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Impact of trainee-driven Antimicrobial Stewardship Program in a high burden resource-limited setting

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SUMMARY

Antimicrobial Stewardship Program (ASP) is one of the most critical interventions required to halt the growing global antimicrobial resistance. The study aimed to evaluate the effect of trainee driven ASP implementation with limited available resources on outcome variables. An ASP team comprising of infectious diseases trainees and consultants was constituted to conduct stewardship activities in the Department of Medicine, All India Institute of Medical Sciences, a tertiary care apex institute in north India. Prospective audit and feedback were conducted by the team, and the following outcome variables were recorded and analysed: the practice of sending cultures, appropriateness of prescribed empiric antibiotics, gross antimicrobial consumption and mortality. ASP intervention led to an increase in blood culture positivity rates by two folds ($p<0.001$). The trend of empiric prescription choices gradually shifted over time towards the use of more effective antibiotics according to the local antibiogram. Redundant usage of antibiotics substantially reduced over time. There was no impact of the antimicrobial stewardship program on the all-cause mortality rate. ASP had a significant effect on the practice of sending cultures and appropriateness of antibiotic usage. In resource-limited settings, trainee-driven antimicrobial stewardship program can succeed in inculcating rational practices among fellow residents and practicing physicians.

Keywords: Antimicrobial resistance, defined daily dose, audit.

INTRODUCTION

India is considered as one of the global hotspots for the emergence of antibiotic resistance [1]. Antimicrobial resistance is continually growing, and the pipeline for new antibiotics is running dry. The scenario is most worrisome with the multidrug-resistant Gram-negative bacteria [2]. Studies on international travellers returning from India have reported high intestinal carriage of multidrug-resistant (MDR) *Enterobacteriaceae* [3-8]. In a recent report communicated from China, the emergence of plasmid-mediated colistin-resistant *Enterobacteriaceae* (col-RE) has been described [9]. Subsequent reports from various parts of the world have confirmed the presence of this latest superbug containing *mcr-1* gene, which is practically resistant to almost all known antibiotics of the present generation [10-14]. Antimicrobial Stewardship Programme (ASP) has been hailed as one of an essential strategy for combating the growing threat and burden of antibiotic resistance [14]. The aim of this study was to investigate the impact of trainee driven antimicrobial stewardship program on the outcome measures (practice of sending cultures, appropriateness of prescribed empiric antibiotics, gross antimicrobial consumption and mortality).

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MATERIALS AND METHODS

Setting

The study was conducted in the medicine wards and intensive care unit at All India Institute of Medical Sciences (AIIMS), a tertiary care apex institute in North India. The wards and the Intensive Care Unit (ICU) of the Department of Medicine at AIIMS receive critically ill patients referred from multiple public and private hospitals from Delhi as well as other states of India. The department has two wards (54 beds) and one ICU (8 beds) under its care. The beds are divided between three units, each unit with two admission days per week (sunday-rotational). The study period ranged from July 2017 to December 2018. The study was conducted after taking permission from the Institute Ethical Committee.

ASP team

Due to the lack of dedicated pharmacists in Indian hospitals, an ASP team was constituted comprising of infectious diseases trainees and consultants from internal medicine/infectious diseases and microbiology/infection control. Three infectious diseases trainees were posted in the ASP team at a time on a monthly rotation basis, and their daily activities were monitored by a faculty in-charge.

Daily ASP rounds

Audit was done by the trainees where relevant parameters were recorded on a pre-defined proforma during the evening rounds, and the feedback was given to the treating team led by the respective unit's consultant during the next day morning round. Evening rounds were taken during the post-admission day evenings of each unit, and feedback was given on pre-admission day mornings. This ensured that the feedback was given 48-72 hours after admission of each patient.

Prospective Audit and Feedback (PAF)

Recorded details were analysed by the trainees, and feedback was given based on the following principles. A regimen was deemed inappropriate if:

a) the empiric use of antibiotic and the total duration were not guided by the hospital antibiotic policy and local antibiogram;
b) the definite therapy was not guided by the antimicrobial susceptibility test reports and hospital antibiotic policy;
c) a redundant coverage was present in the empiric regimen. Intravenous (IV) to oral conversion was suggested wherever possible.

IV to oral conversion was recommended to those patients on IV antibiotics with good oral bioavailability and without mucositis/malabsorption syndrome/gastrointestinal dysmotility/severe nausea, vomiting or diarrhoea for. De-escalation to an antibiotic with a narrower spectrum was suggested if in the culture grew a sensitive organism, or more than 48 hours of defervescence was achieved, or a non-infectious or viral cause was identified, or there was a comprehensive improvement in the condition of the patient.

Weekly meetings

Weekly meetings were held on every Thursday, where, along with didactic education and case presentations, each week's stewardship data was presented and critically analysed.

Outcome measures

The following outcomes were measured.

a) The total number of non-duplicative blood cultures sent in a defined time period and the number of positives.
b) The cumulative monthly antibiotic consumption for the wards calculated according to total grams and that of Defined Daily Doses (DDD) per 100 patient days recommended by the World Health Organization (WHO) [15, 16].
c) The all-cause mortality cases in the medical wards and ICU.

Statistical analysis

Appropriate statistical methods were employed to compare the primary outcome variables. Chi-square test was used for the qualitative variables. Students t-test and Rank sum non-parametric tests were used for the quantitative variables. Results on continuous measurements were presented as Mean ± SD, and results on categorical measurements were presented in number (%). Descriptive statistical analyses were carried out with Stata v11 with Microsoft Word and Excel being used to generate graphs and tables. Normality of data was tested by Anderson Darling test, Shapiro-Wilk, Kolmogorov-Smirnoff test and visually by QQ plot. Chi-square test was used to find the

significance of study parameters on a categorical scale (ordinal or nominal) between two or more groups.

RESULTS

In the second half of 2017, a total of 815 blood cultures were sent with a monthly average of 67.9, out of which, 49 blood cultures came out to be positive at a rate of 6.0%. This rate significantly changed in 2018 with a positivity rate of 12.2% (112 positive blood cultures among 917 sent) with *p*-value <0.0001 (Figure 1).

Piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin, teicoplanin and vancomycin were the seven most commonly prescribed broad-spectrum antibiotics in the medical wards. The individual comparison and the trends of usage of those antibiotics in Daily Defined Dosage (DDD) per 100 patient days showed piperacillin-tazobactam and teicoplanin to be the most commonly used parenteral antibiotics. According to the antibiogram data of our institute, it was found that cefoperazone-sulbactam and imipenem have much better sensitivity as compared to piperacillin-tazobactam and meropenem in most clinically relevant Gram-negative isolates. However, cefoperazone-sulbactam and imipenem remained as an under-prescribed agent compared to piperacillin-tazobactam, particularly when noted during the initial phases of stewardship practice. As a part of the ASP intervention, during the feedback, the use of imipenem and cefoperazone-sulbactam were promoted as empiric agents of choice. The trend of antibiotic consumption data showed that usage of imipenem and cefoperazone-sulbactam increased with time during the study period (Figures 2 and 3). A moving average was calculated to

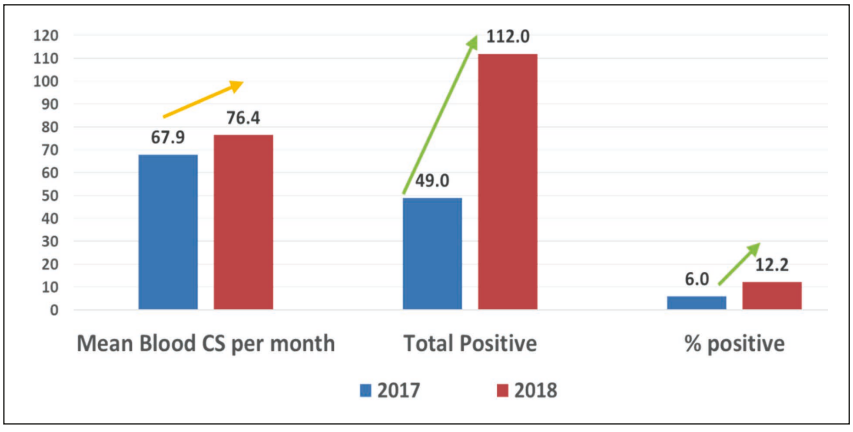

Figure 1 - Mean Blood CS per month and blood culture positivity rates: 2017 vs 2018.

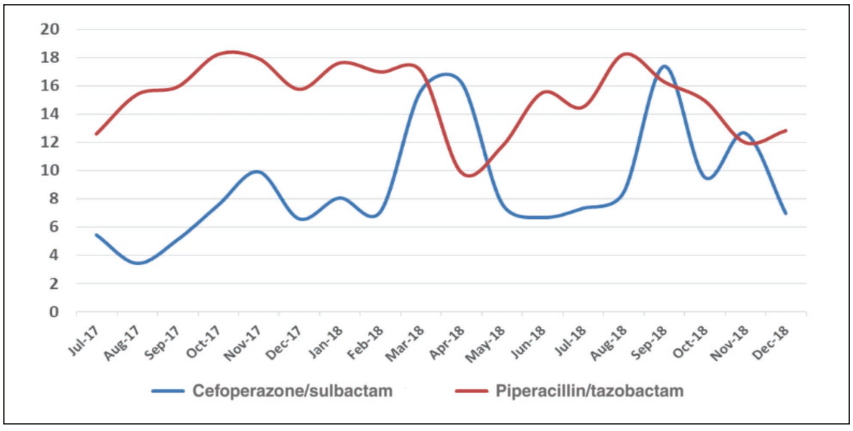

Figure 2 - Cefoperazone-sulbactam versus piperacillin-tazobactam usage trend per 100 patient-days during 18 months (July 2017 to December 2018).

observe the trend of these antibiotics over time, and it was observed that piperacillin-tazobactam and meropenem had a downward slope while cefoperazone-sulbactam and imipenem had an upward slope. Glycopeptide use trend per 100 patient-days during the 18 months showed that usage of teicoplanin was significantly and consistently higher than vancomycin.

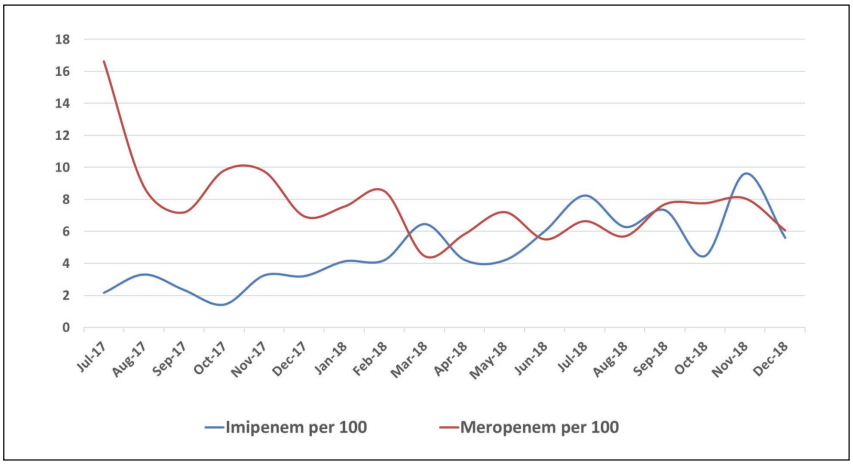

Figure 3 - Imipenem versus meropenem usage trend per 100 patient days during 18 months (July 2017 to December 2018).

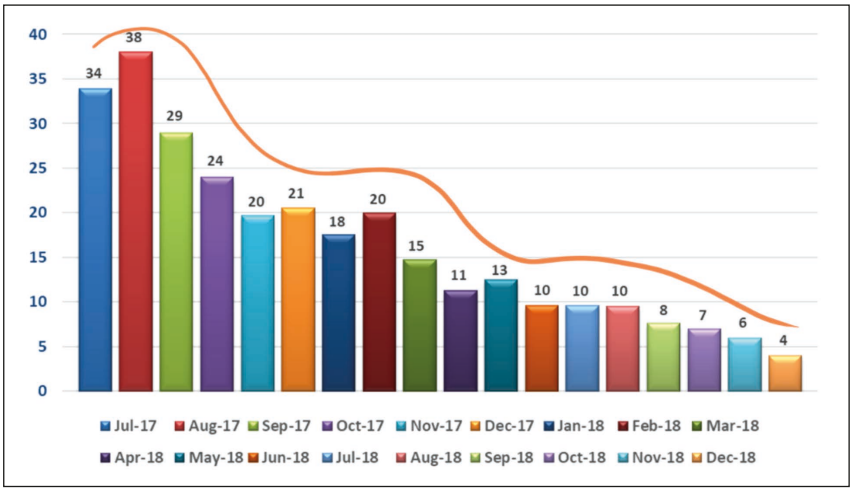

Figure 4 - Reported redundant anaerobic coverage during 18 months (July 2017 to December 2018).

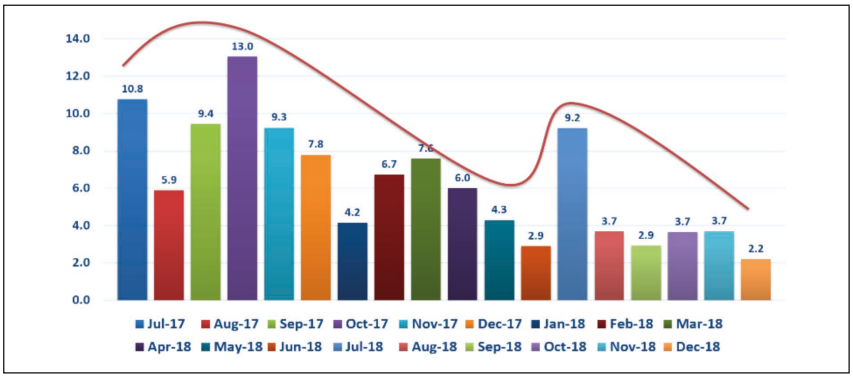

Figure 5 - Cumulative usage trend of Clindamycin and Metronidazole per 100 patient days.

The most commonly practised redundant coverage of antibiotics was reported with respect to anti-anaerobic coverage, where either metronidazole or clindamycin was added to a regimen containing antibiotics with inherent anaerobic coverage like piperacillin-tazobactam or meropenem. Over the time period of 18 months, redundant anaerobic coverage was found to decrease to an absolute value of more than 8-folds, with a gradual and steady decline (Figure 4). This also corroborated to the trend of cumulative usage of metronidazole and clindamycin in the medical wards, plotted over the same time period (Figure 5).

The mortality rates (per 100 patient-days) during the 18 months of antimicrobial stewardship practice from July 2017 to December 2018 did not show any significant trend.

DISCUSSION

A Cochrane meta-analysis confirmed that interventions to reduce excessive prescription of antibiotics could reduce antimicrobial resistance and improve microbiological and clinical outcomes. However, only a few studies provided data about the vital interventional components and the effectiveness of ASP in resource-limited settings [17, 18]. A global survey of stewardship activities revealed that only 14% of respondents in Africa and 53% in Asia had any form of an ASP in place [19]. There is a need for comprehensive and perennial ASP in public sector hospitals in India. Although an ideal ASP team should be comprised of pharmacists, clinical microbiologists, infectious diseases physicians and information technology personnel, it may not always be pragmatic in resource-limited settings. To circumvent the lack of trained pharmacists without any increase in expenditure, we devised an AMSP program led by infectious disease residents under the supervision of senior faculty members. ASP prior to the initiation of the present study was only in the form of small projects in our department. Positive results from those studies paved the way for an improved AMS on a larger scale which can be used as a model in public sector hospitals [20].

Our study showed that ASP intervention leads to improvement in the practice of sending blood culture and an increase in the culture positivity rates. The positivity rate significantly increased in 2018 to 12.21% (112 positive blood cultures among 917 sent) with p-value <0.0001. PAF is the primary strategy of stewardship that has been adopted in our setting, where an infectious diseases trainee, who is not a part of the treating team would evaluate the drugs prescribed to the patient, judge their appropriateness and provide unattached feedback to the treating team. The feedbacks were not binding, and therefore, it did not affect the autonomy of the treating team. PAF has shown to improve antibiotic prescription practices, decrease overall usage of broad-spectrum and parenteral antibiotics and decrease rates of antibiotic resistance among gram-negative pathogens [21-27]. Wherever daily PAF is not possible, limited or weekly PAF has also shown to have significant value.

World Health Organization (WHO) recommends Daily Defined Dosage (DDD) as the measure of antibiotic consumption [15, 16]. The DDD is calculated as the total number of grams of the antimicrobial agent used, divided by the number of grams in an average daily dose. It's generally expressed in DDDs per 1,000 patient-days. The DDD provides a fixed unit of measurement independent of price and dosage form enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. Going by the recommendations of WHO, we preferred to use DDD as the measure of antibiotic consumption.

With the ongoing ASP over the recorded 18 months, concurrent usage of metronidazole or clindamycin with a carbapenem or a BL/BLI combination was considered as redundant anaerobic coverage and feedbacks were provided to the treating team. This strategy was remarkably successful in reducing the redundant coverage over time, as evidenced by the overall decrease in consumption of metronidazole and clindamycin.

Our study shows that even without digital record-keeping, in the absence of trained pharmacists in the program and despite heavy load of high-stakes critically ill patients in our department, a trainee-driven antimicrobial stewardship program can succeed in inculcating rational practices among fellow residents and practising physicians.

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Conflic of interest
None

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