J Korean Med Sci. 2024 Jun 3;39(21):e172
https://doi.org/10.3346/jkms.2024.39.e172
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Infectious Diseases

The Impact of an Antimicrobial Stewardship Program on Days of Therapy in the Pediatric Center: An Interrupted Time-Series Analysis of a 19-Year Study

Kyung-Ran Kim [1*] **Hyo Jung Park** [2,3] **Sun-Young Baek** [4] **Soo-Han Choi** [5] **Byung-Kee Lee** [6] **SooJin Kim** [7] **Jong Min Kim** [8] **Ji-Man Kang** [9] **Sun-Ja Kim** [10] **Sae Rom Choi** [11] **Dongsub Kim** [12] **Joon-sik Choi** [13] **Yoonsun Yoon** [14] **Hwanhee Park** [15] **Doo Ri Kim** [1] **Areum Shin** [1] **Seonwoo Kim** [16] **and Yae-Jean Kim** [1,17]

[1]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Pharmacy, Samsung Medical Center, Seoul, Korea
[3]Sungkyunkwan University School of Pharmacy, Suwon, Korea
[4]Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea
[5]Department of Pediatrics, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea
[6]Department of Pediatrics, Seoulsan Boram Hospital, Ulsan, Korea
[7]Samsung Dream Pediatric Clinic, Suwon, Korea
[8]Department of Pediatrics, Myongji Hospital, Goyang, Korea
[9]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea
[10]Samsung Dream Pediatric Clinic, Jeju, Korea
[11]Wonju Citizen Clinic, Wonju, Korea
[12]Department of Pediatrics, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Korea
[13]Department of Pediatrics, Gangnam Severance Hospital, Seoul, Korea
[14]Department of Pediatrics, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[15]Department of Pediatrics, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea
[16]Academic Research Service Headquarter, LSK Global PS, Seoul, Korea
[17]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Seoul, Korea

Received: Dec 12, 2023
Accepted: Apr 29, 2024
Published online: May 17, 2024

Address for Correspondence:
Yae-Jean Kim, MD, PhD
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Samsung Advanced Institute for Health Sciences and Technology, 115 Irwon-ro, Gangnam-gu, Seoul 06355, Korea.
Email: yaejeankim@skku.edu

*Current affiliation: Department of Pediatrics, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, Korea

ORCID iDs
Kyung-Ran Kim
https://orcid.org/0000-0003-2557-3000
Hyo Jung Park
https://orcid.org/0000-0002-3875-0224
Sun-Young Baek
https://orcid.org/0000-0001-6519-7770
Soo-Han Choi
https://orcid.org/0000-0003-2449-3025
Byung-Kee Lee
https://orcid.org/0009-0009-2533-4756

ABSTRACT

Background: We aimed to analyze the effects of an antimicrobial stewardship program (ASP) on the proportion of antimicrobial-resistant pathogens in bacteremia, antimicrobial use, and mortality in pediatric patients.
Methods: A retrospective single-center study was performed on pediatric inpatients under 19 years old who received systemic antimicrobial treatment from 2001 to 2019. A pediatric infectious disease attending physician started ASP in January 2008. The study period was divided into the pre-intervention (2001–2008) and the post-intervention (2009–2019) periods. The amount of antimicrobial use was defined as days of therapy per 1,000 patient-days, and the differences were compared using delta slope (= changes in slopes) between

SooJin Kim
https://orcid.org/0009-0000-5233-9346
Jong Min Kim
https://orcid.org/0000-0002-5594-4864
Ji-Man Kang
https://orcid.org/0000-0002-0678-4964
Sun-Ja Kim
https://orcid.org/0000-0002-1584-3970
Sae Rom Choi
https://orcid.org/0000-0002-5839-6218
Dongsub Kim
https://orcid.org/0000-0002-9836-6769
Joon-sik Choi
https://orcid.org/0000-0002-5587-2960
Yoonsun Yoon
https://orcid.org/0000-0003-0187-3922
Hwanhee Park
https://orcid.org/0000-0002-3337-408X
Doo Ri Kim
https://orcid.org/0000-0001-5233-4043
Areum Shin
https://orcid.org/0000-0003-3341-0447
Seonwoo Kim
https://orcid.org/0000-0002-9236-560X
Yae-Jean Kim
https://orcid.org/0000-0002-8367-3424

Disclosure
The authors have no potential conflicts of interest to declare.

Author Contributions
Conceptualization: Kim YJ. Data curation: Kim KR. Formal analysis: Baek SY, Kim S. Resources: Park HJ, Park H, Kim DR. Supervision: Kim YJ. Visualization: Kim KR. Writing - original draft: Kim KR. Writing - review & editing: Choi SH, Lee BK, Kim SJ, Kim JM, Kang JM, Kim SJ, Choi SR, Kim D, Choi JS, Yoon Y, Park H, Kim DR, Shin A, Kim YJ.

Presentation
This study, 'The effectiveness of antimicrobial stewardship programs and changes in antibiotic-resistant bacteria,' was partially included as an E-Poster presentation at the 39th Annual Meeting of the European Society for Paediatric Infectious Diseases in 2021.

the two study periods by an interrupted time-series analysis. The proportion of resistant pathogens and the 30-day overall mortality rate were analyzed by the χ^2.

Results: The proportion of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia increased from 17% (39 of 235) in the pre-intervention period to 35% (189 of 533) in the post-intervention period ($P < 0.001$). The total amount of antimicrobial use significantly decreased after the introduction of ASP (delta slope value = −16.5; 95% confidence interval [CI], −30.6 to −2.3; $P = 0.049$). The 30-day overall mortality rate in patients with bacteremia did not increase, being 10% (55 of 564) in the pre-intervention and 10% (94 of 941) in the post-intervention period ($P = 0.881$).

Conclusion: The introduction of ASP for pediatric patients reduced the delta slope of the total antimicrobial use without increasing the mortality rate despite an increased incidence of ESBL-producing gram-negative bacteremia.

Keywords: Antimicrobial Stewardship Program; Pediatric Patients; Pediatric Infectious Disease Attending Physician; Antimicrobial Use; Antimicrobial-Resistant Pathogens

INTRODUCTION

The history of combat between antimicrobial resistance (AMR) in pathogens and human beings started with the discovery of antibiotics in the 1930s and has continued through the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in 1961, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, and carbapenem-resistant (CR) gram-negative bacteria consequently.[1] Appropriate antimicrobial use is a core strategy to improve clinical outcomes and delay the emergence of antibiotic-resistant bacteria. Overuse and misuse of antimicrobials increase adverse effects, length of hospitalization, need for intensive care, morbidity, mortality, and healthcare costs.[2-6] In addition, inappropriate antimicrobial use is associated with developing antibiotic-resistant bacteria due to selective pressure.[3] Infection with antibiotic-resistant bacteria and delaying appropriate antimicrobial use were associated with infection-related poor outcomes.[7] To solve these problems, the Infectious Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society recommended the implementation of an antimicrobial stewardship program (ASP) in hospitals.[8] Korean Society for Antimicrobial Therapy (KSAT), The Korean Society of Infectious Diseases (KSID), and Korean Society of Health-system Pharmacists (KSHP) developed guidelines for implementing ASP in Korea.[9] KSAT, KSID, KSHP, Korean Society of Pediatric Infectious Diseases, and Korean Society for Healthcare-associated Infection Control and Prevention recommended core elements of implementing ASP for general and acute care hospitals in Korea.[10] Studies on antimicrobial use, the effect of antimicrobial strategy for the pediatric population, and pediatric ASP were limited in Korea.[11-13] Most studies on the effects of ASP have been conducted in the adult population,[14-17] and few studies have assessed the pediatric population.[18,19] In addition, previous studies evaluated the short-term effects of ASP implementation and included only certain patient groups, such as general wards, outpatient clinics, emergency departments (EDs), and pediatric intensive care units (PICUs).[20-29] Therefore, long-term studies of the effects of ASP introduction in all hospitalized pediatric patients and the epidemiology of AMR are needed. We analyzed the impacts of ASP introduction on the proportion of antimicrobial-resistant pathogens in bacteremia, the amount of systemic antimicrobial use, and mortality in pediatric patients from 2001 to 2019.

METHODS

Study design and participating hospitals

At the end of the intervention period in 2019, Samsung Medical Center (SMC), Seoul, Korea, was a 1,994-bed university-affiliated tertiary care hospital. The Pediatric Center had approximately 220 beds: 37 in the pediatric medical ward, 50 in the hematology-oncology (HO) and hematopoietic cell transplantation (HCT) units, 60 in the neonatal intensive care unit (NICU), 15 in the PICU, 40 in the pediatric surgery wards, 10 in the pediatric cardiovascular ICU, and eight in the pediatric gastrointestinal and neurosurgery ICU. As of 2019, the number of pediatric physicians was 78, with one pediatric infectious disease (pediatric ID) attending physician and three pediatric ID fellows.

ASP for pediatric patients

The main strategies for our ASP were prospective audit and feedback (PPAF), a computerized decision support system (CDSS, **Supplementary Data 1**), facility-specific clinical practice guidelines, surgical prophylaxis monitoring, and twice-a-week feedback to physicians after infectious disease consultations. The pediatric ID team and ASP team were not separate, and the short-staffed pediatric ID team served for both roles. There was no dedicated pediatric ID team leader as recommended in the ASP guideline.[8] The pediatric ID team (one attending physician and two or three fellows per year) is responsible for ASP, patient care (inpatients and outpatients), and consultation activities. There is no full-time physician designated for ASP activities. In addition to responding to individual consultation requests, the pediatric ID team has regular rounds in the PICU, NICU, pediatric surgery ICU, HCT units, and HO wards. The team reviews the appropriateness of antimicrobial choice, dose, therapeutic drug level monitoring, and duration (if applicable) for cases, especially on combination therapy or broad-spectrum antimicrobials (carbapenem, glycopeptide, and antifungal agents) in advance, visits the ward, discusses with the physicians in charge, and recommends optimal management on Mondays. On Thursdays, a follow-up review is performed electronically or in person. If a new patient is consulted around Thursday first, then a follow-up review is performed on Monday. These activities continue twice a week until the infectious issues are resolved.

In our center, the following list of antibiotics requires authorization to repeat prescription after the initial three-day treatment period: carbapenems (imipenem, meropenem, and ertapenem), vancomycin, and teicoplanin. Fluoroquinolones (levofloxacin, ciprofloxacin) require pre-authorization for the initial prescription in pediatric patients 18 years of age and under. For patients on approved antimicrobials, the pediatric ID consultation was conducted (usually every 4 to 7 days) to evaluate appropriate antimicrobial use.

Definition and data collection

Pre-intervention period: 2001 to 2008

The first pediatric ID attending physician started to work in January 2008. Systems for clinical care in patients with infectious diseases and ASP activities were gradually established. The pre-intervention period was defined as 2001 to 2008. We assessed the amount of prescribed antimicrobials for pediatric patients yearly.

Post-intervention period: 2009 to 2019

After the ASP was started by the pediatric ID attending physician, the post-intervention period was defined as 2009 to 2019. We conducted an additional detailed analysis of the

https://doi.org/10.3346/jkms.2024.39.e172

effect of ASP on antimicrobial use, for which the post-intervention period was divided into six-month intervals (each year had two periods: Period I for January-June and Period II for July-December).

Antimicrobial use

All systemic antimicrobials administrated to inpatients under 19 years were included. Antimicrobial usage data were extracted from the electronic pharmacy database. The amount of antimicrobial use was defined as days of therapy (DOT).[30] DOT documented the total number of antimicrobial DOT. Each antimicrobial was counted separately. This was calculated by counting each antimicrobial that each patient was prescribed. Patient days were a count of the number of days a patient was present in an inpatient unit, measured as calendar days. The rate of antimicrobial use was described as DOT per 1,000 patient-days.[8]

Delta slope (= change in slope, Δ) was defined as an observed slope with intervention (slope of post-intervention period) minus expected slope without intervention (slope of pre-intervention period).[31,32] It means the sustained effect of ASP intervention led by the pediatric ID team. Change in level (immediate effect) was calculated as the mean antimicrobial use in the post-intervention minus the mean antimicrobial use in the pre-intervention period and adjusted using autoregression model (**Supplementary Fig. 1**).[33]

Bacteremia

Bacteremia was counted as one episode if multiple results with the same pathogen were reported within 28 days.

Main outcomes

We defined the main outcomes as the delta slope of DOT per 1,000 patient-days, the trends of the proportion of antimicrobial-resistant major pathogens: *Escherichia coli* (*E. coli*) and *Klebsiella pneumonia* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Staphylococcus aureus* (*S. aureus*), and 30-day overall mortality rate in bacteremias.

Statistical analyses

The impact of ASP on the amount of antimicrobial use was analyzed using segmented regression analyses of interrupted time series with adjustment for autocorrelation.[34] The statistical analyses corrected the number of patients admitted to the NICU, PICU, HCT, and solid organ transplantation. The maximum likelihood estimation method was used in the analyses, and the number of lags was included in the model the using backstep option of the PROC AUTOREG command in SAS® version 9.4 (SAS Institute, Cary NC, USA). We used the Chi-square test to compare the proportion of resistant pathogens and the 30-day overall mortality rate during the two study periods. A P value < 0.05 was considered statistically significant.

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center and informed consent was waived because of the retrospective nature of the study (approval number 2020-08-055).

RESULTS

Changes in the number of admitted patients and proportion of antimicrobial-resistant pathogens

From January 2001 to December 2019, the number of admitted patients younger than 19 years old increased by 153.6%, from 68,803 in the pre-intervention period (2001–2008) to 105,787 in the post-intervention period (2009–2019). The yearly number of total hospitalizations, and HCT recipients increased the post-intervention compared to the pre-intervention period (all; $P < 0.05$; **Supplementary Table 1**).

The proportion of ESBL-producing *E. coli* and *K. pneumoniae* increased from 17% (39/235) in the pre-intervention period to 35% (189/533) in the post-intervention period ($P < 0.001$). The proportion of cefepime-resistant *P. aeruginosa* increased from 11% (7/63) pre-intervention to 23% (25/111) post-intervention, but the change was not statistically significant ($P = 0.062$; **Supplementary Table 2**). The proportion of imipenem-resistant *P. aeruginosa* increased from 16% (10/63) pre-intervention to 30% (33/111) post-intervention ($P = 0.042$). The proportion of methicillin-resistant *S. aureus* (MRSA) among *S. aureus* isolates decreased significantly from 56% (148 of 266) pre-intervention to 38% (114 of 297) post-intervention ($P < 0.001$; **Fig. 1** and **Supplementary Table 2**).

Changes in antimicrobial use

The total amount of antimicrobial use was 453.5 DOT per 1,000 patient-days in 2001, peaked at 584.5 DOT per 1,000 patient-days in 2009, and decreased to 513.0 DOT per 1,000 patient-days in 2019 (**Fig. 2A**). The slope of total antimicrobial use was 7.42 in the

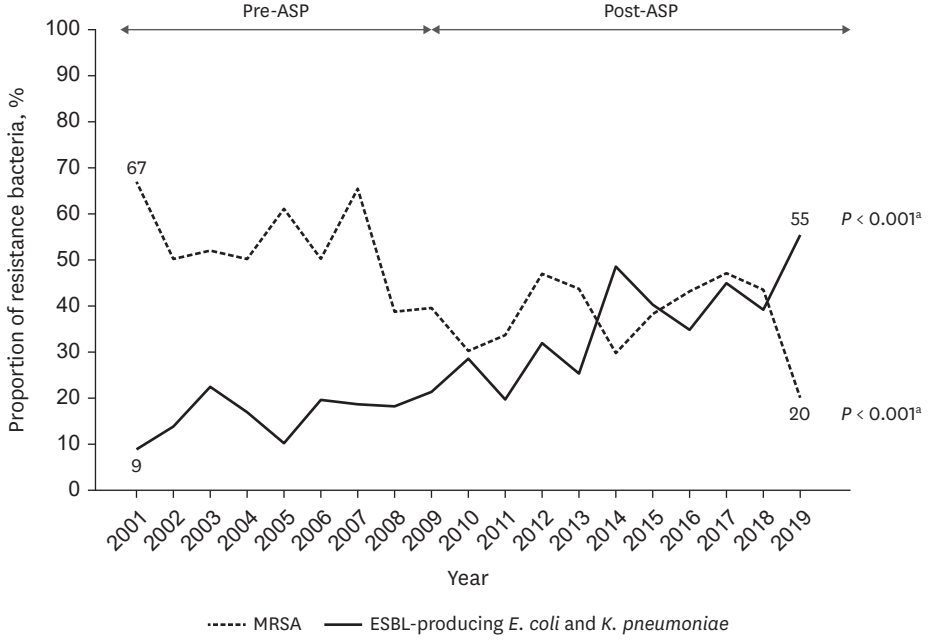

Fig. 1. Change of proportion of major antibiotic-resistant bacteria isolated from bloodstream infections. The black dashed line indicates the proportion of MRSA in *S. aureus* isolated from bloodstream infections. The black solid line indicates the proportion of ESBL-producing GNB in *E. coli* and *K. pneumoniae* isolated from bloodstream infections.
ASP = antimicrobial stewardship program, MRSA = methicillin-resistant *Staphylococcus aureus*, ESBL = extended-spectrum beta-lactamase, GNB = gram-negative bacteria.
[a]Statistically significant.

https://doi.org/10.3346/jkms.2024.39.e172

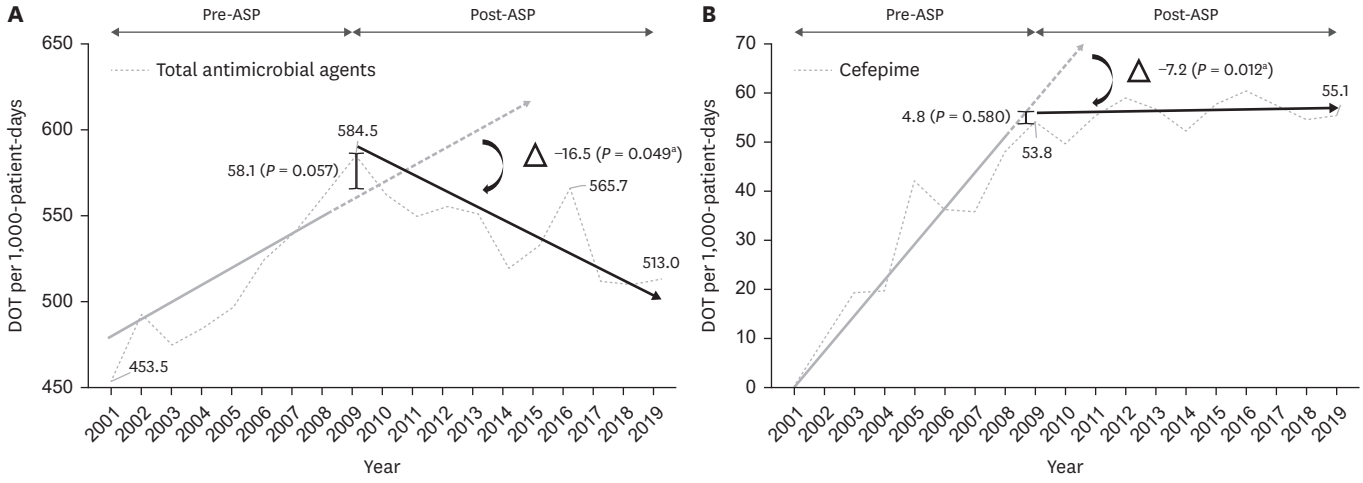

Fig. 2. Interrupted time-series analyses for antimicrobial use from January 2001 to December 2019. (**A**) Total antimicrobial use. The slope of the total antimicrobial use decreased from 584.5 DOT per 1,000 patient-days in 2009 to 513.0 DOT per 1,000 patient-days in 2019 after ASP implementation in March 2008. The delta slopes for the total antimicrobial use were negative. (**B**) Cefepime use. The slope of cefepime use decreased after the ASP implementation, and the delta slopes was negative. The grey dotted line indicates antimicrobial use as DOT per 1,000-patient-days. The grey solid line indicates the observed slope during the pre-intervention period and the grey dashed line indicates the expected slope without the implementation. The black solid line indicates the observed slope with implementation during the post-intervention period. The black triangle indicates the delta slopes (sustained effect): The observed slope with ASP implementation minus the expected slope without the implementation. The 'l' indicates the change in level (immediate effect), the mean antimicrobial use in the post-intervention minus the mean antimicrobial use in the pre-intervention period.
ASP = antimicrobial stewardship programs, DOT = days of therapy.
Statistically significant is defined $P < 0.05$.
[a]Statistically significant.

Table 1. Delta slopes of antimicrobial use as assessed by DOT pre-and post-ASP intervention

Class of antimicrobial agents	Change in level,[b] mean (95% CI)	*P* value	Delta slope,[c] mean (95% CI)	*P* value
Total	58.1 (5.9 to 110.4)	0.057	−16.5 (−30.6 to −2.3)	0.049[a]
Ampicillin	1.1 (−7.7 to 9.8)	0.819	1.0 (−1.4 to 3.4)	0.438
AMP/SUL	−31.0 (−52.9 to −9.0)	0.070	−36.8 (−56.7 to −16.8)	0.037[a]
PIP/TAZ	20.5 (−9.5 to 50.6)	0.214	1.6 (−6.5 to 9.8)	0.702
Cefazolin	−10.3 (−42.0 to 21.4)	0.541	5.6 (−3.0 to 14.2)	0.232
Cefuroxime	26.2 (−7.2 to 59.5)	0.163	−2.2 (−13.6 to 9.2)	0.713
3GCs	−12.9 (−46.1 to 20.2)	0.464	−5.3 (−14.3 to −3.7)	0.278
Aminoglycoside	−3.2 (−27.3 to 20.8)	0.797	7.1 (0.6 to 13.6)	0.061
Cefepime	4.8 (−11.6 to 21.2)	0.580	−7.2 (−11.6 to −2.7)	0.012[a]
Imipenem	−13.6 (−28.4 to 1.3)	0.112	−9.4 (−13.7 to −5.2)	0.002[a]
Meropenem	18.0 (−1.5 to 37.4)	0.103	5.6 (0.3 to 10.9)	0.067
Vancomycin	7.9 (−9.6 to 25.3)	0.399	−4.8 (−9.6 to −0.1)	0.077
Teicoplanin	4.6 (−17.0 to 26.2)	0.686	−3.0 (−8.9 to 2.9)	0.340

DOT = days of therapy, ASP = Antimicrobial stewardship program, CI = confidence interval, AMP/SUL = ampicillin/sulbactam, PIP/TAZ = piperacillin/tazobactam, 3GC = third-generation cephalosporin.
Statistically significant was defined as $P < 0.05$ as significant.
[a]Statistically significant.
[b]Change in level; The mean antimicrobial use in the post-intervention minus the mean antimicrobial use in the pre-intervention period (immediate effect).
[c]Delta slope; Slope of post-intervention period minus slope of pre-intervention (sustained effect).

pre-intervention period and −9.05 in the post-intervention period. The delta slope for total antimicrobial use decreased (delta slope value = −16.5; 95% confidence interval [CI], −30.6 to −2.3; $P = 0.049$). The delta slope of ampicillin/sulbactam and cefepime use also showed decreasing (delta slope value = −36.8; 95% CI, −56.7 to −16.8; $P = 0.037$ and delta slope value = −7.2, 95% CI, −11.6 to −2.7; $P = 0.012$, respectively; **Fig. 2B** and **Table 1**). The delta slopes for aminoglycoside, piperacillin-tazobactam, meropenem, and vancomycin use were unchanged (all; $P \geq 0.05$; **Table 1**).

https://doi.org/10.3346/jkms.2024.39.e172

Transient increase of DOT and concurrent events during ASP intervention

In order to observe the antimicrobial use in detail after ASP intervention, we analyzed the post-intervention period in six-month intervals. In general, antimicrobial use decreased during the post-intervention period. However, three distinct peaks were observed in total antimicrobial use in 2009II, 2012II, and 2015II–2016II (**Fig. 3**). These transient increases coincided with three important events that led to intermittent or reduced ASP activities: the H1N1 influenza pandemic (Period A),[35] the absence of the ID fellow (Period B), and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak in our center[36] and the sabbatical leave of the pediatric ID attending physician after the outbreak closure (Period C; **Fig. 3**). She came back to the hospital and reinforced ASP activities; proactive feedback for appropriate antimicrobial use and interaction with physicians, and regular rounding in the ICUs, HO and transplant units.

We conducted a subgroup analysis since Period C (2015II–2016II) showed the most significant DOT change. The Delta slope of the DOT (total antimicrobial use) decreased during pre-Period C, but the slope significantly increased between pre-Period C and Period C (delta slope value = 38.8, 95% CI, 7.9 to 69.8; $P = 0.028$). After the pediatric ID attending physician came back to the office and strengthened the ASP activities again, the delta slope of total antimicrobial use decreased in post-Period C, although it was not significant yet (delta slope value = −26.8, $P = 0.142$; **Fig. 3** and **Supplementary Table 3**). However, individual changes in level for the total antimicrobial use, meropenem, and vancomycin use decreased significantly post-Period C (all; $P < 0.05$; **Supplementary Table 3**).

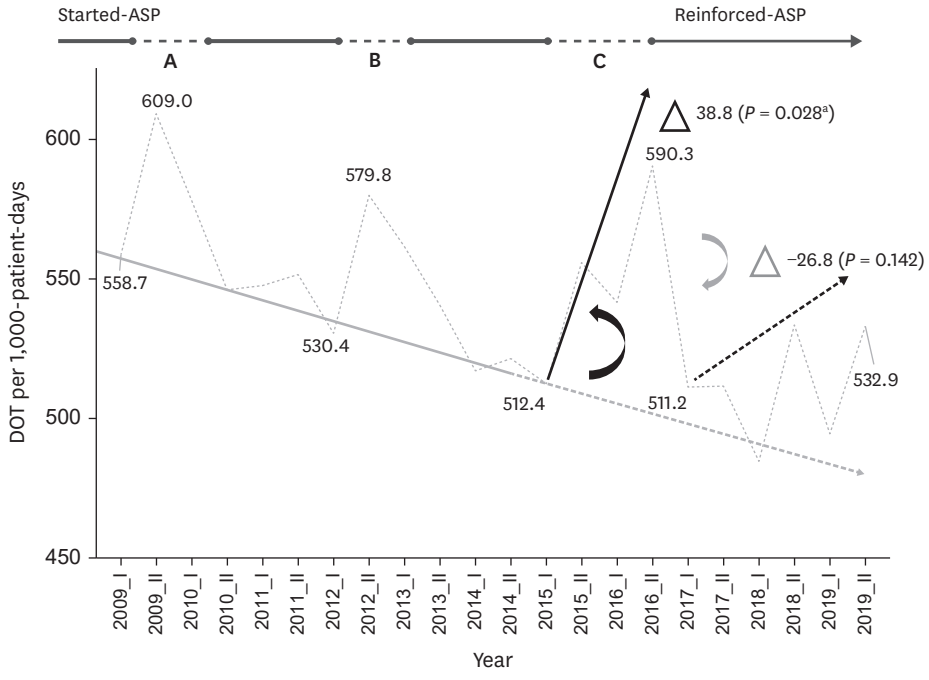

Fig. 3. Transient increase of total antimicrobial use as measured by DOT during the post-ASP intervention period. The grey dotted line indicates total antimicrobial use. The grey solid line indicates the slope before Period C of transiently increased DOT. The grey dashed line indicates the expected slope without Period C of transiently increased DOT. The black solid line indicates the slope during the Period C of the transiently increased DOT period. The black dashed line indicates the observed slope after the reinforcement of ASP procedures by the pediatric ID physician. The triangles indicate the delta slopes. Period A: H1N1 influenza pandemic with no ID fellow(s) from April 2009 to April 2010. Period B: No ID fellow(s). Only an ID attending physician managed the ASP from March 2012 to December 2013. Period C: MERS-CoV2 outbreak in Korea and sabbatical leave of pediatric ID attending physician after the outbreak closure from June 2015 to December 2016. Statistically significant is defined $P < 0.05$. The grey dashed line indicates the period of the transient increase in DOT.
DOT = days of therapy, I = the interval from January to June, II = the interval from July to December, pediatric ID = pediatric infectious disease, MERS-CoV2 = Middle East Respiratory Syndrome coronavirus.
[a]Statistically significant.

https://doi.org/10.3346/jkms.2024.39.e172

Mortality

Although ESBL-producing *E. coli* and *K. pneumoniae* bacteremia increased, the 30-day overall mortality rate among total bacteremia cases was unchanged after the ASP intervention, from the pre-intervention period 10% (55/564) to the post-intervention period 10% (94/941); $P = 0.880$.

DISCUSSION

In this study, we investigated the effects of ASP intervention on antimicrobial use in pediatric patients who were admitted to a tertiary hospital in Korea, as measured by DOT and analyzed using interrupted time-series analyses. The proportion of ESBL-producing *E. coli* and *K. pneumoniae,* and CR *P. aeruginosa* in bacteremia and yearly total number of hospitalized patients and HCT recipients increased during the study period. However, the delta slopes of the total amount of antimicrobials, ampicillin/sulbactam, and cefepime use decreased, and meropenem use was unchanged in the post-intervention period despite the higher proportions of ESBL-producing *E. coli* and *K. pneumoniae* bacteremia. Although the proportion of MRSA bacteremia decreased during the study period, the DOT of vancomycin was unchanged. The 30-day overall mortality rate among bacteremic patients after 11 years of ASP implementation did not increase.

Most pediatric ASP studies were published in the US (52.2%, 59/113) and Europe (24.7%, 28/113), and less than 20% were from Asia (17.7%, 20/113).[28] Previous studies of pediatric ASP have been conducted on the effectiveness of short-term ASP implementation in specific situations, such as NICU, PICU, HO, or ED patients.[28,37-39] Our study is unique in terms of the 19-year study duration and the two distinct periods with/without a pediatric ID attending physician that made the comparison possible. Antimicrobial use showed an inverted V shape after ASP intervention by one pediatric ID attending physician.

The core components of ASP activities are pre-authorization and/or PPAF, recommending a duration of therapy, CDSS for clinicians, facility-specific clinical practice guidelines, physician education, pharmacokinetic monitoring, and a timely transition from intravenous to oral antibiotics as directed by an infectious disease physician. Among these, the key strategy of ASP is the leadership provided by an ID physician(s).[8] In 2000, some hospitals started ASP in Korea.[15] Hwang et al.[15] reported that ASP led by an ID attending physician reduced antimicrobial prescriptions without increasing mortality in adult patients. Our hospital's first and only pediatric ID attending physician started ASP for pediatric patients in 2008. In addition to providing the usual ID consultation services, inpatient care, and outpatient clinics, the pediatric ID attending physician provided PPAF on weekdays and consulted with physicians over the phone in case of an emergency on the weekend. The appropriateness and adequacy of antibiotic prescriptions were evaluated by the pediatric ID team led by the pediatric ID attending physician. Additional feedback for the consultation was suggested to the physicians by the pediatric ID team. At a department-wide conference, the pediatric ID attending physician provided center-specific local AMR trends and yearly updates to pediatricians regarding empiric antibiotic guidelines based on center-specific epidemiology of antibiotic resistance pathogens.[40] The adequacy of center-specific guidelines and appropriate antimicrobial use were also reevaluated.[41] With all these diligent, comprehensive, and multi-faceted approaches provided in ASP as led by one pediatric ID attending physician, a negative value for the delta slope of DOT (total

https://doi.org/10.3346/jkms.2024.39.e172

antimicrobial use) was achieved despite increasing AMR among the major pathogens cultured from patients with bacteremia.

Additional analyses for the post-intervention period showed another remarkable finding with respect to the role of the pediatric ID attending physician in ASP management. After the slope on DOT of total antimicrobial use became negative, transient increases in DOT were recorded in three periods. A common situation in all three periods was that the only pediatric ID attending physician could not spend enough time on ASP activities because of the heavy workload in other areas or absence from work temporarily. One can easily expect that reductions in time and activities in ASP may have led to a transient increase in antimicrobial use. In the 2020 national survey in Korea, with over 150 beds in acute care hospitals, only 12% (25/217) were managed with ASP by pediatric ID physician(s).[42] Kim et al.[43] reported 352 ID physicians (281 adults and 71 pediatric ID physician(s)) worked 61 (interquartile range: 54-71) hours per week: 29 hours in patient care, research 11 hours, infection control 4 hours, ASP 3 hours, and education/training 2 hours. ID physicians were exposed to long work time and multiple tasks simultaneously. Previous studies showed that ASP activities significantly decreased during the coronavirus disease 2019 (COVID-19) pandemic as the ASP members mobilized for COVID-19 infection control and patient care.[44,45] Although the prevalence of bacterial co-infection of COVID-19 infection was low,[46,47] antimicrobial use increased during the pandemic.[44,48] As we have experienced, outbreaks of new pathogens such as MERS-CoV2 and severe acute respiratory syndrome coronavirus 2 can occur anytime. Therefore, securing sufficient human resources is crucial to managing the ASP efficiently and avoiding imposing an excessive workload on one or very limited staff members.

The Centers for Disease Control and Prevention reports that ASP core elements are hospital leadership commitment, accountability, pharmacy expertise, action to improve antimicrobial use, monitoring, reporting, education (to prescribers, pharmacists, and nurses), and government efforts to support stewardship.[49] Overall, the pediatric ASP in our hospital effectively reduced the long-term antimicrobial use without increasing mortality in patients with bacteremia even when all eight ASP core elements were not satisfied during the post-intervention period (**Supplementary Table 4**). However, in our study, pediatric ID team and pediatric ASP team were not separate and short-staffed pediatric ID team served both roles. Therefore, as seen in periods A, B, and C, intermittent availability of the one pediatric ID attending physician for ASP activities resulted in fluctuation of trends of antimicrobial use. It dramatically increased when the pediatric ID attending physician was unavailable for ASP activities due to increased infection control or clinical consultation workloads or she was away from the office for sabbatical leave. Therefore, all ASP core elements should be satisfied to maintain constant and stable, well-functioning ASP activities, with a special emphasis on human resources.

Another important aspect of ASP activities can be related to seniority of the ASP team leader. In our study, during Period C, the pediatric ID attending physician (senior physician) was out of office and junior pediatric ID physician was the pediatric ASP team leader, temporarily. In this situation, factors such as the hierarchy, could have influence the on-site physician's decision-making. In a previous study, the recommendation of appropriate antimicrobial use from a lower hierarchical level was attributed to less effect than higher levels of seniority within the ID team. Therefore, the absence of the senior pediatric ID physician may have influenced the increased antimicrobial use even though the junior pediatric ID physician performed the same tasks in these periods (delta slope value = 38.8, $P = 0.034$; **Fig. 3** and

Supplementary Table 3). It is necessary for a well-established system for anyone who is a well-trained ID physician to effectively manage the ASP without being influenced by hierarchy.

Finally, the delta slope of the DOT for extended-spectrum cephalosporins and carbapenem did not increase after ASP implementation. However, the proportion of ESBL-producing *E. coli* and *K. pneumoniae,* and CR *P. aeruginosa* in bacteremia increased during the post-intervention period. There are controversies regarding the association between antimicrobial use and emerging AMR in pathogens.[28,39] Trends of AMR in pathogens are associated with various factors such as antimicrobial misuse and overuse, hand hygiene compliance, hospital infection-control policies, and epidemics of AMR in pathogens in the community.[8,14] Korean tertiary hospitals have high bed occupancy and patient concentration.[50] AMR in pathogens spreads rapidly between hospitals and person-to-person in these healthcare environments.[50,51] The proportion of ESBL-producing *E. coli* and *K. pneumoniae* was 30.3% (755/2465), and CR *P. aeruginosa* was 19.5% (29/149) in bacteremia, according to Korea's national surveillance report in 2017.[50] In our study, the proportions of ESBL-producing *E. coli* and *K. pneumoniae*, and CR *P. aeruginosa* were 35% (189/533) and 30% (33/111) in the post-intervention period, respectively. Our center is one of the largest tertiary hospitals in Korea. Many patients who are already infected with resistant pathogens are transferred to our center for additional care. Therefore, while we try to control the occurrence of resistant pathogens within our hospital, there is always a risk of exposure to resistant pathogens introduced into our center from other hospitals or the community. For example, the imipenem-resistant *Acinetobacter baumannii* (IRAB) bacteremia outbreak occurred in the PICU from 2009–2012. The IRAB outbreak was successfully managed through collaboration between the pediatric ID team and PICU (medical and nursing) team education and strict infection control. Afterward, an additional IRAB outbreak did not occur.[52] Among ESBL-producing *E. coli* and *K. pneumoniae* bacteremia, 46.1% (105/228) occurred in patients with neutropenic fever. Our empiric antimicrobial therapy strategy for patients with neutropenic fever has been cefepime plus a single dose of amikacin since September 2014.[41] Even under this empiric antimicrobial strategy, the 30-day overall mortality rate for hospitalized patients with bacteremia did not increase.

Our study has some limitations. First, although we analyzed the change in DOT, the proportion of AMR in bacteremia, and 30-day overall Mortality rate after ASP intervention, we did not analyze the changes in healthcare costs or adverse effects related to antibiotic use, such as the prevalence of *Clostridium difficile* infection and allergic reactions. Second, we did not evaluate the efficacy of ASP implementation on the use of antifungal and antiviral agents. Third, this study was conducted at a tertiary hospital in Korea, and the results of our ASP led by the pediatric ID attending physician may not be directly applicable to other hospitals, countries, or adult populations.

The currently increasing pressure created by ever-evolving antibiotic-resistant pathogens requires judicious antibiotic use. In conclusion, our study shows real-world data from a limited human resources environment that evaluated the long-term impact of implementing ASP. The ASP activities led by the pediatric attending physician reduced the delta slope of total antimicrobial use without increasing the mortality rate despite an increasing proportion of ESBL-producing gram-negative bacteremia in pediatric patients.

https://doi.org/10.3346/jkms.2024.39.e172

ACKNOWLEDGMENTS

We thank Soon Jun Kwak for helping with bacteremia data collection.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Supplementary Methods

Supplementary Table 1
Number of admitted cases from 2001 to 2019

Supplementary Table 2
The proportion of antimicrobial-resistant pathogens in bacteremia in the pre-and post-ASP intervention

Supplementary Table 3
The differences in antimicrobial use between Period C and post-Period C

Supplementary Table 4
CDC's core elements of ASP and pediatric ASP in SMC during the post-intervention period

Supplementary Fig. 1
Graphical depiction of the delta slope and change in level (modified from Turner SL et al. 2021[4]). Secular trends (indicated by solid lines) for the pre- and post-intervention periods (indicated by the vertical dashed line) are estimated from the data (indicated by grey dots). A counterfactual trend line (extrapolation of the pre-intervention slope shown as a dashed grey line) is compared with the post-intervention slope to estimate the immediate effect (change in level) and sustained effect (delta slope) of the ASP intervention. Parameters are indicated as the change in level (I) at the ASP intervention and the delta slope (Δ).

REFERENCES

1. Fishman N; Society for Healthcare Epidemiology of AmericaInfectious Diseases Society of AmericaPediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol* 2012;33(4):322-7. PUBMED | CROSSREF
2. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014;5(6):229-41. PUBMED | CROSSREF
3. Kolár M, Urbánek K, Látal T. Antibiotic selective pressure and development of bacterial resistance. *Int J Antimicrob Agents* 2001;17(5):357-63. PUBMED | CROSSREF
4. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect* 2016;22(5):416-22. PUBMED | CROSSREF
5. Naylor NR, Pouwels KB, Hope R, Green N, Henderson KL, Knight GM, et al. The health and cost burden of antibiotic resistant and susceptible *Escherichia coli* bacteraemia in the English hospital setting: a national retrospective cohort study. *PLoS One* 2019;14(9):e0221944. PUBMED | CROSSREF
6. Thorpe KE, Joski P, Johnston KJ. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding $2 billion annually. *Health Aff (Millwood)* 2018;37(4):662-9. PUBMED | CROSSREF

7. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006;42 Suppl 2:S82-9. PUBMED | CROSSREF
8. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016;62(10):e51-77. PUBMED | CROSSREF
9. Yoon YK, Kwon KT, Jeong SJ, Moon C, Kim B, Kiem S, et al. Guidelines on implementing antimicrobial stewardship programs in Korea. *Infect Chemother* 2021;53(3):617-59. PUBMED | CROSSREF
10. Cheong HS, Park KH, Kim HB, Kim SW, Kim B, Moon C, et al. Core elements for implementing antimicrobial stewardship programs in Korean general hospitals. *Infect Chemother* 2022;54(4):637-73. PUBMED | CROSSREF
11. Shin SM, Shin JY, Kim MH, Lee SH, Choi S, Park BJ. Prevalence of antibiotic use for pediatric acute upper respiratory tract infections in Korea. *J Korean Med Sci* 2015;30(5):617-24. PUBMED | CROSSREF
12. Choe YJ, Shin JY. Trends in the use of antibiotics among Korean children. *Korean J Pediatr* 2019;62(4):113-8. PUBMED | CROSSREF
13. Song SY, Shin JH, Hyeon SY, Kim D, Kang WK, Choi SH, et al. Pediatric fluoroquinolone prescription in South Korea before and after a regulatory intervention: a nationwide study, 2007-2015. *PLoS One* 2017;12(5):e0176420. PUBMED | CROSSREF
14. Huh K, Chung DR, Park HJ, Kim MJ, Lee NY, Ha YE, et al. Impact of monitoring surgical prophylactic antibiotics and a computerized decision support system on antimicrobial use and antimicrobial resistance. *Am J Infect Control* 2016;44(9):e145-52. PUBMED | CROSSREF
15. Hwang H, Kim B. Impact of an infectious diseases specialist-led antimicrobial stewardship programmes on antibiotic use and antimicrobial resistance in a large Korean hospital. *Sci Rep* 2018;8(1):14757. PUBMED | CROSSREF
16. Jang W, Hwang H, Jo HU, Cha YH, Kim B. Effect of discontinuation of an antimicrobial stewardship programme on the antibiotic usage pattern. *Clin Microbiol Infect* 2021;27(12):1860.e1-5. PUBMED | CROSSREF
17. Kim SH, Yoon JG, Park HJ, Won H, Ryoo SS, Choi E, et al. Effects of a comprehensive antimicrobial stewardship program in a surgical intensive care unit. *Int J Infect Dis* 2021;108:237-43. PUBMED | CROSSREF
18. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in children: a systematic review. *J Hosp Infect* 2018;99(2):117-23. PUBMED | CROSSREF
19. Turner RB, Valcarlos E, Loeffler AM, Gilbert M, Chan D. Impact of an antimicrobial stewardship program on antibiotic use at a nonfreestanding children's hospital. *J Pediatric Infect Dis Soc* 2017;6(3):e36-40. PUBMED
20. Hersh AL, De Lurgio SA, Thurm C, Lee BR, Weissman SJ, Courter JD, et al. Antimicrobial stewardship programs in freestanding children's hospitals. *Pediatrics* 2015;135(1):33-9. PUBMED | CROSSREF
21. Nzegwu NI, Rychalsky MR, Nallu LA, Song X, Deng Y, Natusch AM, et al. Implementation of an antimicrobial stewardship program in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2017;38(10):1137-43. PUBMED | CROSSREF
22. Aizawa Y, Suwa J, Higuchi H, Fukuoka K, Furuichi M, Kaneko T, et al. Antimicrobial stewardship program in a pediatric intensive care unit. *J Pediatric Infect Dis Soc* 2018;7(3):e156-9. PUBMED | CROSSREF
23. Klatte JM, Kopcza K, Knee A, Horton ER, Housman E, Fisher DJ. Implementation and impact of an antimicrobial stewardship program at a non-freestanding children's hospital. *J Pediatr Pharmacol Ther* 2018;23(2):84-91. PUBMED | CROSSREF
24. Velasco-Arnaiz E, Simó-Nebot S, Ríos-Barnés M, López Ramos MG, Monsonís M, Urrea-Ayala M, et al. Benefits of a pediatric antimicrobial stewardship program in antimicrobial use and quality of prescriptions in a referral children's hospital. *J Pediatr* 2020;225:222-230.e1. PUBMED | CROSSREF
25. Shishido A, Otake S, Kimura M, Tsuzuki S, Fukuda A, Ishida A, et al. Effects of a nudge-based antimicrobial stewardship program in a pediatric primary emergency medical center. *Eur J Pediatr* 2021;180(6):1933-40. PUBMED | CROSSREF
26. Wattier RL, Levy ER, Sabnis AJ, Dvorak CC, Auerbach AD. Reducing second gram-negative antibiotic therapy on pediatric oncology and hematopoietic stem cell transplantation services. *Infect Control Hosp Epidemiol* 2017;38(9):1039-47. PUBMED | CROSSREF
27. Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. *Int J Infect Dis* 2017;64:69-73. PUBMED | CROSSREF
28. Donà D, Barbieri E, Daverio M, Lundin R, Giaquinto C, Zaoutis T, et al. Correction to: implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review. *Antimicrob Resist Infect Control* 2020;9(1):59. PUBMED | CROSSREF

29. Stultz JS, Arnold SR, Shelton CM, Bagga B, Lee KR. Antimicrobial stewardship impact on *Pseudomonas aeruginosa* susceptibility to meropenem at a tertiary pediatric institution. *Am J Infect Control* 2019;47(12):1513-5. PUBMED | CROSSREF

30. Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. *Clin Infect Dis* 2007;44(5):664-70. PUBMED | CROSSREF

31. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. *J Antimicrob Chemother* 2003;52(5):764-71. PUBMED | CROSSREF

32. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;46(1):348-55. PUBMED

33. Turner SL, Karahalios A, Forbes AB, Taljaard M, Grimshaw JM, McKenzie JE. Comparison of six statistical methods for interrupted time series studies: empirical evaluation of 190 published series. *BMC Med Res Methodol* 2021;21(1):134. PUBMED | CROSSREF

34. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27(4):299-309. PUBMED | CROSSREF

35. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). 2009 H1N1 Pandemic (H1N1pdm09 virus). https://archive.cdc.gov/#/details?url=https://www.cdc.gov/flu/pandemic-resources/2009-h1n1-pandemic.html. Updated 2019. Accessed March 1, 2023.

36. Cho SY, Kang JM, Ha YE, Park GE, Lee JY, Ko JH, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet* 2016;388(10048):994-1001. PUBMED | CROSSREF

37. Lee J, Pai H, Kim YK, Kim NH, Eun BW, Kang HJ, et al. Control of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a children's hospital by changing antimicrobial agent usage policy. *J Antimicrob Chemother* 2007;60(3):629-37. PUBMED | CROSSREF

38. Viale P, Tumietto F, Giannella M, Bartoletti M, Tedeschi S, Ambretti S, et al. Impact of a hospital-wide multifaceted programme for reducing carbapenem-resistant Enterobacteriaceae infections in a large teaching hospital in northern Italy. *Clin Microbiol Infect* 2015;21(3):242-7. PUBMED | CROSSREF

39. Horikoshi Y, Higuchi H, Suwa J, Isogai M, Shoji T, Ito K. Impact of computerized pre-authorization of broad spectrum antibiotics in *Pseudomonas aeruginosa* at a children's hospital in Japan. *J Infect Chemother* 2016;22(8):532-5. PUBMED | CROSSREF

40. Chang MS, Sung KW, Kim YJ. Clinical characteristics of bacteremia in children with cancer. *Korean J Pediatr Infect Dis* 2011;18(2):201-6. CROSSREF

41. Lee NH, Kang JM, Lee JW, Huh HJ, Lee NY, Yoo KH, et al. Cefepime versus cefepime plus amikacin as an initial antibiotic choice for pediatric cancer patients with febrile neutropenia in an era of increasing cefepime resistance. *Pediatr Infect Dis J* 2020;39(10):931-6. PUBMED | CROSSREF

42. Lee MJ, Moon SM, Kim B, Park SY, Park JY, Koo H, et al. Status of antimicrobial stewardship programmes in Korean hospitals including small to medium-sized hospitals and the awareness and demands of physicians: a nationwide survey in 2020. *J Glob Antimicrob Resist* 2021;26:180-7. PUBMED | CROSSREF

43. Kim B, Eun BW, Lee E, Kim TH, Park S, Park SY. Professional status of infectious disease specialists in Korea: a nationwide survey. *J Korean Med Sci* 2022;37(47):e320. PUBMED | CROSSREF

44. Ashiru-Oredope D, Kerr F, Hughes S, Urch J, Lanzman M, Yau T, et al. Assessing the impact of COVID-19 on antimicrobial stewardship activities/programs in the United Kingdom. *Antibiotics (Basel)* 2021;10(2):110. PUBMED | CROSSREF

45. Comelli A, Genovese C, Lombardi A, Bobbio C, Scudeller L, Restelli U, et al. What is the impact of SARS-CoV-2 pandemic on antimicrobial stewardship programs (ASPs)? The results of a survey among a regional network of infectious disease centres. *Antimicrob Resist Infect Control* 2022;11(1):108. PUBMED | CROSSREF

46. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect* 2020;26(12):1622-9. PUBMED | CROSSREF

47. Alshaikh FS, Godman B, Sindi ON, Seaton RA, Kurdi A. Prevalence of bacterial coinfection and patterns of antibiotics prescribing in patients with COVID-19: a systematic review and meta-analysis. *PLoS One* 2022;17(8):e0272375. PUBMED | CROSSREF

48. Abelenda-Alonso G, Padullés A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, et al. Antibiotic prescription during the COVID-19 pandemic: a biphasic pattern. *Infect Control Hosp Epidemiol* 2020;41(11):1371-2. PUBMED | CROSSREF

49. CDC. *Core Elements of Hospital Antibiotic Stewardship Programs*. Atlanta, GA, USA: US Department of Health and Human Services, CDC; 2019.

50. Liu C, Yoon EJ, Kim D, Shin JH, Shin JH, Shin KS, et al. Antimicrobial resistance in South Korea: a report from the Korean global antimicrobial resistance surveillance system (Kor-GLASS) for 2017. *J Infect Chemother* 2019;25(11):845-59. PUBMED | CROSSREF

51. Kaier K, Meyer E, Dettenkofer M, Frank U. Epidemiology meets econometrics: using time-series analysis to observe the impact of bed occupancy rates on the spread of multidrug-resistant bacteria. *J Hosp Infect* 2010;76(2):108-13. PUBMED | CROSSREF

52. Kim D, Lee H, Choi JS, Croney CM, Park KS, Park HJ, et al. The changes in epidemiology of imipenem-resistant *Acinetobacter baumannii* bacteremia in a pediatric intensive care unit for 17 years. *J Korean Med Sci* 2022;37(24):e196. PUBMED | CROSSREF