Antimicrobial Stewardship Programs in Freestanding Children’s Hospitals

Adam L. Hersh, MD, PhD; Stephen A. De Lurgio, PhD; Cary Thurm, PhD; Brian R. Lee, PhD; Scott J. Weissman, MD; Joshua D. Courter, Pharm D; Thomas V. Brogan, MD; Samir S. Shah, MD, MSCE; Matthew P. Kronman, MD, MSCE; Jeffrey G. Gerber, MD, PhD; Jason G. Newland, MD, ME

BACKGROUND AND OBJECTIVE: Single-center evaluations of pediatric antimicrobial stewardship programs (ASPs) suggest that ASPs are effective in reducing and improving antibiotic prescribing, but studies are limited. Our objective was to compare antibiotic prescribing rates in a group of pediatric hospitals with formalized ASPs (ASP+) to a group of concurrent control hospitals without formalized stewardship programs (ASP\textsuperscript{2}).

METHODS: We evaluated the impact of ASPs on antibiotic prescribing over time measured by days of therapy/1000 patient-days in a group of 31 freestanding children’s hospitals (9 ASP+, 22 ASP\textsuperscript{2}). We compared differences in average antibiotic use for all ASP+ and ASP\textsuperscript{2} hospitals from 2004 to 2012 before and after release of 2007 Infectious Diseases Society of America guidelines for developing ASPs. Antibiotic use was compared for both all antibacterials and for a select subset (vancomycin, carbapenems, linezolid). For each ASP+ hospital, we determined differences in the average monthly changes in antibiotic use before and after the program was started by using interrupted time series via dynamic regression.

RESULTS: In aggregate, as compared with those years preceding the guidelines, there was a larger decline in average antibiotic use in ASP+ hospitals than in ASP\textsuperscript{2} hospitals from 2007 to 2012, the years after the release of Infectious Diseases Society of America guidelines (11% vs 8%, P = .04). When examined individually, relative to preimplementation trends, 8 of 9 ASP+ hospitals revealed declines in antibiotic use, with an average monthly decline in days of therapy/1000 patient-days of 5.7%. For the select subset of antibiotics, the average monthly decline was 8.2%.

CONCLUSIONS: Formalized ASPs in children’s hospitals are effective in reducing antibiotic prescribing.

WHAT’S KNOWN ON THIS SUBJECT: Antibiotic overuse is common and is a major public health threat. The prevalence of antimicrobial stewardship programs in children’s hospitals is growing. Single-center studies reveal that antimicrobial stewardship programs are effective in reducing unnecessary antibiotic use. Multicenter evaluations are needed.

WHAT THIS STUDY ADDS: Antibiotic use is declining overall across a large network of freestanding children’s hospitals. Hospitals with formalized antimicrobial stewardship programs experienced greater reductions in antibiotic use than other hospitals, suggesting that these interventions are an effective strategy to address antibiotic overuse.
Antibiotics are prescribed during more than 50% of hospitalizations for children, often unnecessarily. This misuse contributes to avoidable adverse events and costs and is an important driver of antibiotic resistance, which is a growing global health and economic threat. Antimicrobial stewardship programs (ASPs) are multidisciplinary, hospital-based interventions designed to ensure that antibiotics are prescribed appropriately to improve patient outcomes and minimize unnecessary costs. The Centers for Disease Control and Prevention, multiple professional organizations including the Infectious Diseases Society of America (IDSA) and The Pediatric Infectious Diseases Society, and a recent report from the President’s Council of Advisors on Science and Technology recommend that all acute care hospitals implement ASPs to help mitigate the harms of antibiotic overuse.

In 2007, the IDSA published Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship and identified pediatrics as a priority area for further research about the effectiveness of stewardship activities. After the release of these guidelines, the number of ASPs has grown substantially in pediatrics and grown substantially in pediatrics and medications prescribed.

Study Design and Data Source
This retrospective, multicenter cohort study used interrupted time-series (ITS) analysis with a concurrent control group to evaluate the impact of ASPs on antibiotic use for hospitalized children. We used data from the Pediatric Health Information System (PHIS), an administrative database representing 44 freestanding children’s hospitals affiliated with the Children’s Hospital Association. The hospitals contributing data to PHIS have broad geographic representation, including 17 of the 20 largest US metropolitan areas. The Children’s Hospital Association and participating hospitals collaborate to ensure data reliability and quality. Data elements for each hospital discharge include discharge diagnoses, patient demographic characteristics, procedures performed, tests used, and medications prescribed.

Study Population and Exposure Groups
This study included children discharged from a subgroup of PHIS hospitals. A previous study included 38 PHIS hospitals and determined whether each had a formalized ASP as of 2011 based on a specified definition, and if so, the date of program initiation. An ASP was defined as “a comprehensive program that functions continuously to monitor antimicrobial use and that dedicates full-time equivalents to support a clinical pharmacist and/or pediatric infectious diseases specialist.” In that study, 16 hospitals had an ASP (ASP+) and 22 hospitals did not (ASP−). For the current study, the 2 exposure groups were hospitals with or without ASPs. We included all ASP− hospitals; however, to have sufficient data for ITS analysis, we only included ASP+ hospitals that had 12 months or more of data after ASP implementation. Thus, the current study included 31 hospitals from the initial group of 38 hospitals where ASP status was known (82%), including 9 of 16 ASP+ hospitals and all 22 ASP− hospitals. All of these ASP+ hospitals began their program after publication of the 2007 IDSA guidelines.

Antibiotic Use
To evaluate trends in antibiotic use, we used days of therapy per 1000 patient-days (DOT/1000 pt-days) as the metric. DOT is calculated as the aggregate sum of antibiotics used per patient per day; a child given ampicillin and gentamicin daily for 2 days would contribute a total of 4 DOT (2 DOT for each day). For each hospital, we calculated the actual antibiotic DOT/1000 pt-days monthly during the study period based on medication charges recorded in PHIS. “All antibiotics” included any antibiotic with intravenous, oral, or intramuscular routes of administration and excluded topical antimicrobial agents, systemic antifungal agents, and antiviral agents. We also examined a subset of “select antibiotics,” which included intravenous vancomycin, carbapenems (meropenem, imipenem, and ertapenem), and linezolid. These 3 classes were chosen because they are monitored nearly universally by ASP+ hospitals. We hypothesized that ASP interventions might lead to greater changes for select compared with all antibiotics, which includes several antibiotics that are not often monitored by ASPs.

Aggregate Analysis Comparing ASP+ and ASP− Hospitals
To understand secular patterns for antibiotic use across study hospitals,
we examined and compared combined monthly antibiotic use between ASP+ and ASP− hospitals from January 2004 (date of complete pharmacy data in PHIS) through December 2012. Rates of antibiotic use for both all and select antibiotics, as measured in DOT/1000 pt-days, were combined and averaged each month and compared between ASP+ and ASP− hospitals.

Outcomes for Aggregate Analysis

We compared trends of aggregate antibiotic use between ASP+ and ASP− hospitals during 2 time periods. Because the ASP− hospitals did not have a specified intervention date, we selected January 2007, the month after the release of the IDSA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship.3 We compared the average antibiotic use between ASP+ and ASP− hospitals as measured by the monthly DOT/1000 pt-days before and after January 2007. All of the ASP+ hospitals started their programs after 2007.7

Hospital Specific Analysis of ASP+ Hospitals

For individual ASP+ hospitals, we examined monthly antibiotic prescribing trends before and after the specific date of program implementation. For each ASP+ hospital, the preintervention period is between January 2004 and the date that their ASP was started, allowing the preintervention period to differ for each ASP+ hospital. For example, if a program was initiated in January 2009, the preintervention period is January 2004 through December 2008. The postintervention period starts at the date of program initiation (minimum 12 months). Using ITS methods,13,14 we modeled pre- and postintervention patterns of antibiotic use at each hospital. This process first involved fitting models to the preintervention period to predict the postintervention DOTs based on preintervention trends, as if an ASP had not been introduced. The next step calculated the differences between the predicted and actual antibiotic DOT during the postintervention period; this served as an estimate of the impact of the intervention. We incorporated multiple contemporary and lagged covariates including concomitant antibiotic use in ASP− hospitals, median patient age, presence of complex chronic conditions, days in the ICU, and overall case mix index as a measure of illness severity. Additionally, we accounted for the patterns of autoregression, moving averages, seasonality, and overall trends in antibiotic use.

Outcomes for Hospital Specific Analysis

For each ASP+ hospital, the primary outcomes are the percentage change for both all and select antibiotics in the postintervention period relative to preintervention trends measured in DOT/1000 pt-days. For example, if the preintervention trend predicted a level of 600 DOT/1000 pt-days and the actual postintervention level was 500 DOT/1000 pt-days, the percentage change would be −17% (100/600). Additionally, we calculated the average percentage change for all ASP+ hospitals combined.

Statistical Analysis

For aggregate analyses that summed usage across each hospital group, the average antibiotic use rates (measured as DOT/1000 pt-days for all and select antibiotics) before and after IDSA guidelines were released were compared by using t tests. For the hospital specific analyses, we used ITS with dynamic regression.13,14 We used P < .05 as a threshold for statistical significance. All statistical analyses and models were estimated by using SPSS 21 (IBM SPSS Statistics, IBM Corporation) and ForecastPro 6.0 (Business Forecast Systems, Inc, Belmont, MA).

RESULTS

Table 1 compares characteristics of the 9 ASP+ hospitals to the 22 ASP− hospitals included in the study. In general, ASP+ and ASP− hospitals were similar. However, ASP+ hospitals had more total beds, a higher percentage of hospital days in the ICU, and a higher volume of solid organ transplants performed.

Aggregate Analysis Comparing ASP+ and ASP− Hospitals

Figure 1 illustrates trends in aggregated monthly values for all and select antibiotic use, measured as DOT/1000 pt-days, for 9 ASP+ and 22 ASP− study hospitals from 2004 to 2012. After the release of the IDSA guidelines in 2007, there is a notable decline in all and select antibiotic use in both ASP+ and ASP− hospitals.

### Table 1 Demographics of Study Hospitals With and Without ASPs in 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospitals Without ASP, n = 22</th>
<th>Hospitals With ASP, n = 9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total beds</td>
<td>252 (219–287)</td>
<td>316 (286–348)</td>
<td>.019</td>
</tr>
<tr>
<td>Case Mix Index</td>
<td>2.4 (2.1–2.6)</td>
<td>2.5 (2.3–2.8)</td>
<td>.157</td>
</tr>
<tr>
<td>Total patient days</td>
<td>77 326 (57 497–92 811)</td>
<td>78 744 (77 100–86 183)</td>
<td>.306</td>
</tr>
<tr>
<td>Percent NICU days</td>
<td>21.2 (14.6–28.8)</td>
<td>18.8 (14.7–25.4)</td>
<td>.744</td>
</tr>
<tr>
<td>Percent PICU days</td>
<td>11.5 (9.0–15.7)</td>
<td>16.1 (15.0–22.8)</td>
<td>.022</td>
</tr>
<tr>
<td>Percent surgical patients</td>
<td>23.3 (21.5–26.1)</td>
<td>24.0 (22.0–26.2)</td>
<td>.557</td>
</tr>
<tr>
<td>Solid organ transplants</td>
<td>10 (1–43)</td>
<td>18 (9–38)</td>
<td>.471</td>
</tr>
<tr>
<td>Bone marrow transplants</td>
<td>30 (4–47)</td>
<td>31 (31–34)</td>
<td>.76</td>
</tr>
<tr>
<td>Census region, no. (%) of hospitals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>2 (9.1)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>8 (36.4)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td>North central</td>
<td>6 (27.3)</td>
<td>5 (55.6)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>6 (27.3)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

Data are median value (interquartile range).
All Antibiotic Use

In the years before guideline release in 2007, a period during which no ASP+ hospitals had started programs, there was no difference in average antibiotic DOT/1000 pt-days between ASP+ and ASP− hospitals (775 vs 771 DOT/1000 pt-days; \( P = .40 \)). After the guidelines were released, ASP+ hospitals experienced a greater decline in use of all antibiotics than observed in ASP− hospitals; the decline was 11% in ASP+ compared with 8% in ASP− hospitals (\( P = .04 \)). Changes in both ASP+ and ASP− hospitals were significant compared with previous years (\( P < .001 \) for both).

Select Antibiotic Use

In years before 2007, use of select antibiotics was nearly identical in ASP+ and ASP− hospitals (115 vs 114 DOT/1000 pt-days; \( P = .80 \); Fig 1). After the IDSA guidelines were released in 2007, use of select antibiotics in ASP+ hospitals declined by 4% to an average of 110 DOT/1000 pt-days (\( P = .06 \)), whereas minimal change occurred in ASP− hospitals (115 DOT/1000 pt-days; \( P = .67 \)).

Hospital Specific Analysis of ASP+ Hospitals

All Antibiotic Use

The average percent changes in all antibiotic DOT/1000 pt-days for each of the 9 ASP+ hospitals relative to what was predicted based on preintervention trends are summarized in Fig 2A. These values ranged from −11.4% to +7.0%; 8 of 9 (89%) ASP+ hospitals had percentages <0%, indicating that during the postimplementation period, actual antibiotic DOT/1000 pt-days was lower than predicted from the preintervention period. A representative example for 1 hospital is shown in Fig 3. For this hospital, the reduction in DOT/1000 pt-days during the postintervention period for all antibiotics was −8.7%. When all 9 ASP+ hospitals were combined, the average percentage change in DOT/1000 pt-days was −5.7% (95% confidence interval: −4.3% to −7.2%).

Select Antibiotic Use

The average percentage change in select antibiotic DOT/1000 pt-days relative to predicted trends from the preintervention period for the 9 ASP+ hospitals is shown in Fig 2B. Percentage change values ranged from −25.5% to +28.5%. When combined, the average percentage change in select antibiotic use was −8.2% (95% confidence interval: −6.75% to −9.7%).

DISCUSSION

After release of the IDSA guidelines for ASPs in 2007, overall antibiotic use decreased throughout a network of freestanding children’s hospitals, in both hospitals with and without ASPs. However, these changes were more pronounced among those hospitals that established formalized ASPs during this period compared with those that did not. Relative to trends before program initiation and accounting for concurrent secular trends, overall antibiotic use declined more than was expected in nearly 90% of hospitals after starting an ASP, with an average reduction of 6% relative to previous antibiotic use patterns. This decline was greater for a select group of antibiotics (vancomycin, carbapenems, linezolid) that are universally monitored in these programs. These findings suggest that formalized ASPs in freestanding children’s hospitals are effective in reducing antibiotic usage in postintervention months, particularly for antibiotics that are routinely monitored.

Our study has several strengths. Most notably, we examined the impact of ASP initiation in a sample of 9 freestanding children’s hospitals. This multicenter evaluation of antibiotic use after ASP implementation provides strong evidence that ASPs are effective in reducing antibiotic use. Our study is further strengthened, especially compared with single-center studies, by the use of ITS with a large number of pre- and
postintervention data points and a group of concurrent control hospitals to account for simultaneous secular trends in antibiotic use. Because there may be important between-hospital differences in case-mix that could influence antibiotic prescribing practices, we accounted for several potential confounders, including the prevalence of comorbid conditions and critical illness at each hospital.

Our findings are generally similar to and build on the existing evidence-base of previously published studies in single-centers that examined the impact of pediatric ASPs. Newland et al.\textsuperscript{11} reported a decline of 7% in overall DOT/1000 pt-days after implementing an ASP compared with control hospitals within the PHIS network. This previous study, however, was limited in that the control hospitals included all other hospitals within PHIS and did not distinguish between those controls with and without ASPs. Based on the current findings, the design used by Newland et al.\textsuperscript{11} may have had the effect of blunting the actual estimated impact of their stewardship program in that hospitals with formalized ASPs appear to experience greater declines in antibiotic use compared with those without programs. Di Pentima et al.\textsuperscript{10} reported a significant decline in antibiotic use after implementing an ASP, with a reduction of \(~30\%) in overall antibiotic doses/1000 pt-days. In another study, an ASP was associated with an 11.6\% decline in the number of dispensed antibiotic doses for pediatric patients.\textsuperscript{9} A direct comparison with findings from our study is not possible because the metric used in these studies was doses and not days of therapy. But, similar to our findings and to the study from Newland et al.\textsuperscript{11} the reduction in antibiotic use was most pronounced for those agents that were actively monitored or restricted.

We found that declines in antibiotic use occurred throughout this group of children’s hospitals, in both those with and without ASPs alike. The changes could be attributable to a variety of stewardship initiatives within children’s hospitals collectively, ranging from implementation of a few effective strategies to development of a formalized ASP. In a previous study, we found that many hospitals without formal ASPs nonetheless incorporated important components of stewardship such as previous authorization or guideline development and implementation.\textsuperscript{7} Despite the fact that favorable changes occurred in ASP– hospitals, our findings suggest that the development of a formalized stewardship program, defined to include commitment of financial resources for personnel, translates into declines in antibiotic use that are above and beyond those achieved without similar investment.

Little is known about which specific stewardship strategies are most effective for improving the quality of antibiotic prescribing. For example, some ASPs exclusively use prior authorization, whereas others use prospective audit-and-feedback or a combination of the two.\textsuperscript{7} Although hospitals with ASPs did reduce antibiotic use to a greater degree than those without formalized programs, this was not universal. In 1 ASP+...
hospital, antibiotic use increased relative to preintervention trends after the program was begun; further analysis is needed to identify factors that may explain why antibiotic use trends in this hospital were different than other ASP+ hospitals. It is likely that some of the individual ASP—hospitals are indeed performing antimicrobial stewardship as effectively as those with formalized programs. We need to better understand which types of ASP activities are most effective, especially those interventions requiring lower levels of financial support, which will therefore be most cost-effective. This is particularly important given that many children are cared for outside of children's hospitals where dedicated pediatric infectious disease physicians or pharmacists (and therefore formal ASPs) may not be available on site.

There are several important benefits derived from ASP activities that we did not measure in this study and as such, we have likely underestimated the true value of these programs. One important focus of ASPs is to guide clinicians in de-escalation from broader-spectrum to narrower-spectrum therapy as indicated by clinical information including culture results. Changes in antibiotic selection from 1 agent to another for de-escalation would not be detected by the DOT/1000 pt-days metric. Additionally, several other important outcomes related to ASPs include changes in antibiotic costs, rates of multidrug resistant organisms and Clostridium difficile infection, dose optimization, and intravenous to oral conversion, none of which were measured in this study.3,4

We acknowledge that there are other limitations to our study design and data source. First, although reducing antibiotic overuse is a stewardship priority, and reductions in DOT may reflect reductions in overuse, we cannot be certain that these observed changes reflect better quality antibiotic prescribing. Another potential limitation to DOT is that changes from multiple agents to a single agent (eg, ceftriaxone and metronidazole to piperacillin-tazobactam) would cause DOT to decline without a meaningful reduction in antimicrobial exposure. This can be addressed by using a complementary metric, length of therapy, which accounts for the treatment duration in days, independent of the number of agents prescribed.15 The trends observed using length of therapy were identical to DOT, suggesting that conversion to fewer agents was not responsible for our findings. Our study only focused on antibacterial agents and we have therefore not accounted for changes in antifungal or antiviral agents, many of which are associated with high rates of potential toxicity and cost.

Third, PHIS is an administrative database where data for antibiotic use are derived from charges. Although PHIS has been used extensively to study antibiotic prescribing,1,16 using antibiotic charges as a measure of actual use has not been validated. For instance, in some cases, a patient may have been charged for an antibiotic but not actually received it. Next, due to the requirements of ITS analysis, we excluded some ASP+ hospitals with insufficient data after program initiation. Excluded hospitals were similar to study hospitals in terms of bed size and case mix index, but had a higher number of solid organ/bone marrow transplants. The exclusion of hospitals that recently started programs may have biased our results toward a smaller magnitude of impact because declines in antibiotic consumption and DOT are typically realized soon after program initiation. Finally, the generalizability of our findings to nonfreestanding children's hospitals is uncertain.

CONCLUSIONS

We found that 8 of 9 pediatric hospitals experienced significant declines in antibiotic use after...
introducing ASPs. These declines were greater than the concurrent secular trends of declining antibiotic use in similar hospitals without ASPs. Although these individual institutions are likely aware of the impact their ASP has had on antibiotic use, these results provide evidence to support the value of ASPs in leading to reductions in antibiotic prescribing for hospitalized children. This multicenter study strengthens recommendations for universal implementation of ASPs in acute care hospitals.


DOI: 10.1542/peds.2014-2579

Accepted for publication Oct 24, 2014

Address correspondence to Adam L. Hersh, MD, PhD, 295 Chipeta Way, Salt Lake City, UT 84103. E-mail: adam.hersh@hsc.utah.edu

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

Copyright © 2015 by the American Academy of Pediatrics

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

FUNDING: Dr Hersh received support from the Primary Children’s Foundation and from grant K08HS023320 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official view of the Agency for Healthcare Research and Quality.

POTENTIAL CONFLICT OF INTEREST: Drs. Hersh, Weissman, Gerber, and Newland receive funding from Pfizer/Joint Commission for a grant to study antimicrobial stewardship, the other authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page XXX, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-3501.

REFERENCES


Antimicrobial Stewardship Programs in Freestanding Children's Hospitals
Adam L. Hersh, Stephen A. De Lurgio, Cary Thurm, Brian R. Lee, Scott J. Weissman, Joshua D. Courter, Thomas V. Brogan, Samir S. Shah, Matthew P. Kronman, Jeffrey G. Gerber and Jason G. Newland
Pediatrics originally published online December 8, 2014;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/early/2014/12/02/peds.2014-2579

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Antimicrobial Stewardship Programs in Freestanding Children's Hospitals
Adam L. Hersh, Stephen A. De Lurgio, Cary Thurm, Brian R. Lee, Scott J. Weissman, Joshua D. Courter, Thomas V. Brogan, Samir S. Shah, Matthew P. Kronman, Jeffrey G. Gerber and Jason G. Newland
Pediatrics originally published online December 8, 2014;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2014/12/02/peds.2014-2579