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Optimizing Antimicrobial Drug Utilization through Antimicrobial Stewardship programme in a tertiary care referral hospital in south India

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ABSTRACT

Antimicrobial stewardship is defined as a rational, systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes. The primary objective (strategy) of the study was to reduce the use of antimicrobial agents by the development and implementation of an Antimicrobial Stewardship Programme.(ASP) The secondary strategies comprised intravenous to oral conversion of antimicrobial agents, de-escalation therapy, reduction of medication errors etc. The study was executed as an observational phase for 75 days in general medicine inpatients and developed an Antimicrobial stewardship committee. Interpretation of the pre-interventional phase data committee selected the primary and secondary strategies. Corrective actions for the findings were made and the monitoring was re-initiated in the post interventional phase with proper recommendations by the clinical pharmacist in prospective design for the next 75 days in the same set of population. The primary strategy was indexed in terms of DDD/100 bed days for the utilization of antimicrobial agents and the secondary strategies are represented in terms of numbers and percentage difference. The significance differences were made by the statistical analysis for different strategies. The Antimicrobial stewardship programme was executed and developed with fulfilled quorum committee. The primary strategy, 54% (0.5730DDD/100beddays) reduction in the use of antimicrobial agents were achieved in comparison to the observational phase, significance reduction were achieved in the doxycycline (0.296 to 0.022), oral ciprofloxacin (0.392 to 0.115) and oral moxifloxacin (0.184 to 0.021). By the proper educations, monitoring and the recommendations by the clinical pharmacist the rate of conversions of intravenous to conversion of antimicrobial agents increased from 6% to 72%(p=0.0001), the usage of multiple broad spectrum (De-escalation) antimicrobial agents decreased from 17.31% to 15% and the medication errors such as prescription error, dispensing errors and administration errors were reduced from 71.25% to 28.28%. By the programme some impact were fallen to other strategies such as number of culture sensitivity tests, duration of the therapy and resistance panel of the study site. The functioning of the program with heterogeneous goals in each cycle can effectively optimize the antimicrobial use and pathogen susceptibility patterns.

INTRODUCTION

The accidental finding of the scientist Alexander Fleming in 1928 in his laboratory a substances from the micro-organism helps to kill or inhibit the growth of the other organisms still influencing the modern era of multiple infectious diseases[1] Antibiotics are substances produced by micro-organisms which specifically alter the growth or kill other microorganisms at a very low concentration.[2] Because of the unavailability of the other antimicrobial agents and the unawareness of the resistance leads to increase the usage of antimicrobial agents and finally allow to start the journey of the resistance in between 1940-1950[3]. Infections may be fatal unless the severity is ameliorated by the antimicrobial agents; imprudent use over the past half century has resulted in humanity facing the prospect of losing the battle against many bacterial diseases [4].Antimicrobial stewardship programme is aimed at achieving optimal outcomes with antimicrobial therapy in patients as well as population as a whole through its usage optimization by a rational and systematic approach [5]. Through a prospective analysis of the antimicrobial prescribing practices, stewardship programs made changes in the usage of antimicrobial agents and leads to enhanced patient care, reduce imprudent use and resistance. Through its impact and implications, the program has garnered the status of the most important public health intervention in the last century [6]. Coupled with infection control, hand hygiene and surveillance, it is a salient feature of local and national programs for preventing emergence of antimicrobial resistance and preventable healthcare infections [7]. The current programme was initiated based on the stewardship programme developed by the Great New York Hospital Association (GNYHA)[5]. Their stewardship programme followed some steps for the implementation, which are followed in the current work.

Assessment of Current Practice:

The assessment of the current practice involved the identification of the usage of antimicrobial usage in the facility, knowledge of the physician regarding the usual antibiotic therapy, frequency of the medication errors such as prescription, administration and dispensing error etc. Based on the culture reports collected in the assessment period developed a local antibiogram to analyse the sensitivity as well as the resistance pattern in the community.

Establishing an Antimicrobial Stewardship Committee:

To develop an antimicrobial stewardship committee, proper quorum is required. Stake holders from the various health care positions are included such as physicians, infection control physician, clinical pharmacist, pharmacist, nurse, laboratory technician and administrators. As an educational purpose or as a pilot programme the doctor of pharmacy student leads the programme with close communication with the other committee members.

Planning and Implementation:

Addressing the multiple issues and correcting the all is a difficult process and may leads to diverge the aim of the stewardship programme. From the initial assessment, the committee can able to find out the strategies to be focused on the initial stages of the programme. The strategies used to tackle the issues should be based on the current practices and resource availability.

Strategies:

As per the NYHA antimicrobial stewardship tool kit consist of two modes of strategies, core strategies and supplemental strategies. The core strategies are prospective audit with intervention and feedback, formulary restriction and preauthorization. Whereas, supplemental strategies include IV (Intravenous) to oral conversions, de-escalation, medication errors, education, dose optimization etc.[8].

As per the initial assessment the committee decided to choose one core strategy, prospective audit with intervention and feedback and all the supplemental strategies.

ANTIMICROBIAL STEWARDSHIP PROGRAMME

ASSESSEMENT OF THE CURRENT PRACTICE – ACUTE CARE FECILITY

FECILITY: ..... DATE: .....

1. Working time of the pharmacy
   a) 24/7 hours or less
   b) If not 24hr describe off hours
   .....
   c) Antimicrobial usage described in
   d) 1) Amount 2) Rupees 3) Defined Daily Dose 4) Other .....
2. We have any microbiology lab?
   a) If no, Where is the microbiology lab service performed?.....
   b) Resistance information reporting frequency?
   c) How u can access the data?
   d) Did u previously got the unit specific data on as needed basis?
3. Does our hospital have any antibiogram?
   a) If yes how often? ....
4. Do we have any antimicrobial protocol?
5. Is there any antimicrobial use monitoring in our institution? .....
6. If we have any monitoring programme, what are the possible specialities included? .....
   a) Infectious disease trained physician
   b) Clinical pharmacist
   c) Clinical microbiologist
   d) Hospital epidemiologist
7. Do we have any computer physician order entry system?
8. What are the common infectious diseases in our facility?
9. Which antibiotics are commonly used as broad spectrum antimicrobial agents?
10. What are the factors influencing the intravenous to oral conversion of the antimicrobial agents?
11. What is de-escalation of antimicrobial agents?
12. What are the common medication errors occurring in our hospital setting as prescription related, dispensing related and administration related?

Image No. 1

MATERIALS AND METHODS

National Accreditation Board for Hospital (NABH) accredited 350 bedded hospital at the Kerala state, India was the setting of this prospective interventional study. Six month span study conducted from April 2015 to September 2015 with an approximate strength of 180 patients per day. The study population was limited to patients admitted in the general medicine department of the hospital. The study protocol was approved by the Institutional ethical committee through official letter [IEC/ASH/2015/PB/106] dated 20 March 2015. The sample size of this pre and post interventional study was estimated with proportional risk difference null hypothesis of the equally distributed large population. The risk difference of the two hands pre intervention and post intervention is 0.6 with a proportion of 0.2 and 0.8. Because of the high acceptance of clinical pharmacist mediated interventions the power of the study was kept as 95 with an error of 0.5 were given the required population size as 24 for the each hand [9,10] This pre and post interventional study conducted with 75 days of monitoring phase and the rest of the periods are interventional phase. The knowledge of expected committee members such as physicians, pharmacist, nurse laboratory technician etc. regarding the antimicrobial stewardship programme and management of the antimicrobial agents in the hospital were accessed by the ethical committee approved questionnaire (Image no: 1).

It might be important to evaluate the knowledge of physician regarding the usage of antimicrobial agents and their prescription pattern. Currently there are no definite antibiotic selection criteria existing in the institution. Questionnaire was prepared based on the popular infectious diseases around the community, standard antimicrobial usage, dosage adjustment and usual activities of an antimicrobial stewardship programme. The questionnaire was peer reviewed by the committee members and validated by the chief infection control physician of the hospital. The important area included in the questionnaire are, selection of empirical antimicrobial agents for the endemic diseases, dose, frequency and duration of the therapy, dosage adjustment in the special population, escalation and de-escalations, intravenous to oral conversion, spectrum and resistance pattern of the antimicrobial agents. (Image no: II).

To evaluate the current management of the antimicrobial agent's management clinical pharmacist developed a data retrieving chart. Data of the all patient are collected in this format. In this data collection form (Image no: III) included the details such as patient demographics, microbiology details, antimicrobial agents, medication error related to antibiotics and finally medication error related to antibiotics.

When analysing the initial assessment data of the current practice, lead of the stewardship team and clinical pharmacist decided to develop an antimicrobial stewardship committee to fulfil the strategies of the antimicrobial stewardship programme. The quorums of the committee are infection control physician, internal medicine physician, Clinical pharmacist, pharmacist, Clinical microbiologist, senior administrator, information technology representative.Data analysis of the current practice was communicated to the team members and decided to develop corrective actions for the strategies need to be concentrate. The antimicrobial resistance is the global outcome and within this short span of the study could not make any difference in the resistance pattern, so the primary outcome of the study was to setup a stewardship programme and thereby reduce the consumption of antimicrobial agents. The strategies selected for that include - improve the knowledge of the physicians, de-escalation of the antibiotics, and early conversion of parenteral to oral formulations, errors associated with the antimicrobial agents such as prescription error, administration error and dispensing error.

DATA COLLECTION FORM FOR ANTIMICROBIAL STEWARDSHIP PROGRAMME IN AL-SHIFA HOSPITAL PVT.LTD

PATIENT DEMOGRAPHICS	Name	Age	Sex	Weight		Age category		Physician	
	Hospital ID	DOA	DOD	Diagnosis		Department		Location	
MICROBIOLOGY DATA	Collected specimen	Collection date	Reporting date	Time of sample receipt		Test		Within or outside the hospital :	
	Isolated organisms	Sensitive drugs		Resistant drugs					
ANTIBIOTIC DRUG CHART	Antibiotic No:1	Dose	Days						
	Indication	Frequency	D1 / D2 / D3	Stat & Stop date	Total days	Total units	Unit cost	Total cost	
No: of broad spectrum antibiotics	No: of narrow spectrum antibiotics	No: of parenteral antibiotics		Conversion of IV to oral formulations		No: of deescalated drugs		Duration of therapy before Surgery	
Days taken for the conversion	Parenteral antibiotics for discharged patient	No: of drugs without culture		Empirical treatment respond or not		Surgery		Duration of therapy after Surgery	

MEDICATION ERROR

	Prescription error	Administration error	Dispensing error
Date	1. Illegible handwriting a)Dose not mentioned b) Dosage form not mentioned c) Unit not specified d) Frequency not mentioned e) Inappropriate use of decimal 2. Use of abbreviations 3. Monitoring error 4. Wrong drug 5. Wrong dose a) Over dose b) Under dose 6. Wrong duration 7. Wrong dosage form 8. Wrong unit 9. Wrong frequency 10. Wrong route	1. Omission error 2. Wrong time 3. Wrong dose a) Over dose b) Under dose c) Extra dose 4. Wrong dosage form 5. Wrong drug 6. Wrong drug preparation 7. Deteriorated drug error 8. Wrong patient 9. Wrong route 10. Wrong administration technique 11. Improper documentation 12. Compatibility error 13. Monitoring errors 14. Failure to check patient's identity	1. Wrong drug 2. Wrong patient 3. Wrong dose a) Over dose b) Under dose 4. Extra dose 5. Missed dose 6. Wrong dosage form 7. Unordered dose 8. Wrong package 9. Incorrect labelling a) Incorrect patient name b) Incorrect drug name c) Incorrect strength 10. Incorrect instruction 11. Deteriorated drug 12. Omission of item 13. Inappropriate substitute
Details of the error			
Recommended Intervention			
Performed interventions			
NCCMERP Category of medication error			

Image No. 3

Education of the healthcare professionals

The education of the health care professional was performed by the clinical pharmacist. Clinical pharmacist educated the physician regarding the antimicrobial stewardship programme and the current antimicrobial prophylactic, empirical and definitive therapy. The educational materials were approved by the committee members and classes were performed at the beginning of the interventional study. After the study period the knowledge of the physicians were reassessed with the same assessment module used at the beginning of the study.

De-escalation of antibiotics

For all patients selection of empirical therapy is based on the local antibiogram or the existing hospital antimicrobial guideline. Most of the time empirical therapy may be sufficient for the control of the existing disease status. The de-escalation is the process by which changing antimicrobial agents based on their spectrum from broad spectrum antimicrobial agents to narrow spectrum. The de-escalation is always the conversion from empirical therapy to definitive therapy based on the culture and sensitivity report.

Parenteral to oral conversion of antibiotics

Most of the times, preferred route of administration of antimicrobial agents is intravenous route (IV). So the heading can be modified as IV to oral conversion of antimicrobial agents.

IV TO ORAL CONVERSION DATA

PATIENT DEMOGRAPHICS

HOSPITAL ID	NAME	AGE	SEX	DATE

CONVERSION SATISFYING FACTORS

FEBRILE ☐ AFEBRILE ☐	BLOOD PRESURE FLUCTUATIONS	YES ☐ NO ☐	ORAL INTAKE YES ☐ NO ☐	CONSCIOUS ☐ UNCONSCIOUS ☐	NON COMPELLING FACTORS ....

ANTIMICROBIAL AGENT DETAILS

ANTIMICROBIAL AGENT	DOSE	ROUTE	FREQUENCY	COST OF DRUG	DEFINED DAILY DOSE	START & STOP DATE	RECOMMEND ATIONS
(IV FORMULATION)							
(PO FORMULATION)							

Image No. IV

CONVERSION GUIDE LINE FOR ANTIMICROBIAL AGNETS

IV FORM	ORAL FORM	IV FORM	ORAL FORM
SEQUENTIAL THERAPY		SWITCH THERAPY	
LEVOFLOXACIN	LEVOFLOXACIN	CEFTAZIDIME	CIPROFLOXACIN
CIPROFLOXACIN	CIPROFLOXACIN	CEFAZOLIN	CEPHALEXIN OR CLOTRIMAZOLE
FLUCONAZOLE	FLUCONAZOLE		
METRONIDAZOLE	METRONIDAZOLE	CEFOTAXIME	CIPROFLOXACIN
CLINDAMYCIN	CLINDAMYCIN	AMPICILLIN SULBACTAM OR AMOXICILLIN CLAVULANATE	LEVOFLOXACIN + METRONIDAZOLE OR AMOXICILLIN CLAVULANATE
CLOTRIMAZOLE	CLOTRIMAZOLE		
AMOXYCILLIN	AMOXYCILLIN		
CEPHAZOLIN	CEPHALEXIN OR CEFUROXIME	IMIPENEM/ CILASTATIN	CIPROFLOXACIN + METRONIDAZOLE
		STEP DOWN THERAPY	
MOXIFLOXACIN	MOXIFLOXACIN	CEFTRIAXONE	CEFIXIME
FLUCLOXACILLIN	FLUCLOXACILLIN		
AMPICILLIN*	AMPICILLIN	Sequential therapy: Similar bioavailablilty Switch therapy: same class with Similar spectrum Step down therapy: Same class with different sprectrum. *Characterized by time over MIC principle	
CEFUROXIME*	CEFUROXIME		
ERYTHROMYCIN*	ERYTHROMYCIN		
AZITHROMYCIN*	AZITHROMYCIN		

Image No. V

Intravenous formulation is required for the faster onset of action as well as to control the initial infectious severity. The IV to oral conversions were made those who have the conversion favourable conditions such as absence of fever, normal blood pressure(BP), consciousness and ability to take drugs orally were used as parameters for deciding the quality of the IV to oral conversions and making recommendation to physicians. The study site has no currently existing guideline for the conversion of IV parenteral formulations. Clinical pharmacist developed an institutional IV to oral conversion guideline based on the existing antimicrobial manual as well as the drug information resources that focused on the parenteral conversion of antimicrobial agents. The IV to oral conversions can be performed based on the prescribed IV agent such as sequential therapy, switch therapy and step down therapy. Sequential therapy is the conversion of parenteral formulations to its original oral formulations. If the exact counter portion is not available conversion will be to an oral equivalent; within the same class and with same level of potency, but of a different compound and it is termed as switch therapy. Finally "Step down therapy" in which an injectable medication is substituted with an oral agent in another class or, a different medication within the same class where the frequency, dose, and the spectrum of activity may not exactly be similar. The conversion satisfying factors are recorded in the data collection template (Image no: IV) and if these factors are acceptable clinical pharmacist recommended the conversions based on the conversion tool (Image no: V). The acceptance of the recommendations is contributed as the strength of the antimicrobial stewardship programme.

Medication error

The medication errors are again grouped based on the NCCMERP (National Coordination council for Medication Error Reporting Programme) categorization, again classified into A, B, C,..,E based on the severity of action such as circumstances to cause error to death.

The medication error related to the antibiotics was measured from the three aspects such as prescription, dispensing and administration. The three modes of medication errors were identified by the proper review of the prescription chart, administration cross check and monitoring of the dispensed medications. The identified medication error was classified based on the Pharmaceutical Care Network of Europe. (PCNE) and the severity of the medication error were accessed by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Educational class provided to the stack holders such as physicians, nurses and pharmacist based on the medication errors identified in the pre implementation phase. The medication errors developed during the post implementation phase were compared with the pre implementation to access the impact of the education by the committee. In different perspective, for physician educational classes are given based on the existing guideline and medication therapy, selection of dose, route, frequency and duration of therapy and dosage adjustment in case of special population such as elderly, paediatrics and pregnant women, renal and hepatic impaired patients etc, clinical pharmacist cross checked every prescriptions and the errors are rectified with the proper recommendations. The proper administration techniques, dilution and timely administration of the antimicrobial agents to cover the golden hours of sepsis were educated and monitored. And finally for the pharmacist the pre-interventional period based errors are informed them and advised them how to tackle those errors with the proper labelling and dispensing process.

Institutional antibiogram

An institutional antibiogram was developed with the help of World Health Organization Network (WHONET), a software powered by WHO and the antibiogram were compared with the existing institutional antibiotic manual. The fewer number of organism and their sensitive pattern was not sufficient to modify the manual, so the manual is not updated with the antibiogram. Similarly the resistance pattern of the organism in the local community won't deteriorate with the low term antimicrobial stewardship programme. Because of the global strategy antimicrobial resistance reduction is not included in the study.

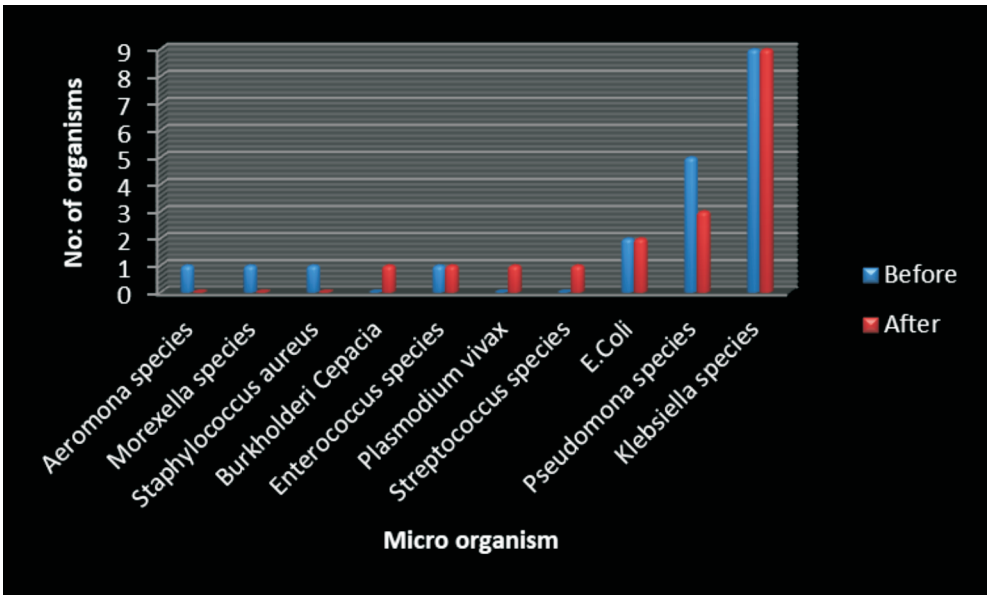

Image No. VI

Antimicrobial agent consumption

The impact of the all strategies finally measured in terms of consumption of the antimicrobial agents. To compare with the international standards the usage of the antimicrobial agents were measured in terms of (Daily Defined Dose) DDD/100bed days. The DDD *is the assumed average maintenance dose per day for a drug used for its main indication in adults.*

The consumption of the individual agent is measured using the Windows free software Antimicrobial Consumption (AMC) Tool Ver 1.40 developed by Arno Muller under the guidance of European Centre for Disease Prevention and Control (ECDC).

RESULTS

Characteristics of study population

During the study period, total 300 patients was admitted in the general medicine department, from that inclusion criteria satisfied 102 patients were involved in the study. 52 and 50 subjects constituted the pre and post programme study groups respectively and the difference in gender distribution (55.77% versus 46% males) among them was found to be non-significant with p=0.17 and there is no difference in the antimicrobial therapy based on the gender. The age distribution of study population were found to be 42-52% are geriatrics and 56-48% are adults in the pre and post interventional stage with an exception of 2 pediatric patients in the pre interventional period.

Interpretation of the secondary objectives

Assessment of the current practice and improvement

The current practice of the pharmacy, microbiology and usage of antimicrobial agents were accessed from the health care professional such as physician, pharmacist, nurses and laboratory technicians. Five experienced staffs are selected from the department such as physicians, microbiology, nursing and pharmacy. The pre and post training score obtained as Pharmacy 30-52, microbiology 26-48, nursing 35-51, physicians 36-56. The first value is before the training and the second value after the proper training. In the initial period of the study all of the departments were correctly answered only 50% of the questions were as in the post trained phase answered more than 90% of the questions correctly. The baseline assessment of physician knowledge and attitudes towards antimicrobial usage was measured. Five physicians in the internal medicine were evaluated for the antimicrobial usage. 26 questions were given to these physicians before and after the programme with an education prior to start of interventional period. Initially an awareness class was conducted for the whole quorum regarding stewardship programme. After that, for the individual group of stakeholders given the details of the roles and responsibilities towards stewardship programmes, mainly the end users such as pharmacist, physicians, nurse etc. For the physicians the existing prophylaxis and treatment protocol were educated, along with that the dosage adjustment in the concomitant conditions, de-

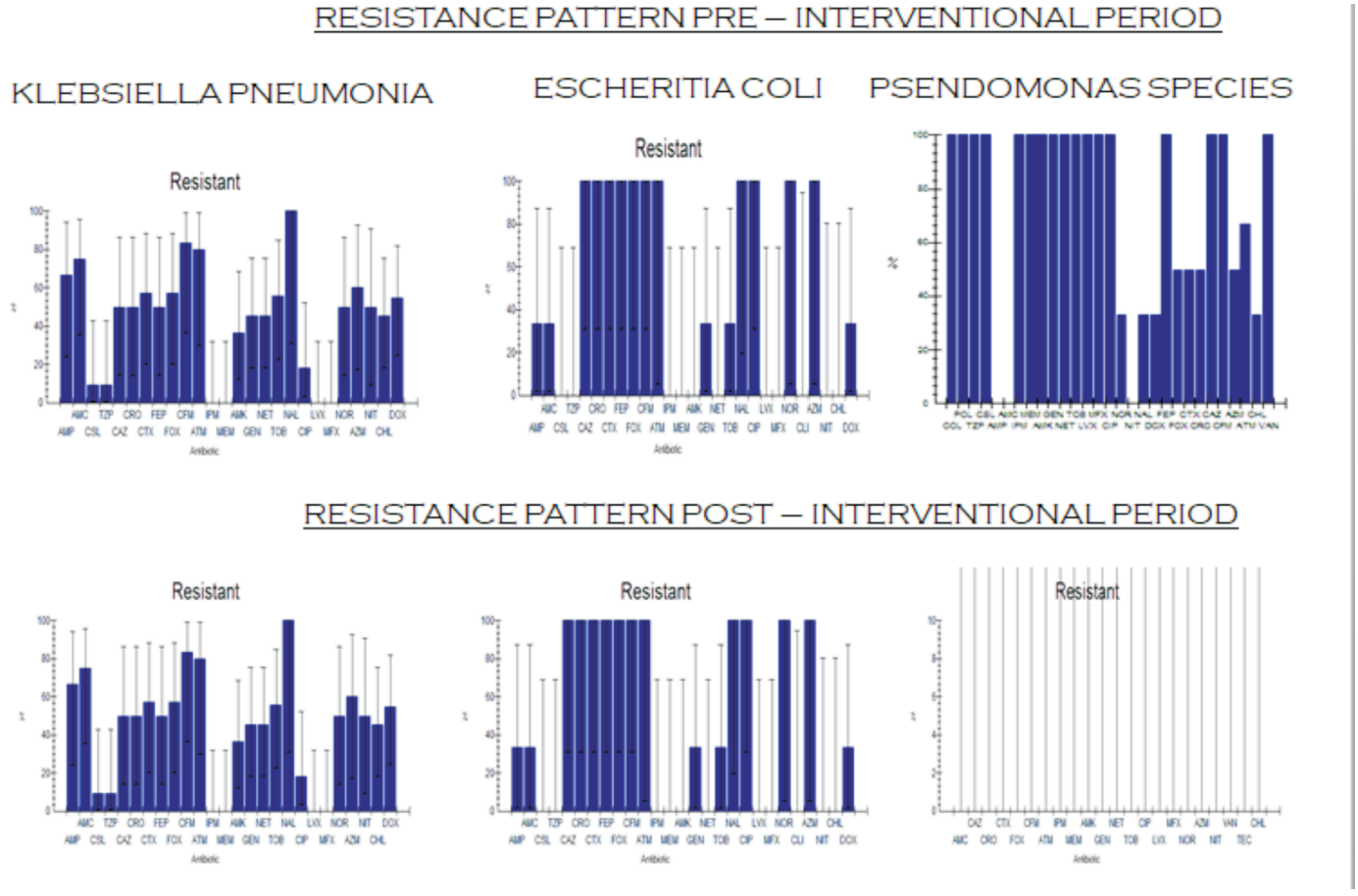

Image No. VII

Table 1 :

Antibiotic name	%R		%I		%S	
	Before	After	Before	After	Before	After
Ampicillin	84.6	75	0	7.7	40	53.8
Cloxacillin	76.9	46.2	0	0	100	100
Amoxicillin/Clavulanic acid	65	47.1	0	0	35	52.9
Cefoperazone/Sulbactam	61.1	75	0	0	100	94.7
Piperacillin/Tazobactam	60	38.5	0	0	100	94.4
Ceftazidime	58.3	27.3	0	0	47.4	46.2
Ceftriaxone	57.9	58.3	0	0	42.1	41.7
Cefotaxime	52.6	53.8	0	0	47.4	42.9
Cefepime	52.6	57.1	0	0	50	36.4
Cefoxitin	50	63.6	0	0	57.9	35.7
Cefixime	50	60	0	0	38.9	25
Aztreonam	47.1	50	0	0	50	40
Imipenem	42.1	64.3	0	0	94.7	94.1
Meropenem	42.1	33.3	0	0	100	94.1
Amikacin	38.1	42.1	0	4.8	90	76.2
Gentamicin	33.3	33.3	15	4.8	65	61.9
Netilmicin	23.8	25	0	0	80	75
Tobramycin	20	33.3	15	5.3	65	57.9
Nalidixic acid	20	25	0	0	15.4	25
Ciprofloxacin	20	36.8	5.3	4.8	52.6	61.9
Levofloxacin	14.3	4.8	15	14.3	80	81
Moxifloxacin	10	19	14.3	9.5	71.4	85.7
Norfloxacin	5.3	5.9	0	0	23.1	53.8
Clindamycin	5	4.8	0	0	100	80
Colistin	0	0	0	0	100	100
Polymixin B	0	5.3	0	0	100	0
Azithromycin	0	5.6	0	0	52.9	50
Erythromycin	0	5.9	0	0	66.7	66.7
Nitrofurantoin	0	20	0	0	41.7	72.7
Linezolid	0	0	0	0	100	100
Vancomycin	0	100	0	0	100	100
Teicoplanin	0	0	0	0	100	100
Chloramphenicol	0	0	0	0	76.2	75
Doxycycline	0	0	9.5	10.5	52.4	47.4

escalation process, IV to oral conversion of antimicrobial agents were also educated with the prepared slides. For the pharmacist and nursing staffs educated the dispensing methods as right drug, dose, frequency, time, preparation (dilution) and maintaining the time of administration also conveyed prior to interventional period.The physicians were answered only 5- 15 questions correctly priory but later they answered more than 20 questions. Statistical analysis resulted in an average score of 7.33 ±2.76. The re-evaluation of the same parameter after the administration of ASP awareness class and guideline dissemination generated a mean score of 13.83 ± 0.39 with the resulting difference being significant ($p<0.0001$).

Culture and Sensitivity (C&S) tested population

There was no significant alteration (P=0.5) in the evaluation of C&S test between the two phases of study with 46.2% (no: 24) not receiving the test during initial phase and 40% (no: 22) during the later phase. 28 patients of the initial phase and 30 patients of the implementation phase performed culture and sensitivity test. But the numbers of test performed were increased from 34 to 49,

which distributed from one to three numbers per patient. The increased number of cultures increased the definite therapy in the post interventional period. Because of the increased number of culture sensitivity tests the definitive therapies are increased 15% in post interventional period compared to the pre-interventional period.

Resistance panel of the endemic area

The resistance, intermediate sensitive and sensitivity of the identified organism against available antimicrobial agents were given below table no: 1. 38 organisms were isolated in the whole study period in which 20 numbers in the initial phase and 18 numbers in the post phase. The division is given in the following Image no: VI.

Klebsiella, pseudomonas and E.coli are the predominant species isolated from patients admitted in the general medicine department. The resistance pattern of the above mentioned species is given below (Image no: VII), separated as pre-interventional period and post interventional period.

De-escalation of antibiotics

In the pre interventional period for all the antimicrobial therapy (Drugs: 111) started with broad spectrum agents and based on the sensitivity pattern 13 drugs are deescalated to narrow spectrum agents in 9 patients. Similarly to the post interventional phase for the patients broad-spectrum agents are used to start empirical therapy (Drugs: 104), from that 6 drugs are deescalated to narrow spectrum agents such as Linezolid, Cotrimoxazole, Fosfomycin, Rifampicin, Ethambutol etc . But there was found to be a decrease in the usage of multiple broad spectrum agents within a patient from 17.31% in the pre-ASP phase to 15% which too proved to be non-significant with p=0.66. Approximately 50% of the drugs in the pre and post stage of study responded to empirical therapy, there is no significant difference was found to be in the effectiveness of empirical therapy indicating the necessity of more emphasising strategies in the next cycle of stewardship programme.

Parenteral to oral conversion of antibiotics

More than 50% of the antimicrobial agents used in the both phases are injectable preparations. Similarly 86% of the pre interventional period and 84% of the post phase patients are administered with parenteral antimicrobial agents. Maximum of 4 parenteral antibiotics are administered for a patients in the pre and post period, for 5 patients in the former and 4 patients in the later class. The maximum numbers of antibiotics required conditions are upper respiratory tract infection, cellulitis, urinary tract infection with the medications such as cefoperazone sulbactum, piperacillin tazobactum, metronidazole, levofloxacin, meropenem, imipenem cilastatin etc. In both groups only one parenteral antibiotic was administered for most of the patients. 86% and 84% of the pre and post study patients are fulfilled the condition for IV to oral conversion, but unavailability of the intense monitoring and active recommendation for conversion limited to only 6% conversions in the pre interventional period. Education and the active recommendations of the clinical pharmacist increased the rate conversion in the post interventional period from 6% to 72%, the difference is significant (P=0.0001). But in the both groups less than 20% of the IV agents are not converted because of the unsatisfactory conditions such as severity of the infection, fluctuations in the blood pressure, intermittent fever. Days taken for IV to per oral conversion also compared between the two phases. The average days of parenteral therapy is continued for 3.87days (~4days) were as in the post interventional stage the IV therapy is only prolonged for 2.25days(~2days).

Parenteral and oral antimicrobial agents for discharge patients

Because of the early discharge 21% of the patients were discharged with parenteral antimicrobial agents in the pre-phase were as in the post interventional phase only for 6% of the patients are dispensed with IV agents. In the pre as well as post stewardship period only one IV antimicrobial agent was dispensed as a discharged medication.Even if the patients are eligible for the conversion, when the antibiotics are started just prior to the discharge date the physicians are forced to continue the parenteral formulations. The difference was having significance with p= 0.03 implying the success of the program in this context. By the recommendations the unwanted continuation of the oral antimicrobial therapy were reduced. In the pre interventional period the average duration of therapy was 3.33 and the in the post interventional period it was 2.83. Most of the infections are controlled with the empirical therapy of intravenous preparations and the so the definitive therapy only need to be completed few days in the hospital period. When the patient got discharged the duration of the antimicrobial therapy was also optimised by the proper discharge summery review. The average duration of therapy in the pre phase was 6.89 days and for the post phase was 5.82 days. More than 10 days of discharge treatment was given for urinary tract infection with sepsis and chronic obstructive pulmonary disease.

Medication error related to antibiotics

The study perspective also incorporated an obligation to reduce the number of medication errors associated with antimicrobial agents in the hospital. Sum of medication errors found in the pre and post period study period were found to be 132.The major portion of the medication errors are in the pre interventional period 71.2%(n=94) and 28.78% (n=38), and the division of the medication error's as prescription error 38.63%, administration error 25%, dispensing error 7.57% are reduced to 20.45%, 7.576, 0.758% in the post interventional period respectively. The significant difference found for the medication errors are p=0.00019, p=0.001, p=0.005 for prescription related, administration related and dispensing related.

The types of errors founds in the different stack holders are, the selection of agents, inappropriate dose and dosage form, renal dose adjustment and improper duration of the therapy. In the case of administration side, wrong timing of the administration and wrong dilution methods and the dispensing of wrong medicine, wrong dose and wrong dosage form. The nursing and dispensing errors are reduced by the double checking before the dispensing and administration of the antimicrobial agents. The severity of the medication errors are also reduced from medication errors reached to the patient. Class A, B and C errors were reduced by 3.84% (A; Circumstances to cause errors), 1.07% (B; Prevented before reaching the patient) and 23.69 %(C; Errors reached the patient and no harm) respectively with the difference in Category C proving to be significant (p=0.00019).

Interpretation of the primary objectives

Consumption of antimicrobial agents

One of the impact measurement tool for the effect of

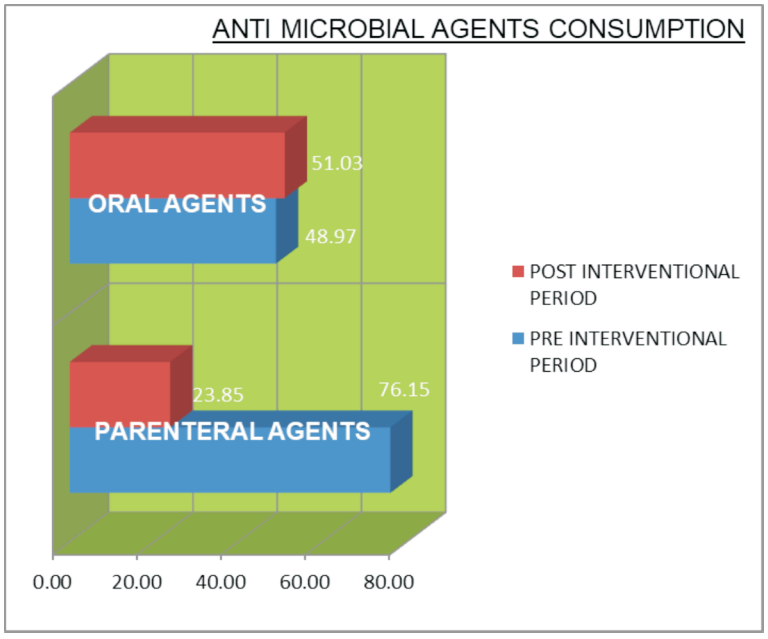

Figure 5 : Concomitant Administered antibiotics

antimicrobial stewardship is the reduction in the consumption of the antimicrobial agents based on the patient population. Drug utilization measured in DDD/100bed days showed significant difference between the two phases. The overall usage the antimicrobial agents are comparable because most of the infectious disease conditions are similar in both time periods. But the individual differences in DDD for drugs are not comparable because certain drugs are not used in either of the population. So an average of 54% (0.5730) reduction was achieved in the post interventional study period.

Comparing the consumption of the antimicrobial agent usage in the both hand of the study population 884 units of agents used in the pre interventional period in that 597 in the inpatient period and rest in the outpatient basis. 97.32% of the IP basis drugs are parenteral and rest of them are administered via enteral route, the medication included as when the patient got discharged 22.3% are parenteral and larger percentage is enteral agents. Similarly in the post interventional period total 509 units were only used to treat infectious diseases in that 206 are used in IP and 299 are used as discharge medications. IP basis used drugs 90.29% are parenteral agents and rest re enteral agents. Were as in the discharge basis only 5% are parenteral agents and rest are enteral route agents.

The DDD/100 bed days were found out by the ATC obtained from the data base of WHO. From the 31 generics used 13 agents are parenteral and 18 agents are enteral route of administration. The DDD/100 bed days of the following drugs are reduced when comparing the pre and post interventional period for the following oral agents Doxycycline, Amoxicillin and enzyme inhibitors, Cefuroxime, Azithromycin, Ciprofloxacin, Levofloxacin, Moxufloxacin, Linezolid, Fluconazole, Metronidazole and the parenteral agents Imipenem and enzyme inhibitors, Amikacin, Moxifloxacin. When applying the statistical difference in terms of Z test, the significance differences were only obtained for only for the following agents such as doxycycline (0.296 to 0.022), ciprofloxacin (0.392 to 0.115) and moxifloxacin (0.184 to 0.021) in terms of DDD/100 bed days. The DDD/ 100 bed days of the selected population is given the below table no: 2

When describing in terms of monetary value in the usage of antimicrobial agents the cost of the therapy was found to be reduced for the post interventional population. The indirect cost of the treatment such as cost of the syringe, diluent fluid etc are not included in the measurement, only cost of the antibiotic is added. The stewardship programme not made a significant difference (0.042) in the treatment cost per population; the mean difference of the cost per populations is 1352.38. But the cost of the parenteral antibiotic usage in the IP setting and the discharge medications cost are reduced in the post interventional period when comparing with the pre- period. The cost antimicrobial agents consumption in terms of cost were depicted in the table no: 3.

Clinical pharmacist recommendations

Clinical pharmacist based recommendations are the key interventions in this antimicrobial stewardship programme that made a difference in the usage of antimicrobial agents. There was no recommendation in the pre interventional period; the direct interaction of the clinical pharmacist with physicians as well as with other health care professionals influenced the unwanted usage of antimicrobial agents. Majority of the interventions are done as IV to oral conversion of antimicrobial agents. Based on the guideline developed 39 recommendations were provided for the conversion, out of which, 36 recommendations were accepted by the physician and the remaining 3 were rejected due to non-satisfactory patient parameters. The study was effective in causing significant increase in number of IV to oral conversions from 5.76% in the pre-ASP phase to 72% in the post-ASP phase yielding $p<0.0001$. Timely conversion was regarded as a vital aspect while making the IV to PO switch and the number of days to implement the same was reduced to an significant level with $p<0.0001$. Dose de-escalation was another thrust area of the current program with the outcome being an increase in the

Table 2

Sl no	DRUGS	DDD/100 BED DAYS		Z value	Significance
		Before	After		
1	Doxycycline	0.296	0.022	4.11	S
2	Chloramphenicol, O	0.007	0	0.61	NS
3	Benzylpenicillin	0	0.081	2.10	NS
4	Amoxicillin and enzyme inhibitor,P	0	0.003	0.39	NS
5	Amoxicillin and enzyme inhibitor,O	0.079	0.038	0.89	NS
6	Cefuroxime,P	0	0.0007	0.19	NS
7	Cefuroxime,O	0	0.095	2.29	S
8	Ceftriaxone,P	0.008	0.094	2.00	S
9	Cefixime,O	0.019	0.01	0.38	NS
10	Cefpodoxime,O,	0	0.011	0.75	NS
11	Cefoperazone, combinations,P	0.044	0.009	1.11	NS
12	Aztreonam, P	0.0001	0.011	0.74	NS
13	Meropenem P	0.0018	0.002	0.02	NS
14	Imipenem and enzyme inhibitor,P,	0.005	0.003	0.16	NS
15	Azithromycin,O	0.02	0.007	0.57	NS
16	Clindamycin,O,	0	0.007	0.59	NS
17	Amikacin,P	0.007	0.0012	0.46	NS
18	Ciprofloxacin,P	0	0.0014	0.26	NS
19	Ciprofloxacin, O	0.392	0.115	3.40	S
20	Levofloxacin, P	0	0.029	1.22	NS
21	Levofloxacin, O	0.077	0.053	0.49	NS
22	Moxifloxacin, P	0.075	0.004	1.89	NS
23	Moxifloxacin, O	0.184	0.021	2.84	S
24	Metronidazole,P,	0	0.002	0.32	NS
25	Linezolid, P	0.0004	0	0.14	NS
26	Linezolid,O	0.022	0.005	0.75	NS
27	Fluconazole,O	0.013	0.004	0.50	NS
28	Rifampicin	0	0.004	0.45	NS
29	Isoniazid	0	0.04	1.44	NS
30	Ethambutol	0	0.003	0.39	NS
31	Metronidazole, ,O	0.018	0.019	0.04	NS

Table 3

COST IN INDIAN RUPEES	PREINTERVENTIONAL PERIOD				POST INTERVENTIONAL PERIOD				NET COST OF THERAPY
	PARENTERAL AGENTS		ENTERAL AGENTS		PARENTERAL AGENTS		ENTERAL AGENTS		
	UNIT COST	TOTAL COST	UNIT COST	TOTAL COST	UNIT COST	TOTAL COST	UNIT COST	TOTAL COST	
INPATIENT MEDICATIONS	23,270.18	21,7115.27	347.842	1,294.282	7,211.87	41,927.37	132.27	263.21	4,57,335.496
DISCHARGE MEDICATIONS	1,733.87	12,668.96	537.302	5,215.26	818.2	6,453.2	712.834	5,618.56	3,16,712.000

practice of dose reduction by 16.94% which was significant with p=0.019. The rest of the recommendations are distributed as de-escalation, prevention of the medication errors. Based on the culture and sensitivity the clinical pharmacist recommended the conversions to narrow spectrum agents. Almost 6 drugs are de-escalated to narrow spectrum and also switched to sensitivity based broad spectrum agents. In the post interventional period found 38 medication errors even the prior education given and all the errors are prevented before reaching the patient by clinical pharmacist interventions. The recommended interventions are patient specific and recommended interventions mainly prevent the selection of wrong drug, wrong dose, wrong direction and wrong duration of the drug therapy, dispensing and administration errors.

DISCUSSION

The unavailability of the effective antimicrobial stewardship programme or the improper management of the infectious disease with the antimicrobial agents leads to the development of multi resistant organisms. For each and every institution dealing with antimicrobial agents needs proper monitoring and management. In this study we observed that, some impact is made by the team in the primary as well as the secondary strategies. The reduction in the usage of antimicrobial agents, improved de-escalation, IV to oral conversions and reduction of medication errors associated with the antimicrobial agents by the influence of the antimicrobial stewardship programme as well as the recommendations of the clinical pharmacist. The assessment of the primary outcome of the antimicrobial stewardship programme, antimicrobial resistance reductions is not measured because of the lesser time period of the study. A study conducted in Lebanan hospital by Mohammed Ibrahim et al [11] documented as the pre and post implementation study of antimicrobial stewardship programme improves the perception and knowledge of physicians towards the use of antimicrobial agents and antimicrobial stewardship programme improved. In the same way the physicians and other healthcare professional's knowledge and management of antimicrobial agents were improved by the impact of current study.

Culture sensitivity reports

Compared to the pre interventional study period the number of culture sensitivity test done was more in the post interventional phase. In accordance with the programme the number of empirical therapy was less in the post interventional period. The conducted studies not reported the number of tests done before and after the programme. The definitive therapies are more in the post interventional period. In the post interventional period number of definitive therapies are fifteen % higher than the prior study period,

De-escalation of antibiotics

Prescribing trends before and after implementation of antimicrobial stewardship was analysed by the Cairns KA *et al* [12], whose interventions mainly focused on the control of broad spectrum antimicrobial agents. The Cairns study results in the reduction 17% in the use of critical care broad-spectrum agents were as 10% reduction in the non-critical area. With the proper recommendations 15% reductions was made in the use of broad-spectrum antimicrobial agents in the current study. The mainly used broad-spectrum agents are cephalosporin and beta-lactum antibiotics and they are converted to Linezolid, Cotrimoxazole, Fosfomycin,Rifampicin, Ethambutol etc .An outpatient ASP by Jeffrey. S *et al*[13]on broad spectrum antibiotic prescribing produced a reduction from 26.8% to 14.3%. However, the present study had no significant effect on the reduction of broad spectrum antimicrobial agents with yield of negligible proportion of 0.966%. This clearly indicated a necessity for intervention with more emphasis with an active rather than passive approach to produce significant impact.

Parenteral to oral conversions

In 2009, Dominik*et al*[14] evaluated the outcomes following implementation of checklist with criteria for IV to PO conversion on patients of two general medical wards for four months and 61.38% were switched and length of stay decreased by 19% whereas, in the current study by the conversion tool and clinical pharmacist recommendations 72% of IV agents are converted to PO equivalents, instead of length of hospital stay the duration IV therapy changed from 4days to 2 days.

From the study of Przybylski *et al*[15], the oral therapy of the IV to oral converted group the therapy was prolonged 1.53 days less than the non - converted group. In the current study 0.5 days were only reduced in the hospital period of the converted oral therapy, from 3.33 to 2.83 days. But the oral therapy after the patient got discharged was 1.04 days reduced from average of 6.89 days to 5.82 days.

Medication error

The medication errors are a major contributor for the improper use of the antimicrobial agents. All the primary and secondary strategies of the antimicrobial stewardship can be considered as medication error as per the PCNE classification of medication errors. Study conducted by Sanders J, et al [16] on the reduction of medication errors in anti-retroviral's as part of the antimicrobial stewardship programme was found to be 46% and the current study included all types antimicrobial agents and the reduction was 43.42%

Consumption of antimicrobial agents

Consumption in terms of DDD

Reham Kaki *et al* [17] performed literature study utilizing systematic search on Ovid Medline, Embase and Cochrane electronic databases from 1996-2010 which revealed reductions ranging from 11% to 38% DDD/100 bed days in various studies. The reduction obtained in the current study is much higher (54%) than the above mentioned percentage range. Study of Dilip Nathwani *et al*[18] on the improvement of antibiotic prescribing by the interventions obtained a change of 0.27 DDD/ 100 bed days and from this study was found to be 0.573 DDD/100 bed days.Study by Fung T *et al* [19], on impact of a multidisciplinary antibiotic management programme showed 22% reduction in the use of parenteral antimicrobial agents while current study result obtained a 27.2 % reduction in the use of parenteral antimicrobial agents.

Consumption in cost

Study of Bantar C *et al* [20] on impact of intervention programme over prescribing practice; progressive decline in AMA consumption resulted in savings of $913,236 over 18 months. The study resulted in significant increase in microbiology based prescribing by 63% and the current study was effective in enhancing the same by 52.73%.Study conducted by Standiford HC *et al* [21] on cost analysis before and after implementation of antimicrobial stewardship programme produce a reduction in cost by 45.8%, only 65% of the

antimicrobial cost of the pre-interventional period is utilized for the post period therapy.

Recommendations

94% of the total recommendations by Valerie Leung *et al* [22] accepted on the basis of a pilot antimicrobial stewardship program was accepted; the acceptance proportion of recommendations in the current study was higher by 0.59%. Waters CD [23] in a pharmacist driven stewardship programme 91.8% recommendations were accepted by the physician and in the similar way 92% of the recommendations were accepted in the current study.

Drawbacks / Limitations of the study

The short duration of study period was inadequate to have an impact on the resistance pattern of microorganisms to antimicrobial agents. Therefore, longer study period is required for influencing the emergence of the resistance and reduction of the existing resistance rate. High cost of narrow spectrum antimicrobial agents was a major limiting factor in increasing the practice of de-escalation therapy. To counteract this scenario, there is necessity to develop of low cost narrow spectrum antimicrobial agents coupled with selective use of broad spectrum antimicrobial agents. Limiting the areas of focus during an ASP is quintessential for its success; a contradictory approach has more chances of culminating in implementation failure. The de-escalation is not always possible in the community because of the early discharge of the patient. Once the patient got relief from the disease on 2nd or 3rd day of admission the patients are requesting for the discharge. Because of this reason the culture based or definitive therapy was unable to be performed for these patients.

CONCLUSION

The overall outcome of the stewardship program indicated that the constitution and execution of antimicrobial stewardship committee and its activities were performed efficiently. The primary outcome, reduction of the use of antimicrobial agents and secondary outcome de-escalation and parenteral to oral conversion were the emphasis areas of the study and the strategies selected for the implementation strategies used to enhance the same was met with positive outcomes as evident from the results. Further cycles of the program with different thrust topics can be effective in further optimizing the antimicrobial usage. However, while pursuing novel goals; a simultaneous attempt must be made to ensure that the outcomes of the prior cycles do not diminish in the long run.

CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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