Research Article

A Prospective Observational Study on Drug Utilisation Pattern of Restricted Antibiotics: Colistin, Teicoplanin and Tigecycline in a Tertiary Care Hospital

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ABSTRACT

Introduction: The emergence of antimicrobial resistance is a global threat. Now micro- organisms manage to overcome the antibiotics via various resistance mechanisms. This study was carried out to evaluate the appropriate usage and resistance pattern of the restricted antibiotics. **Methods:** A prospective observational study on Drug Utilization Pattern of Colistin, Teicoplanin and Tigecycline were conducted during the period of February 2016 – July 2016 at G. Kuppusamy Naidu Memorial Hospital, coimbatore, Tamil Nadu. **Results:** Out of 103 patients, 55 patients were treated empirically and 48 were treated based on their culture report. The antibiotics were prescribed mostly for patients with positive culture report followed by neutropenia patients and De-escalation was done only in 14 cases. The antibiotics were mostly consumed by patients in oncology department. On calculating the defined daily dose (DDD) Colistin was used predominantly, followed by teicoplanin and tigecycline. **Conclusion:** A stewardship Program must be implemented in the hospital to improve overall antibiotic usage in hospital. By this, we could reduce the emergence of antibiotic resistance up to a certain extent, by implementing a restricted antibiotic order form and proper follow up could add up to reduced antibiotic consumption.

Key words: Drug use evaluation, Restricted antibiotics, Colistin, Teicoplanin, Tigecycline, Defined daily dose, Restricted antibiotic form.

INTRODUCTION

DUE ensures safety and efficacy of drugs to improve patient's health status. It also promotes the rational use of drugs and reduces health care cost.[1,2,3] It is a vital component of clinical pharmacy practice.[4,5,6] DUE is a framed process which could be used for analysing the pattern of drug usage in various healthcare settings. Conducting DUE studies also contribute to reducing healthcare cost and incidence of adverse drug events.[7,8] For the comparison of drug utilization among various departments or among various healthcare Settings, WHO launched a technical unit of measurement in conjunction with the Anatomic Therapeutic Chemical classification which is referred as Defined Daily Dose (DDD). The World Health Organization Anatomical Therapeutic Chemical / Defined Daily Dose (WHO ATC/DDD) has been accepted as a gold standard and is used by researchers for calculating the drug consumption throughout the world.

DDD is the presumed average daily dose for a drug prescribed for its prior indication in adults. It doesn't give an exact picture of the drug consumption but provide a rough

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estimate of the drug usage. DDD is independent of the dosage form and cost thus enabling the researchers for the assessment of trends in drug utilization. DDD is a potent tool for comparing the drug utilization. The goal of calculating DDD is to improve drug usage.[9] The WHO ATC/DDD transcribes dosage forms of drugs (tablets, vials, capsules, inhalers etc.) to a standard unit called DDD. Usually DDD's are assigned for those drugs which are marketed and approved in at least one country and DDD is not assigned for those medicines which are used in rare disorders or diseases, dermatology, vaccines, anesthetics, sera and contrast media.[10]

Colistin, Teicoplanin and Tigecycline are the High end restricted antibiotics mostly used for the treatment of MDR (Multi Drug Resistance) infections. Among them Colistin is active against G negative organisms, teicoplanin against G positive organisms and tigecycline is active against both G positive and G-negative organisms. The purpose of our study was to evaluate the appropriateness of the usage of these antibiotics, then to value their indication for use in different wards, to determine the de-escalation process based on culture report and to calculate the defined daily dose for these antibiotics in the study period and compare the drug utilization in different departments. Data's were collected from the case sheets of Inpatients who were treated with colistin, teicoplanin and tigecycline.

OBJECTIVES

To evaluate the indication for use of Colistin, tigecycline and teicoplanin in different wards.

To evaluate the de- escalation process based on culture report.

To calculate the defined daily dose for these antibiotics during the study period and to compare the drug utilization in different departments

Study Design

A prospective observational study on drug utilization pattern of Colistin, Teicoplanin and Tigecycline was conducted in G. Kuppusamy Naidu Memorial Hospital, Coimbatore with a sample size of 103 patients.

Inclusion and Exclusion Criteria

All inpatients receiving Teicoplanin, Tigecycline and Colistin during the study period from February 2016-July 2016 were included in the study. We excluded the inpatients who discharged against medical advice.

Method of Data Collection

During our study, we reviewed the case sheets of all patients who met the inclusion criteria. Data was collected using a well-structured data collection proforma which includes patient's demographics, drug allergies, patient's case history, medication chart, culture reports and laboratory parameters. We reviewed the laboratory parameters regularly to check any variations. The culture and sensitivity reports were analyzed to assess the appropriateness of the antibiotic selection. Any medication errors that were found in our cases were also recorded. Follow up of de- escalation process was done and the usage of Colistin, teicoplanin and tigecycline was calculated using DDD. All the discrepancies observed have been documented appropriately in the data collection form designed for our study.

Data Analysis

The data was analyzed using Graph pad version 5.03. Chi square test was used to analyze the drug utilization in various departments, its indication for use and the de-escalation process. A p-value of ≤ 0.05 was considered to be significant. Using this value the significance for our results was calculated.

RESULTS AND DISCUSSION

In our study, we collected details from 103 patients, who were treated with Colistin, Teicoplanin and Tigecycline and found that Colistin was mostly used and majority of patients were male (81.53%) as compared to females (18.46%) Table 1. Mostly these antibiotics were prescribed in the age group of 51-70yrs, among them Colistin was prescribed frequently i.e. nearly 32.81% (n=21) followed by age group 29.68% (n=19) Table 1.

The restricted antibiotics were mostly prescribed as empiric therapy 53.92% (n=55) in majority of patients Table 2. Similar studies was conducted by Marie Thuong *et al*., in 2000 and Aparna Williams *et al*., in 2011 and their study also indicated that implementation of empiric and direct therapy reduces the multi-drug resistance, over use of antibiotics and unnecessary side effects.

Restricted antibiotics were used frequently in oncology patients [25% (n=34)] for neutropenic condition and MDR strains Table 3. A similar study was conducted by D. Averbuch *et al.,* in 2013, concluded that treatment with intravenous Colistin with renal dose adjustment, was relatively safe for cancer patients, even with concomitantly administered nephrotoxic medications and commonly prescribed restricted antibiotic in oncology patients was

Colistin [50% (n=17)] followed by Tigecycline [38.2% (n=13)], showed good outcome. Giampaolo Bucaneve *et al.,* in his study found that combination of *Piperacillin/ Tazobactam* and *Tigecycline* is safe, well tolerated, and more effective than *Piperacillin/ Tazobactam* alone in febrile, high risk, neutropenic hematologic patients with cancer. The sec mostly used indication of Colistin was Respiratory Tract Infection (n=15) Table 3. An analogous study was conducted by Magdalena E. Sobieszczyk *et al.*, in 2004 and concluded that Polymyxin B in combination with other antimicrobials can be considered a reasonable and safe treatment option for MDR G-negative respiratory tract infections in the setting of limited therapeutic options.

The spread of MDR micro-organisms is a global threat. Compared to previous years, the number of micro–organisms isolated is increasing tremendously. During our study, Klebsiella species have been isolated mostly in the cultures, nearly 27.08% (n =26) Table 4 and was managed primarily with Colistin and it was effective. When Karabiners. A *et al.*, in 2003 reveals that Klebsiella pneumonia was resistant to all antibiotics including carbapenem and can be successfully treat with Colistin.

We also determined that the sec most frequently isolated organism was Acinetobacter baumannii 18.75% (n=18) Table 4 and like Klebsiella species, Acinetobacter was also treatable with Colistin. Gary Martens *et al.,* in 2009 also studied the distribution pattern of organism and finalized that in-spite of the risk of nephrotoxicity, Colistin is highly efficacious to multi-drug resistant Acinetobacter baumannii infections.

Resistant mechanisms observed in our study was Carbapenem resistance 60.31% (n=38), ESBL 26.98% (n=17), methicillin resistance 11.11% (n =7) and Colistin resistance 1.58% (n =1) Table 5 and for this the preferred choice of drug was Colistin, Teicoplanin and Tigecycline. A similar study was conducted by Joon Young Song *et al.,* in 2007 concluded that Colistin and Tigecycline showed good *in vitro* activities against carbapenem resistant Acinetobacter Baumannii isolates.

From our study we concluded that proper de-escalation of restricted antibiotics was not performed in 86.40% (n=89) Table 5 cases and a similar study was conducted by Garnacho - Montero. J *et al.,* in 2015 concluded that antibiotic de-escalation is a well-tolerated management strategy in critically ill patients but unfortunately is not widely adopted.

We concluded that the use of restricted antibiotic was almost the same in all wards, 50.48% (n=52) and ICU

Table 1: In gender wise distribution males received 76.69% of these antibiotics and patients in age group of 51-70 contributed 23.3% to the consumption. On classifying based on diagnosis, patients with carcinoma received the antibiotics more.

Prescribing pattern				
	Colistin	Teicoplanin	Tigecycline	Percentage
Direct	26	12	9	46.07
Empirical	38	6	11	53.92

Table 2: Out of 103 patients who received these antibiotics, empirical therapy was more as compared to specific therapy.

INDICATION				
	Colistin	**Teicoplanin**	**Tigecycline**	**Percentage**
Based on sensitivity report	32	5	8	37.1
Sepsis	0	1	0	0.82
Lung infection	1	0	0	0.82
Worsening clinical condition	17	11	8	29.7
Skin and soft tissue infection	4	0	0	3.30
Neutropenic	18	4	7	23.9
Others	3	2	0	4.13

Table 3: shows the indication for which these antibiotics were prescribed, and the report was that they were mainly prescribed for worsening clinical condition followed by neutropenic condition.

	Organisms			
	Colistin	Teicoplanin	Tigecycline	Percentage
E coli	6	1	2	9.37
Streptococcus	2	2	0	4.16
Staphylococcus	1	4	1	6.25
Acinetobacter	15	0	3	18.75
Pseudomonas	6	0	2	8.33
Klebsiella	17	2	7	27.08
MR Cons	2	1	0	3.12
MS Cons	4	0	3	7.29
Enterococcus	3	2	2	7.29
Ralstonia Picketi	0	0	1	1.04
Shewanella	1	1	0	2.08
Stenotrophomonas	1	0	0	1.04
Citrobacter	1	1	0	2.08
Proteus	1	0	1	2.08

Table 4: Indicates that out of the 14 isolated organisms, klebsiella were mostly treated with these antibiotics followed by acinetobacter.

	RESISTANCE			
	Colistin	Teicoplanin	Tigecycline	Percentage
Carbapenem resistance	26	2	10	36.89
ESBL	13	2	2	16.50
Methicillin resistance	2	3	2	6.79
Colistin resistance	1	0	0	0.97
De- Escalation				
De-Escalation done	14	0	0	13.59
De-Escalation not done	57	17	19	86.40

49.51% (n=51) Figure 1 and better outcome was seen with the use of these antibiotics. A similar study was conducted by Michalopoulos. A. S *et al.,* in 2004 which indicated that Colistin was mostly used in ICU setups in critically ill patients and showed good clinical response.

For the comparison of drug utilization among various departments, WHO launched a technical unit of measurement in conjunction with the anatomic therapeutic chemical classification which is referred as DDD. We calculated DDD of these antibiotics and found its usage in ICU and wards. Colistin was used most

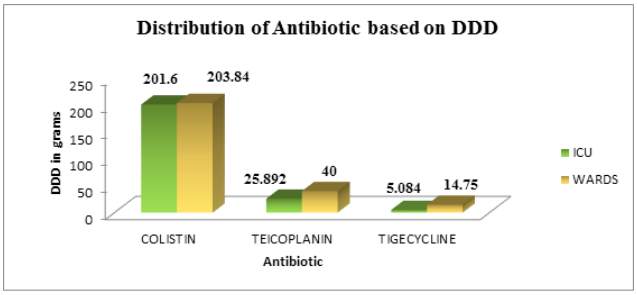

Figure 1: Distribution of Antibiotic Based on DDD.

Table 5: Among the resistance mechanisms found, carbapenem resistance was treated mostly with these antibiotics. On investigating the de-escalation pattern, it was seen that de-escalation was done only in 13.59% of patients who received these antibiotics.

	GENDER			
	Colistin	**Teicoplanin**	**Tigecycline**	**Percentage**
Male	53	11	15	76.69
Female	12	7	5	23.3
Age (in years)				
0-1	9	3	1	12.7
1-15	4	0	0	3.9
16-30	4	1	1	5.8
31-50	19	4	5	27.4
51-70	21	9	9	38.2
>70	7	1	4	11.7
DIAGNOSIS				
Renal disease	0	5	6	8.08
Cancer	17	4	13	25
Sepsis	8	7	4	13.9
RTI	15	5	2	16.1
UTI	3	0	0	2.2
Skin and soft tissue	3	2	1	4.41
Preterm condition	6	0	0	4.41
Cardiac disease	3	5	4	8.82
CNS infection	10	1	0	8.08
Others	11	1	0	8.82

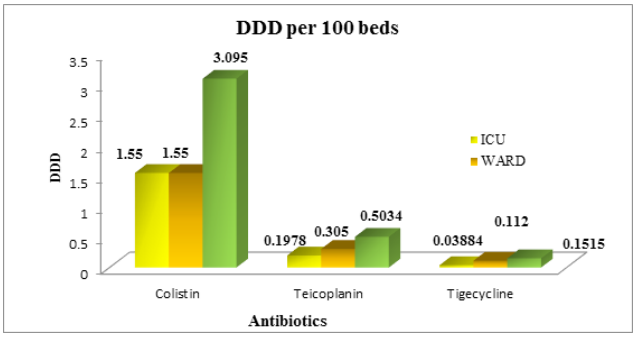

Figure 2: DDD PER 100 BEDS.

frequently, 82.54 % (202.720 g), followed by Tigecycline 13.41 (32.946 g) and Teicoplanin 4.03 (9.917 g) Figure 2.

CONCLUSION

Antibiotics are most widely prescribed for majority of the patients at the time of admission. Antibiotics continue to be widely prescribed in critically ill patients and form a significant proportion of the total drug consumed in the ICU's. A serious bacterial infection requires prompt and appropriate treatment to minimize the cost of treatment, length of hospital stay and the risk of morbidity and mortality. To achieve this goal, broad-spectrum antibiotics are recommended as initial empirical therapy, followed by streamlining to a more specific therapy after receiving Culture reports. This minimizes the development of antibiotic resistance.

Our study shows that implementation of an antibiotic order form for restricted antibiotics and follow up by

clinical pharmacists can lead to marked reduction in antibiotic usage, improved, appropriate and effective use of antibiotics. This research work emphasizes the strict regulation are essential to promote rational use. We found that Colistin was mostly prescribed out of these three restricted antibiotics for neutropenic condition followed by respiratory tract infections. The usage statistics of these three restricted antibiotics in various departments was analyzed which showed that Colistin was in most of the cases, de-escalation was not done even though, only half of them had MDR strains (50.8%). These restricted antibiotics were given for other conditions. These restricted antibiotics were given for other conditions other than MDR strains including neutropenic conditions in cancer patients and also for pre-term conditions. In such scenario as well de-escalation was not found in practice (22.5%). If proper de- escalation is not done, it may result in increased emergence of antimicrobial resistance and lead to increased health care cost.[14,15,16,17,18,19,20,21]

The medication related problems associated with these three restricted antibiotics was low during the study period.

The consumption of the Colistin, tigecycline and teicoplanin in various departments was calculated based on DDD which revealed that Colistin was highly consumed compared to tigecycline and teicoplanin.

A stewardship Program must be implemented in the hospital to improve overall antibiotic usage in hospital. By this, we could reduce the emergence of antibiotic resistance up to a certain extent. If not there won't be any choice of antibiotic for the treatment of MDR infections. By implementing this, we could promote the rational use of drugs, reduce hospital stay, minimize health care cost and prevent medication related problems.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATION USED

DUE: Drug utilization evaluation; **DDD:** Defined Daily Dose; **ATC:** Anatomical therapeutic chemical; **WHO:** World Health Organization; **MDR:** Multi Drug Resistance; **ESBL:** Extended spectrum beta-lactamase.

REFERENCES

1. Palumbo FB, *et al*. Drug use evaluation Principles and practices of managed care pharmacy: Academy of managed care Pharmacy. 1995;51-60.
2. Rupp MT, *et al*. A drug utilization evaluation primer: operational and conceptual aspects, Proceedings of the group health Associations of America, Annual meeting. 1991. New York.
3. Academy of Managed care Pharmacy. The concepts in Managed Care Pharmacy Series and pharmaceutical care. 1997.
4. Demsey JW, *et al*. Drug utilization a regional approach. Leader of Health Service. 1995;4(1):34-7.
5. The hospital pharmacist's society Australia. Specialty practice in drug use evaluation. Standard practice for drug use evaluation of Australian hospitals. Aust J Hosp Pharm. 1996;26:240-6.
6. Eshraghi A. Drug utilization evaluation study of amphotericin B in neutropenic patients in a teaching hospital of Iran. Iranian J Pharm Res. 2012;11(1):151-6.
7. Mirrahimi B, *et al*. Drug use evaluation of three widely prescribed antibiotics in a teaching hospital of Iran. J Pharm Care. 2013;3(1):100-3.
8. Defersah AD. Drug utilization review of ciprofloxacin in the outpatient department of boru meda hospital, south wollo zone, Ethiopia. International Journal of Basic Clinical Pharmacology. 2014;3:171-8.
9. Averbunch D, *et al*. Colistin is relatively safe in hematological malignancies and hematopoietic stem cell transplantation patients. British Journal of Clinical Pharmacology. 2013;41(5):991-7.
10. Bucaneve G, *et al*. Results of a multicenter, controlled, randomized clinical trial evaluating the combination of piperacillin / tazobactam and Tigecycline in High-Risk Hematologic patients with cancer with Febrile Neutropenia. J Clin Oncology. 2014;32(14):1463-71.
11. Beena PM, Prabhakar S, *et al*. Blood Culture – A must and of utmost importance in medical intensive care wards. Journal of Clinical and Biomedical Sciences. 2014;4(20):297-9.
12. Thuong M, *et al*. Appropriate use of restricted antimicrobial agents in hospitals: the importance of empirical therapy and assisted re-evaluation. Journal of Antimicrobial Chemotherapy. 2000;46(3):501-8.
13. Williams A, *et al*. Antibiotic prescription patterns at admission into a tertiary level intensive care unit in Northern India. 2011;3(4):531-6.
14. Karabiners A, *et al*. *Colistin for Klebsiella* pneumonia associated sepsis. Clinical Infectious Diseases. 2004;38(1):7-9.
15. Martens G, *et al*. Safety and effectiveness of Colisin compared with tobramycin for multidrug resistant Acinetobacter *baumannii infections*. BMC Infectious Disease. 2009;26(10):1471-2334.
16. Song JY, *et al*. *In vitro* activities of carbapenem/sulbactams combination, Colistin, *colistin/rifampicin combination* and tigecycline against carbapenem-resistant *Acinetobacter Baumannii*. Journal of Antimicrobial Chemotherapy. 2007;60(2):317-22.
17. Garnacho-Montero J, *et al*. Antibiotic de-escalation in the ICU: How is it best done?. Current Opinion in Infectious Diseases. 2015;28(2):193-8.
18. Hartzell JD, *et al*. Nephrotoxicity Associated with *intravenous Colistin* (*colistimethate sodium*) Treatment at a Tertiary Care Medical Centre. Clinical Infectious Disease. 2011;48(12):1724-8.
19. Michalopoulos AS, *et al*, Colistin treatment in patients with ICU-acquired infections caused by multi resistant G-negative bacteria: the renaissance of an old antibiotic. Clinical Microbiology and Infection. 2005;11(2):115-21.