ORIGINAL ARTICLE

Impact of an Antimicrobial Stewardship Program on Broad Spectrum Antibiotics Consumption in the Intensive Care Setting

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Abstract

Background and objectives: Antibiotics are the most commonly exploited agents in intensive care units. An antimicrobial stewardship program (ASP) helps in the optimal utilization of antibiotics and prevents the development of antibiotic resistance. The aim of this study was to assess the impact of ASP on broad-spectrum antibiotic consumption in terms of defined daily dose (DDD) and days of therapy (DOT) before and after the implementation of an ASP.

Materials and methods: It was a prospective, quasi-experimental, pre- and post-study. Group A consisted of 5 months of ASP data, ASP activities were implemented during the next 2 months and continued. Group B (post-ASP) data was collected for the next 5 months. Total and individual DDDs and DOTs of broad-spectrum antibiotics utilized were compared between group A and group B.

Results: Total DDDs used per 100 patient bed days were reduced by 18.72% post-ASP implementation (103.46 to 84.09 grams). The total DOT per 100 patient bed days used was 90.91 vs 71.25 days (21.62% reduction). As per the WHO classification of antibiotics use, the watch category (43.4% vs 43.04%) as well as reserve category (56.6% vs 56.97%) used between the two groups were found similar. The average length of stay (8.9 ± 2 days) after ASP was found significantly lesser than baseline (10.8 ± 3.4 days) ($p < 0.05$), however, there was no significant change in mortality between the two groups.

Conclusion: Antimicrobial stewardship program implementation may reduce overall antibiotic consumption both in terms of DDD and DOT.

Keywords: Antimicrobial stewardship, Antibiotic consumption, Days of therapy, Defined daily dose.

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Introduction

Antibiotics are the most prescribed and misused drugs worldwide in outpatient as well as critical care unit settings. Up to 30% of the prescribed antibiotics were deemed unnecessary or inappropriate in one of the published literature, the most common reasons for unnecessary therapy included administration of antimicrobials for longer than recommended durations, administration of antimicrobials for non-infectious or nonbacterial causes, and treatment of colonizing or contaminating microorganisms.[1] Indiscriminate use of antibiotics has led to the global threat of antimicrobial resistance (AMR) and the emergence of multidrug-resistant (MDR) organisms in intensive care units (ICU).[2–5]

Intensive care units contribute to a significant proportion of broad-spectrum antibiotic prescriptions.[6] Resultant antibiotic pressure then selects the development of resistant MDR organisms.[7] Majority of MDR organisms (approximately 64.5%) in ICUs belong to the notorious ESKAPE (*Enterococcus faecium, Staphylococcus aureus* including MRSA, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* species) group.[8] Development of New Delhi beta-lactamase carbapenamase amongst gram-negative organisms poses a specific problem with few options left to treat such cases.[9]

Micro-organisms are highly capable of developing new resistance mechanisms and there are very few new antibiotics being introduced to combat these superbugs.[10] We have stepped

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Table 1: Antimicrobial Stewardship Program activities

- A team of Physician intensivists, infectious disease specialists, microbiologists, nursing in charge, hospital infection control (HIC) personal and clinical pharmacists was formed.
- Unit antibiogram was prepared and made available for the use of all the stakeholders.
- Justification letter was introduced, required for the prescription of broad-spectrum antibiotics.
- Regular audit review meetings were conducted with the team on a regular basis and feedback was given to the primary treating physician with regard to antibiotic selection, its dose, and duration of therapy.
- Strict hand hygiene compliance training and implementation of infection control activities were carried out.
- The WHO AWaRe classification of antibiotics (A, Access group; Wa, Watch group; Re, Reserve group) was made available for use.
- Hospital administration and HIC were involved and kept in the loop for all the activities.

into a dystopian crisis of a post-antibiotic era where these existing antibiotics will no longer work and even a minor infection can kill in the absence of an effective cure.[11]

Antimicrobial stewardship program (ASP) is defined as the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.[12] Antimicrobial stewardship program can help promote rational use of antibiotics, decrease their utilization, and reduce financial burden.[13]

Antibiotic utilization can be measured by computing a defined daily dose (DDD) or days of therapy (DOT). Defined daily dose is defined by the World Health Organization (WHO) as the average maintenance dose of a drug per day used for its main indication in adults. World Health Organization publishes standard assigned DDDs annually which are available on their website.[14] The Advantage of DDD is its ease of calculation, it can be used for inter-hospital comparison or comparison between different countries. The problems with DDD is that WHO-assigned DDD and actually prescribed doses can be different, DDD may be underestimated in cases of renal failure and DDD cannot be used in pediatric populations as no WHO-assigned DDDs are available for pediatric age group.

Days of therapy is the total number of days for which the patient is administered an antibiotic regardless of its dose or frequency. Days of therapy is the recommended metric by Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for antibiotic utilization.[15] Days of therapy is patient level data that might be difficult to obtain where facilities are not available but can be used in pediatric population.

Indian data is sparse both in terms of antibiotic utilization metrics and in evaluating the impact of ASPs on antibiotic utilization. A recent study published in the Lancet has shown that antibiotic consumption in India in the year 2019 was around 5,071 million DDDs, which is a huge number. The study also revealed that although the per capita consumption of antibiotics is relatively low in India as compared to many countries, India consumes a large proportion of broad-spectrum antibiotics which should otherwise be used judiciously.[16]

World Health Organization (WHO) categorizes essential antibiotics into three groups based on their potential to induce and propagate resistance. These antibiotics are classified into access (A), watch (Wa), and reserve (Re) categories. This classification is also known as the AWaRe classification.[17] This can be used as a tool to understand the impact of ASP and antibiotic consumption trends.

Indian data is lacking regarding the ASP implementation, overall antibiotic consumption in Indian ICUs, and impact on ASP metrics. We designed this study to compare the change in broad-spectrum antibiotic consumption pre- and post-ASP implementation, both in terms of DDD and DOT. Broad-spectrum antibiotics are the class of antibiotics that acts against both gram-positive and gram-negative bacteria and can be used in a wide variety of infections. We also aim to know the common prescription pattern of broad-spectrum antibiotics as per the AWaRe classification.

Materials and Methods

This was a prospective, quasi-experimental, pre- and post, single-center study, done at a level 3 intensive care unit in Pune, India. Institutional ethics committee approval was obtained.[18] All patients above 18 years of age who were prescribed broad-spectrum antibiotics were included in our study. The study was planned for a period of 1 year from April 2021 to March 2022.

The study was divided into two parts, group A, or pre-ASP implementation period, and group B, or post-ASP implementation period. In the first 5 months (April 2021 to August 2021), we collected the pre-ASP implementation data. Data was collected from daily ICU patient charts and recorded manually in dedicated case record forms. It included basic demographic information, the type of antibiotic prescribed, its dose, the route of administration and the duration of antibiotic therapy.

For the next 2 months (September and October 2021) various antibiotic stewardship implementation and awareness activities were carried out and continued during ASP period (Table 1).

Similar data on antibiotic utilization was collected prospectively during the next 5 months of the post-ASP implementation period or group B (November 2021 to March 2022).

Defined daily dose (DDD) calculation:

- Drug usage in DDDs = Number of packages issued × Amount of drug in each package/WHO defined DDD[15]
- DDD per 100 patient days = Number of DDDs used/Number of in-patient days × 100
- Where the number of in-patients days was obtained from the relation – Number of Patients Day = O × N × T, with: O = specific rate of beds occupation of the service; N = number of available beds; T = time period in days.

Days of therapy – It was calculated as the total number of days for which a patient is given an antibiotic regardless of its dose.

Outcome Measures

Primary outcome measures were to know the change in antibiotic consumption in terms of DDDs and DOTs before and after implementation of ASP activities and to know the prescription pattern of broad-spectrum antibiotics at our unit based on WHO AWaRe classification system.

Secondary outcome measures were to know the effect of ASP implementation on mortality and length of stay.

Statistical Analysis

Statistical Analysis Method

Statistical analysis was done on IBM SPSS statistics version 20. Categorical variables were represented in the form of frequencies and percentages and cross tabulations were done for the chosen parameters and compared using Chi-square test or Fisher's exact test. Continuous variables were expressed in the descriptive statistics tables as means and standard deviation and were compared using an independent sample *t*-test. The *p*-value < 0.05 was considered significant and *p*-value < 0.01 was considered highly significant.

Results

During the Pre ASP period (group A), 504 patients were admitted to our ICU, of whom 149 patients (29.56%) received broad-spectrum antibiotics. During post ASP period (group B) total of 358 patients were admitted and 107 patients received (29.88%) broad-spectrum antibiotics. Both groups were comparable in terms of age, gender, and severity of illness (average APACHE II score) (Table 2).

Overall, there was a reduction in total antibiotics consumption post ASP implementation in terms of both DDD and DOT. Defined daily dose per 100 patient bed days was 103.46 in group A which was reduced to 84.09 per 100 patient bed days in group B (18.72% reduction). Days of therapy per 100 patient bed days was 90.91 in group A vs 71.25 in group B (21.62% reduction) (Table 3).

In terms of DDDs there was a significant reduction in consumption of meropenem (562.78 to 375), polymyxin (78.93 to 51.63), colistin (258.44 to 189.47), teicoplanin (188 to 85), fosfomycin (106 to 24.66) and aztreonam (123.75 to 49.75), all *p*-values < 0.05. Consumption of ceftriaxone increased significantly from 165.5 to 194.5 DDDs and of cefepime-tazobactam increased from 109.67 to 146.24 DDDs (both *p*-values < 0.05).

Similarly, DOTs of the above antibiotics were significantly reduced ($p < 0.05$). Days of therapy of meropenem was reduced from 418 to 267, polymyxin from 105 to 50, colistin from 315 to 228, teicoplanin from 124 to 53, fosfomycin from 58 to 15 and aztreonam from 82 to 50 days. Days of therapy usage of cefepime-tazobactam significantly increased from 75 to 104 days (Table 4).

The most common antibiotic prescribed in our unit was ceftriaxone (35.6% and 44.9%) and meropenem (38.3% and 45.6%) in both groups (Fig. 1).

World Health Organization watch category antibiotics were used in 43.4% of cases in group A and group B it was used in 43.04% of cases. Reserve category antibiotic use was in 56.6% of cases in group A and in 56.97% cases group B (Table 5). There was no significant change between them. We did not include any access category antibiotics in our study.

The average Length of stay (8.9 ± 2 days) after the Antibiotic stewardship program was found significantly lesser than the baseline (10.8 ± 3.4 days) ($p < 0.05$), however, there was no significant change in mortality between the two groups (Table 1).

Table 2: Comparison of baseline characteristics of the study participants between periods before and after implementation of Antibiotic Stewardship Program

Demographic parameters	*Group A (N = 149)*		*Group B (N = 107)*		
	Number	*%*	*Number*	*%*	*p*
Gender					
Male	104	69.80	72	67.29	0.67
Female	45	30.20	35	32.71	
	Mean	*SD*	*Mean*	*SD*	*p*
Age	53.0	17.5	50.5	19.1	0.27
Weight	62.4	8.7	62.3	9.1	0.9
APACHE-II score	13.1	6.4	11.7	5.5	0.06
Mortality	29	19.46	13	12.15	0.1
Length of stay	10.8	3.4	8.9	2.1	0.007

APACHE-II, acute physiological and chronic health evaluation score II; SD, standard deviation; $p < 0.05$ is significant

Table 3: Comparison of average DDD use before and after implementation of Antibiotic Stewardship Program

	Group A (N = 149)				*Group B (N = 107)*				
Antibiotic	*Total DDD*	*N*	*Mean*	*SD*	*Total DDD*	*N*	*Mean*	*SD*	*p*
Ceftriaxone	165.5	53	3.1	1.2	194.5	48	4.1	1.5	<0.01
Meropenem	562.78	68	8.3	2.3	375	54	6.9	2.2	0.01
Polymyxin	78.93	11	7.3	3.1	51.36	10	5.0	1.5	0.04
Colistin	258.54	27	9.6	2.2	189.47	21	8.1	1.9	0.01
Cefepime/tazobactam	109.67	19	4.8	1.4	146.245	26	6.6	2.9	0.01
Piperacillin/tazobactam	59.14	31	1.9	1.4	60.74	12	5.1	2.1	0.12
Teicoplanin	188	31	6.9	1.8	85	14	5.1	2.1	<0.01
Linezolid	110	25	4.4	2.7	98.5	23	4.3	2.6	0.9
Minocycline	86	11	7.8	2.4	71	7	10.1	2.8	0.08
Fosfomycin	106	11	9.6	3.2	24.66	7	3.5	1.5	<0.01
Ceftazidime/avibactam	98.39	12	8.2	2.8	74.575	9	8.3	3.1	0.94
Aztreonam	123.75	13	9.5	3.1	49.75	8	6.2	2.2	0.01
Vancomycin	10.75	5	2.2	1.0	12.25	9	1.4	0.4	0.43
Tigecycline	5	1	5.0	0.0	6	3	2.0	0.5	0.38
Total DDDs	1962.45				1439.05				
DDD per 100 patient bed days	103.46				84.09				–18.72%

DDD, defined daily dose; SD, standard deviation; $p < 0.05$ is considered significant; *p*-value < 0.01 considered highly significant

Table 4: Comparison of average DOT use before and after implementation of Antibiotic Stewardship Program

	Group A (N = 149)				*Group B (N = 107)*				
Antibiotic	*Total DOT*	*N*	*Mean*	*SD*	*Total DOT*	*N*	*Mean*	*SD*	*p*
Ceftriaxone	194	53	3.7	1.2	155	48	3.2	2.3	0.16
Meropenem	418	68	6.1	1.9	267	41	4.5	2.1	0.03
Polymyxin	105	11	9.5	3.2	50	10	5.0	2.3	<0.01
Colistin	315	27	11.7	1.6	228	21	8.9	1.9	0.02
Cefepime/tazobactam	75	19	3.9	2.3	104	26	5.8	2.2	<0.01
Piperacillin/tazobactam	91	31	4.4	1.2	53	12	3.4	1.2	<0.01
Teicoplanin	124	31	4.0	1.9	53	14	2.8	1.6	0.04
Linezolid	85	25	3.4	1.2	92	23	4.0	1.4	0.12
Minocycline	93	11	8.5	2.3	68	7	9.7	3.2	0.37
Fosfomycin	58	11	5.3	1.8	15	7	2.1	0.9	<0.01
Ceftazidime/avibactam	71	12	5.9	1.2	70	9	7.8	2.2	0.48
Aztreonam	82	13	6.9	1.8	50	8	4.3	2.1	0.04
Vancomycin	20	5	4.0	2.1	29	9	3.2	1.8	0.47
Tigecycline	5	1	5.0	0.0	8	3	2.7	1.1	0.67
Total DOT	1,736				1,242				
DOT per 100 patient bed days	90.92				71.25				–21.62%

DOT, days of therapy; SD, standard deviation; $p < 0.05$ is considered significant; p-value < 0.01 considered highly significant

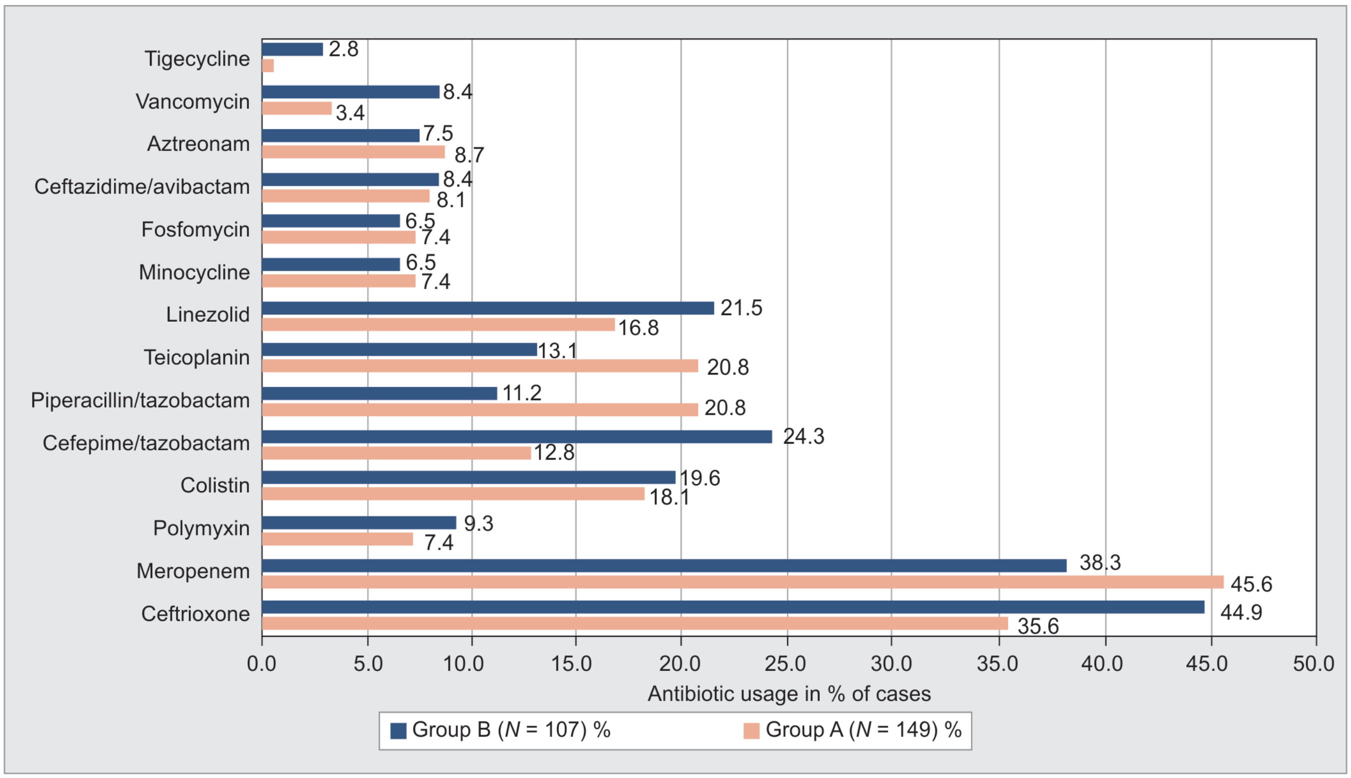

Fig. 1: Distribution of antibiotics usage in % of cases, before and after implementation of Antibiotic Stewardship Program

Discussion

Antimicrobial stewardship is still a poorly understood, complex, and difficult-to-employ concept in most healthcare settings. It requires a comprehensive understanding and teamwork from a variety of stakeholders including the administration and leadership. As the saying goes "if we cannot measure it, we cannot improve it," is important to measure the background information on current ASP practices and metrics for better understanding and further improvements in implementation.

The major effects of a properly implemented ASP program are three-fold. Reduction in antibiotic consumption reduced antibiotic resistance and development of MDR organisms, and decreased antibiotic use-related complications like clostridium difficile positivity rate and nephrotoxicity.

Table 5: Comparison of % DDDs as per AWaRe Classification before and after implementation of Antibiotic Stewardship Program

	Group A (N = 149)		*Group B (N = 107)*	
AWaRe class	*Total DDD*	*%*	*Total DDD*	*%*
Watch category	852.0	43.4	619.25	43.03
Reserve category	1110.4	56.6	819.8	56.97

DDD, defined daily dose; AWaRe, Access group (A) Watch group (Wa) Reserve group (Re); WHO, World Health Organization access watch and reserve class of antibiotics

In our study, there was an overall 18.72% reduction in consumption of antimicrobials in terms of DDDs post-ASP implementation (from 103.46 per 100 patient bed days to 84.09 per 100 patient bed days). Similar results were observed with DOT usage. Overall, DOT used was reduced by 21.62% during post ASP period. In a recent (2023) systematic review and meta-analysis of the association of ASPs with antimicrobial consumption, ASPs were associated with reduced antibiotic consumption in both hospital and nonhospital settings.[19] Antimicrobial Stewardship Program were associated with a 10% (95% CI, 4–15%) reduction in antibiotic prescriptions and a 28% reduction in antibiotic consumption (rate ratio, 0.72; 95% CI, 0.56–0.92%). Antimicrobial Stewardship Program were also associated with a 21% (95% CI, 5–36%) reduction in antibiotic consumption in pediatric hospitals and a 28% reduction in WHO watch group antibiotics (rate ratio, 0.72; 95% CI, 0.56–0.92%). The results are similar to our study.

Consumption of important WATCH category antibiotics like meropenem, teicoplanin, and aztreonam was significantly reduced during post-ASP analysis. More importantly, DDD usage of reserve category antibiotics polymyxin, colistin, and fosfomycin was reduced significantly after ASP implementation. Defined daily dose usage of cephalosporins like ceftriaxone and cefepime-tazobactam increased post-ASP implementation.

Days of therapy of meropenem, teicoplanin, polymyxin, colistin, and fosfomycin were significantly reduced during post-ASP period. Days of therapy usage was increased for cefepime-tazobactam in post-ASP period.

These mixed results could be because of a variety of reasons. Increased awareness amongst physicians may have caused targeted and specific treatment of community-acquired infections especially pneumonia over hospital-acquired infections. This can explain the increased use of beta-lactams and beta-lactamase inhibitors like ceftriaxone and cefepime-tazobactam. Similarly, antibiotics justification forms may have curtailed the use of inappropriate gram-positive coverage by teicoplanin and reserve categories of antibiotics like polymyxin, colistin, and fosfomycin.

Multiple previous studies have consistently shown a significant reduction in overall and individual antibiotic consumption post-ASP implementation. These results are comparable with our study.[20–24] Increase in consumption of antibiotics like cefepime-tazobactam may be because of a lack of awareness amongst primary caregivers and prescription opposition.

Our results suggest that ASP implementation can effectively cut down the overall use of broad-spectrum antibiotics in intensive care units. Antimicrobial Stewardship Program is a complex process and its implementation involves multiple challenges.

It is a matter of debate whether to use DDD or DOT for assessment of antibiotic consumption, with many organizations like IDSA recommending DOT for the same because of the benefits mentioned earlier.[25] We calculated both DDD and DOT in our set-up.

Continuous prospective audits of antibiotic consumption give us insights into our prescription pattern. In our set-up approximately 30% of the admitted patients in ICU were prescribed broad-spectrum antibiotics, ceftriaxone and meropenem being the most common agents. Watch and reserve category antibiotics use was comparable between the two groups, an overall decreasing trend was seen which was not significant.

Indian Society of Critical Care Medicine has issued a comprehensive guideline for antibiotic prescription in intensive care units which can be utilized for empirical choice of antibiotic for most infections in Indian ICUs.[26]

The length of ICU stay was significantly reduced post-ASP period in our setup. However direct cause and effect cannot be established here. Antimicrobial Stewardship Program are known to cause a decrease in the length of stay. In a study by Khdour MR et al., the median (interquartile range) of the length of stay was significantly reduced post-ASP [11 (3–21) vs 7 (4–19) days; $p < 0.01$).[27] Whether decreased antibiotic consumption has caused a reduction in length of stay or vice versa is difficult to understand.

Limitations

It was a single-center study. The major benefit of the ASP is a decrease in antibiotic resistance, our study did not account for changing patterns of antibiotic resistance. Furthermore, the cost factor can be considered to see the financial gains of the successful ASP implementation.

Conclusion

Our study highlights the positive impact of ASP implementation on overall broad-spectrum antibiotic consumption, both in terms of DDD and DOT. The average length of stay was significantly reduced post-ASP implementation, however, there was no difference in mortality.

Clinical Significance

Effective antimicrobial stewardship programs may significantly reduce broad-spectrum antibiotics consumption in intensive care settings.

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