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A STUDY ON DRUG USE EVALUATION OF RESTRICTED ANTIBIOTICS (MEROPENEM AND VANCOMYCIN) IN A TERTIARY CARE HOSPITAL

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Abstract: ***Background:*** Antimicrobial resistance among microorganisms is a global concern. We conducted a Drug Use Evaluation study to evaluate the appropriateness of use of restricted antibiotics in the context of the existing Antibiotic Order Form using sequential prospective audits of prescriptions. ***Methods:*** A prospective observational Drug Utilization Review (DUR) study was conducted in patients receiving Restricted Antibiotics (Meropenem, Vancomycin) among Adult/Paediatric Inpatients in various wards and ICUs of a tertiary care hospital, Coimbatore, Tamil Nadu for a period of 6 months from February 12, 2014 to July 12, 2014. ***Results:*** Out of 113 prescriptions, 67 (59.29%) were empirically treated, 30 (26.54%) were specific therapy and 16 (14.15%) were prophylactic. Before restriction policy DDD per 100 patient days of Meropenem was 1.52 and Vancomycin 1.24. After restriction policy it reduced to 1.38 and 0.58 for Meropenem and Vancomycin respectively during 2013 and further reduced to 1.12 for Meropenem and 0.35 for Vancomycin during 2014 (p *value* <0.05). Hence, significant differences were observed in DDDs before and after the regulation. Thus the study proved that evaluation of Antibiotic utilization improved the appropriate and effective use of antibiotics and is also economical to the patient. ***Conclusion:*** Our study shows that implementation of an antibiotic order form for restricted antibiotics and follow-up by clinical pharmacist can be associated with a marked reduction in antibiotic consumption, improved appropriate and effective use to the patients. This research work emphasize that strict regulations on the use of antibiotics is essential to promote the rational use.

Keywords: Drug Use Evaluation, Restricted Antibiotics, Meropenem, Vancomycin, Antibiotic Order Policy, Defined Daily Dose.

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INTRODUCTION

Drug Utilization Evaluation (DUE) is an effective tool for monitoring the appropriateness of the usage of various medications [1]. DUEs have traditionally focussed on drugs with high price tags, complicated dosage schedules, Narrow Therapeutic Indices and regular side effects [2]. It is an ongoing systematic process designed to maintain the appropriate and medication data before, during and after dispensing in order to assure appropriate therapeutic decision making and positive patient outcome [3].

Antibiotics are powerful and effective drugs that fight against infectious diseases caused by bacteria that account for a significant proportion of total hospital drug expenditures [4]. Furthermore irrational use of antibiotics can be associated with a number of serious consequences to the patients and the community. To optimize the clinical outcomes by minimizing unintended consequences of microbial use, including toxicities, resistance and irrational use can be minimized by Antibiotic Stewardship Program (ASP). Developing resistance has been worrisome early after these agents became available for widespread use. Drug Use Evaluation (DUE) for commonly used antibiotics not only will improve treatment efficacy, but also in conserving cost and preventing unwanted adverse effects [5].

Meropenem, a carbapenem group of antibiotic and Vancomycin, a glycopeptides antibiotic are the drugs most commonly prescribed among all of the restricted drugs in the hospital setting were the study was conducted. The purpose of this observational study was to evaluate the appropriateness, the indication of administration, dosage, adverse drug events (ADE's), calculating defined daily dose(DDD) to analyze drug utilization with the ultimate goal of improving use and consumption of these antibiotics. Data's were collected from the case sheets of Inpatients who were treated with Meropenem and Vancomycin.

MATERIALS AND METHODS:

Study Design: A prospective observational Drug Utilization Review (DUR) study was conducted in patients receiving Restricted Antibiotics (Meropenem, Vancomycin) among Adult/Paediatric Inpatients in various wards and ICUs of a tertiary care hospital, Coimbatore, Tamil Nadu.

Study site: A Tertiary Care Hospital, Coimbatore, Tamil Nadu.

Study Period: The study was conducted during a period of 6 months from February 12, 2014 to July 12, 2014.

Inclusion Criteria: The Adult and Paediatric In-patients who received Restricted Antibiotics (Meropenem and Vancomycin) during the study period.

Exclusion Criteria: Patients who are hypersensitive to Meropenem and Vancomycin and patients with Restricted Antibiotic course duration < 48 hours are excluded from the study.

METHODOLOGY:

Data was collected using a well structured data collection form (Annexure I) which includes patient's demographics, clinical data, antibiotic regimens and dosing, indications for antibiotic use, culture reports, laboratory values, co-administration of other antibiotics, possible drug interactions, adverse drug reaction and outcomes of therapy. Microbiological data and adverse events were collected from patient's record. The data were followed until the discontinuation of Vancomycin, Meropenem or when patient was discharged from the hospital or patient death. All hospitalized patients who received Restricted Antibiotics were evaluated using the data collected from the Restricted Antibiotic Form (Annexure II).

The Defined Daily Dose values for previous year is collected from the pharmacy store system and data were converted to defined daily dose according to Anatomic and Therapeutic Chemical Classification System (ACT/DDD). Ratio prescribed daily dose per DDD was calculated.

Subjects receiving Meropenem and Vancomycin were identified by the order submitted to the pharmacy department of the hospital and also from daily patient review in different ward's and ICU's.

EVALUATION OF ANTIBIOTIC USE IN ACCORDANCE WITH

ANTIBIOTIC ORDER FORM (AOF)

The patient's charts and all relevant clinical data were received within 72 hours of drug dispensing. They included underlying diseases, site of infection, place where the infection was acquired, reasons for using drug, suspected or known causative bacteria and microbiological investigation of each patient. The patients were followed from the first day to the third or fifth day of treatment when the microbiological results were available. The clinical progress notes of the attending physicians were used to evaluate the clinical outcome on the follow-up day.

Appropriateness of these Restricted Antibiotics was assessed according to the following criteria:

- Firstly, Evaluation of antibiotic prescribing as stated in the AOF (Antibiotic Order Form).
- Secondly, Appropriateness of dosage regimen which included route of administration, dosage, dosing interval as well as dosage adjustment in Geriatrics, in patients with hepatic or Renal Function Impairment.

- Thirdly, Re-evaluation of the Empirical treatment when the microbiological and susceptibility data were obtained. Discontinuation, continuation, changing of antimicrobial or dosage regimens was recorded.

STATISTICAL METHOD

The information collected regarding all the selected cases were recorded in a Master Chart. Chi-square test and Unpaired t-test were performed and a p-value of <0.05 was considered to be significant. Using this, percentages, means, standard deviations were calculated.

To compare appropriate and inappropriate antibiotic therapy in terms of patient's outcomes and changes in clinical parameters, chi-square test was used. Unpaired t-test used to find out the reduction of antibiotic usage before and after the restriction policy in the hospital.

RESULTS AND DISCUSSION

The Inappropriate and Irrational use of Antibiotics is a common practice in healthcare settings [6]. It has been observed that Irrational use of Antibiotics lead to an increase in the morbidity and mortality rate in community, healthcare settings and resistance development against antibiotics [7, 8]. Appropriate use of antibiotics could be promoted by use of an Antibiotic Stewardship Programme (ASP's) like drug utilization evaluation with a name of maximizing the therapeutic response by limiting the unintended side effects [9]. Drug utilization studies are helpful in understanding the current practice in clinical settings.

A total of 113 patients enrolled into the study in which 71 (62.83%) were males and 42 (37.16%) were females and the demographic details of the patients were showed in table no.1. In our hospital, five antibiotics namely Meropenem, Vancomycin, Colistin, Teicoplanin and Tigecycline are considered as Restricted Antibiotics. To minimize the emergence of bacterial resistance the Restricted Antibiotic Policy was introduced in the hospital and documentation of the indication was emphasized to these antibiotics.

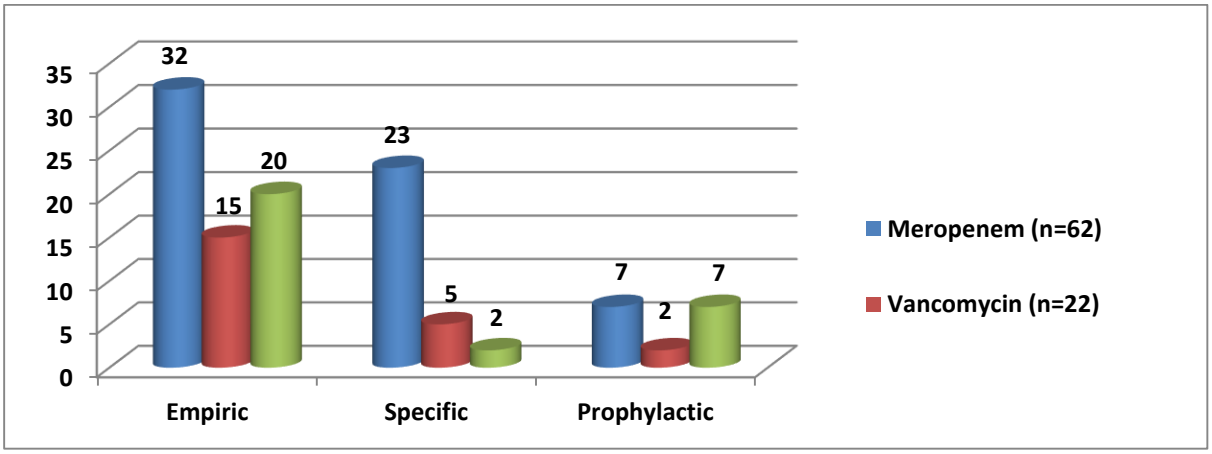
Table 1: Patient Demographic details:

Sex	NO. OF PATIENTS	PERCENTAGE
Male	71	62.83%
Female	42	37.16%
Age		
20-40 years	38	
40-60 years	44	Median: 50 years
60-80years	31	
Indication for the use of Meropenem and Vancomycin		

Based on Sensitivity report	25	22.12%
Worsening Clinical Condition	59	52.21%
Continuation of Antibiotic	3	2.65%
Febrile neutropenia	26	23%
Suspected MRSA	2	1.76%

Out of these five restricted antibiotics, Meropenem and Vancomycin are the most commonly used restricted antibiotics and were started empirically (based on clinical evidence) in 59.29%, Specific (based on culture result) in 26.54% and Prophylactic (without evidence of infection) in 14.15% of the total population (113 patients) which was depicted in Graph 1. The result shows that Empiric therapy was justified in most of the cases (72%), but continuation of treatment according to the culture reports in several cases was unjustified (45%). This result with vast number of Empirical cases indicates that Meropenem is used mainly on the basis of clinical judgement and experience without considering the Standard Treatment Guidelines [10]. Our results shows that most antibiotic therapy was empirically selected based on clinical judgement and the continuation of the treatment followed by culture results which is comparable with several other previous Drug Use Evaluation studies [1]. Whereas Vancomycin, another cell wall inhibitor, used empirically in 98% of cases in study conducted by Vazin et al., 2012 [11] supports our results.

Graph 1: Treatment Pattern



In the current study, 66.12% of the cases were treated with Meropenem in ICCU's and General wards, as the patients in these wards have underlying co-morbid conditions, there may not be clear-cut indications for the prescription of Meropenem and the drug is used synergistically with other drugs such as Vancomycin, Colistin, Ceftriaxone, Amikacin and Metronidazole. Vancomycin was frequently used in Paediatric wards and paediatric ICU's (68.18%) along with Meropenem and Ceftriaxone combination (Table 2). However about 91.15% of patients

responded to Meropenem and Vancomycin therapy but it is hard to say that this was due to the direct therapeutic effect of Meropenem or Vancomycin.

Meropenem is most commonly used for the treatment of sepsis 15(24.19%), Pyelonephritis 13(19.35%) and pneumonia 8(12.90) caused by *Klebseilla pneumoniae*, *Escherichia coli* and *Acinetobacter species*. Vancomycin is predominantly used in Meningitis 7(31.81%) caused by *Staphylococcus aureus* and *Pseudomonas aeruoginosa*. Combination of Meropenem and Vancomycin were more commonly used in treatment of sepsis 10(34.48%) and pneumonia 3(10.34%) (Table 3).

Table 2: Antibiotics administered before, concurrent and after Meropenem and Vancomycin

MEROPENEM			VANCOMYCIN		
BEFORE	**CONCURRENT**	**AFTER**	**BEFORE**	**CONCURRENT**	**AFTER**
Cefaxone, Linezolide, Metronidazole	Colistin	-	Amikacin, (Cefoperazone+Sulbactam)	Meropenem	-
Amikacin, (Cefoperazon + Sulbactam)	-	-	-	Cefaxone	Amikacin, Meropenem
Amikacin, (Cefoperazone + Sulbactam)	Amikacin, (Cefoperazone +Sulbactam)	-	-	Ceftriaxone, Azithromycin, Meropenem	-
Amikacin + Ampilox	Amikacin	-	-	Rifampicin, Amikacin, (Cefoperaxone + Sulbactam)	-
-	Ceftriaxone + Azithromycin	-	-	Ceftriaxone, Rifampicin	-
-	Clindamycin, Metronidazole	-	-	Meropenem	-

(Cefoperazon + Sulbactam), Azithromycin	Doxycycline + Linezolide	-			
Ceftriaxone	-	Cefoperazone + Sulbactam, Levofloxacin			

Table 3: TYPES OF INFECTION AMONG PATIENTS RECEIVING RESTRICTED ANTIBIOTICS

TYPE OF INFECTION	MEROPENEM	VANCOMYCIN	MEROPENEM + VANCOMYCIN
SEPSIS	15	1	10
PYELONEPHRITIS	13	0	0
PNEUMONIA	8	2	3
ENDOCARDITIS	2	1	0
INTRA ABDOMINAL INFECTION	2	2	2
MENINGITIS	0	7	0
SKIN AND WOUND INFECTION	0	4	0

Regarding drug utilization monitoring, we observed that out of 34 patients, 21(33.87%) patients were dose adjusted during the therapy with Meropenem and 2(9.09%) patients with Vancomycin therapy, based on baseline BUN and serum Cr assessment and 11(17.74%) patients were not adjusted the dose with Meropenem. Also dosing interval of the patients treated with Meropenem and Vancomycin was found to be hundred percent. Duration of treatment was calculated and 16% of total cases shows under use (1-3 days), 67.25% shows rational use (4-7 days, 7-14 days), and in 8.8% of cases observed over use of Meropenem and Vancomycin (Table 4). The other study conducted shows 84% adherence to guidelines in relation to the routine drug monitoring of Meropenem [12]. It reflects neglecting monitoring parameters in our practice settings too, since our study shows 67.64% adherence to guidelines for the routine drug monitoring. The other study conducted in Iran shows that appropriate dose adjustment was done in all the study participants [13] which supports our results.

Table 4: Appropriateness of Meropenem and Vancomycin therapy (n=113)

APPROPRIATE UTILIZATION	MEROPENEM	VANCOMYCIN
Maintenance dose		
Dose adjusted during therapy	21(32)	4(7)
Dose not adjusted during therapy	11(32)	3(5)
Dosing interval	78(100%)	35(100%)
Dilution	78(100%)	12(100%)
Duration of treatment		
1-3 days	12(15.3%)	6(17.1%)
4-7 days	36(46.1)	12(34.2%)
7-14 days	23(29.4%)	15(42.8%)
More than 14 days	7(9.0%)	2(5.7%)

Notifying physicians about long-term cost-saving quality of TDM and use of a consultant clinical pharmacist for dosing adjustments can improve the treatment standardization. Dose adjustments were necessary for about 11 patients due to diminished renal function that were not performed accordingly in study population. Vazin et al., also reported that in the setting of diminished renal function, appropriate Vancomycin dose adjustments were not performed. This again demonstrates the strong need for more widespread implementation of Clinical Pharmacist's role in Hospital wards [14].

Lack of documented microbial growth and anti-biogram results may be associated with prolonged courses of unnecessary combined antibiotic regimens. Such methods of antibiotic usage are associated with development of microbial resistance. Optimization of sampling methods and laboratory techniques can improve the culture yield. Therapeutic Drug Monitoring (TDM) is a well-established and necessary requirement for patients treated with Meropenem and Vancomycin and relevant guidelines have been published. Based on strong recommendations for employing TDM in patients treated with Meropenem and Vancomycin, it was performed for most of treated patients.

Meropenem is one of the most commonly used broad spectrum with relatively fewer side effects. However studies have shown that two major adverse effects do occur during Meropenem therapy i.e., diarrhea and rashes which should always be considered while using this drug [15]. Another study showed that abdominal discomfort was the most common adverse effect occurred with the use of Meropenem [16].

During our study 3 patients were developed seizures, 4 patients with diarrhea and 3 patients with skin rashes as an adverse drug event of Meropenem and it is over-comed by dose adjustment and no adverse event was observed during the treatment with Vancomycin. However none of these side effects observed was of life threatening intensity. This indicates that these drugs were well tolerated by patients and has an acceptable safety profile. In spite of that, Meropenem dosing strategies must be optimized to further decrease in the incidence of side effects.

Microbial resistance to the Antimicrobial treatment is a global issue. In our study, Meropenem shows Resistant to *Klebseilla pneumonia* in three cases and those were treated with the combination of Meropenem and Colistin to overcome this Resistance problem. One of the key contributors to Resistance is prolonged use of Antibiotics. In order to overcome this issue, every institution should bear the responsibility to address the Microbial Resistance Problem [17]. Table 5 shows the bacterial profile of the patients treated with Meropenem and Vancomycin. Infection with the gram-negative bacteria 59.4% was found to be more when compared to gram-positive bacteria 40.5%.

Table 5: Bacterial profile of the patients treated with Meropenem and Vancomycin

Gram-negative bacteria	
Acinetobacter spp.	**6(14.2%)**
E coli	**11(26.1%)**
Enterobacter	**4(8.79%)**
Klebseilla spp	**15(35.7%)**
Pseudomonas aeuroginosa	**8(19.0%)**
Subtotal	**44(59.4%)**
Gram-positive bacteria	
Coagulase negative staphylococcus	**6(20.6%)**
Bacillus species	**4(13.7%)**
Staphylococcus aureus	**9(31.0%)**
Streptococcus species	**6(20.6%)**
Enterococcus species	**5(16.7%)**
Subtotal	**30(40.5%)**
Total	**74**
SUSCEPTIBLE PATTERNS OF ISOLATED ORGANISMS	

ANTIBIOTICS	SENSITIVITY	RESISTANCE
MEROPENEM	71	7
VANCOMYCIN	33	2

In our study, 91.15% of patients treated with Meropenem and Vancomycin showed positive clinical outcome, 8.83% patients showed therapeutic failure, thus they discharged from the hospital against medical advice and death (Table 6).

Table 6: Clinical outcomes of patients treated with Meropenem and Vancomycin

GROUPS	SUCCESS		FAILURE		X^2 VALUE
	No. of Patients	Percentage	No. of Patients	Percentage	
Patients treated with Meropenem (62)	55	88.7	7	11.3	2.977
Patients treated with Vancomycin (22)	22	100	-	-	

'p' value <0.05 is consider as significant (X2 standard value is 3.84

The total quantities of Antibiotics consumed were analyzed using Defined Daily Doses (DDDs) technique. Before restriction policy DDD per 100 patient days of Meropenem was 1.52 and Vancomycin 1.24. After restriction policy it reduced to 1.38 and 0.58 for Meropenem and Vancomycin respectively during 2013 and further reduced to 1.12 for Meropenem and 0.35 for Vancomycin during 2014. Hence, significant differences were observed in DDDs before

and after the regulation (Table 7). Thus the study proved that evaluation of Antibiotic utilization improved the appropriate and effective use of Antibiotics and is also economical to the patient. The similar results were found in a study conducted Thammasart University Hospital, Pratumthani Thailand shows the rate of use of Third Generation Cephalosporins (31 vs. 18 DDD/1000 patient-days, $p < .001$) and Glycopeptides (3.2 Vs 2.4 DDDs/1000

patient-days, $p = .002$) were significantly reduced [18]. The other study results shows that the reduction in the use of third generation cephalosporins (35.4-26.6 DDDs/100 bed days) and Carbapenems (21.4-16.9 DDDs/100 bed days) conducted in Royal Melbourne Hospital, Victoria, Australia [19].

Table 7: DDD for Meropenem and Vancomycin during 2012 -2014

DRUG	PARAMETER	2012	2013	2014	t-DISTRIBUTION
MEROPENEM	DDD	4662.39	4073.42	3155.23	0.00365
	DDD for total admission	7.06	6.34	5.59	
	DDD/ 100 patients	1.52	1.38	1.12	
VANCOMYCIN	DDD	3796	1727.50	996.50	0.00123
	DDD for total admission	5.74	2.69	1.76	

'p' value is calculated by using unpaired t-test and 'p' value <0.05 is considered as significant.

This study can be an alert for physicians to restrict the Antibiotic administrations in unnecessary situations, and to emphasize in dose adjustment for drugs like Meropenem and Vancomycin when needed, in order to reduce adverse drug reactions such as seizures. In addition, the DUE programs should be performed as a routine program in hospitals to evaluate and improve the quality of patient care, especially in treatment with antimicrobial agents. The data documented about inappropriate use of antibiotics must be distributed to the physicians to discuss and optimize their medication orders [20]. It is also very helpful for health systems decision makers to reduce the costs of treatment by utilizing the TDM and culture and sensitivity testing in hospitals [14].

CONCLUSION

Our study shows that implementation of an antibiotic order form for restricted antibiotics and follow-up by clinical pharmacist can be associated with a marked reduction in antibiotic consumption, improved appropriate and effective use to the patients. This research work emphasize that strict regulations on the use of antibiotics is essential to promote the rational use.

Drug use evaluation of Meropenem and Vancomycin with respect to indication, duration of therapy and frequency of administration follows the current prescription practices.

Auditing antibiotic usage and reinforcing practice guidelines through direct counselling thus appears to be warranted. A combination of both restrictive and educational measures appears to be necessary to improve overall antibiotic usage in hospital. It has been stated that a collaborative team for improving antimicrobial use in hospital is very necessary. Key members

should include Infectious Disease specialist, clinical pharmacist, the microbiologist, and infection-control personnel to provide continuing education to hospital employees. In addition, it seems desirable that each hospital conduct surveillance studies on antimicrobial usage, to identify unique indications of inappropriate drug use which could be employed as educational tools to improve Antibiotics use by physicians.

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