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Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality

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ABSTRACT

Objective: The impact of pediatric antimicrobial stewardship programs (ASP) on antimicrobial resistance (AMR) remains largely unknown. This study aimed to evaluate the AMR for carbapenem of Gram-negative bacilli (GNB) and carbapenem use with infectious diseases consultation after the implementation of an ASP.
Methods: This quasi-experimental study was conducted at Tokyo Metropolitan Children's Medical Center in Japan. The pre- and post-intervention periods were April 2010 to September 2011 and October 2011 to March 2017, respectively. The pre-intervention phase consisted of consultations with the infectious diseases service alone. The ASP was implemented during the post-intervention phase. The carbapenem resistance rates of GNB were calculated. The correlation between carbapenem resistance rates and carbapenem day of therapy (DOT) was examined. The outcome metrics were compared by average length of hospitalization, all-cause mortality, and infection-related mortality.
Results: A positive correlation was observed between the carbapenem resistance rate in *Pseudomonas aeruginosa* and DOT (0.76, $p = 0.04$). The carbapenem resistance rate in *P. aeruginosa* ($p < 0.01$) and DOT ($p < 0.01$) decreased significantly in the post-intervention period. The length of hospitalization ($p < 0.01$) and infection-related mortality ($p = 0.05$) decreased in the post-intervention period.
Conclusions: A sustained ASP with additional consultation with the infectious disease service reduced carbapenem use and resistance in *P. aeruginosa*, leading to favorable outcomes in terms of length of hospitalization and infection-related mortality.

Introduction

Antimicrobial resistance (AMR) is a serious threat to human health requiring action at every level (Gootz, 2010; Michael et al., 2014). During the G7 summit in 2016, the Japanese government released a national AMR action plan to promote the judicious use of antibiotic agents to reduce AMR (Government of Japan, 2016). In the healthcare setting, an antimicrobial stewardship program (ASP) in combination with effective infection prevention and control practices is essential to combat AMR (Nichols et al., 2017). In 2016, the Infectious Diseases Society of America published new guidelines on ASPs to recommend evidence-based interventions and assessment metrics (Barlam et al., 2016). Although both process and outcome metrics should be monitored to evaluate the effectiveness and safety of ASPs, outcome metrics for AMR have often shown less impact from ASPs, especially in pediatrics, despite

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a reduced use of antimicrobial agents (Smith et al., 2015; Davey et al., 2017; Principi and Esposito, 2016). A previous report by the present study group on a short-term ASP also failed to find a significant reduction in AMR from reduced antimicrobial use (Horikoshi et al., 2016).

Data on the effects of sustained ASPs in the pediatric population are still scarce. Removing ASP interventions in an adult population resulted in a loss of the benefits of decreased antimicrobial use (Himmelberg et al., 1991). One study of outpatients demonstrated the same loss of effect in children after the ASP interventions were ended (Gerber et al., 2014). A sustainable ASP should be designed with available resources. The duration of pediatric ASP studies on AMR outcomes is also generally limited, with the majority of studies examining a period of 1 to 3 years (Smith et al., 2015). One study had an intervention period lasting 4 years, but found no significant difference in the infection rate by resistant Gram-negative bacilli (Di Pentima et al., 2011). An ASP with a longer intervention period may result in improvements with regard to AMR.

The aim of this study was to assess the impact of a sustained ASP by focusing on carbapenem use and the antibiotic sensitivity of Gram-negative bacilli after the introduction of an ASP in a pediatric population.

Materials and methods

This quasi-experimental study was conducted at Tokyo Metropolitan Children's Medical Center. The pre- and post-intervention ASP periods were April 2010 to September 2011 and October 2011 to March 2017, respectively. The study hospital, located in the western part of Tokyo, Japan, and equipped with 561 pediatric beds, is a public children's hospital, which was formed from the merger in 2010 of three children's hospitals and a community hospital. The Division of Infectious Diseases was opened in the same year with one attending physician; the former hospitals had had no infectious disease service. The number of attending physicians increased to two in the post-intervention period, and the number of infectious diseases fellow physicians had increased from one to six by 2017.

Carbapenem use was measured by day of therapy (DOT) per 1000 patient-days for each Japanese fiscal year starting in April. The resistance rate was defined as the percentage of isolates with non-susceptibility (intermediate and resistant). In each fiscal year, the resistance rate of *Pseudomonas aeruginosa* to meropenem and the resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* to imipenem were calculated. The detection of the same species within 1 month in the same patient was excluded from analysis to avoid duplication. Identification and sensitivity testing were performed with the MicroScan WalkAway-96 Plus system (Siemens, Germany). Susceptibility was interpreted according to the Clinical and Laboratory Standards Institute M100-S27 document.

Pre-intervention period

During the pre-intervention period, physicians were required to submit a paper-based report after each carbapenem prescription. These reports were not checked and no feedback was given. Voluntary consultation on carbapenem use with an infectious disease physician was encouraged. The hospital formulary included meropenem and panipenem. Imipenem was purchased upon request.

Post-intervention period

An ASP subcommittee comprising infectious disease physicians, pharmacists, microbiologists, and clerks was formed. In October 2011, computerized preauthorization and a prospective audit for carbapenem were implemented as core elements of the ASP (Dellit et al., 2007). An electronic chart-based drug ordering system was designed to block orders for carbapenem automatically. Approval of an infectious diseases physician was required to proceed with any carbapenem prescription. All patients on carbapenems were followed prospectively by the infectious disease service to provide recommendations within 72 h as to whether the drug should be continued for a specific period, discontinued, or switched to a narrower agent based on clinical status and microbiology results. Restrictive reporting was also implemented to prevent physicians from viewing the sensitivity results for carbapenem in the electronic charts. If a strain was resistant to all β-lactam agents besides carbapenem, carbapenem sensitivity was disclosed on an individual basis. Panipenem was removed from the hospital formulary because it was seldom used, and imipenem and panipenem were purchased upon request. PCR-based diagnostics were provided upon request after consultation. PCR was performed in-house, mainly for critically ill, immunocompromised, or undiagnosed patients. A standard manual for antibiotic dosing and initial treatment for common infectious diseases was developed and posted on the electronic charts. A therapeutic drug monitoring (TDM) service with in-house measurement of drug concentrations and computer simulations became available at the pharmacy during day-time hours, including at weekends. A yearly antibiogram in the electronic charts was updated by microbiologists.

Primary outcomes and secondary outcomes

The primary outcomes were DOT with carbapenem, the carbapenem resistance rate for *P. aeruginosa*, *E. coli*, and *K. pneumoniae*, and the correlation between DOT and resistance rates. The secondary outcomes were average days of hospitalization, all-cause mortality, and infection-related mortality in the pre- and post-intervention periods. Infection-related mortality was defined as mortality cases with a microbiologically confirmed infection or infection clinically diagnosed by an infectious disease physician. Patients in the terminal stage of their primary disease were excluded from the analysis of infection-related mortality.

Statistical analysis

The DOT with carbapenem was compared between the pre- and post-intervention periods using the Mann–Whitney *U*-test and interrupted time-series analysis for level and trend changes after intervention (Wagner et al., 2002; Schweizer et al., 2016). The carbapenem resistance rate in each fiscal year was analyzed using the Cochran–Armitage test for trends. Significantly reduced drug and resistance rates of the organisms were analyzed for correlation using Spearman's rank correlation coefficient. The average length of hospitalization, all-cause mortality, and infection-related mortality were also compared using the Mann–Whitney *U*-test. Significance was set at $p < 0.05$ (two-tailed test). IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA) was used for the analysis.

This study was approved by the Institutional Review Board of Tokyo Metropolitan Children's Medical Center (H29b-21).

Results

The carbapenem DOT in the post-intervention period decreased significantly by 59.3% from 4.94/1000 patient-days (standard deviation (SD) 2.90) to 2.01/1000 patient-days (SD 1.59) ($p < 0.01$). An interrupted time-series analysis did not detect a significant