binomial logistic regression models that incorporated interrupted events, seasonality, and autocorrelation. Allowing calculation of immediate changes due to specific interventions and trends in use over each time period. The primary outcome was use of ampicillin as recommended in the guidelines versus ceftriaxone, the historical standard. Secondary outcomes included other antimicrobial use, length of stay, mortality, and readmission.

RESULTS: One thousand two hundred forty-six children met study criteria. Ampicillin use increased from 2% at baseline to 6% after ASTF formation and 44% after guideline release. Ceftriaxone use increased slightly (from 56% to 59%) after ASTF formation but decreased to 28% after guideline release. An immediate change in prescription occurred in the month after guideline publication and remained stable over the following year.

CONCLUSIONS: Guidelines and education can have an impact on antimicrobial use in the pediatric setting. Although the optimal strategies for pediatric antimicrobial stewardship programs still are being determined, we believe that our approach offers an inexpensive and low-risk step in the right direction. *Pediatrics* 2012;129:e1326–e1333

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KEY WORDS

antibiotic use, pneumonia

ABBREVIATIONS

ASP—antimicrobial stewardship program

ASTF—antimicrobial stewardship task force

CAP—community-acquired pneumonia

ICD-9—*International Classification of Diseases, Ninth Revision*

IDSA—Infectious Diseases Society of America

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The prevalence of infections caused by antimicrobial-resistant bacteria is rising, in part because of the inappropriate use of antibiotics. Since 2007, the Infectious Diseases Society of America (IDSA) has formally recommended that hospitals develop antimicrobial stewardship programs (ASPs) to monitor and direct antimicrobial use at the institutional level.¹ Prospective audit with feedback and previous approval are the recommended core strategies for ASPs. These strategies require dedicated personnel that may not be available in all children's hospitals. Indeed, a recent survey of pediatric infectious diseases physicians found that lack of time and funding were the most common barriers to implementing an ASP.² Our institution does not have a prospective audit or previous approval system. As a first step in antimicrobial stewardship efforts, we developed guidelines for empirical antimicrobial use.

Streptococcus pneumoniae is the most common pyogenic bacterial etiology of community-acquired pneumonia (CAP) in children.³ Before the development of our guidelines, ceftriaxone was the standard empirical agent used for uncomplicated CAP in children at our institution. In recent years, ampicillin has re-emerged as the preferred agent for empirical therapy for uncomplicated CAP and is now recommended as first-line therapy in the joint Pediatric Infectious Diseases Society and IDSA clinical practice guidelines.³ As a first step in assessing the effectiveness of our guidelines, which also recommend ampicillin as first-line therapy, we analyzed trends in antimicrobial use for CAP at our institution over a 3-year period, including the formation of a stewardship working group, generation of the guidelines, and public introduction of the guidelines.

METHODS

Setting and Guideline Development

Kosair Children's Hospital is a tertiary-care pediatric center with 263 beds, including a 97-bed NICU and a 26-bed pediatric ICU. Our antimicrobial stewardship task force (ASTF) was formed in October 2007. This multidisciplinary team consists of all pediatric faculty members from the division of infectious diseases and at least 1 faculty member from critical care, emergency medicine, and hospitalist medicine. The chief residents and directors of the medical staff, infection control team, pediatric pharmacy, and microbiology laboratory are also members of the ASTF. Our first goal was to develop guidelines for empirical antimicrobial use for common pediatric presentations. From October 2007 through October 2008 the group met monthly to generate an inclusive list of common diagnoses and discuss appropriate antimicrobial management. In September 2008, the guidelines were sent to division and service chiefs from each medical and surgical specialty for review, resulting in a few minor revisions. An excerpt from this document is presented in Fig 1. Typical pathogens, suggested empirical therapy, alternate agents, and other clinical comments are included for each diagnosis. The guidelines were presented and approved at the hospital Medical Executive Committee in October 2008. Later that month the chair of the ASTF presented the guidelines at departmental grand rounds as part of a lecture on the importance of antimicrobial stewardship. The guidelines were e-mailed to all medical staff and made available on the hospital Intranet. All pediatric residents were provided with electronic and hard copies of the guidelines, and an antimicrobial stewardship lecture was incorporated into the annual resident core curriculum. Our institution does not yet use computerized physician-order entry but

does use several preprinted order sets. The order sets for CAP and rule-out sepsis were aligned with the empirical guidelines in the spring of 2009.

Data Source

Hospital administrative records were reviewed to identify all children with an *International Classification of Diseases, Ninth Revision* (ICD-9) billing code consistent with pneumonia from January 2007 through September 2009. Specific inclusionary ICD-9 codes are presented in Table 1. Only inpatients with a primary ICD-9 diagnosis of pneumonia were included in this study. Because this study focused on empirical use, only antimicrobial agents received during the first 24 hours of hospitalization were included. Children who did not receive an antimicrobial agent within 24 hours of admission were excluded from the analysis. This exclusion validated pneumonia as the primary diagnosis and also reduced the likelihood of children with hospital-acquired pneumonia being included in the study. Because we wanted to ensure that ampicillin monotherapy was not prescribed inappropriately, children with chronic medical conditions were not excluded.

Data Analysis

The main outcome of interest was the use of ampicillin and ceftriaxone. Secondary outcomes included use of other antimicrobial agents (ie, vancomycin, clindamycin, and azithromycin), length of stay, mortality, and readmission within 30 days of initial hospitalization. The proportions of children prescribed each antimicrobial were summarized by month over 3 periods of time: (1) before ASTF formation (January 2007–September 2007), (2) during guideline development (October 2007–October 2008), and (3) after guideline release (November 2008–September 2009). Trends in antimicrobial use over time were assessed with quasi-binomial

Kosair Children's Hospital Empiric Antimicrobial Guidelines (October 2008)

This table, which is based on local antimicrobial susceptibility patterns, provides a guide to the initial selection of antimicrobials in patients who have a high likelihood of infection. Cultures should be obtained from the appropriate sources prior to initiation of antimicrobial therapy, except when this will cause a delay in treatment that may harm the patient. Culture results should be used to guide definitive therapy. Previous culture results and the patient's antimicrobial history should be reviewed. Antimicrobials may not be necessary, or drug selections may need to be modified, depending on the particular medical situation.

The table is organized by organ system and site of infection, with the exception of fever syndromes and neonatal infections, which are contained in a separate section at the end.

Diagnosis or Clinical Scenario	Common Pathogens (in order of likelihood)	Preferred Drug(s)	Alternative Drug(s)	Comments
Respiratory Tract (continued)				
Community-acquired pneumonia				
Lobar, without effusion	<i>S pneumoniae</i> <i>H influenzae</i>	ampicillin	ceftriaxone	MSSA and MRSA rarely implicated
Lobar, with effusion	<i>S pneumoniae</i> MSSA or MRSA group A streptococcus	clindamycin plus ceftriaxone		Consider Pediatric Surgery consult
Atypical, infant	<i>C trachomatis</i> <i>B pertussis</i>	azithromycin		
Atypical, age ≥5 yr	<i>M pneumoniae</i> <i>C pneumoniae</i>	azithromycin	doxycycline	Consider mycoplasma PCR throat swab Atypical pneumonia is unusual between infancy and 4 yr of age
Viral	Influenza virus	oseltamivir		Send rapid influenza antigen and VRP Treat only influenza-positive patients when: – age >1 yr and – symptoms <48 hr or immunocompromised or patient in ICU

FIGURE 1

Excerpt from empirical guideline. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; VRP, viral respiratory panel.

logistic regression models that incorporated the effect of interrupted events and accounted for seasonality and autocorrelation.⁴ These models allowed for calculation of immediate changes due to specific interventions and trends in use of each antimicrobial agent during the 3 different time periods. Results from these models are presented as odds ratios. The odds ratios for immediate changes represent the odds of prescription in a month immediately after an intervention (ie, guideline release) as compared with the odds of prescription in the preceding month. The odds ratios for trends represent the odds of prescription for each month in a given interval as compared with the previous month. Trends are modeled to be constant across each interval and therefore assess patterns of antimicrobial prescribing over time after a given intervention.

The full model included terms for trend for each time period, immediate change due to each intervention, and seasonality. A reduced model with insignificant terms removed was compared with the full model, with these terms included using the deviance test. This process was repeated, with higher-order terms being removed first, until a final model was selected. Autocorrelation was assessed by using the Durbin-Watson statistic.^{5,6} Further details of our statistical modeling have been reported separately.⁷ All analyses were performed by using the statistics software package R, version 2.10.1 (<http://www.r-project.org>) and Stata version 11 (StataCorp, College Station, TX). This quality improvement project was approved by the institutional review board at the University of Louisville.

RESULTS

An ICD-9 code consistent with pneumonia was listed for 2320 hospitalizations during the study period. Of these, 1373 (59%) represented a primary diagnosis (Fig 2). One hundred twenty-seven children were excluded because they did not receive antibiotics during the first 24 hours of hospitalization, leaving a final sample size of 1246. Among children with a primary diagnosis of pneumonia, the most common ICD-9 code was 486, "pneumonia; organism nos," which was associated with 1101 admissions (88.4%). Forty-four hospitalizations (3.5%) received ICD-9 code 482.9, "bacterial pneumonia nos," 32 (2.6%) received the code 482.1, "pseudomonal pneumonia," and 26 (2.1%) received the code 481, "pneumococcal pneumonia." All other ICD-9 codes were associated with <1% of admissions.

TABLE 1 ICD-9 Codes Used to Identify Patients With Pneumonia

ICD-9	Diagnosis
481	Pneumococcal pneumonia
482	Other bacterial pneumonia
482.1	Pseudomonal pneumonia
482.2	H. influenzae pneumonia
482.3	Streptococcal pneumonia
482.30	Streptococcal pneumonia NOS
482.31	Pneumonia due to Streptococcus A
482.32	Pneumonia due to Streptococcus B
482.39	Pneumonia other streptococci
482.4	Staphylococcal pneumonia
482.40	Staphylococcal pneumonia NOS
482.41	<i>Staphylococcus aureus</i> pneumonia
482.42	Methicillin-resistant pneumonia due to staphylococci
482.49	Staphylococcal pneumonia NEC
482.8	Bacterial pneumonia NEC
482.83	Pneumonia due to other gram-negative bacteria
482.89	Pneumonia due to other specific bacteria
482.9	Bacterial pneumonia NOS
486	Pneumonia; organism NOS
510.0	Empyema
510.9	Empyema without fistula
511.1	Bacterial pleural effusion/not due to tuberculosis

NEC, not elsewhere classified; NOS, not otherwise specified.

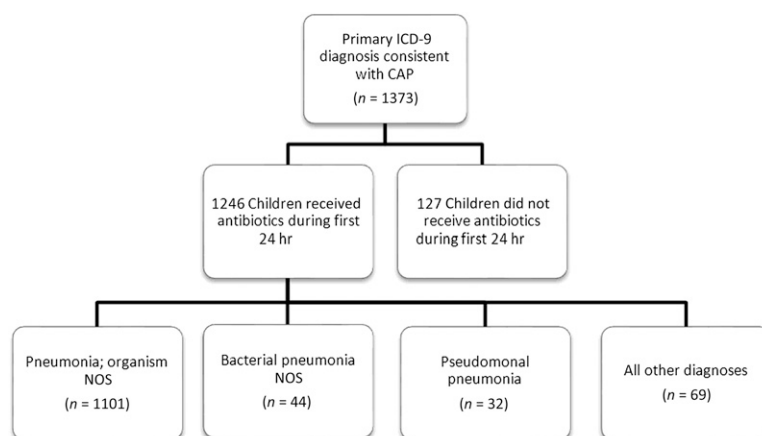


FIGURE 2

Breakdown of patients with a primary diagnosis of CAP. NOS, not otherwise specified.

Trends in ceftriaxone and ampicillin use by month are depicted graphically in Fig 3. Ampicillin use increased from 2% before guideline release to 8% during guideline formation and 44% after guideline release. Ceftriaxone use increased slightly from 56% to 59% during guideline formation and then fell to 28% after guideline release. Trends in vancomycin use are presented in Fig 4. Vancomycin use decreased from 10.0% to 6.7% after ASTF formation, and it decreased to 4.7% after guideline release.

There were no statistically significant changes in use of clindamycin (12.0% to 8.0% to 10.3%) or azithromycin (20.9% to 20.8% to 16.8%) during the overall study period (Fig 5).

The results of the final quasi-binomial logistic regression model are presented in Table 2. Use of ampicillin and ceftriaxone were increasing in the 9 months before ASTF formation. There were no immediate changes in prescription of either antibiotic after ASTF formation. During the guideline-formation

period ceftriaxone use was slightly decreasing while ampicillin use continued to increase. After guideline release, there was an immediate and statistically significant increase in ampicillin use and an immediate and statistically significant decrease in ceftriaxone use. In the 11 months after guideline release, there were no significant changes in use of either drug.

Use of vancomycin fluctuated during the study period. The final model demonstrates that the use of vancomycin was slightly increasing during each study period, but that this increase was more than offset by immediate decreases associated with ASTF formation and guideline release. The net result is an overall decrease in usage. Although clindamycin usage did not change overall during the 3-year study period, there were immediate decreases associated with ASTF formation and guideline release offset by increasing use during guideline development and after guideline release. Azithromycin use remained stable during each study period.

There were no adverse events in the study population associated with the antimicrobial change from ceftriaxone to ampicillin as recommended by the guidelines. Specifically, there were no deaths, and there was no difference in mean length of stay before (3.11 days) and after (3.13 days) guideline release. Nineteen children were readmitted within 30 days of hospital discharge; 5 in the pre-ASTF period, 7 during guideline development, and 7 after guideline release. Seventeen of 19 had underlying asthma or chronic lung disease. One otherwise healthy patient was discharged on oral cefdinir after 6 days of treatment with ceftriaxone. He was readmitted the following day owing to increased work of breathing and completed a 10-day course of ceftriaxone. The other previously healthy patient received intravenous ceftriaxone and was

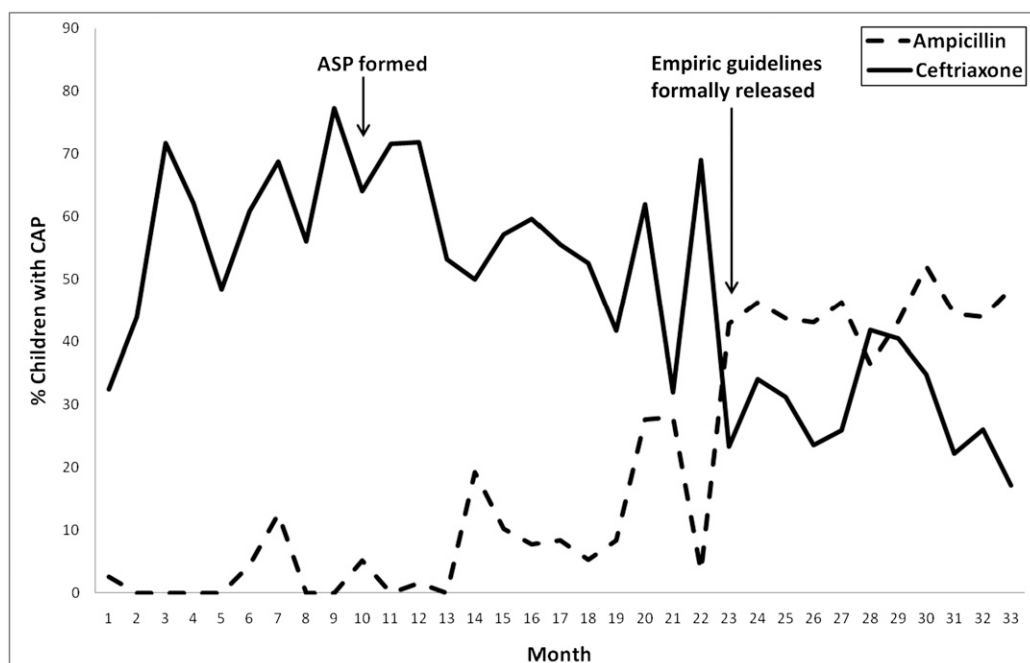


FIGURE 3
Ampicillin and ceftriaxone use by month, January 2007 to September 2009.

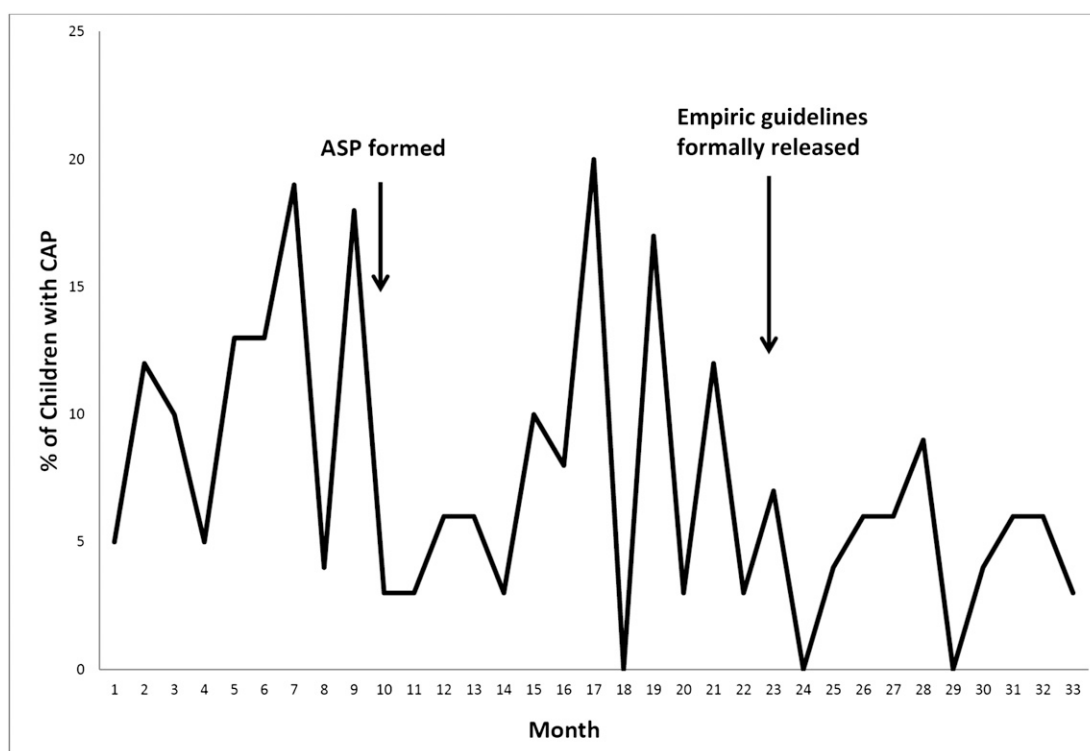


FIGURE 4
Vancomycin use by month, January 2007 to September 2009.

discharged on oral amoxicillin. He was readmitted 2 days after discharge owing to a pleural effusion and underwent video-assisted thorascopic surgery.

We also reviewed medical records of children with ICD-9 codes representing diagnoses that would not have been treated adequately with ampicillin

monotherapy. Among the 32 children discharged with a primary ICD-9 code of 482.1, “pseudomonal pneumonia,” post-hoc analysis revealed that this group

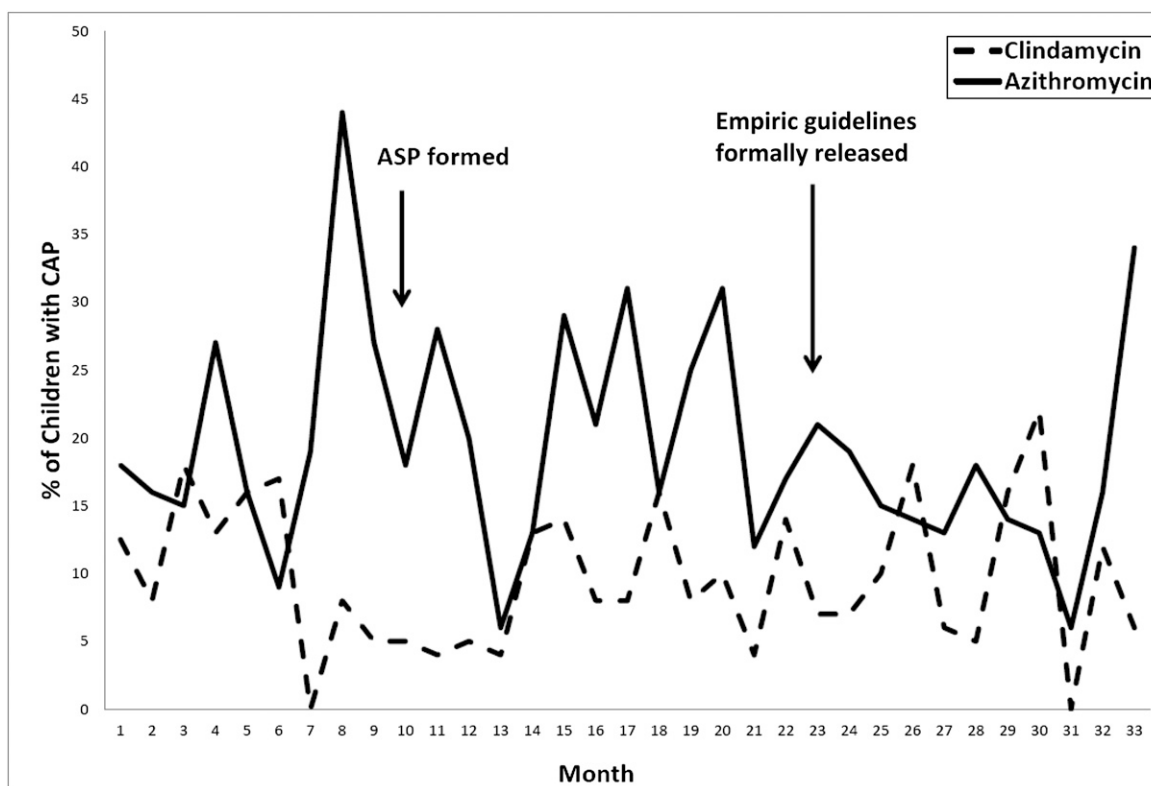


FIGURE 5
Clindamycin and azithromycin use by month, January 2007 to September 2009.

included 17 patients with cystic fibrosis, 14 patients with tracheostomy, and 1 patient with chronic lung disease. Twenty-nine were started appropriately on empirical antipseudomonal therapy. Two patients were switched to appropriate therapy after a tracheal culture sample grew *Pseudomonas*. The third patient did not receive empirical therapy because the isolate was deemed to

represent colonization rather than infection by an infectious diseases consultation on the day of admission.

Of 19 children with a discharge diagnosis consistent with staphylococcal pneumonia, 14 started treatment with empirical antistaphylococcal therapy. Four were switched appropriately after results of tracheal culture samples were known. The last child never had

microbiologic confirmation of *Staphylococcus aureus* infection but was empirically switched to clindamycin on hospital day 3 after infectious diseases consultation because of persistent fever. All 16 children with an administrative code consistent with empyema received antistaphylococcal therapy (either clindamycin or vancomycin) on the day of admission.

TABLE 2 Odds Ratios and 95% Confidence Intervals (CIs) for Antibiotic Prescription at Various Time Points From January 2007 Through September 2009

Antibiotic	Baseline Trend ^a Before ASTF Formation		Immediate Change ^b Due To ASTF Formation		Trend During Guideline Development		Immediate Change Due To Guideline Release		Trend After Guideline Release	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Ampicillin	1.18	1.10–1.28	NS	—	1.18	1.10–1.28	2.93	1.37–6.28	NS	—
Ceftriaxone	1.11	1.03–1.20	NS	—	0.94	0.89–0.99	0.39	0.21–0.74	NS	—
Vancomycin	1.06	0.99–1.14	0.47	0.14–0.89	1.06	0.99–1.14	0.33	0.12–0.94	1.06	0.99–1.14
Clindamycin	NS	—	0.43	0.24–0.78	1.09	1.02–1.16	0.43	0.17–1.06	1.09	1.02–1.16
Azithromycin	NS	—	NS	—	NS	—	NS	—	NS	—

Interventions during this period include ASTF formation (October 2007) and guideline release (October 2008). NS, terms not significantly different from those that were excluded from the final model.

^a A “trend” is the ratio of the odds of prescription in month M + 1 of a given interval to the odds in month M. It is constant across the interval and is linear on the log odds ratio scale during the specified time interval.

^b An “immediate change” is the ratio of the odds of prescription in the month immediately after an intervention (such as the initiation of ASTF formation) to the odds in the month immediately before the intervention.

DISCUSSION

There were statistically significant changes in prescription patterns of ampicillin and ceftriaxone for CAP associated with the development of our ASTF. These changes began with ASTF formation, were most pronounced after guideline release, and remained stable during the first year after guideline release. Our use of time-series analyses with multiple data points suggests that these changes in clinical practice were likely due to our intervention and not to secular changes alone. There were no adverse events associated with guideline implementation.

Although IDSA recommendations call for ASPs with prospective audit with intervention and feedback or formulary restriction and preauthorization,¹ many centers do not have sufficient time or funding to implement them.^{2,8} Although the optimal strategies for pediatric ASPs remain to be elucidated, our data suggest that clinical guidelines and educational campaigns created by a multidisciplinary team can have a significant impact on antimicrobial use. At a minimum, such strategies can serve as an important first step in antimicrobial stewardship. Our intervention incurred little risk or cost and was associated with a 50% decrease in ceftriaxone use. Two recent nationally representative studies have estimated rates of childhood hospitalization for pneumonia to be 199 to 281 per 100 000 children each year.^{9,10} From this perspective, even a modest decrease in cephalosporin use for children hospitalized with pneumonia would have a significant impact at the population level.

Loss of provider autonomy has been reported to be a barrier to ASP development.² We included physicians from multiple pediatric subspecialties on our ASTF, and we believe this effort was an important part of guideline acceptance. Ampicillin use increased after our ASTF

formation but before the empirical guidelines were released publicly, which suggests that our group was effective in engaging key stakeholders in antibiotic prescribing before the guidelines became official hospital policy. Easy accessibility of the guidelines to residents and faculty likely contributed to compliance as well. A previous study demonstrated that the introduction of laminated cards with antimicrobial recommendations clipped onto a hospital identification badge resulted in a statistically significant increase in appropriate antimicrobial use for pneumonia although identical guidelines were available elsewhere.¹¹ Although we did not formally survey the pediatric residents, most of them carry hard copies of the guidelines with them when they are on-call.

One of the strengths of this study is its methodology. Quasi-experimental study designs offer strong epidemiological evidence for effectiveness when randomization is not possible.¹² Our use of multiple time points before and after the intervention controls for underlying secular trends and regression to the mean.¹³ We also evaluated use of azithromycin, which was not a direct target of our intervention. Although azithromycin is recommended as therapy for atypical pneumonia in our guidelines, this recommendation was not a change from previous clinical practice. There were no changes in azithromycin usage across the overall study period or at any of the intervention points, offering further evidence that the observed change in antimicrobial therapy was not due to underlying secular trends.

Our use of administrative data introduces some limitations. Medical records were not reviewed to confirm the diagnosis of pneumonia for all children included in the study; however, because this study was designed to assess the

choice of empirical therapy, rather than validate the diagnosis of pneumonia, this limitation is less relevant to the study objectives. Additionally, our choice of administrative codes included children with cystic fibrosis, tracheostomy-associated infections, and other chronic medical conditions. Ideally, such children would be excluded from studies of guideline effectiveness. For this initial quality improvement project, however, it was important to ensure that such children were not treated inappropriately with ampicillin monotherapy. None of the patients with the diagnosis of pseudomonal pneumonia received ampicillin during the study period. The inclusion of children with chronic medical conditions made our guidelines only appear to be less effective. Post-hoc analysis excluding 233 children with multiple admissions for pneumonia had a small favorable effect; ampicillin use after guideline release increased to 47% as compared with 44%, by using the entire database.

As with any single-center study, these results may not be generalizable to other institutions. Although our guidelines and study methodology may be replicated by using the data presented here, other factors such as local leadership, culture, and traditions may not.¹⁴ We are fortunate to have the support of hospital administration and medical staff and included administrators and senior clinicians in the guideline development process. We suspect that “buy-in” of these key opinion leaders played an important role in our success.¹⁵ Additionally, although the infectious diseases faculty members are not involved in the care of patients with uncomplicated CAP, they are highly visible during patient care and resident education activities on a daily basis. These factors may have made our stewardship efforts more effective. Nevertheless, our hospital is likely more representative of

other children's hospitals in the United States than those with published descriptions of their pediatric ASPs. For instance, a successful ASP at a large tertiary-care pediatric hospital is managed by 2 doctoral-level clinical pharmacists with postgraduate training in pediatrics and infectious diseases during business hours and infectious diseases fellows during nights and weekends.¹⁶ Such personnel

may not be available at many children's hospitals.

CONCLUSIONS

This study demonstrates that guidelines and educational campaigns can have an impact on antimicrobial use in the pediatric setting. It has been suggested that nonmandatory changes are short-lived, but the impact of our guidelines was

still observed 1 year after introduction. Future studies to assess the longer-term impact of our guidelines for pneumonia and other clinical presentations are ongoing. Although the optimal strategies for pediatric antimicrobial stewardship are still being determined, we believe our approach offers a low-risk step in the right direction for centers that currently lack the time and resources to develop a formal ASP as outlined by the IDSA.

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