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Assessing the impact of antimicrobial stewardship programs in tertiary hospitals for UTI: does it work alone?

Prahara Yuri[1]*, Katsumi Shigemura[2,3], Andaru Dahesihdewi[4], Andy Zulfiqqar[1], Koichi Kitagawa[5], Masato Fujisawa[2]

[1]Division of Urology, Department of Surgery, Faculty of Medicine, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Division of Urology, Department of Urology, Kobe University Hospital, Kobe, Japan, [3]Department of International Health, Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan, [4]Department of Clinical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, [5]Department of Advanced Medical Science, Kobe University Graduate School of Science, Technology and Innovation, Kobe, Japan.

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ABSTRACT

Antibiotic resistance is currently an emergent global challenge. Urinary tract infection (UTI), one of the most commonly reported infections, are is becoming a difficult case to treat considering the increasing prevalence of antimicrobial resistance (AMR). The objective of this study was to assess the impact of a hospital antibiotic stewardship program on AMR in managing UTI at a tertiary referral hospital in Yogyakarta, Indonesia, while considering the absence of the program in lower-tier referral hospitals. A retrospective cross-sectional study was conducted from January 2017 to December 2020, classified into pediatric and adult samples. Urine samples were collected and cultured from all patients with UTI hospitalized in the Dr. Sardjito General Hospital, Yogyakarta. The UTI causative bacteria and antibiotic susceptibilities were investigated in the comparison of the first 2 years (2017-2018, prior to the hospital antibiotic stewardship program) and the last 2 years (2019-2020, following the implementation of the hospital antibiotic stewardship program). The isolates from 717 adult urine samples were cultured. *Escherichia coli* (39.1%), *Acitenobacter baumanii* (9.3%), and *Pseudomonas aeruginosa* (8.5%) were identified as the most common bacteria prior to the hospital antibiotic stewardship program. Extended-spectrum β-lactamase-producing *E. coli* and *Burkholderia cepacia* were still increasing in the following the implementation of the hospital antibiotic stewardship program. Our study indicated that the stewardship program does not exhibit a significant change during the first two years considering the absence of the program in lower-tier referral hospitals.

Keywords:
antimicrobial stewardship;
urinary tract infection;
antibiotic resistance;
Indonesia;
extended-β-lactamase

ABSTRAK

Resistensi antibiotik saat ini merupakan tantangan global yang muncul. Infeksi saluran kemih (ISK), merupkan salah satu infeksi yang paling umum dilaporkan, menjadi kasus yang semakin sulit untuk di atasi mengingat prevalensi resistensi antimikroba yang meningkat. Tujuan dari penelitian ini adalah untuk menilai dampak dari program *stewardship on antibiotic* di rumah sakit terhadap resistensi antimikroba dalam mengelola UTI di rumah sakit rujukan tersier di Yogyakarta, Indonesia, tanpa kehadiran program yang sama di RS referral lebih rendah lainnya. Penelitian potong lintang dilakukan dari Januari 2017 hingga Desember 2020, diklasifikasikan menjadi sampel pediatrik dan dewasa. Sampel urin dikumpulkan dan dibiakkan dari semua pasien dengan ISK yang dirawat di Rumah Sakit Umum Pusat Dr. Sardjito, Yogyakarta. Bakteri penyebab infeksi saluran kemih dan kerentanannya terhadap antibiotik dievaluasi dengan membandingkan 2 tahun pertama (2017-2018, sebelum program pengelolaan antibiotik rumah sakit) dan 2 tahun terakhir (2019-2020, setelah penerapan program pengelolaan antibiotik rumah sakit). Dari 717 sampel urin dewasa telah dibiakkan *Escherichia coli* (39.1%), *Acitenobacter baumanii* (9.3%), dan *Pseudomonas aeruginosa* (8.5%) diidentifikasi sebagai bakteri paling umum sebelum program pengelolaan antibiotik rumah sakit. *Escherichia coli* yang memproduksi β-laktamase spektrum luas dan *Burkholderia cepacia* masih meningkat setelah penerapan program pengelolaan antibiotik rumah sakit. Penelitian ini menunjukkan bahwa program pengelolaan tidak menunjukkan perubahan nyata selama dua tahun pertama mengingat ketidakhadiran program tersebut di rumah sakit rujukan tingkat lebih rendah.

*corresponding author: prahara.yuri@ugm.ac.id

INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections. Globally, 150 million people were estimated to be affected by UTI,[1] with all age groups being susceptible. The pattern of infection differs between gender and age groups and patients with predisposing factors.[2] Alarmingly, standard antibiotic treatments have shown decreasing success in UTI management due to increasing antimicrobial resistance (AMR). This problem has been reported globally. According to the World Health Organization (WHO) in 2014, antimicrobial resistance is increasing all over the globe, adding the threat of further complications and mortality from UTI.[3] However, these studies are mostly from developed countries. There have been few reports from Indonesia, the world's fourth-largest population. Some reports have evaluated AMR in UTI from Indonesia in both population-based and laboratory-based research. Sugianli *et al*.[4] assessed the difference in resistance prevalence between laboratory-based and population-based surveillance (PBS) among uropathogens in Indonesia. Sugianli *et al*.[5] also assessed the prevalence of AMR to commonly used antimicrobial drugs in *Escherichia coli* and *Klebsiella pneumoniae* isolated from patients with community- or healthcare-associated UTIs in Indonesia.

Appropriate empirical treatment for UTI plays a key role in treatment success and the prevention of complications. Understanding the demographics and resistance profiles of uropathogens is crucial for determining the appropriate antibiotics.[6,7] However, the rise of AMR has made selecting appropriate empirical antibiotics more challenging. Current microbial susceptibility patterns must be known to treat UTI cases empirically. Bryce *et al*.[8] reported that the global prevalence of AMR in pediatric UTI is largely due to *E. coli* and that the routine use of antibiotics in primary care contributes to AMR in pediatric UTI. In this study, we evaluated the presence of UTI-causative bacteria and their susceptibility patterns in Yogyakarta after the antibiotic stewardship program (ASP) (initiated in the middle of 2018) over four year to establish an appropriate empirical therapy and evaluate our ASP, after classifying the data into pediatrics and adults and comparing with epoch changes as well (2017-2018: before ASP vs 2019-2020: after ASP).

MATERIALS AND METHODS

Study design

This was a hospital-based cross-sectional study. The data were retrospectively gathered from electronic medical records in Dr. Sardjito General Hospital, Yogyakarta a tertiary referral hospital in Yogyakarta, Indonesia, which is also the largest hospital in Central Java with over 813 beds and 23 departments. Antibiotic stewardship program were established at the middle 2018. Antibiotics were grouped into three groups in our ASP using the Carmeli scoring system.[9]-

Antibiotic stewardship program teams closely regulate certain antibiotics, which are grouped in lines 2-3 displayed in Supplemental TABLES 1-3, pre-authorized antibiotic prescriptions are required on line 3, while line 2 items are monitored and evaluated consecutively by ASP teams. The aforementioned groups of antibiotics were only prescribed with approval by the members of antibiotic stewardship boards. This means the physicians cannot use these kinds of broad-spectrum antibiotics by their own judgments from the middle of 2018. To assess how ASP works, this study analysed UTI data from before and after ASP beginning. In the region, the implementation of ASP is not yet widely adapted. Our hospital initiated

an ASP during the time of this study, but lower-tier referral hospitals have not yet implemented the program.

The data were collected consecutively from the laboratory data on electronic medical records of hospitalized UTI or UTI-suspected patients from the internal medicine, surgery, and pediatric departments. Microbiology and antibiotic susceptibility data were collected for all patients with clinical signs and symptoms of UTI, pyuria, at least 50,000 bacterial cfu/mL as well as diagnostic codes for suspected UTI or UTI from January 2017 to January 2020. All urine was collected mid-stream or by catheter. To determine changes over time, we divided the data into four groups, the first 2 years (January 2017- December 2018: prior ASP, pediatrics and adults) and the second 2 years (January 2019- December 2020: following ASP initiation, pediatrics and adults). This is because of the deference between pediatric and adults UTI the underlying disease and history of antibiotic exposures. Furthermore, these four categories for ASP evaluation may aid in providing more precise data on which half (paediatrics or adults) is better controlled. The Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (KE/0395/04) approved this study.

Sample collection

Clinical symptoms of UTI including fever, dysuria, urinary frequency, hematuria, abdominal pain, pain in the bladder area, back pain, and new daytime incontinence were used as criteria for requesting a urinalysis and culture. Urine cultures were performed just after the aseptic urine collection. Patients were selected according to their coding systems that indicate UTI. Bacterial counting, identification, and susceptibility test was done by both conventional methods and the Vitek 2 automated system (bioMerieux, France). Incubate 1 µL of well-mixed urine on cystine-lactose-electrolyte-deficient (CLED) and MacConkey agar plates in an aerobic environment at 37°C for 24 hr. Bacterial growth was observed and the colonies were counted as cfu/mL. Colonies on both types of plates were identified and the resistance pattern were examined based on the minimal inhibitory concentration (MIC) using VITEK 2 automated system as well as the inhibition diameter zone using disc diffusion method.[10]

Antimicrobial susceptibility tests

The antimicrobial susceptibilities of isolates were tested by the micro dilution broth using Vitek 2 automated system as well as the disk diffusion method using Mueller-Hinton medium according to the Clinical and Laboratory Standards Institute (CLSI) recommendations. The antimicrobial agents tested were amoxicillin (AMX), ampicillin-sulbactam (SAM), ceftazidime (CAZ), nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (SXT), ampicillin (AMP), piperacillin-tazobactam (TZP), Ciprofloxacin (CIP), amoxicillin-clavulanic acid (AMC), and tigecycline (TGC). Extended-spectrum β-lactamase (ESBL)-producing bacteria were diagnosed with a positive ESBL test.

RESULTS

Bacteria isolated from pediatric patients

A total 487 samples of urine, and 455 were positive cultures from pediatric patients (93.01%) were collected. *Escherichia coli* (35.1%) was the major causative microbe for UTI, with *E. faecalis* (15.2%) as the second and *K. pneumoniae* (14.9%) the third most causative UTI microbes' prior ASP (2015-2017) (TABLE 2). In the second

period, among 341 samples that were collected, 279 shown positive cultures (81.8%). Although causative bacterial resistance rates remained similar in the second 2-year period the proportion of ESBL increased. Susceptibility tests of *E. coli* ESBL improved toward NIT (96.2%), CIP (37.7%), SXT (24.5%), and TGC (24.5%) after ASP, compared to before ASP. *Escherichia faecalis* had less susceptible to some of tested antibiotics such as AMX, AMC, or TZP but was more susceptible to CAZ, SXT, AM, and TGC. The susceptibilities test result on both *E. coli* ESBL (+) and *K. pneumonia* ESBL (+) were observed steady on this study.

TABLE 1. Antimicrobial susceptibility of isolated bacteria from adult patients

Microbes	n	AMX		SAM		CAZ		NIT		SXT		AMP		TZP		CIP		AMC		TGC	
		%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p
E. coli (2017-2018)	197	-		42.1		46.7		91.9		30.5		14.7		79.7		29.9		1.5		98.0	
			N/A		0.438		0.002		0.000		0.004		0.074		0.000		0.004		0.637		0.000
E. coli (2019-2020)	149	-		46.3		63.1		72.2		45.6		22.1		60.4		45.0		0.7		79.1	
E. coli ESBL (+) (2017-2018)	83	-		31.3		8.4		96.4		15.7		0		77.1		12.0		-		98.8	
			N/A		0.409		0,000		0.000		0.026		0.549		0.023		0.040		N/A		0.000
E. coli ESBL (+) (2019-2020)	161	-		36.6		36.0		62.7		28.6		1.2		62.7		23.0		-		74.2	
K. pneumoniae (2017-2018)	25	-		44.0		56.0		64.0		64		4		60		52.0		-		76.0	
			N/A		0.234		0.753		0.146		0.924		0.287		0.589		0.974		N/A		0.887
K. pneumoniae (2019-2020)	62	-		58.1		59.7		46.8		62.9		0		66.1		51.6		-		77.4	
K. pneumoniae ESBL (+) (2017-2018)	23	-		0.0		8.7		52.2		26.1		0		56.5		30.4		-		78.3	
			N/A		0.553		0.06		0.97		0.857		1.000		0.797		0.957		N/A		0.918
K. pneumoniae ESBL (+) (2019-2020)	57	-		5.3		28.1		52.6		28.1		1.8		59.6		29.8		-		77.2	
P. aeruginosa (2017-2018)	61	1.6		1.6		59.0		0.0		1.6		1.6		63.9		49.2		1.6		0.0	
			0.430		1.000		0.859		0.000		0.000		1.000		0.315		0.981		0.430		0.000
P. aeruginosa (2019-2020)	81	0		2.5		60.5		23.5		29.6		1.2		55.6		49.4		0		30.9	
E. faecalis (2017-2018)	3	-		100		66.7		66.7		66.7		0		0		66.7		-		0.0	
			N/A		0.143		1.000		0.107		0.464		1.000		1.000		0.464		N/A		0.464
E. faecalis (2019-2020)	5	-		20.0		60.0		0.0		20		20		20		20.0		-		40.0	
E. cloacae (2017-2018)	20	89.5		5.0		50.0		50.0		65		5		65		70.0		-		86.4	
			0.002		0.317		0.337		0.337		0.171		0.317		0.087		0.024		N/A		0.268
E. cloacae (2019-2020)	43	25.0		0.0		37.2		62.8		46.5		0		41.9		39.5		-		74.4	

Extended-spectrum β-lactamase; Chi Square analysis ($p < 0.05$); Fisher test analysis ($p<0.05$); amoxicillin (AMX); ampicillin-sulbactam (SAM); ceftazidime (CAZ); nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (SXT); ampicillin (AMP); piperacillin-tazobactam (TZP); ciprofloxacin (CIP); amoxicillin-clavulanic acid (AMC); tigecycline (TGC).

TABLE 2. Antimicrobial susceptibility of isolated bacteria from pediatric patients

Microbes	n	AMX		SAM		CAZ		NIT		SXT		AMP		TZP		CIP		AMC		TGC	
		%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p	%	p
E. coli (2017-2018)	107	-	N/A	23.4	0.002	46.7	0.000	96.3	0.100	32.7	0.186	9.3	0.004	50.5	0.001	49.5	0.013	1.9	1.000	60.7	0.000
E. coli (2019-2020)	48	-		47.9		89.6		89.6		43.8		27.1		79.2		70.8		0.0		94.0	
E. coli ESBL[1)] (+) (2017-2018)	53	-	N/A	17.0	0.360	7.5		96.2		24.5		-		18.9		37.7		-	N/A	24.5	
							0.079		0.648		0.092		N/A		0.000		0.137				0.000
E. coli ESBL[1)] (+) (2019-2020)	64	-		25.0		18.8		95.3		17.2		-		75.0		25.0		-		98.4	
K. pneumoniae (2017-2018)	30	-	N/A	23.3	0.08	40.0		60.0		40.0		-		30.0		60.0		80.0	0.478	56.7	
							0.114		0.825		0.825		N/A		0.000		0.825				0.004
K. pneumoniae (2019-2020)	19	-		47.4		63.2		63.2		36.8		-		84.2		63.2		71.4		94.7	
K. pneumoniae ESBL (+) (2017-2018)	37	-	N/A	-	N/A	0.0		75.7		27.0		-		10.8		64.9		-	N/A	18.4	
							0.054		0.051		0.032		N/A		0.000		0.000				0.000
K. pneumoniae ESBL (+) (2019-2020)	37	-		-		13.5		54.1		8.1		-		64.9		21.6		-		91.9	
Enterococcus faecalis (2017-2018)	69	59.4	0.033	1.4	0.310	2.9	0.094	84.1		5.8		62.3		27.5		37.7		59.4	0.033	0.0	
									0.143		0.252		0.290		0.567		1.000				0.190
E. faecalis (2019-2020)	4	0.0		0.0		25.0		50.0		25.0		100		0.0		25.0		0		7.7	
Pseudomonas aeruginosa (2017-2018)	33	-	N/A	-	N/A	57.6	0.009	0.0		0.0		-		21.2		75.8		-	N/A	47.8	
									0.256		0.441		N/A		0.000		0.093				0.122
P. aeruginosa (2019-2020)	26	-		-		88.5		3.8		3.8		-		76.9		92.3		-		0.0	
Enterobacter cloacae (2017-2018)	13	-	N/A	-	N/A	15.4	1.000	84.6		30.8		-		15.4		84.6		-	N/A	53.3	
									0.202		1.000		N/A		0.645		0.202				0.043
E. cloacae (2019-2020)	6			-		16.7		58.3		33.3		-		25.0		58.3		-		91.7	

Extended-spectrum β-lactamase; Chi Square analysis (p< 0.05); Fisher test analysis (p<0.05); amoxicillin (AMX); ampicillin-sulbactam (SAM); ceftazidime (CAZ); nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (SXT); ampicillin (AMP); piperacillin-tazobactam (TZP); ciprofloxacin (CIP); amoxicillin-clavulanic acid (AMC); tigecycline (TGC).

Antimicrobial susceptibility

The results of antimicrobial susceptibility test were confirmed positive with the formation of an inhibition zone by clavulanic acid (CLA) on the middle ceftazidime (CAZ)/CLA disc gert-year period (90,3%). Among the isolates, *E. coli* (n=280, 39.1%), *Acinetobacter baumanii* (n=67, 9.3%), and *Pseudomonas aeruginosa* (n=61, 8.5%) were identified as the most common bacteria. In the second two-year period (following ASP), approximately 943 samples were collected, and 882 samples shown positive cultured (93.5%). The changes over time showed that *E. coli* and *K. pneumoniae* significantly declined as causative microbes for UTI Following ASP Program (2019-2020) compared to the prior ASP program (2017-2018). The proportion of ESBL-producing *E. coli* increased from 11.6% prior ASP to 18.5 % following ASP, and *P. aeruginosa* increased from 8.5% to 9.2% (TABLE 1). *Escherichia coli* showed better susceptibility to CIP (29.9% in 2017-2018 and 45% in 2019-2020, p= 0.004) as well as ESBL-producing *E. coli* (12% before ASP and 24% after ASP). We also found *Enterococcus faecalis* resistance to most antibiotics increased after ASP-compared to prior ASP (p < 0.05).

Susceptibility test results for *P. aeruginosa* remained steady over the entire study period, with susceptibility tests showing favorable results for CAZ compared to SXT, TZP, and CIP satisfactory susceptibility (TABLE 3).

TABLE 3. Isolated bacteria

Microbes	Adults				Pediatrics			
	2017-2018		2019-2020		2017-2018		2019-2020	
	n	%	n	%	n	%	n	%
E. coli	197	27.5	149	16.9	107	23.5	50	18.0
E. coli ESBL[1)] (+)	83	11.6	163	18.5	53	11.6	64	23.0
K. pneumoniae	25	3.5	62	7.0	30	6.6	19	6.8
K. pneumoniae ESBL (+)	23	3.2	57	6.5	38	8.3	37	13.2
E. gallinarum	9	1.25	11	1.2	2	0.4	3	0.6
P. aeruginosa	61	8.5	81	9.2	33	7.2	26	9.3
Candida tropicalis	79	11.2	80	9.0	18	3.9	6	2.1
E. faecalis	3	0.4	5	0.6	69	15.2	4	1.4
Sphingomonas paucimobilis	1	0.1	3	0.3	2	0.4	0	0.0
Acinetobacter baumannii	67	9.3	88	10.0	16	3.5	4	1.4
Citrobacter freundii	9	1.3	8	0.9	2	0.4	1	0.4
E. cloacae	22	3.1	43	4.9	15	3.2	12	4.3
Staphylococcus haemolyticus	24	3.3	15	1.7	23	5.0	12	4.3
Proteus mirabilis	15	2.1	12	1.4	5	1.0	4	1.4
Burkholderia cepacia	22	3.1	24	2.7	8	1.7	19	6.8
S. aureus	17	2.4	19	2.1	6	1.3	2	0.7
C. krusei	3	0.4	4	0.4	3	0.7	0	0.0
S. epidermidis	4	0.6	2	0.2	3	0.7	4	1.4
K. oxytoca	2	0.3	3	0.3	1	0.2	0	0.0
C. lusitaniae	17	2.4	12	1.4	1	0.2	3	1.0
C. parapsilosis	10	1.7	13	1.5	9	1.8	2	0.7
S. hominis	4	0.5	3	0.3	2	0.4	2	0.7
P. putida	7	1.0	11	1.2	1	0.2	0	0.0
Aeromonas hydrophila/caviae	3	0.4	1	0.1	2	0.4	0	0.0
C. koseri	2	0.3	1	0.1	2	0.4	2	0.7
E. casseliflavus	3	0.4	3	0.3	0	0.0	2	0.7
S. saprophyticus	4	0.6	8	0.9	0	0.0	1	0.4
Salmonella enterica	1	0.1	1	0.1	0	0.0	0	0.0
Total	717	100	882	100	453	100	279	100

DISCUSSION

Microbial drug resistance is common worldwide and is increasing year after year. Our hospital implemented Rational Use of Medicine and ASP to address increased antibiotic resistance, but the high AMR has not changed in first two years. After the implementation of the national universal health coverage, infection management in Indonesia strategically focused on the secondary and tertiary health centers. Patients with more complicated or unresolved infections, such as ESBL or antibiotic-resistant infections, are more likely to be referred to tertiary hospitals, thus registering as an increase in antibiotic-resistant infections despite the current ASP. Pre-authorization and formulary restrictions of antibiotics are part of the strategy that has been implemented in

our hospital. These strategies involve several antibiotics listed in lines 2 and 3 according to Carmeli scoring systems which cannot be prescribed without permission and approval from the ASP team, and prescriptions are reviewed case by case. ASP has been set up in a limited number of regional hospitals with various difficulties, and our hospital has been the program initiator in our region.

Antibiotic resistance is caused in part by over-prescription and inappropriate usage of broad-spectrum antibiotics such as fluoroquinolones.[11-13] The increasing proportion of ESBL is an alarming sign of the imminent threat of untreatable UTI. The rise of UTI caused by ESBL-producing bacteria has been observed in both developed and developing countries.[14,15] Bacterial susceptibility to AMP, AMX, and AMC was also decline in this study.

Unnecessary prescriptions due to the lack of properly administered ASP may contribute to declines in bacterial susceptibility.[11,13,16] The high rate of NIT TZP TGC resistance in *E. coli* spp. in this study is not surprising in the adult population, since the intrinsic resistant phenotypes of these bacteria have been widely reported.[17,18] In contrast, AMS, CAZ, and SXT had good susceptibility for non-ESBL-producing *E. coli*[14] and remained around 45% in ESBL-producing *E. coli* over the study period. Similar results were also reported by Cantas *et al.*[15] who found that ESBL-producing *E. coli* were highly susceptible to ERT and MER. Another report in Surabaya Indonesia, found that susceptibility to AMI was 100% for ESBL-producing *E. coli*. Our results in Yogyakarta Indonesia, were lower, with a susceptibility to AMI for ESBL-producing *E. coli* of 90.9%,[14] which may indicate the need for caution in UTI treatment, considering the antibiograms in each institution.

Nitrofurantoin is not commonly available at primary health centers in Indonesia and is seldom used in secondary health centers. Sekyere *et al.*[19] discussed the vertical spread of nitrofurantoin resistance genes through clonal and multiclonal expansion, commonly found locally. Abia *et al.*[20] also reported *E. coli* resistance to nitrofurantoin genes in South Africa. Our results are consistent with Procop *et al.*[21] and Garau *et al.*[22] demonstrating that ESBL spp. have lower susceptibility to nitrofurantoin than non-ESBL, as seen now in Indonesia. Our results showed that some bacteria such as *E. coli* and *E. coli*-producing ESBL, increased susceptibilities to nitrofurantoin after ASP initiation.

Susceptibility tests for *K. pneumoniae* showed a more alarming result. We found high rates of resistance toward a wide variety of antibiotics. In this study, *K. pneumoniae* showed lower susceptibility levels to most available antibiotics for both the adult and pediatric age groups. High incidence rates of ESBL and extended resistance were found in Australia, Israel, Greece, Colombia, and China, but susceptibilities consistently remained high.[23-25] Cautious usage and close observation are essential to maintain the efficacy of AMI, ERT, and MER.

Enterococcus faecalis is a common cause of UTI and forms a biofilm responsible for persistent UTI and treatment resistance.[25,26] In this study, *E. faecalis* showed significant changes of increasing resistance to most of the antimicrobials tested. Living in a competitive environment and exposed to a myriad of antibiotics, this bacterium has developed a variety of responses and considerable genetic plasticity to cope with threats.[27,28] Our susceptibility tests showed that SAM (100%), CAZ (66.7%), NIT (66.7%), SXT (66.7%), and CIP (66.7%) were initially suitable for *E. faecalis* UTI in adults before ASP, and rapidly declined after the ASP. Other antibiotics had similar results, with similar patterns for both pediatric and adult patients despite the implementation of ASP in

our hospital. This may indicate that ASP need to be implemented at a region-wide level as part of a comprehensive policy.

This study showed good satisfactory susceptibility of *P. aeruginosa* to CAZ (88.5%) and CIP (92.3%) in pediatric patients before the implementation of ASP, and a decline to 57.6% (TAZ) and 75.8% (CIP) after implementation of ASP, which was alarming even though it did not reach statistical significance. Our study found favorable susceptibilities of FTN and TGC for ESBL-producing *E. coli* in pediatric patients. Favorable susceptibilities of CAZ and TGC were also found in the adult population.

This study has several limitations, including the use of retrospective cross-sectional design and potential selection bias. We were also unable to exclude cases caused by anatomical abnormality or distinguish between nosocomial and non-nosocomial UTI. Our data also did not include complete antibiotic dosing history or intrinsic antibiotic resistance data. In addition, resistance patterns of bacteria in water and sludge were not investigated previously; this may be a confounding factor in this study. We collected whole-hospital data consecutively without distinguishing between clinical departments. Lastly, we lacked the evaluation data of ASP performance in detail, for instance, how much such intervention was done or what was the physicians' response or patients' outcome, and the link with bacterial data. Further studies are needed to determine the best alternative treatments after obtaining and applying antibiotic susceptibility results. The study provides valuable insights into the effectiveness of ASPs and emphasizes the need for a collaborative and integrated approach to antimicrobial stewardship across the healthcare continuum.

CONCLUSION

In conclusion, we found that our ASP the implementation of ASPs in tertiary hospitals is significantly unable to overcome the effects of antibiotic use in lower-referral hospitals. The findings of this study have important implications for the design and implementation of ASPs. It suggests that ASPs should be complemented by additional interventions, such as enhancing antibiotic prescribing in lower-referral hospitals, in order to be effective in modifying antibiotic susceptibility pattern. We highlight the importance of a comprehensive and coordinated approach to antimicrobial stewardship across all healthcare settings.

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