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ORIGINAL ARTICLE

Decreased antimicrobial resistance and defined daily doses after implementation of a clinical culture-guided antimicrobial stewardship program in a local hospital

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KEYWORDS
antimicrobial resistance;
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defined daily dose

Abstract *Background:* We aimed to report the implementation of an antimicrobial stewardship program (ASP) guided by clinically significant cultures in a hospital to assess its pharmaceutical, microbiological, financial, and outcome effects.
Methods: A 3-year cohort study of an antimicrobial restriction policy implementation was performed. The ASP with culture-guided de-escalation of antibiotics was instituted in a local hospital since January 1, 2012. The cost of antimicrobials, defined daily dose (DDD), susceptibility to antimicrobials, and outcome of all admitted patients were calculated and evaluated before and after the ASP implementation.
Results: Average monthly length of stay of admitted patients decreased from 7.8 ± 0.5 days in 2011 to 6.9 ± 0.3 days in 2013 ($p < 0.001$). The average monthly cost of antimicrobials decreased 46.9% from US$30,146.8 in 2011 to US$16,021.3 in 2013 ($p < 0.001$). Total

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intravenous antimicrobial DDDs per 100 bed-days of the inpatients were 66.9, 54.1 and 48.4 in 2011, 2012 and 2013, respectively. A total of 18.6 DDDs per 100 bed-days of inpatients (27.7%) decreased from 2011 to 2013. By comparing data in 2013 to those in 2011, the ASP reduced antimicrobial resistance of Gram-positive bacteria ($p = 0.013$), Gram-negative bacteria ($p < 0.001$), and predominant species (all $p < 0.05$). The yearly mortality also decreased from 1.3% in 2011 to 1.1% in 2012 and 1.0% in 2013.

Conclusions: The ASP with a culture-guided de-escalation of antibiotics successfully reduced length of stay, mortality, the cost of antimicrobials, DDDs, and antimicrobial resistance rate, and that is highly recommended for local hospitals.

Introduction

Antibiotic overuse and resistance problems have become a major public health issue worldwide.[1–8] In addition to increased treatment expenditures, inappropriate or excessive antibiotic usage results in the emergence and spread of antibiotic-resistant bacteria, which lead to increased morbidity, inpatient stays, and higher mortality.[9–18] The use of antimicrobials against bacterial infections is pivotal in the emergence of antimicrobial resistance of bacteria due to antibiotic selective pressure.[4–6] In order to improve patient outcomes by reducing the unintended consequences of antibiotic use, the Infectious Disease Society of America, the Society for Healthcare Epidemiology of America and the Centers for Disease Control, Taiwan have published guidelines for developing antimicrobial stewardship programs (ASPs).[1–3] Procalcitonin-guided or blood-culture-guided de-escalation strategies have been shown to reduce antimicrobial exposure without any impact on the mortality rate and treatment failure in critically ill patients.[19–21] However, procalcitonin and blood culture are seldom available in noncritical patients. For noncritical patients, it is more feasible to guide usage of antibiotics by clinically significant cultures from urine, pus, sputum, blood, and stools.

It is difficult to implement an ASP in a local, small hospital without adequate resources.[8] The Anatomical Therapeutic Chemical Classification/Defined Daily Dose (**ATC/DDD**) classification from the World Health Organization in 2013, widely used as a standard to measure drug use in hospitals and community settings, was used to calculate antibiotic usage, which was presented as the numbers of DDDs and DDDs/100 bed-days.[22–26] In this study, we monitored the efficacy of the ASP on DDD, antimicrobial cost, and bacterial susceptibility before and after ASP implementation.

Methods

Study designs

All patients admitted to Nan Men General Hospital (NMGH), a 141-bed local hospital in Northern Taiwan, including 116 acute illness beds, 15 hemodialysis beds, and 10 intensive care center beds, from 2011 to 2013 were enrolled in this study. Prior to January 2012, traditional antimicrobial restriction policy other than the culture-based regimen was performed in this hospital. The Antibiotic Restriction Committee (ARC) monitored and controlled the consumption of all antimicrobials. All ARC doctors were senior physicians and well trained in antibiotic control. Computerized Physician Order Entry (CPOE) and Computerized Antimicrobial Approval System (CAAS) were also implemented. The antibiotic prescriptions that failed to pass the above audit were discontinued within 48 hours. Prescriptions of restricted and unrestricted antimicrobials, antibiotic prescriptions in the outpatient department, and prophylactic antimicrobials for surgery were post-prescriptively audited under the control of infectious disease specialists. Pediatric patients were the most frequently admitted patients, contributing to more than half of the total admitted to this hospital (Table 1). A new antimicrobial restriction policy with a culture-guided ASP was implemented in this hospital and supported by a medical center from January 1, 2012. Routine monitoring of antibiotic use based on infected culture by the web-based justification was initiated on January 1, 2012 to decrease antimicrobial resistance and expenditure. The new restriction policy was initially implemented on January 1, 2012. Before the ASP, the specialists, administration and technologists of NMGH were well trained by Chang Gung Memorial Hospital (CGMH), a 3700-bed teaching medical center. However, NMGH is not part of a larger CGMH system that shares/pools resources before ASP implementation. This study was designed as a cohort "before and after" study to compare pharmaceutical, microbiological and financial changes before and after implementation of the policy over a 3-year period from 2011 to 2013, and data in 2011 (before the culture-guided ASP) were used as controls. All 27 physicians remained the same during this study period. This study was approved by the Institutional Review Board of NMGH.

New antimicrobial restriction policy

The new antimicrobial restriction policy of the culture-guided ASP was created by the ARC, including infectious disease physicians, clinical pharmacists, microbiologists, and administrators of NMGH and CGMH, and it was implemented on January 1, 2012. All prescriptions of restricted

Table 1 Patient characteristics during baseline (2011) and intervention periods (2012–2013).

Patient characteristics	*n* (%), 2011 (*n* = 4181)	*n* (%), 2012 (*n* = 4230)	*n* (%), 2013 (*n* = 4435)	*p* ($Data_{2012}$ *vs.* $Data_{2011}$)	*p* ($Data_{2013}$ *vs.* $Data_{2011}$)
Age distribution					
≤ 10 y	1653 (39.5)	1674 (39.6)	1729 (39.0)	0.971	0.601
11–20 y	1253 (30.0)	1298 (30.7)	1296 (29.2)	0.475	0.448
21–60 y	367 (8.8)	375 (8.9)	387 (8.7)	0.888	0.932
61–80 y	558 (13.3)	557 (13.2)	584 (13.8)	0.810	0.500
> 80 y	350 (8.4)	326 (7.7)	439 (9.2)	0.229	0.164
Male sex	2035 (48.7)	2075 (49.1)	2196 (49.5)	0.726	0.434
Primary ICD-9 diagnosis codes					
Pulmonary disease	1367 (32.7)	1375 (32.9)	1397 (31.5)	0.788	0.464
Gastrointestinal disease	1045 (25.0)	1054 (24.9)	1157 (26.1)	0.071	0.550
Urinary tract disease	427 (10.2)	437 (10.3)	442 (10.0)	0.858	0.704
Neoplastic disease	346 (8.3)	356 (8.4)	362 (8.2)	0.816	0.848
Cardiac disease	254 (6.1)	263 (6.2)	275 (6.2)	0.786	0.808
Soft tissue disease	287 (6.9)	295 (7.0)	306 (6.9)	0.843	0.948
Neurological disease	287 (6.9)	294 (7.0)	316 (7.1)	0.939	0.636
Endocrinal disease	168 (4.0)	156 (3.7)	180 (4.1)	0.431	0.873
Pitt bacteremia score					
≥ 4 points	416 (9.9)	430 (10.2)	433 (9.8)	0.742	0.772
3 points	632 (15.1)	627 (14.8)	673 (15.2)	0.706	0.939
2 points	937 (22.4)	966 (22.8)	1031 (23.2)	0.641	0.356
≤ 1 point	2196 (52.5)	2207 (52.2)	2298 (51.8)	0.749	0.511
Charlson score					
≥ 4 points	209 (5.0)	219 (5.2)	227 (5.1)	0.710	0.800
3 points	266 (6.4)	276 (6.5)	271 (6.1)	0.761	0.629
2 points	370 (8.8)	376 (8.9)	385 (8.7)	0.949	0.782
1 point	424 (10.1)	432 (10.2)	453 (10.2)	0.913	0.911
0 points	2912 (69.6)	2927 (69.2)	3099 (69.9)	0.653	0.818

ICD-9 = International Classification of Diseases, 9th Revision.

antimicrobials for admitted patients required approval from ARC physicians by CAAS to prevent suboptimal regimens. For the second review, the microbiological laboratory sent an alarm message for results of positive cultures, including urine, pus, sputum, blood, and stools, to the prescribed attending doctor and preassigned ARC physician by mobile phone. Both the prescribed attending doctor and preassigned ARC physician evaluated the clinical significance of the microbial cultures, and re-evaluated all antimicrobial agents, relevant medical information, updated culture results, and antimicrobial susceptibilities within a 48-hour buffer period through the bidirectional communication platform. Assessment of the clinical significance (colonization or infection) of each bacterium and the type of infection was performed by infectious diseases specialists and followed the US Centers for Disease Control and Prevention criteria, which was defined in the presence of not only bacteria from clinical specimens, but also clinical symptoms or signs of infection.[27] After each new clinically significant culture was reported, the attending doctor adjusted the antimicrobials by CPOE according to the culture result, and ARC physician audited the new prescription by CAAS.

This policy was based on five components in detail: (1) adjust antimicrobials according to the results of clinically significant cultures; (2) for prospective audit, establishing an antibiotic audit via a web-based CAAS verified by the ARC; (3) providing systematic education on stewardship concepts associated with this policy; (4) enhancing the participation of infection specialists and pharmacists in antimicrobial use evaluations based on this policy; and (5) discussing inappropriate prescriptions with the attending doctors. Many experts in infection, microbiology, computers and pharmacy from CGMH taught and helped with the implementation in this local hospital. Unrestricted or less expensive antibiotics were recommended to replace the restricted or more expensive ones if both were indicated according to clinically significant cultures. For example, restricted antimicrobials such as cefuroxime, ceftriaxone, or ceftazidime were recommended to replace imipenem, levofloxacin, moxifloxacin, or tazocin if the indications or susceptibilities were similar. Cases of overuse or inappropriate use of antimicrobials were reported to the ARC, who discussed it with the prescribers. All staff, especially the prescribers, were educated to enhance general adherence to the new policy. Rational use of antimicrobials guided by clinically significant culture and infection control was instructed in the morning meetings.

Antimicrobial category control policy

The antibiotic prescription control policy classified by unrestricted and restricted antimicrobials was initiated.

Unrestricted antimicrobials were first-line antimicrobials, including first-generation cephalosporins, penicillin derivatives, aminoglycosides, and other macrolides, such as cefazolin, clindamycin, and gentamicin, which could be used clinically by all physicians but were verified regularly by infectious disease physicians. Restricted antimicrobials included second-, third-, and fourth-line antimicrobials, and physicians were required to submit applications to the members of ARC through the web-based antimicrobial approval system for their prescription. Restricted antimicrobial agents in our institution were: second-, third-, and fourth-generation cephalosporins (cefuroxime, ceftriaxone, ceftazidime and flomoxef); broad-spectrum penicillin derivatives (ampicillin/sulbactam and piperacillin/tazobactam); fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin); glycopeptides (vancomycin and teicoplanin); carbapenems (imipenem); and others (isepamicin and tigecycline).

Second-line antimicrobials included second-generation cephalosporins and aminopenicillins with enzyme inhibitors. Third-line antimicrobials were broad-spectrum antimicrobial agents such as third- and fourth-generation cephalosporins, antipseudomonal penicillins with enzyme inhibitors, and fluoroquinolones. Fourth-line agents, such as imipenem, colistin and tigecycline, were restricted for the treatment of multiple drug-resistant bacteria. ARC members conducted clinically significant culture-guided and bedside evaluations before approving online prescriptions. However, emergency antibiotic prescriptions for $<$ 2 days were available for instantaneous dispensing to prevent impeding the treatment of severely sick patients. Antibiotic usage, dosage, frequency and duration were re-evaluated by a pharmacist via telephone.

Bacterial isolates and antimicrobial susceptibility

All bacteria cultured from any sources, including urine, pus, sputum, blood, and stools, among patients admitted to NMGH were collected from 2011 to 2013. All these bacteria were analyzed for changes in their antibiotic susceptibility during the study period. Antimicrobial susceptibility was determined using the disk diffusion method according to the Clinical and Laboratory Standards Institute standards.[28]

DDD

Antibiotic data were determined based on the number of packages and doses from the retrospective pharmacy database of the hospital for 2011—2013. These raw data were entered into Microsoft Excel and converted into DDDs. The World Health Organization ATC system was used to identify antimicrobials (ATC/DDD version 2013) and their adult DDDs as revised in 2012.[23] Data were expressed as the number of DDDs per 100 bed-days of the inpatients. DDDs/100 bed-days = annual consumption of antimicrobials (g) $\times$ 100 / DDD (g/d) $\times$ total hospitalization days.[22—26] Data on all intravenous antimicrobials administered to patients were evaluated in this study.

Questionnaire

The ARC designed questionnaires were used in the hospital for evaluating the satisfaction of the attending doctors. These questionnaires were validated and audited by independent administrators, and approved by the hospital superintendent and sent to the attending doctors. All related staff, including attending doctors and nurses, answered the questionnaires anonymously in their individual offices. The questionnaires were collected and summarized by administrators.

Statistical analysis

Data were recorded and entered into a database. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Student t test, χ^2 test or Fisher's exact test was used when appropriate to compare proportions. All statistical analyses were two-sided, and the significance was set at $p < 0.05$.

Results

Patient characteristics

There were 4181 admissions in 2011 during the 1-year baseline period, and 4230 and 4435 admissions in 2012 and 2013, respectively, during the 2-year intervention period. Number of monthly admissions increased from 348.4 $\pm$ 36.5 in 2011 to 369.6 $\pm$ 29.6 ($p = 0.015$). Average length of stay decreased from 7.8 $\pm$ 0.5 days in 2011 to 7.2 $\pm$ 0.3 days in

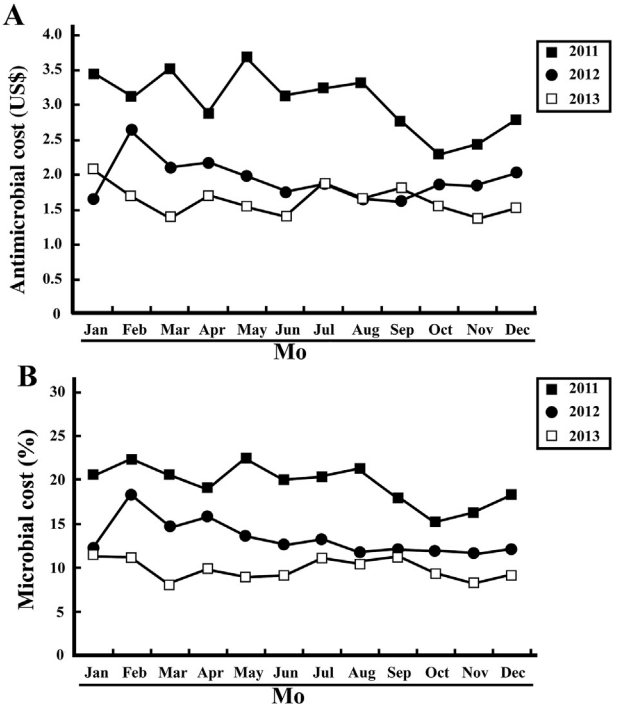

Figure 1. (A) Average antimicrobial cost (US$) and (B) percentage of antimicrobial costs in comparison to total costs of all drugs in each month from 2011 to 2013.

2012 ($p = 0.002$), then decreased to 6.6 ± 0.3 days ($p < 0.001$). Patient characteristics were analyzed. Age, sex, primary diagnoses, Pitt bacteremia score and Charlson score were similar between the baseline (2011) and intervention (2012–2013) periods (all $p > 0.05$; Table 1).

Antimicrobial cost

The average monthly cost of antibiotics decreased by 37.0% from US$30,146.8 in 2011 to US$18,993.2 in 2012 ($p < 0.001$; Figure 1A) and by 15.6% from $18,993.2 in 2012 to $16021.3 in 2013 ($p = 0.022$; Figure 1A). The percentage of antimicrobial cost compared with total cost of all drugs decreased from 19.17% in 2011 to 13.15% in 2012 ($p < 0.001$; when comparing monthly data throughout the year; Figure 1B). This percentage decreased from 13.15% in 2012 to 9.59% in 2013 ($p < 0.001$; Figure 1B).

DDDs

The DDDs of most intravenous antimicrobials, including cefuroxime, ampicillin/sulbactam, piperacillin/tazobactam, levofloxacin, gentamicin, ceftazidime, isepamicin, tigecycline, imipenem, flomoxef, clindamycin, and moxifloxacin decreased from 2011 to 2013 after implementation of the new policy (Table 2). However, the DDDs of cefazolin, ceftriaxone, amikacin, sulbactam, tinidazole, ciprofloxacin and vancomycin increased.

Total intravenous antibiotic DDDs of the inpatients were 21,876.1, 16,534.9, and 14,238.3 in 2011, 2012, and 2013, respectively (Table 2). The yearly sum of all intravenous antibiotic DDDs of all intravenous antimicrobials decreased by 7637.8 (34.9%) from 2011 to 2013. The total bed-days in 2011, 2012 and 2013 were 32,679, 30,584 and 29,429, respectively. After calculation, the total antibiotic DDDs per 100 bed-days of inpatients were 66.9, 54.1 and 48.4 in 2011, 2012 and 2013, respectively. A total decrease of 18.6 DDDs (27.7%) per 100 bed-days of the inpatients occurred from 2011 to 2013.

Microbiological assay

There was no significant difference among distribution of bacterial sources (urine, pus, sputum, blood, and stools) from 2011 to 2013 (all $p > 0.05$). Species identified by culture are summarized in Table 3. *Staphylococcus* and *Streptococcus* species were predominant among Gram-positive bacteria (Table 3). *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were leading species among Gram-negative bacteria. Total number of all bacteria was reduced by 298 isolates (17.1%) from 2011 to 2013 (Table 3).

Antimicrobial susceptibilities

After comparing susceptibilities to various antimicrobials in 2012 or 2013 to those in 2011, the susceptibilities to antimicrobials for treating all Gram-positive bacteria increased from 2011 to 2012 ($p = 0.024$, Figure 2A) and also increased from 2011 to 2013 ($p = 0.013$). Susceptibilities to all antimicrobial agents increased after the ASP, except cefazolin. The susceptibilities to antimicrobials for treating *Staphylococcus aureus*, the predominant Gram-positive bacteria, increased from 2011 to 2012 ($p = 0.002$, Table 3) and also increased from 2011 to 2013 ($p = 0.019$). The percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) in

Table 2 Comparison of defined daily doses (DDDs) of all intravenous antimicrobials used from 2011 to 2013.

Antimicrobials	Numbers of DDDs				DDDs/100 bed-days			
	2011	2012	2013	Change[a]	2011	2012	2013	Change
Cefuroxime	6984.5	3825.0	4001.8	−2982.8	21.4	12.5	13.6	−7.8
Cefazolin	2071.7	3399.7	2658.0	586.3	6.3	11.1	9.0	2.7
Ceftriaxone	2064.5	2631.0	2113.5	49.0	6.3	8.6	7.2	0.9
Augmentin	2916.7	1377.3	948.7	−1968.0	8.9	4.5	3.2	−5.7
Piperacillin/tazobactam	2007.0	1244.0	897.0	−1110.0	6.1	4.1	3.0	−3.1
Levofloxacin	811.5	368.0	547.5	−264.0	2.5	1.2	1.9	−0.6
Amikacin	236.0	370.0	406.0	170.0	0.7	1.2	1.4	0.7
Gentamicin	1099.3	428.3	374.3	−725.0	3.4	1.4	1.3	−2.1
Ceftazidime	376.8	560.8	374.3	−2.5	1.2	1.8	1.3	0.1
Ampicillin/sulbactam	217.5	180.5	348.0	130.5	0.7	0.6	1.2	0.5
Isepamicin	657.0	500.0	282.5	−374.5	2.0	1.6	1.0	−1.1
Ciprofloxacin	139.6	377.6	272.8	133.2	0.4	1.2	0.9	0.5
Tigecycline	350.0	163.0	253.0	−97.0	1.1	0.5	0.9	−0.2
Imipenem	584.0	319.8	251.0	−333.0	1.8	1.0	0.9	−0.9
Vancomycin	231.5	218.3	236.3	4.8	0.7	0.7	0.8	0.1
Flomoxef	199.8	77.0	127.3	−72.5	0.6	0.3	0.4	−0.2
Clindamycin	817.8	320.7	105.5	−712.3	2.5	1.0	0.4	−2.1
Moxifloxacin	111.0	174.0	41.0	−70.0	0.3	0.6	0.1	−0.2
Sum	21,876.1	16,534.9	14,238.3	−7637.8	66.9	54.1	48.4	−18.6

[a] Change = $Data_{2013} - Data_{2011}$.
DDD = defined daily dose.

Table 3 Total numbers of bacteria and antibiotic resistance from all Gram-positive cultures from patients admitted in 2011—2013.

Bacterial species	Year of data	Total no. of bacteria (%)[a]	Antibiotic resistance (%)										
			Clindamycin	Gentamicin	Penicillin	Flucloxacillin	Cefazolin	Ceftriaxone	Ciprofloxacin	Levofloxacin	Moxifloxacin	Vancomycin	Tigecycline
Staphylococcus aureus	$Data_{2011}$	238 (13.7)	45	26.9	87.8	50.8	30.3	48.7	18.9	13.9	7.6	0	0
	$Data_{2012}$	228 (13.9)	53.1	21.5	79.8	19.7	25	31.6	9.2	7.9	4.8	0	0
	$Data_{2013}$	220 (15.3)	36.8	15.8	71.8	10.5	32.6	30.5	10.0	10.0	5.9	0	0
Enterococcus species	$Data_{2011}$	199 (11.4)	—	54.8	10.1	70.4	—	—	37.7	36.2	0	0	0
	$Data_{2012}$	187 (11.4)	—	50.3	10.2	19.8	—	—	22.4	15	0	0	0
	$Data_{2013}$	179 (12.4)	—	43	2.2	12.3	—	—	18.4	16.2	0	0	0
Streptococcus agalactiae	$Data_{2011}$	92 (5.3)	26.1	—	22.8	23.9	—	28.3	—	31.5	31.5	0	0
	$Data_{2012}$	78 (4.7)	25.6	—	23.1	21.8	—	11.5	—	14.1	15.4	0	0
	$Data_{2013}$	63 (4.4)	25.4	—	4.8	3.2	—	0	—	11.1	11.1	0	0
Streptococcus pneumoniae	$Data_{2011}$	31 (1.8)	32.3	—	67.7	67.7	—	29	—	6.5	6.5	0	0
	$Data_{2012}$	23 (1.4)	30.4	—	69.6	30.4	—	13	—	6.5	6.5	0	0
	$Data_{2013}$	21 (1.5)	23.8	—	4.8	14.3	—	9.5	—	9.5	9.5	0	0
Gram-positive bacilli	$Data_{2011}$	21 (1.2)	33.3	23.8	57.1	57.1	19	38.1	33.3	28.5	19	0	0
	$Data_{2012}$	23 (1.4)	26.1	26.1	56.5	43.4	17.4	13	13	28.5	19	0	0
	$Data_{2013}$	20 (1.4)	30	10	45	40	30	25	30	25	25	0	0
Streptococcus viridians	$Data_{2011}$	16 (0.9)	37.5	—	37.5	31.3	—	31.3	—	18.8	18.8	0	0
	$Data_{2012}$	18 (1.1)	33.3	—	38.9	22.2	—	22.2	—	18.8	18.8	0	0
	$Data_{2013}$	11 (0.8)	36.3	—	27.2	18.2	—	9.1	—	18.2	9.1	0	0
Streptococcus pyogens	$Data_{2011}$	14 (0.8)	28.6	—	0	0	0	0	—	0	0	0	0
	$Data_{2012}$	15 (0.9)	26.7	—	0	0	0	0	—	0	0	0	0
	$Data_{2013}$	13 (0.9)	0	—	0	0	0	0	—	0	0	0	0
Coagulase -negative staphylococci	$Data_{2011}$	12 (0.7)	33.3	50	66.7	50	41.7	41.7	25	25	16.7	0	8.3
	$Data_{2012}$	9 (0.5)	33.3	44.4	66.7	44.4	22.2	22.2	22.2	25	16.7	0	0
	$Data_{2013}$	6 (0.4)	33.3	16.7	50	33.3	16.7	16.7	16.7	16.7	8.3	0	0

[a] Presented as total number of this species (percentage of all Gram-positive bacteria and Gram-negative bacteria, including those in Table 4).

this species decreased from 50.8% (121/238) to 10.5% (23/220). No vancomycin-resistant enterococci were found in the study period.

The susceptibilities to antimicrobials for treating Gram-negative bacteria increased from 2011 to 2012 ($p < 0.001$, Figure 2B), and also from 2011 to 2013 ($p < 0.001$). The susceptibilities to antimicrobials for *E. coli*, the leading Gram-negative bacteria, increased from 2011 to 2012 ($p = 0.002$, Table 4), and increased from 2011 to 2013 ($p = 0.002$). Susceptibilities to all antimicrobial agents increased after the ASP, except ampicillin/sulbactam. The percentage of imipenem-resistant *Acinetobacter baumannii* (IRAB) decreased from 74% (37/50) in 2011 to 52.5% (21/40) in 2013. The percentage of *E. coli* containing extended-spectrum β-lactamase decreased from 5.1% (30/592) to 1.1% (6/545). The percentage of extended-spectrum-β-lactamase-producing *K. pneumoniae* decreased from 3.9% (7/181) to 2.2% (3/139).

Mortality

The total number of patient deaths decreased from 53 in 2011 to 48 in 2012 and 45 in 2013. The yearly mortality also decreased from 1.3% in 2011 to 1.1% in 2012 and 1.0% in 2013.

Questionnaire

According to the questionnaire results from 155 related staff, including 27 attending doctors, 56 nurses, and 72 other staff, > 90% of the doctors believed the new policy was effective in antibiotic restriction, and reducing antibiotic abuse, resistance, and related side effects (Table 5). More than 85% of the attending doctors were satisfied with the new policy, antibiotic audit system, and antibiotic restriction.

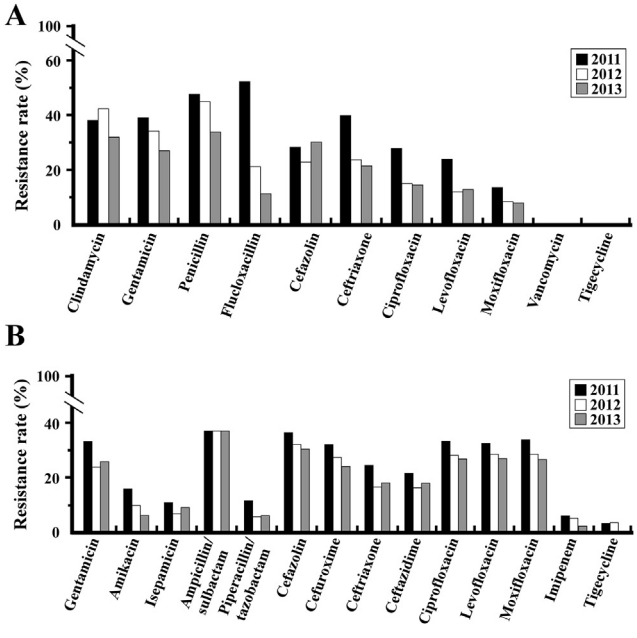

Figure 2. Changes in antibiotic resistance of (A) Gram-positive and (B) Gram-negative bacteria to antimicrobials from 2011 to 2013. Resistance rate = number of susceptible bacteria to the antimicrobial / number of total tested bacteria.

Discussion

After assessing the economic benefit of this culture-guided ASP, the average antimicrobial cost and the percentage of antimicrobial costs in comparison with the total cost of all drugs were improved from 2011 to 2013. The results indicated that the new antimicrobial restriction policy reduced the treatment expenditure successfully in this hospital. Similarly, the extensive implementation of the ASP by specialized staff was found recently to be effective in reducing the inappropriate use of antimicrobials and their costs in Japan, the US and Taiwan.[29–36] The decreased antimicrobial cost around October might be correlated with less bacterial infections due to the warmer temperatures in Taiwan.

Antimicrobial resistance decreased in Gram-positive and Gram-negative bacteria in this hospital. The predominant species included *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Staphylococcus aureus*. The new antimicrobial restriction policy reduced the antimicrobial resistance towards almost all antimicrobials for these bacteria. Only the resistance to cefazolin increased for Gram-positive bacteria, whereas the resistance to ampicillin/sulbactam also increased for Gram-negative bacteria. Cefazolin, if the infection pathogen was susceptible to it, was recommended by the ARC as a substitution for second-, and third- line antimicrobials or other expensive first-line antimicrobials. Ampicillin/sulbactam, if the pathogen was susceptible to it, was recommended in lieu of other expensive restricted antimicrobials, such as piperacillin/tazobactam, levofloxacin, tigecycline, imipenem, flomoxef, and moxifloxacin. The increased resistance to cefazolin and ampicillin/sulbactam could be explained by increased DDDs after ASP implementation. Therefore, the increased resistance to the two antimicrobials may be attributed to the implementation of the new restriction policy. In other studies, the ASPs had significant effects on decreasing the use of a number of broad-spectrum antimicrobials, but use of some other antimicrobials might have increased.[29–35] After implementing the ASP, for example, prolonged antimicrobial usage for > 2 weeks was significantly reduced. Significant reductions in antimicrobial use were observed for second-generation cephalosporins, carbapenems, and aminoglycosides,[31] and the use of the three antimicrobials also decreased in our study.

Bias may exist in antimicrobial costs due to the variations in different antimicrobial prices. DDD is a valuable tool for assessing the overall quality of prescribed antimicrobials.[22–26] The reductions of 7637.8 DDDs (34.9% of the total DDD_S in 2011) and 18.6 DDDs per 100 bed—days of inpatients (27.7% of the value in 2011) in 2013 demonstrated successful restriction in antimicrobial usage. Only the DDDs of cefazolin, ceftriaxone, ceftazidime, amikacin, ampicillin/sulbactam, ciprofloxacin, and vancomycin increased after the restriction policy. However, the increased use of these antimicrobials was attributed to the recommendation by the ARC to substitute the restricted or expensive antimicrobials.

Table 4 Total numbers of bacteria and antibiotic resistance of all Gram-negative cultures from patients admitted in 2011—2013.

Bacterial species	Year of data	Total no. of bacteria (%)[a]	Antibiotic resistance (%)													
			Gentamicin	Amikacin	Isepamicin	Ampicillin/ sulbactam	Piperacillin/ tazobactam	Cefazolin	Cefuroxime	Ceftriaxone	Ceftazidime	Ciprofloxacin	Levofloxacin	Moxifloxacin	Imipenem	Tigecycline
Escherichia coli	$Data_{2011}$	592 (34.0)	30.6	9	0	35.6	7.8	29.9	27.5	21.8	14.9	29.7	28.7	27.7	0	0
	$Data_{2012}$	563 (34.2)	25	2	0	36.4	1.8	30	24	17.1	12.8	25	25	25	0	0
	$Data_{2013}$	545 (37.8)	24	0.9	0	30.1	21.7	17.2	11.6	24	24	24	38	0.9	0	0
Klebsiella pneumoniae	$Data_{2011}$	181 (10.4)	40.9	32	33.1	32	11	60.2	51.9	47	37	48.1	48.1	48.1	0	0
	$Data_{2012}$	171 (10.4)	12.9	22.2	12.3	45.6	11.1	50.9	45	22.2	12.9	34.5	38	33.3	0	0
	$Data_{2013}$	139 (9.6)	22.3	12.9	33.1	39.6	39.6	28.8	39.6	28.8	28.8	28.8	39.6	10.1	0	0
Pseudomonas aeruginosa	$Data_{2011}$	184 (10.6)	17.9	3.8	3.8	0	9.8	0	0	0	13	29.9	29.9	29.9	15.2	20.1
	$Data_{2012}$	157 (9.5)	14	3.2	2.5	0	5.1	0	0	0	14	28	27.4	27.4	10.8	14
	$Data_{2013}$	119 (8.3)	21.6	1.7	1.7	0	0	0	3.4	29.4	29.4	24.3	0	4.2	1.7	4.2
Acinetobacter baumannii	$Data_{2011}$	50 (2.9)	96	92	92	82	80	0	0	0	94	94	92	92	74	0
	$Data_{2012}$	50 (3.0)	88	86	84	78	46	0	0	0	94	92	92	92	68	30
	$Data_{2013}$	40 (2.8)	85	80	80	0	0	0	92	92	90	90	62.5	80	52.5	0
Proteus mirabilis	$Data_{2011}$	35 (2.0)	40	20	0	28.6	0	37.1	17.1	11.4	11.4	20	20	20	0	0
	$Data_{2012}$	68 (4.1)	20.6	10.3	0	8.8	0	11.8	17.1	11.4	7.4	11.8	8.8	8.8	0	0
	$Data_{2013}$	25 (1.7)	20	0	0	8	0	0	0	8	8	8	4	0	0	0
Salmonella species	$Data_{2011}$	58 (3.3)	0	0	0	39.7	0	0	0	0	0	0	0	0	0	0
	$Data_{2012}$	28 (1.7)	0	0	0	10.3	0	0	0	0	0	0	0	0	0	0
	$Data_{2013}$	21 (1.5)	0	0	0	0	0	4.8	0	4.8	4.8	0	14.3	0	0	0
Escherichia fergusonii	$Data_{2011}$	16 (0.9)	25	12.5	0	25	12.5	18.8	18.8	12.5	6.3	18.8	12.5	12.5	0	0
	$Data_{2012}$	26 (1.6)	26.9	11.5	0	26.9	11.5	15.4	15.4	11.5	11.5	15.4	11.5	11.5	0	0
	$Data_{2013}$	19 (1.3)	26.3	10.5	0	15.8	10.5	10.5	5.3	10.5	10.5	10.5	15.8	0	0	0

[a] Presented as total number of this species (percentage of all Gram-positive and Gram-negative bacteria, including those in Table 3).

Table 5 Results of the questionnaire about the novel antibiotic restriction policy with the antimicrobial stewardship program.

Questions	Excellent or very satisfied *n* (%)	Yes or satisfied *n* (%)	No or dissatisfied *n* (%)	Poor or very dissatisfied *n* (%)
Is the policy effective in antibiotic abuse?	76 (49.0)	79 (51.0)	0 (0)	0 (0)
Is the policy effective in reducing antibiotic resistance?	56 (36.2)	85 (54.8)	14 (9.0)	0 (0)
Is the policy effective in decreasing antibiotic-related side effects?	81 (52.3)	72 (46.5)	2 (1.3)	0 (0)
Is the policy effective in antibiotic restriction?	63 (40.6)	86 (55.5)	6 (3.9)	0 (0)
Are you satisfied with the policy in antibiotic restriction?	29 (18.7)	108 (69.7)	18 (11.6)	0 (0)
Are you satisfied with web-based antibiotic audit system?	28 (18.1)	104 (67.1)	23 (14.8)	0 (0)
Are you satisfied with antibiotic audit system?	29 (18.7)	115 (74.2)	11 (7.1%)	0 (0)
Are you satisfied with the novel policy?	29 (18.7)	120 (77.4)	6 (3.9%)	0 (0)

We excluded the bias of disease severity because there was no significant difference in Pitt bacteremia score and Charlson score from 2011 to 2013 (Table 1). In order to avoid confounding by antibiotic policy other than the culture-based regimen, we used the data in 2011 as a control since traditional antibiotic policy other than the culture-based regimen has been performed in 2011. We excluded the bias of difference in admission population because there was no significant difference among age, sex, and primary ICD-9 codes and Charlson score of admitted patients during the control and study periods (Table 1). Since there was no significant population difference among admitted patients from 2011 to 2013, the bias caused by antimicrobial resistance in the community before admission was equally distributed in the control group in 2011 and the study group in 2012—2013; thus, the bias could be excluded after comparing the data of the study group and control group. There was no different infection control policy leading to any confounding factor during the study period.

This study highlighted the decreased antimicrobial resistance associated with the reduced DDDs. Similarly, in a previous multivariate analysis, the piperacillin/tazobactam, quinolones, and/or total consumption at the advanced treatment hospitals showed a significant correlation with the incidence of *P. aeruginosa* resistant to imipenem, meropenem, ciprofloxacin, and amikacin.[29] The incidence of *A. baumannii* resistant to imipenem correlated with the use of broad-spectrum antimicrobials for at least 5 days.[4–6] The prevalence of multi-drug-resistant *A. baumannii* isolated during the carbapenem non-restricted period was at least twofold higher than that during the carbapenem-restricted period.[37]

Use of cephalosporins and fluoroquinolones is an independent risk factor for MRSA infections.[38,39] By this principle, decreased total consumption of cephalosporins (—4.1 DDDs/100 bed-days from 2011 to 2013) and fluoroquinolones (—0.3 DDDs/100 bed-days from 2011 to 2013) could explain the decreased percentage of MRSA in this species (50.8% in 2011 to 10.5% in 2013). Prior use of broad-spectrum antibiotics is an independent risk factor for IRAB infections.[4,5] Thus, the decreased percentage of IRAB (74% in 2011 to 52.5% in 2013) could be explained by the decreased total consumption of broad-spectrum antibiotics in this study (Table 2).

In conclusion, we report successful implementation of a culture-guided ASP, an antimicrobial restriction policy, leading to medical expense savings, and decreases in the inappropriate use of antimicrobials, average length of stay, mortality, and development of antimicrobial resistance. With the advantage of our experience, the implementation of practical ASP is highly recommended for local hospitals.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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