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Evaluation of carbapenem antimicrobial stewardship program at a tertiary care hospital: A prospective interventional study

Fizzah Ali[1], Tabassum Zehra[1], Nazir Ahmed Solangi[1], Karim Ullah Makki[2], Haris Aziz Siddiqui[3] and Shama Abidi[3]

[1]Department of Pharmacology, Liaquat National Hospital and Medical College, Karachi, Pakistan
[2]Department of Medicine and Allied, Liaquat National Hospital and Medical College, Karachi, Pakistan
[3]Department of Pharmacy Services, Liaquat National Hospital and Medical College, Karachi, Pakistan

Abstract: This study aimed to determine physicians' acceptance rate of the Antimicrobial Stewardship Program ASP interventions in critically ill patients and to compare the clinical outcomes between accepted and rejected ASP groups. The study included patients on carbapenem therapy who were advised ASP interventions between 18-75 years of age and admitted in ICU/HDU from December 2020 to May 2021 at Liaquat National Hospital Karachi. Based on acceptance by the primary physician, data is divided into two groups. Outcomes were observed based on clinical improvement within seven days, 30-day mortality and readmission rates. Among 134 non-adherent prescriptions, Carbapenem ASP interventions were accepted in 117 (87.3%) patients. The accepted interventions improved clinical outcomes for most patients within seven days, 99 (84.6%). An insignificant association in death between the accepted versus rejected group within 30 days (p=1.000) was observed. On the other hand, a significant association in readmission was seen between both groups within 30 days (p=0.036). This study concluded that carbapenem prescriptions guided by the 'Antimicrobial stewardship program' are widely accepted in Pakistan and have improved clinical outcomes within 30 days of intervention.

Keywords: Antimicrobial stewardship program, carbapenem, dose de-escalation, respiratory tract infection. antibiotic resistance.

INTRODUCTION

Antibiotic resistance is a major health issue worldwide. According to the World Health Organization, around 2049,422 individuals have been affected annually, with a recorded 23,000 fatalities (Johnk *et al*., 2019). The misuse of antibiotics and lack of development of newer agents might have contributed to the emergence of antimicrobial resistance (AMR) (Bhattacharjee, 2020; Poline *et al*., 2021). AMR is also increasing at an alarming pace in Pakistan due to incorrect antimicrobial use and the development of novel mutant strains (Rehman *et al*., 2018). The Antimicrobial Stewardship Program (ASP) is a systemic strategy designed to rationalize the use of antimicrobial medicines to treat or prevent illness while reducing the risk of undesirable side effects and bacterial resistance (Dellit *et al*., 2007; Hajiabdolbaghi *et al*., 2020). This program was established following the recommendations of the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA) and the American Society of Health-System Pharmacists (ASHP) for enhancing antimicrobial stewardship efforts (Bhattacharjee *et al*., 2020; García-Rodríguez *et al*., 2019; Seah *et al*., 2017).

The program is led by the participation of a multidisciplinary team and includes the following: The development of antimicrobial use recommendations per worldwide standards; modification of medications according to organisms/ culture and sensitivity(C/S) reports; restriction of broad-spectrum antibiotics by the approving authority; feedback to the primary care physician; reporting antibiotic susceptibility data following institutional policy; education of staff (on appropriate prescribing and antibiotic resistance); and ward rounds (advice on treatment duration, transitioning from empirical to guided therapy and dose recommendations) (Morency-Potvin *et al*., 2017).

The Infectious Disease Society of America has mentioned evaluating the efficacy of ASP methods as a research priority (Dellit *et al*., 2007). Numerous studies have assessed the efficacy of ASPs in different contexts, e.g., in-patient wards, critical care units, antibiotic resistance and several others. However, most of the researches have been undertaken in the United States or European countries; very few studies have been conducted in other locations; thus, there is a paucity of data covering other regions, including Pakistan (Ababneh *et al*., 2021; Akazawa *et al*., 2019; Hussain *et al*., 2022). Therefore, it is crucial to report the impact of ASP from various regions, particularly in Asia, to promote ASP globally. Thus, we conducted prospective research to ascertain the ASP's effect in Pakistan. This study demonstrates the ASP implementation in our institution and will improve rationalization in the utilization of Carbapenem.

**Corresponding author:* e-mail: fizzah.ali@lnh.edu.pk

Considering these perspectives, we evaluated the acceptance rate of ASP interventions by physicians in critically ill patients and compared the clinical outcomes between accepted and rejected ASP groups.

MATERIALS AND METHODS

Study design, setting and sample size

This prospective interventional study was conducted at Liaquat National Hospital Karachi and this study was conducted according to the principles of the Declaration of Helsinki as stated in the Fortaleza Brazil 2013. The study duration was six months, from December 2020 to May 2021. The study included in-patients on carbapenem therapy who were advised ASP interventions between 18 and 75 years of age admitted to medical ICU/HDU. Patients with concomitant invasive fungal infections, those taking four or more antibiotics and those who died within three days of treatment were excluded from the study.

Ethical approval

This study was conducted after Ethical Committee's approval (Ref: App#0592-2020 LNH-ERC; dated December 2020) using a non-probability consecutive sampling technique.

Data collection method

The ASP team at Liaquat National Hospital included a physician, a microbiologist and a clinical pharmacist. After approval of the research committee, patients on carbapenem therapy were recruited. The ASP team reviewed the data daily, including demographic and clinical data. Demographic data included age, gender and body weight with valid serial numbers, while clinical data included prescribed drug, dose, dosage frequency, route and diagnosis. The appropriateness of drug therapy was assessed according to international guidelines (Pollack & Srinivasan, 2014; Pope *et al*., 2009). Recommendations for interventions were made when required. Interventions included were; dose, duration and frequency adjustments; pharmacotherapeutic recommendations and antibiotic de-escalation. The ASP team reviewed each recommendation to determine if it was accepted or rejected. The reason(s) for rejection were documented. After the physician's acceptance, interventions were made. All these details were kept on a specially designed log sheet. Outcomes were assessed and compared between the cases with accepted intervention (modification of antibiotic) and cases with rejected intervention. Individual patients' medical records were reviewed for clinical outcomes of data.

Ethical consideration

This study was conducted according to the principles of the Declaration of Helsinki as stated in the Fortaleza Brazil 2013.

STATISTICAL ANALYSIS

SPSS (Statistical Package for the Social Sciences, version 21.0) was used for the analysis. Frequencies and percentages were calculated for categorical factors such as gender, diagnosis, C/S report, frequency, pharmacist intervention and acceptance and rejection of interventions. Continuous variables were given as a mean and standard deviation, including age, weight, carbapenem dosages and treatment duration. Fischer's exact/chi-square test was used to determine the relationship between categorical variables. The chi-square test or fishers' exact test on Mann-Whitney was used to compare groups' variables. A P-value of less than 0.05 was considered a significant level.

RESULTS

Keeping in view the guidelines, 134 prescriptions were found non-adherent from December 2020 to May 2021. Out of 134 prescriptions, 89 (66%) were male and 45 (33.65%) were female. The patient age ranges were between 45 to 95 years, with a mean age of 59.49±11.624 years. The duration of the drug given varied between 1 to 15 days, with an average mean of 10.79±3.573 days. Culture and sensitivity (C/S) reports were sent in 100 cases. In the C/S reports, 10 (7.5%) cases were isolated *Pseudomonas aeruginosa,* 7 (5.2%) isolated *Klebsiella pneumonia* and 8(6.0%) isolated growth of methicillin-resistant Staphylococcus aureus (MRSA), while no growth was found in 48 (35.8%) cases. Prescribed frequencies of the drug were once daily 2 (1.5%), twice daily 71 (53.0%), thrice daily 55 (41.0%) and four-time daily 6 (4.5%), as shown in table 1.

The most common diagnosis was respiratory tract infection 55 (41.0%), followed by sepsis 18 (13.4%) and peri/post-operative cases 14(10.4%). One gram IV was the most frequently prescribed dose (69.4%), followed by 500mg (29.1%). Carbapenem ASP intervention was accepted in 117(87.3%) patients, whereas it was rejected in 17 (12.7%) patients. The revision of antimicrobial prescriptions by the ASP team was carried out as follows: The dose was adjusted in 68 (50.7%) patients, duration was adjusted in 12 (9%); the pharmacotherapeutic recommendation in 16 (11.95%) cases; and 34 (25.4%) patients received de-escalation of carbapenem therapy; the frequency of adjustments was observed in 4 (3%) prescriptions. The reason for ASP intervention in the majority of the cases is creatinine clearance 84(62.7%), followed by inappropriate dosing 46(34.3%) and others 2 (1.5%), as shown in table 2.

Clinical outcomes of the ASP Intervention revealed an insignificant association between accepted and rejected groups with improved clinical outcomes within seven days (p=0.171). Despite this, most patients 99 (84.6%) from the accepted group, had improved clinical outcomes within seven days. Furthermore, an insignificant association was observed between the accepted and rejected groups with death within 30 days (p=1.000). On the other hand, a significant association was seen between the accepted and rejected groups with readmission within 30 days due to the recurrence of infections (p=0.036), as shown in table 3.

The reasons for readmission are ascites in 1 (0.7%) of patients, breast cancer complications in 1 (0.7%), chronic liver disease in 1 (0.7%), hemorrhage in 1 (0.7%) and re-infection in 6 (4.5%) of patients, as shown in table 4.

DISCUSSION

To our knowledge, this may be the first local research that evaluated the effect of an ASP intervention in adults for whom carbapenem usage was deemed inappropriate by the ASP team. Antimicrobial stewardship initiatives are underfunded; therefore, focusing on treatments with a better spectrum of activity is essential. We selected carbapenem as our reference antibiotic because they have the broadest antibacterial coverage with the vulnerability of beta-lactamases (García-Rodríguez *et al*., 2021). The measures advised by our ASP did not compromise patient safety in terms of clinical outcomes, such as clinical improvement and 30-day mortality rates. The approved intervention group had a significantly lower readmission rate than the rejected intervention group.

Carbapenems are widely prescribed medications with a broad spectrum of activity. The present study primarily used it to treat the respiratory tract in 41.0% of patients, followed by sepsis in 13.4% of patients and urinary tract (UTI) in 3.7% of patients. In a similar context, a Malaysian study concluded that Meropenum was mainly used in treating respiratory tract infections (28.5%) (Ong *et al*., 2020). The results of this study were in agreement with our study. On the contrary, a Spanish study found that urinary tract infection was the most common treatment site (36.2%) (García-Rodríguez *et al*., 2021). Most of the patients in our research were treated for respiratory infections; this outcome discrepancy is likely attributable to the COVID epidemic. These results also demonstrated how often Carbapenem was utilized in Pakistan.

An analysis by Shively and colleagues on pharmacist-guided ASP documented comparable acceptance rates (88.9%); they also observed a statistically significant decrease in antimicrobial utilization (p<0.001) (Shively *et al*., 2020). Likewise, another study by Jover-Sáenz and colleagues depicted a descriptive research on ASP and documented similar findings encouraging physician acceptance rates (Jover-Sáenz *et al*., 2020). Our study was in accordance with the above-cited studies and indicated that the Intervention accepted rate was 117 (87.3%), giving favorable clinical outcomes. Another study documented that more patients in the rejected group had a wide range of antibiotic use before hospitalization and were more critical than the accepted group, which might be elucidated by the comparatively low acceptance rate of their ASP interventions. In their research, the intervention acceptance rate was 48%, regardless of their potential review-and-feedback policy effort (Seah *et al*., 2017). The present study was inconsistent with the above-reported study and revealed that the overall intervention accepted rate was reportedly high 117 (87.35). This high acceptance rate demonstrates the better adoption of these strategies in our institute and gives us insights into how ASP can be practically applicable in developing countries with limited resources. The rejection rate in the present study was 12.7%; according to previously published findings, the frequency of intervention rejection seemed to be more related to physicians' attitudes in various in-patient units and not to the seriousness of the comorbidity of the individual (García-Rodríguez *et al*., 2021).

In the clinical setting, inappropriate antibiotic prescriptions are frequent; moreover, recent researches have indicated that carbapenem medication prescriptions are inaccurate or inefficient in over 50% of instances. In the present study, the carbapenem dose is adjusted in 68 (50.7%) patients and dose de-escalation in 34 (25.4%) patients. The primary reason (62.7%) of interventions was related to dose adjustment due to renal mal-function. In conformity, a more recent national study also revealed that approximately 60% of cases with needed renal dose adjustment were not adjusted, constituting a significant chunk of medication errors (Hassan *et al*., 2021). The 2nd main reason for intervention was incomplete carbapenem regimens in approximately 46 (34.3%) instances. These findings were in agreement with the literature. These de-escalation techniques are linked with minimal antibiotic resistance and mortality rates without jeopardizing the safety of patients (El-Masri *et al*., 2022; Faraone *et al*., 2020; Mitchell *et al*., 2019).

The mean duration of antibiotic prescription was 10.69 ± 3.790 and the duration was adjusted in 12 (9.0%) patients in our research. Numerous international guidelines recommend doctors to reduce the duration of antimicrobial treatment for various diseases. For urinary tract infections and pneumonia, shorter regimens are now suggested. Despite the inclusion of these recommendations, recent studies reveal that antibiotics are still being given over long periods, providing more potential for ASP. On the other hand, short-course therapy may harm patient outcomes in some cases, particularly in cases of chronic neutropenia, a lack of sufficient source control, infection with XDR Gram-negative organisms and other infections (Timsit *et al*., 2019).

Table 1: Patient's demographics, characteristics and data on carbapenem prescription guided by ASP.

Variable		Mean ± SD n=134 n (%)
Age(years)		59.49 ± 11.624
Weight(kg)		72.58 ± 9.891
Duration (days)		10.69 ± 3.790
Duration	1	2 (1.5%)
	10	39 (29.1%)
	14	56 (41.8%)
	15	6 (4.5%)
	3	11 (8.2%)
	5	3 (2.2%)
	7	17 (12.7%)
Total		134 (100.0%)
Dose time	Once daily	2 (1.5%)
	Twice daily	71 (53.0%)
	Thrice daily	55 (41.0%)
	Four times daily	6 (4.5%)
Total		134 (100.0%)
Culture & Sensitivity: Organism identified on C/S n=100	Acinetobacter	8 (8.0%)
	Escherichia coli (EC)	1 (1%)
	Klebsiella pneumonia	7 (7%)
	Mixed	2 (2%)
	Methicillin-resistant Staphylococcus aureus (MRSA)	8 (8%)
	Staphylococcus aureus	3 (3%)
	Streptococcus	5 (5%)
	Pseudomonas aeruginosa	10 (10%)
	No growth	48 (48%)
	Others	8 (8.0%)
Total		(100.0%)

Table 2: Diagnosis Physicians' response, type and reason for carbapenem intervention.

Variable		n	(%)
Diagnosis	Nervous system infection	3	2.2
	Urinary tract infection (UTI)	5	3.7
	Peri/post-operative	14	10.4
	Respiratory tract infection	55	41.0
	Sepsis	18	13.4
	Others	39	29.1
Total		134	100.0
Intervention Accepted	Yes	117	87.3
	No	17	12.7
Total		134	100.0
Type of intervention	Dose adjustment	68	50.7
	Duration adjustment	12	9.0
	Pharmacotherapeutic recommendation	16	11.9
	Antibiotic de-escalation	34	25.4
	Frequency adjustment	4	3.0
Total		134	100.0
Reason for intervention	Creatinine clearance	84	62.7
	Inappropriate dosing	46	34.3
	Multiple antibiotics	2	1.5
	Others	2	1.5
Total		134	100.0

Table 3: Association of clinical outcome in 7 days, mortality rate and readmission within 30 days with accepted and rejected groups.

Variable		Intervention Accepted		Total	p-value
		Yes n (%)	No n (%)		
Clinical improvement in 7 days	Yes	99 (84.6%)	12 (70.6%)	111 (82.8%)	0.171
	No	18 (15.4%)	5 (29.4%)	23 (17.2%)	
Total		117 (100.0%)	17 (100.0%)	134 (100.0%)	
Death within 30 days	Yes	13 (11.1%)	2 (11.8%)	15 (11.2%)	>0.999
	No	104 (88.9%)	15 (88.2%)	119 (88.8%)	
Total		117 (100.0%)	17 (100.0%)	134 (100.0%)	
Readmission within 30 days	Yes	16 (13.7%)	6 (35.3%)	22 (16.4%)	0.036*
	No	101 (86.3%)	11 (64.7%)	112 (83.6%)	
Total		117 (100.0%)	17 (100.0%)	134 (100.0%)	

*p value significant at <0.05).*Fisher-exact test was applied

Table 4: Frequency & reasons for readmission

Variable		n	(%)
Reason for Readmission	Acute Kidney injury (AKI)	1	0.7
	Ascites	1	0.7
	Breast cancer	1	0.7
	Chronic Liver Disease	1	0.7
	Covid	1	0.7
	Exacerbation of disease	2	1.5
	Gastrointestinal disorder	2	1.5
	Hemorrhage	1	0.7
	Re-infection	6	4.5
Total		134	100.0

The outcomes of ASP interventions were analyzed in multiple studies based on clinical improvement, readmission rate, mortality, antibiotic resistance and economic impact. In the current study, we found improvement in clinical outcomes with a non-significant change (p=0.171), a significant decrease (p=0.036) in hospital readmissions and a non-significant impact (p>0.999) on the 30-day mortality rate. Jover-Saenz *et al.* (2020) found no change in the hospital readmission rate during the first month. However, similar to the present investigation, he found a constant crude mortality rate after Asp treatments. This research somewhat partially concurs with the present findings (Jover-Sáenz *et al.*, 2020).

Another study found a correlation between acceptance of ASP suggestions, declining hospitalization stays and infection-related readmissions. They reported a decline in hospitalization duration and a considerable decrease in readmission rates within 30 days in critically ill patients (Lee *et al.*, 2017). Our study reflected consistency with the research mentioned above and revealed the significant association between acceptance and rejection of ASP recommendations with readmission within 30 days related to re-infection (p=0.036). On the other hand, improvement in clinical outcomes was observed in accepted and rejected interventions with an insignificant association (p=0.171) and a reduction in death rate within 30 days was also found in accepted and rejected intervention groups with an insignificant association (p>0.999).

Antimicrobial stewardship entails the best choice, prescribed amount and period of antimicrobial treatment that leads to the most favorable clinical outcome for the management or avoidance of infection, with negligible toxicity to the patient and the least impact on resulting resistance (Ababneh *et al.*, 2021). Our study was in agreement with the above review that the Antimicrobial stewardship' program not only optimized the antimicrobial effect of the drug but also improved the clinical outcomes by reducing the hospital stay and mortality rate.

The novelty of the research is one of its greatest strengths. To the best of our knowledge, this is the first prospective study done in the local region to investigate the usage of carbapenems in adult populations after the implementation of ASP. It includes information on inappropriate Carbapenem usage and pattern of culture and sensitivity in Pakistan. It also emphasizes the need to develop antibiotic stewardship strategies at the local level to reduce antibiotic abuse and combat microbial resistance. In this era, when we are actively seeking strategies to reduce the spread of antibiotic-resistant microbes and preserve the existing antibacterial drugs, deploying these strategies can benefit our future generations.

We acknowledge several limitations in our study. Firstly, this is the perspective of a particular centre, which limits the generalization of the results. Still, it contributes to the publicized work on ASP deployment in a specific area, notably Pakistan. Secondly, due to the brief duration of the study, the sample size of the participants is comparatively smaller. We could not analyze the antibiotic resistance pattern and the program's economic impact could also not be assessed due to hospital policy. Lastly, since the official ASP is already implemented in our institution, restriction on the use of specific antimicrobials was in practice; as a result, the ASP interventions' effect might have been more significant if data before limitations were available.

CONCLUSION

This study concluded that the Antibiotic Stewardship program is acceptable and applicable in developing countries like Pakistan, similar to developed countries. Carbapenem guided by ASP improved the rationality of recommended antibiotics and showed an impact in ameliorating clinical outcomes and mortality rates. Moreover, extended period studies are needed for further elaboration.

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