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ORIGINAL RESEARCH

The Impact of an Antibiotic Stewardship Program on the Consumption of Specific Antimicrobials and Their Cost Burden: A Hospital-wide Intervention

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Background: Inappropriate use of antimicrobials (AM) is a major concern worldwide that leads to the propagation of antimicrobial resistance (AMR). In addition to its clinical implications, AMR imposes an economic burden on communities, especially developing countries with more infectious diseases and less available resources. Antimicrobial stewardship programs (ASPs) have been found to be effective in reducing AMR. This study was designed to evaluate the effect of implementing an ASP in reducing AM consumption, its economic burden, and AMR as a consecutive result.

Materials and Methods: Consumption of caspofungin, amphotericin B, voriconazole, colistin, linezolid, vancomycin, and carbapenems was compared in a prospective cross-sectional study between two time periods introduced as pre- and post-ASP. Drug use density presented as anatomical therapeutic chemical (ATC)/defined daily doses (DDD) and normalized per 1000 bed days, cost savings, and AMR patterns were evaluated.

Results: A total of 9400 AM prescriptions were analyzed during a 2-year period. Consumption measured in DDD/1000 bed days dropped by 24.8, 25.0, 35.3, 47.0, 39.2, 10.5, and 23.2 percent for amphotericin B, caspofungin, colistin, voriconazole, meropenem, imipenem, and vancomycin, respectively. Linezolid consumption increased by 26.8% after implementing ASP. The expenditure of target AMs in the average value of USD decreased by 41.3% after the intervention compared to the time before using ASP (P-value=0.001). Implementing ASP also increased AM susceptibility of *Pseudomonas aeruginosa*, while the susceptibility of methicillin-resistant *Staphylococcus aureus* did not change significantly.

Conclusion: The results of this study suggest that establishment of ASP can lead to a reduction in improper administration of AMs and their expenditure resulting in economic benefit and lowering AMR at hospitals with minimum resources. Clinical pharmacists' role was critical to the success of this ASP and was uniquely empowered at our center.

Keywords: antimicrobial stewardship programs, appropriate prescribing, antimicrobial use, DDD, defined daily dose

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Introduction

The introduction of antimicrobials (AM) as promising agents against infections was a major breakthrough in man's history. Much attention was drawn to these agents that their vast, uncontrolled and inappropriate consumption soon became a major threat to all mankind by developing resistance patterns.[1] Drug resistance is a strategy that infective species acquire in time to escape destruction. This process

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leads to development of antimicrobial resistance (AMR) and lowers cure chances of previously treatable infections resulting in high mortality and morbidity rates.[2–4] Limited introduction of new and effective antimicrobials to the healthcare market has magnified the burden of AMR worldwide.[5] Unfortunately in most societies the destructive impact of AMR as a result of AM misuse is underestimated showing favorable short-term outcome, neglecting its vicious long-term influence.[6] This issue can be even more evident in low income countries due to their inefficient vaccination policies, higher rates of infectious diseases, the unavailability of a variety of effective antibiotics, and even laboratory techniques, instruments, and media required for the accurate identification of a -pathogen.[7,8] Considering that antimicrobial consumption has almost doubled in Iran during the past decade,[9] and inappropriate empiric antibiotic therapy has been reported to be high,[10] without doubt AMR is an issue in the country that must be looked into. In addition to significant mortality, AMR has been reported to add as high as trillions of dollars of cost burden to nations.[11] The economic impact of AMR in the hospital setting can be attributed to longer hospital stays, the need for alternative AMs that are often more expensive, and even higher doses of anti-infective medication.[1,12] Special policies have been thought upon regarding AMR worldwide. Antibiotic stewardship programs (ASPs) were introduced as a global action plan (GAP) by the WHO in 2015, in order to help save the current status of the antibiotics and raise a chance for their future effectiveness.[13] Authorizing use of AMs can occur by developing guidelines and restricting their use with the help of the core members of the ASP team.[14] According to the latest essential medicines list (EML) presented by WHO, antibiotics have been categorized according to their priority in use; Antibiotics such as linezolid and colistin have been reserved as "last-resort" options and vancomycin, meropenem, and imipenem have high potential for resistance.[15] This puts forth the necessity of controlling use of high-cost broad spectrum AMs. While the impact of ASPs has been repeatedly demonstrated in developed and some developing countries, a paucity of literature examining ASP interventions in our country is evident and this conveys the lack of such programs being implemented or are possibly performed in an unstructured manner.[16] In this study we decided to evaluate the impact of performing ASP in a large, teaching tertiary care center in southern Iran on AM consumption and its related cost.

Materials and Methods

Study Site

This cross-sectional single-center prospective study was performed at a large referral university-affiliated, 497-bed hospital with emergency, internal medicine, surgery, cardiology, obstetrics/gynecology, and dermatology wards.

Ethical Approval

This study was approved by the institutional review board and ethics committee of Shiraz University of Medical Sciences (approval code: IR.SUMS.REC.1398.749) and was conducted according to the Declaration of Helsinki regarding ethical principles for medical research.

Study Time Periods

Two time periods were designated for comparison, the pre-ASP phase (April 2016–April 2017) and the post-ASP phase (May 2017–May 2018).

Intervention

In the pre-ASP phase, data regarding consumption of the AMs selected based on their wide spectrum of activity, high cost, and relevant high risk of resistance (caspofungin, amphotericin B, voriconazole, colistin, linezolid, vancomycin, meropenem, and imipenem) were obtained from the Hospital Information System (HIS) and medical records of all patients that had administered one of the listed antimicrobials were reviewed. In May 2017 (post-ASP phase) a formal ASP consisting of two infectious disease (ID) specialists, two clinical pharmacists, a hospital administrator, a microbiologist, and an IT specialist was started which included four components: guideline revision and "AM order forms" development, respectively, performed and prepared by the ID specialists and clinical pharmacists' collaboration, information and education provided by the clinical pharmacists, regular ward rounds by the clinical pharmacists, and intensified infectious disease consultations and feedback provided by the ID specialists. Microorganism susceptibilities and their resistance patterns were evaluated by the microbiologist before and after implementing ASP, as this information primarily helped towards selection of AMs for which restriction was planned to be performed. The IT specialist helped in organizing an electronic program towards informing the clinical pharmacists of an AM prescription and restricting the AM order by requiring the ID specialist consultation and confirmation. At last the hospital

administrator supported the ASP by establishing an institutional policy towards making this program happen.

Briefly, an initial focus of the ASP was to develop treatment protocols that follow local susceptibility patterns along with national guidelines focusing on post-prescriptive audit with feedback and intervention. ASP education included initial short division-specific team briefings, summarizing the revised guidelines, and explaining the overall strategy. Workflow demonstrating the process of the ASP audit is shown in Figure 1.

For caspofungin, amphotericin B, voriconazole, colistin, and linezolid, order-forms consisting of the patient's name, indications according to guidelines, dose, route, frequency, and duration of antimicrobial treatment and culture results were prepared. This form was to be filled out by the treating physician and validated by a clinical pharmacist/ID specialist to confirm accuracy of prescription. The ASP team reviewed clinical charts every weekday. Appropriate use was encouraged with positive feedback to prescribers. Inappropriate use was discussed with prescribers and coupled with a stewardship recommendation, which was filed in the patient's record and discussed with the care providers on the phone. The hospital pharmacy checked the availability and completeness of the filled-out forms before confirming the dispense of the mentioned AMs to the ward for each patient.

Considering that restriction on the use of selected broad spectrum AMs might shift physicians to ordering other AMs, another restraint was applied for vancomycin, meropenem, and imipenem as other broad spectrum AMs available at the hospital. This restraint was applied as a level of prescription audit, requiring a specialist physician's order, knowing that the hospital that the study took

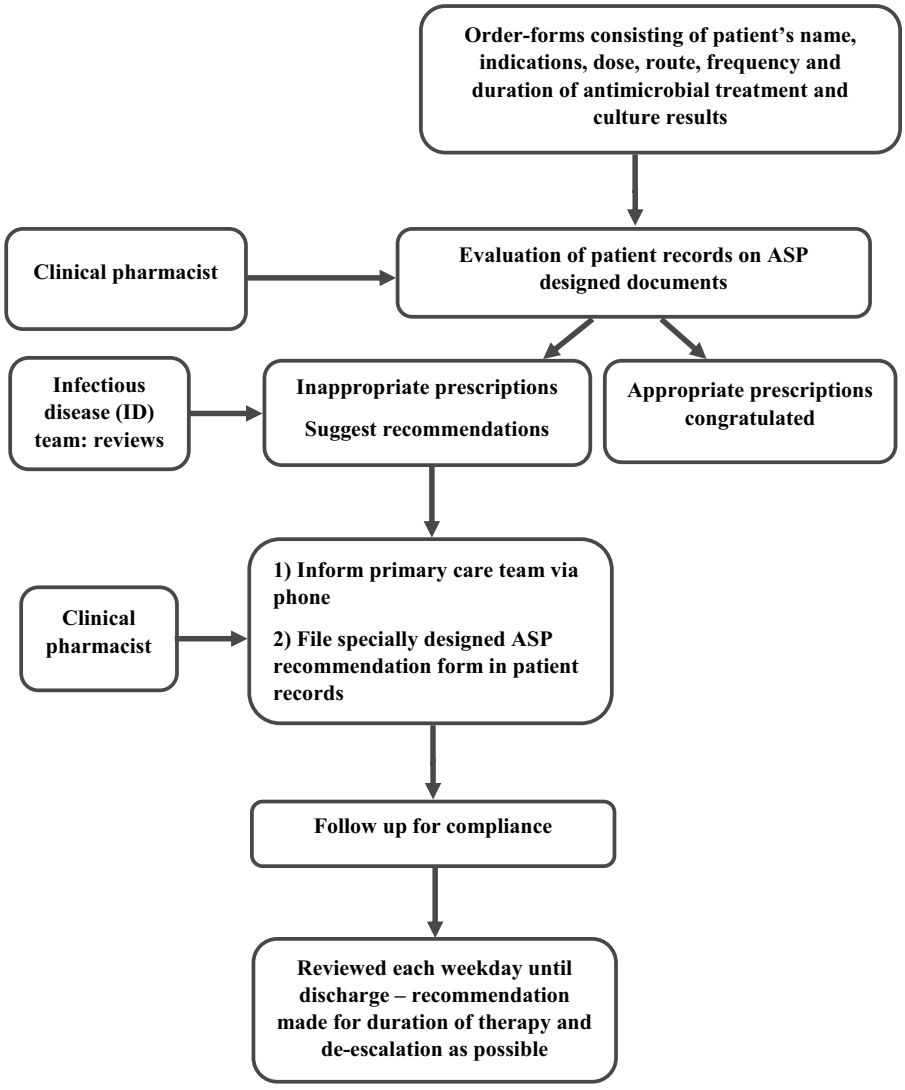

Figure 1 Antimicrobial stewardship program (ASP) workflow for audit and review.

place in is a teaching hospital and medical interns and residents are also able to order AMs.

Study Design and Data Collection

All patients' medical records, including their demographic data, length of hospital stay, duration of AM use, lab data (chemical and microbial), mortality rates, and monthly direct drug expense for each AM charged for patients based on its value provided to the ASP team by the hospital pharmacy, were evaluated before and after implication of intervention.

Drug use density expressed according to the WHO definition presented as anatomical therapeutic chemical (ATC)/defined daily doses (DDD) and normalized per 1000 bed days, cost savings, and AMR patterns were also evaluated.

The primary objective of the study was to compare data of AM use which were expressed as DDD between the pre-ASP and the post-ASP period. Secondary objectives were to compare the total cost of AMs and also change in AM resistance patterns in the two study phases at our institution. The cost data evaluated were based on purchasing costs provided by the hospital pharmacy.

Bacterial Resistance and Antibiotic Use

To evaluate the impact of changes in antibiotic use on bacterial resistance, all isolates from patients' samples received from different wards were collected including blood, pus/wound swabs, sputum, drain fluids, and urine. Criteria for antimicrobial susceptibility testing were carried out according to Clinical Laboratory Standard Institute (CLSI) guidelines.[17] Antimicrobial sensitivity testing was done on Muller Hinton Agar (MHA) by Kirby-Bauer's disc diffusion method. Changes in the resistance pattern were compared between the two study periods.

Statistical Analysis

After gathering all data, SPSSvs16 software was used to perform the statistical analysis. Smirnov-Kolmogorov test was used to evaluate the normal distribution of data, and according to their distribution, *t*-test, Mann–Whitney, or Wilcoxon tests were utilized for statistical analysis. *P*-values<0.05 were considered significant for all tests.

Results

A total of 14,820 patients who received at least one of the target antibiotics during their inpatient stay at the two time periods were included in the study, with 7320 and 7500 subjects representing the pre-ASP and post-ASP groups, respectively. No significant differences in age and sex distribution were found between the two groups (Table 1).

A total number of 9400 AM prescriptions were evaluated. An overall 26.3% decrease in consumption was observed between the pre-ASP and post-ASP phases measured in DDD/1000 bed days for target AMs. The most significant reduction was observed in the use of voriconazole (−47%) and colistin (−35.3%) amongst the restricted high cost audited AMs including amphotericin B, caspofungin, voriconazole, colistin, and linezolid; However, an increasing rate of consumption was observed for linezolid (+26.8%). Also reduction in carbapenem and vancomycin consumption was observed following audit performed at the level of prescription; the highest rate of decrease was observed for meropenem (−39.2%) (Table 2).

The mean monthly cost for restricted AMs significantly dropped by 41.3% in the post-implementation phase of ASP in comparison with the pre-implementation phase (*P*-value<0.001). The average monthly cost saving during the intervention phase was $183,052. As shown in Table 3, the highest cost saving belonged to voriconazole consumption, showing a 60.6% reduction in mean monthly hospital cost attributed to use of the mentioned AM. Linezolid consumption showed an increasing trend of 10.3% in terms of its mean monthly cost burden parallel to its increased consumption rate. Table 4 demonstrates the amount of AM prescribed in terms of average vial per patient, and as shown once again voriconazole has the

Table 1 Baseline Data of the Study Population

Variables	Study Phase		*P*-value
	Pre-ASP	Post-ASP	
Sex n (%)			
Male	3677 (50.2)	3638 (48.5)	0.15
Female	3643 (49.8)	3862 (51.5)	
Age (years; mean±SD)	58.1±19.84	57.9±18.5	0.53
Ward n (%)			
Intensive Care Unit	549 (7.5)	548 (7.3)	0.64
Internal medicine	1954 (26.7)	2047 (27.3)	0.41
General Surgery	2064 (28.2)	2063 (27.5)	0.34
Cardiac Surgery	608 (8.3)	683 (9.1)	0.08
Gynecology	696 (9.5)	652 (8.7)	0.09
Dermatology	351 (4.8)	390 (5.2)	0.26
Neurology	600 (8.2)	585 (7.8)	0.37
Coronary Care Unit	498 (6.8)	532 (7.1)	0.47

Abbreviation: ASP, antimicrobial stewardship program.

Table 2 Defined Daily Dose (DDD) per 1000 Patient-Days for Selected Antimicrobials During the Two Phases of the Study (Pre- and Post-Intervention)

Antimicrobial Agent	DDD/1000 Patient Days		Percent of Change
	Pre-ASP	Post-ASP	
Antifungal			
Amphotericin B	16.5	12.4	−24.8%
Caspofungin	1.2	0.9	−25.0%
Voriconazole	19.8	10.5	−47.0%
Antibacterial (spectrum of activity)			
Colistin (G^-)	45.1	29.2	− 35.3%
Linezolid (G^+)	16.9	23.1	+26.8%
Meropenem (G^+, G^-)	22.1	13.1	−39.2%
Imipenem (G^+, G^-)	1.9	1.7	−10.5%
Vancomycin (G^+)	5.6	4.3	−23.2%
Total	129.1	95.2	−26.3%

Abbreviations: ASP, antimicrobial stewardship program; DDD, defined daily dose.

Table 3 Comparison of Mean Monthly Costs of Antimicrobial Administration in the Average Value of USD During the Two Phases of the Study (Pre- and Post-Intervention)

Antimicrobial Agent	Study Phase		Percent of Change	*P*-value
	Pre-ASP	Post-ASP		
Antifungal				
Amphotericin	123,300	66,940	−45.7%	<0.001
Caspofungin	7000	3700	−47.1%	<0.001
Voriconazole	11,160	4400	−60.6%	<0.001
Antibacterial (spectrum of activity)				
Colistin (G^-)	26,312	13,500	−48.7%	<0.001
Linezolid (G^+)	18,100	20,170	+10.3%	0.002
Carbapenems (G^+, G^-)	182,600	99,270	−45.6%	<0.001
Vancomycin (G^+)	69,100	46,540	−32.6%	<0.001
Total	437,572	254,520	−41.8%	<0.001

Abbreviations: ASP, antimicrobial stewardship program; USD, United States dollars.

highest rate of reduction during the two study phases. The least reduction is accredited to amphotericin B.

During the pre- and post-ASP phases, a total of 280 and 295 samples were received from different wards of the hospital, respectively, and were further processed for susceptibility testing. Two hundred and nine (74.64%) and 215 (72.88%) organisms were isolated in each study phase, respectively. A total number of organisms isolated

Table 4 Amount of Prescribed Antimicrobial in Average Value of Vial per Patient (Mean±SD) During the Two Phases of the Study (Pre- and Post-Intervention)

Antimicrobial Agent	Study Phase		*P*-value
	Pre-ASP	Post-ASP	
Antifungal			
Amphotericin B	28.68±13.32	25.35±11.6	0.013
Caspofungin	13.94±4.28	11.32±5.12	<0.001
Voriconazole	18.25±5.38	11.50±2.60	<0.001
Antibacterial (spectrum of activity)			
Colistin (G^-)	45.60±12.49	39.33±15.76	<0.001
Linezolid (G^+)	21.84±4.33	23.44±5.17	0.003
Meropenem (G^+, G^-)	33.27±14.09	29.79±11.23	0.009
Imipenem (G^+, G^-)	23.17±19.89	19.51±11.66	0.25
Vancomycin (G^+)	20.74±16.69	15.93±11.5	0.001

Abbreviation: ASP, antimicrobial stewardship program.

from various clinical samples and their resistance patterns are shown in Table 5.

Susceptibility of *Pseudomonas aeruginosa* showed a significant difference between the two study phases (*P*-value<0.05), demonstrating increased sensitivity towards mentioned AMs in the post-ASP phase. *Staphylococcus aureus* sensitivity did not change significantly for most antibiotics (Table 5).

Mortality rates were evaluated in patients that had received the target antimicrobials in the pre- and post-ASP phase. Total mortality rate decreased from 16.8% to 15.2%; however, this decrease in rate was not statistically significant (*P*-value=0.725).

Length of hospital stay (mean±SD) showed a significant decrease (P-value=0.0201) in post-ASP phase (10.94±5.42) compared to the pre-ASP phase (12.24±6.75).

Discussion

AMR is known as a global threat to mankind causing mortality and morbidity. The goal of preserving AM effectiveness has reached its utmost importance during the recent decade.[18,19] Following this major worldwide concern, in this study we decided to develop and carry out a program that restricts the use of high-cost, broad spectrum AMs at our institution. This plan was performed with the help of the core members of an ASP team, clinical pharmacists, and ID specialists. Necessary approval of five high-cost broad spectrum AMs by an ID specialist before their administration for admitted patients at all our hospital

Table 5 Antibiotic Sensitivity Pattern for Different Microorganisms Before and After Implementing ASP

Microorganism	Antimicrobial agent	Pre-ASP		Post-ASP		*P*-value
		Sensitivity Rate (%)	n (%)	Sensitivity Rate (%)	n (%)	
Pseudomonas aeruginosa	Colistin	90.5	42 (20.10)	100	44 (20.47)	<0.001
	Cefepime	32		50		<0.001
	Amikacin	42		55		<0.001
	Ciprofloxacin	60		65		0.047
	Carbapenems	82.4		86.2		0.044
	Piperacillin/Tazobactam	90		92		0.178
Klebsiella pneumoniae	Imipenem	45	23 (11.0)	58	22 (10.23)	<0.001
	Amikacin	70		77.8		<0.001
	Ciprofloxacin	11.1		27.5		<0.001
	Cefepime	18.3		25		0.001
	Gentamicin	35		45.6		<0.001
	Colistin	98		100		<0.001
Staphylococcus aureus	Oxacillin	54.2	36 (17.23)	57	40 (18.60)	0.278
	Vancomycin	68		72		0.093
	Linezolid	91.3		90		0.685
	Clindamycin	12.5		25		0.005
	Cefazolin	75		56.9		<0.001
Escherichia coli	Gentamicin	65	40 (19.14)	82.3	41 (19.07)	<0.001
	Ciprofloxacin	30		40.4		0.0483
	Amikacin	89.5		94.1		0.108
	Cefepime	40		43.8		0.481
	Ampicillin/Sulbactam	33.3		38.9		0.288
Enterococcus spp.	Ampicillin	3.6	18 (8.61)	6.1	22 (10.23)	0.202
	Amikacin	4.6		5.4		0.740
	Meropenem	1.5		3.5		0.270
	Vancomycin	50		48.6		0.797
	Linezolid	92		96		0.103
Enterobacteriaceae spp.	Cefepime	6.3	13 (6.22)	15	11 (5.12)	0.0145
	Piperacillin/Tazobactam	66.7		70		0.514
	Ceftriaxone	33.3		42		0.102
	Imipenem	75		76.2		0.797
	Amikacin	75		81		0.177
	Ciprofloxacin	45		59.2		0.009
Acinetobacter spp.	Imipenem	2.2	37 (17.70)	8.5	35 (16.28)	0.0148
	Cefepime	1.5		6.6		0.0304
	Piperacillin/Tazobactam	4.2		11.5		0.0166
	Amikacin	13.6		20.6		0.0968
	Ciprofloxacin	8.7		10.7		0.542

Abbreviation: ASP, antimicrobial stewardship program.

wards was implemented. Our results indicate great reduction in the consumption of four of the studied AMs; however, linezolid showed an increase in approval and administration after the ongoing program. As it has been previously described by researchers, different cultural, contextual, and behavioral attitude exists towards the management of an infection. AM prescription has been associated to higher levels of therapeutic power for the physician and the patient, overcoming the physician's fear of uncertainty in managing a patient.[1] Therefore it is obvious that lack of authority and knowledge in the management of infectious diseases can lead to higher and

inappropriate AM consumption.[20] In this study we decided to take the first step by preparing order-forms according to guidelines that can help the ID specialist make a better decision on approving or disapproving the administration of an AM medication. Previous reports also approve ID consultation as a way of increasing rational antibiotic use.[21,22] Knowledge of pathogens' susceptibility, resistance patterns at the institutions, and the spectrum of AM activity are all crucial knowledge required in the management of an infection that not every physician might be trained for.[1] Inappropriate AM prescription and administration has been reported as high as 79% for severe infections.[23] This fact highlights the role of an ID specialist, clinical pharmacist with ID training, and an overall AM prescription audit performed by preparing guidelines and order forms for AM prescription in a healthcare institution.[24]

Similar to other reports,[21,25] the total consumption of high-cost AMs following prescription audit was reduced except for linezolid. This reduction presented as DDD/1000 patient days was considerable (26.3%) compared to recent ASP reports from US acute-care hospitals (15.8%).[26] An increase in linezolid consumption could be due to expansion of vancomycin resistant *Enterococcus spp* (VRE) that are a main issue in the resistance patterns at our institution. Relevant reports have shown very high consumption of linezolid at their institutions as well due to its great activity against MRSA.[27] However, the inadvertent excessive use of linezolid has been reported to cause resistant patterns in the gram positive microorganisms.[28,29] It has also been concluded that vancomycin usage as an anti-MRSA agent has not fully been substituted by linezolid and the latter has been added on top of previous antibiotic managements, although MRSA burden was consistent.[30] This fact can add to resistance patterns;[31] therefore following this study use of linezolid at our institution should be carefully assessed to control the emergence of linezolid resistant microorganisms.

In our study population the most approved AM prescriptions were based on culture results (Figure 1), considering the fact that the applied ASP policy required justification for the approval of the relevant AM medication. We should take into account that disagreement with established guidelines is a common attitude of AM prescribers that can be controlled by such restriction policies.[1] In our report the highest colistin consumption was for *Acinetobacter spp*, linezolid was mainly used in patients with vancomycin resistant *Enterococci* (VRE) positive cultures, and high rates of caspofungin had been used for resistant Candida non-albicans positive cultures that are all examples of appropriateness of AM prescription approval. Culture based therapy has been highly approved for severe infections rather than empiric therapy that has been reported to increase mortality rates and length of hospital stay.[23,32]

Our data indicate financial savings after implementing the restriction policy. Although carrying out these programs are costly themselves, many previous reports have confirmed an overall economic benefit in restricting unapproved use of high cost medication.[33–35] The overall cut in the hospital's cost regarding AMs to 41.3% in this report is higher than a similar study reporting a 32% decline in expenditures.[25] The need for earlier intervention in AM therapy rather than just focusing on its length of administration has been evident in this study and also previous reports helping towards reducing imposed financial burden.[36]

The increase in antibiotic susceptibility of microorganisms is a result of implementing restriction on AM use and reduction in AMR. In our study, this benefit of ASP was evident in changing *Pseudomonas aeruginosa's* sensitivity towards antibiotics that is comparable with previous ASP studies,[37–38] although compared to available literature,[37] susceptibility of other microorganisms did not change significantly. Limiting use of antibiotics that have anti-pseudomonal activity, may be the reason for change in susceptibility of the mentioned microorganism.

Duration of hospital stay and AM administration can be affected by correct AM therapy. In our study the overall length of stay at the hospital was decreased after implementing the restriction policy. Reduced hospital stay has been reported following application of antibiotic policies in healthcare institutions, most probably due to the correct AM selection and its prompt anti-infective action consequently.[33,39] Some researchers have on the contrary confirmed the non-inferiority of implementing ASP policies by reporting that hospital stay is not prolonged although antibiotic use is restricted.[25,36]

According to this study's results we must highlight the fact that mortality rates did not significantly change after restriction of AM use. Considering that a part of the audit was restriction on the use of carbapenems and vancomycin as other available broad spectrum AM options, we could at least be certain that restricting primary use of AMs did not impact patients' outcome with respect to mortality rates. This fact has also been supported previously[26] and can

help reduce the bias on presuming that excessive AM use can improve safety and outcome.

Limitations of this study could be the probable bias towards positive results of implementing ASP as it has been also reported as a downside of such studies. On the other hand, focusing only on AM consumption of the study population and not considering their baseline clinical status that may have affected mortality and outcome, could be another limitation of this study. Considering that this was a single center study, future multi-center studies are mandated for auditing AM consumption. Also a future study is recommended to study the rise in consumption of linezolid at our institution and its probable causes.

Conclusion

In this study we could demonstrate the significant reduction in use of high-cost broad spectrum AMs and their cost burden by performing restriction policies on their prescription at our institution. It was shown that the obligation for an ID specialist's approval before administration of such AMs did not affect mortality rates and patient outcome. According to this single center study, performing ASPs may help towards correct clinical practice, reduction of AMR, and cost savings that may be beneficial for low income countries with a budget deficit.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Considering that in this study only cumulative data were evaluated and data specific to each patient was not reported, therefore confidentiality of data was respected and patient consent was not required for performing the study. This study was approved by the institutional review board and ethics committee of Shiraz University of Medical Sciences (approval code: IR.SUMS.REC.1398.749;).

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Disclosure

The authors report no conflicts of interest in this work.

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