Impact of a Prospective Audit and Feedback Antimicrobial Stewardship Program in Pediatric Units in Tertiary Care Teaching Hospital in Thailand

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ABSTRACT  

BACKGROUND: Antimicrobial stewardship programs (ASPs) have been proven to be beneficial in reducing the use of antimicrobial agents, antibiotic resistance, and health care costs. The data supporting the utility of ASPs has come largely from adult hospital units, but few pediatric hospital units have implemented ASPs. Our objective for this study was to assess the impact of ASPs in pediatric units in tertiary care teaching hospitals.  

METHODS: We conducted a retrospective chart review to compare antimicrobial use pre- and post-ASP over a 6-month period in a tertiary care hospital in which an ASP had been in use since July 2017. Meropenem, vancomycin, and colistin were selected to be monitored. ASP rounds were conducted twice a week to assess and provide feedback on antimicrobial prescriptions. Antimicrobial use was measured as days of therapy (DOTs) per 1000 patient-days and was compared pre- and post-ASP by using independent t tests.  

RESULTS: Charts of children hospitalized who were in antimicrobial treatment pre-ASP (44.3%) and post-ASP (41.7%) were reviewed. The percentages of children who received selected antimicrobial agents did not differ between pre- and post-ASP. During the post-ASP period, a significant reduction in DOT with vancomycin and colistin was observed. Vancomycin use decreased from 58.5 to 40.2 DOTs per 1000 patient-days (P = .038), and colistin decreased from 36.3 to 13.8 DOTs per 1000 patient-days (P = .026). Meropenem use decreased from 126.8 to 111.2 DOTs per 1000 patient-days (P = .467). Between the 2 periods, there was no effect on length of stay and mortality.  

CONCLUSIONS: ASPs can lead to a significant reduction in selected antimicrobial use in children who are hospitalized, with no effect on length of stay or mortality rate.
Antimicrobial resistance is 1 of the greatest public health threats worldwide. Infections from antimicrobial-resistant bacteria and *Clostridium difficile* lead to increased morbidity and mortality, longer hospital stays, and dramatically increased health care costs. The Centers for Disease Control and Prevention estimates that drug-resistant bacteria cause 2 million illnesses and ~23,000 deaths each year in the United States. In the European Union, ~25,000 patients die of infections caused by the selected multidrug-resistant bacteria each year. In Thailand, antimicrobial-resistance infections resulted in at least 3,24 million days of hospitalization and 38,481 deaths. Overuse and inappropriate use of antibiotics are important factors that lead to worldwide antibiotic resistance. Data from pediatric studies have revealed that 37% to 60% of children will receive at least 1 antimicrobial during hospitalization. Furthermore, up to 35% of inpatient antibiotic prescriptions are either unnecessary or inappropriate.

In 2007, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America published guidelines on the development of antimicrobial stewardship programs (ASPs) within health care institutions. In 2014, the Centers for Disease Control and Prevention developed ASP guidance to assist hospitals in either starting or expanding programs to improve antibiotic prescribing and suggested that hospitals should have institute ASPs. The primary purpose for ASPs is to optimize clinical outcomes while minimizing the unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *C. difficile*), and antibiotic resistance.

ASPs have proven beneficial in reducing the frequency and duration of target drug prescribing, the occurrence of *Clostridium difficile*-associated diseases, and health care costs. Although data supporting the utility of ASPs have come largely from adult units, few pediatric units have implemented comprehensive ASPs. Recent studies have revealed that the successful implementation of antimicrobial stewardship strategies has had a significant impact on reducing selected and nonselected antimicrobial use, thus improving the quality of care of children who are hospitalized and preventing antibiotic resistance.

In Asia, many countries have implemented ASPs for children who are hospitalized, including Japan, Singapore, and China. In Thailand, previous research has revealed that the utility of ASPs has come largely from medical schools, but there has been a lack of evidence regarding the impact of ASP implementation, particularly in pediatric units. The study hospital was a tertiary care teaching hospital in Bangkok, Thailand, with a 200-bed pediatric unit. The ASP was fully implemented in the pediatric unit in July 2017. To address the limitations in the existing evidence regarding the impact of pediatric ASPs, our main objective was to describe the structure, function, and clinical impact of a pediatric ASP on antimicrobial use and patient outcomes at the tertiary care teaching hospital in Thailand and to provide an interim analysis after the ASP had been fully implemented for a 6-month period.

**METHODS**

**ASP**

The strategy for ASPs has been to use the “prospective audit and feedback” approach. Since the program’s inception in July 2017, its membership has included infectious disease (ID) pediatricians and pharmacists with ID training. The ASP team selected the antimicrobial agents (meropenem, vancomycin, and colistin) to be monitored in terms of their use and appropriateness of treatment. These agents were selected because meropenem is a broad-spectrum antimicrobial agent most commonly used in the hospital, vancomycin is an antimicrobial agent used for multidrug-resistant Gram-positive bacterial infections, and colistin is an agent used for multidrug-resistant Gram-negative bacterial infections. The goals for the ASP were to (1) decrease use of the selected antimicrobial agents; (2) facilitate the early de-escalation or discontinuation of the selected antimicrobial agents’ empirical regimens, guided by the microbiologic results; (3) ensure dosing accuracy; and (4) improve patient safety and avoid drug errors. The ASP team developed practice guidelines and implemented prospective day 3 audits of the selected antimicrobial agents with education and feedback. Practice guidelines of appropriate indications and dosage of the selected antimicrobial agents were developed and distributed to physicians during the annual conference held for health care providers working in the pediatric unit of the hospital.

Regarding the process of prospective audit and feedback, the ASP team received a list of all active selected antimicrobial orders generated every morning by the pharmacist team. The ASP ward rounds were conducted twice a week on Monday and Thursday. For example, if a child starts antimicrobial agents on Sunday, the first assessment of indication and dosage would be performed during the ASP rounds on Monday. On Thursday, the second assessment would be conducted, with feedback to the primary team. Therefore, the duration of antimicrobial treatment might vary from 3 to 6 days from the primary to the secondary assessment. All assessments on selected antimicrobial use and recommendations given were recorded in the drug use evaluation (DUE) form (Fig 1). Acceptance of the recommendations was checked within 72 hours after the recommendations were made during regular ward rounds by the pediatric ID physicians.

**Setting and Study Design**

The study was conducted at a tertiary care teaching hospital in Bangkok, Thailand. Thirteen pediatric units, including 9 general unit, 1 oncology unit, 2 PICUs, and 1 surgical unit, were included, with a total of 200 beds and ~500 admissions per month. Electronic medical records and a computerized information system relating to the antibiotics dispensed to the patients were not available at the time of the study.

We conducted a retrospective chart review using data from patients who were discharged from the hospital between November 2016 and April 2017 (pre-ASP period) and between July 2017 and December 2017 (post-ASP period) and
received ≥1 antimicrobial agent of interest to this study. We excluded May 2017 and June 2017 from the study because the program was launched during this period. Our goal for the study was to assess the impact of an ASP on selected antimicrobial use, hospital length of stay (LOS), and number of deaths, comparing pre- and post-ASP periods.

**FIGURE 1** DUE form. CNS, central nervous system; CSF, cerebrospinal fluid; NA, not applicable.
Data Collection
Medical records of all patients who were discharged from the hospital during these periods were reviewed. A data set from all patients who received antimicrobial therapy was prepared and included the following: demographic parameters (age and sex), antimicrobial(s) prescribed, route of administration, duration of antimicrobial use, clinical indication, patient admission day(s), and patient outcome at discharge. Medical records that could not be obtained for review were excluded from the analysis (Fig 2). Total patient-days were calculated for all patients who were discharged from the hospital during the study periods, and ASP recommendations and acceptance were tracked by using data collected from the DUE form, which was used to evaluate and record recommendations given during ASP ward rounds.

Measures of Antimicrobial Use
To evaluate trends in antimicrobial consumption, we used days of therapy (DOTs) per 1000 patient-days as the metric. DOTs are calculated as the aggregate sum of antimicrobial agents used per patient per day. For example, a child given meropenem daily for 2 days for any dosage given would result in a total of 2 DOTs.

The term "all antimicrobials" refers to any antimicrobial with intravenous, oral, or intramuscular routes of administration and excludes topical antimicrobial agents, systemic antifungal agents, and antiviral agents. In this study, we also examined a subset of selected antimicrobial agents, including intravenous meropenem, vancomycin, and colistin. To ensure that a decrease in the use of the selected antimicrobial agents had no effect on increasing the use of other antimicrobial agents, nonselected antimicrobial agents, including intravenous third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime), piperacillin/tazobactam, ampicillin/sulbactam, cefoperazone/sulbactam, and levofloxacin, were also included in the study.

Statistical Analysis
The average antimicrobial use rates (measured as DOTs per 1000 patient-days for selected and nonselected antimicrobial agents) pre- and post-ASP were compared by using independent t tests. The duration of each selected and nonselected antimicrobial therapy and LOS during the pre- and post-ASP periods were compared by using the Mann–Whitney U test. In-hospital mortality during the pre- and post-ASP periods was compared by using the \( \chi^2 \) test. All statistical analyses were estimated by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS
Study Population and Demographic Data
A total of 1055 patients receiving antimicrobial treatment were enrolled during the pre-ASP period. During the post-ASP period, 1184 patients were enrolled. Overall, no statistically significant differences in the demographic data were observed between the 2 study groups (Table 1).

ASP Recommendations and Acceptance
During the 6-month post-ASP period, a total of 241 selected antimicrobial treatments were reviewed, and the ASP team made 170 recommendations on the selected antimicrobial agents in cases of inappropriate use. Discontinuation of the selected antimicrobial agents was the most common recommendation (51.2%), followed by de-escalation (38.6%) and dose adjustment (10.2%). The most accepted recommendation was dose adjustment (85.7%), followed by de-escalation (47.9%) and discontinuation (21.5%). The overall acceptance of the recommendations was 43.5%.

Selected Antimicrobial Use
After ASP implementation, the percentage of hospitalized children receiving selected antimicrobial agents (meropenem, vancomycin, and colistin) did not significantly change (16.0% and 14.7% [\( P = .368 \)], 8.5% and 6.4% [\( P = .057 \)], and 4.1% and 2.8% [\( P = .093 \)], respectively). However, consumption of vancomycin and colistin significantly decreased during the post-ASP period. DOTs per 1000 patient-days with vancomycin decreased by 31.3%, from 58.5 to 40.2 (\( P = .038 \)), whereas DOTs per 1000 patient-days with colistin decreased by 61.9%, from 36.3 to 13.8 (\( P = .026 \)). DOTs per 1000 patient-days with meropenem revealed
a reduction trend of 12.3%, from 126.8 to 111.2, but no statistically significant difference \((P = .467)\) (Fig 3). The median duration of colistin prescriptions, but not meropenem or vancomycin prescriptions, decreased during the post-ASP period (Table 2).

Nonselected Antimicrobial Use

During the post-ASP period, the percentage of hospitalized children receiving ceftriaxone and/or cefotaxime was 43.1%, the percentage of hospitalized children receiving piperacillin/tazobactam was 14.1%, the percentage of hospitalized children receiving ampicillin/sulbactam was 1.1%, and the percentage of hospitalized children receiving levofloxacin was 1.8%. These figures were not significantly different from those obtained during the pre-ASP period. In contrast, the percentage of cefazidime prescriptions increased from 9.4% (pre-ASP period) to 12.6% (post-ASP period) \((P = .014)\), whereas the percentage of cefoperazone/sulbactam prescrptions, a third-generation cephalosporin/\(\beta\)-lactamase inhibitor combination with anti-\textit{Pseudomonas} activity, decreased from 2.6% to 1.1% \((P = .009)\). The consumption of cefoperazone/sulbactam and levofloxacin decreased from 22.8 to 5.9 DOTs per 1000 patient-days \((-74.3%, P = .005)\) and from 14.6 to 7.6 DOTs per 1000 patient-days \((-48.0%, P = .013)\), respectively. No significant differences between the 2 periods for other nonselected antimicrobial agents were observed on the DOT (Fig 3).

**DISCUSSION**

To our knowledge, in this study, we are the first to evaluate the prospective audit and feedback of ASPs in a pediatric tertiary care setting in Thailand after implementation of the program for a 6-month period. This study reveals that this type of ASP strategy can successfully reduce the frequency of use and DOTs for selected antimicrobial agents in children who are hospitalized, with no change in the increase of the use of nonselected antimicrobial agents. Furthermore, in the study, we provide insight into antimicrobial agents, patient outcomes, types of ASP recommendations, and acceptance that a prospective audit and feedback ASP in a tertiary care setting will encounter.

**FIGURE 3** Comparison of average selected antimicrobial and nonselected antimicrobial use as DOTs per 1000 patient-days during the pre- and post-ASP periods. \(* P < 0.05\).
Our findings align with those of previous reports of ASP effectiveness from various settings in other countries. In recent studies, including 1 by Newland et al, authors have studied the impact of ASPs at 25 children’s hospitals in the United States. They demonstrated that prospective audit and feedback had a significant impact on decreasing the use of selected antibiotics monitored by ASPs at children’s hospitals. Kreitmeyer et al studied the impact of ASPs on broad-spectrum antibiotic use in general pediatric wards in Germany. The results also revealed that the same ASP strategy decreased antimicrobial use in children who were hospitalized. In addition, Willis et al and Klatte et al studied the impact of a prospective audit with feedback on antimicrobial use. Both studies revealed that the use of antimicrobial agents decreased.

Although our intervention (prospective audit and feedback) has been focused on providing feedback on the use of selected antimicrobial agents during regular ASP ward rounds, the clinical guidelines employed by the ASP might also contribute to improving antimicrobial use before prescribing decisions are made. This might reduce the selected antimicrobial use as an empirical therapy. However, the results of this study revealed that the use of meropenem remained unchanged. The DOTs tended to decrease post-ASP but not significantly. This finding revealed an area in which improvements could be made regarding the use of meropenem, and the ASP team should investigate the cause; otherwise, other interventions should be initiated.

For nonselected antimicrobial agents, the results revealed that there were no significant differences in DOTs between the 2 periods. There could be several potential reasons the DOTs of nonselected antimicrobial agents did not change. These reasons include the fact that most recommendations were for discontinuation and not change of agent, that therapy was continued for at least 72 hours before any ASP intervention (by which time the culture results or clinical evidence would have confirmed the absence of infection and the possibility of the antimicrobial being stopped), or that microbiologic test results confirmed initial therapy as the appropriate choice. These findings also reveal that there is room for improving interventions by the ASP team through further implementation and research. Regarding the reasons for changing the consumption of nonselected antimicrobial agents, we need microbiologic data that can be used to explain the variability results, but such data were not included in this study. There were no shortages of antimicrobial agents in the study hospital during the study periods.

Although we can significantly decrease broad-spectrum antimicrobial use in the hospital, ASP-recommendation acceptance rates appear low in this study (43.5%). However, a greater acceptance rate can be obtained by providing education regarding the benefit of ASPs, by encouraging corroboration in ASP implementation among health care providers, and by identifying the barriers related to ASP-recommendation refusal among pediatricians. For example, a recent study in a pediatric setting in the United States revealed that barriers related to stewardship programs included the need to educate incoming housestaff and other new recruits on a routine basis and to find mechanisms to change long-standing antimicrobial prescribing practices. Both barriers likely require significant education efforts.

The additional metrics of implementing ASP measurement, including improved patient clinical outcomes in terms of LOS and mortality, are also important. The results of this study revealed that ASP could reduce the use of selected broad-spectrum antimicrobial agents without changing the LOS or mortality rate. The long-term effects of ASPs on patients’ clinical outcomes must be further investigated. Recent studies, including a study by Lee et al, revealed that the average LOS during the pre- and postimplementation years was 6 and 6.13 days, respectively. There was no difference in the rate of discharge from the critical care units due to death during the preimplementation period versus the postimplementation period. Similarly, a study by Turner et al over a 2-year postintervention period revealed that LOS and mortality rates were unchanged.

There were several limitations to this study. We did not evaluate the severity of the patients’ conditions. The pre- and post-ASP periods were <1 year given that antimicrobial use might have depended on the seasonality of pediatric illnesses. However, the demographic data that we collected of the study population revealed...
that the 2 study groups were similar. We also did not collect the culture results of patients, which might be associated with the use of selected antimicrobial agents. The objective for this study was not linked to resistance data, which might have benefited from successful ASP evaluation. In addition, there were no data regarding compliance with institutional antimicrobial prescribing guidelines before ASP implementation to compare the pre- and post-ASP periods, which might be a better metric for judicious antimicrobial use instead of simply consumption because this data could also be another success point of the program's effort. Observed changes in this study could be due to the differences in the patient case mix during the observation periods that were not tracked in the study. Lastly, because we could not access an individual patient’s antimicrobial cost, we did not evaluate the true cost of antimicrobial agents. Consequently, an ASP cost-benefit analysis was not conducted in this study.

CONCLUSIONS

A prospective audit and feedback ASP can lead to a significant reduction in selected antimicrobial use among children who are hospitalized. The median LOS and in-hospital mortality rate were similar pre- and post-ASP. The study ASP has been in effect for 6 months, which is a short observation period. We aim to continue to measure the sustained impact of the program over time.

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