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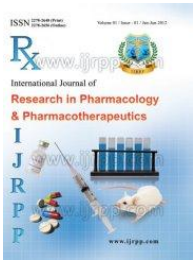

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Potential observational study of exploitation of pharmacokinetic principles of antibiotics used for indoor patients

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ABSTRACT

The use of pharmacokinetic-pharmacodynamic (PK/PD) properties of certain antibiotics, if used judiciously, could be an effective way to improve drug concentration in body and hence, clinical outcomes. The aim and objective of this study was to observe the prescription pattern of selected antibiotics in indoor patients who were admitted in ICU and ward. In this study it was observed whether antibiotics were prescribed following PK/PD properties. This study focused on drug dosing pattern along with adjustment with creatinine clearance in renal impairment and duration of antibiotic infusion during individual dose of the antibiotics. This observational single center study was conducted for 256 patients. Among them, 16 patients were excluded and 240 patients were finally analyzed as they met the inclusion criteria. In the demographic parameter described it was found that the mean age was in elderly population. It was a male predominant cohort and mostly patients were included from intensive care area. It was observed that culture growth occurred in 53% cases and rest 47% showed negative culture. In majority of cases appropriate antibiotics were given. About 94.74 % were appropriate antimicrobials. The sources of sepsis were lung, and renal in majority however, other sources like GIT, skin and soft tissue, or hepato- bilary, were also there. The major sources of infections in this study were lung and renal (n=70), followed by unknown source (n= 42). The correlation of drug dose adjustment with renal clearance was also investigated in this study. Adjustment of drug following creatinine clearance was mostly found in intensive care area as compared to ward. From this study it could be commented that dose adjustment following creatinine clearance is not that prevalent in ward and should be emphasized to improve clinical outcome and to avoid drug toxicity.

Keywords: Pharmacokinetic Parameter, Pharmacodynamic Parameter, Creatinine Clearance, Meropenem, Vancomycin, Colistin

INTRODUCTION

Pharmacokinetics (PK) is concerned with the time course of drug concentrations in the body, while pharmacodyamics (PD) is concerned with the relationship between those concentrations and the effect of drug. PK parameters quantify the serum

level time course of a drug. The three PK parameters that are most important for evaluating the efficacy of drug are the peak serum level (Cmax), the trough level (Cmin), and the Area Under the serum concentration time Curve (AUC). While these parameters quantify the serum level time course, they do not describe the efficacy of a drug.

The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro. While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity. Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic: the Peak/MIC ratio, the T>MIC (time above MIC), and the 24h-AUC/MIC ratio.

The three pharmacodyamic properties of antibiotics that best describe killing activity are time-dependence, concentration-dependence, and persistent effects. The rate of killing is determined by either the length of time necessary to kill (time-dependent), or the effect of increasing concentrations (concentration-dependent). Persistent effects include the Post-Antibiotic Effect (PAE). PAE is the persistant suppression of bacterial growth following antibiotic exposure.

The incidence of sepsis in intensive care units (ICUs) internationally has been shown to be as high as 51% with 71% of patients receiving an antibacterial during their ICU stay [1]. The treatment of sepsis remains a significant challenge and is the cause of high mortality and morbidity. Critical care patients often have profound effects on the PK parameters like volume of distribution (V_d) and clearance (Cl) of antibacterial agents, both of which may affect the pharmacokinetics (PK) / pharmacodynamics (PD) of the drug [2]. Knowledge of PK and PD of commonly used antibiotics may help to select appropriate dosage regimens and schedule intervals that will contribute to therapeutic efficacy and improve clinical outcome. A recent large study that measured beta-lactam concentrations in critically ill patients showed that many patients did not achieve PK/PD targets and therefore may be less likely to achieve a positive clinical outcome [3].Sub-therapeutic dosing of antibiotics may lead to the development of antibiotic resistance and/or therapeutic failure if appropriate dose adjustments are not made [4].

Fluoroquinolones are lipophilic and have a high V_d. They have extensive distribution characteristics and achieve good extracellular and intracellular concentrations. The V_d of most drugs in this class is minimally affected in the critically ill patient. They exhibit concentration-dependent PK, and a Peak/MIC ratio of 10 predicts bacterial eradication [5]. However, this requires high doses, which has raised concerns about neurotoxicity and therefore precludes its clinical use. Therefore, the AUC/MIC ratio is the parameter that is usually associated with dosing.

For beta-lactam antibiotics, higher drug concentrations do not result in significantly greater bacterial kill. Beta-lactams have shown a slow continuous kill that is almost entirely related to T > MIC and if antibiotic concentrations fall below the MIC, bacteria proliferate almost immediately. As a minimum standard for carbapenems, the percentage of the dosing interval that free drug concentration remains above the MIC should be maintained at 40%. However, patients with severe bacterial infections T >MIC of 100% have shown to display significantly greater cure and bacterial eradication than patients with T <100% [6].

Studies in critically ill patients have demonstrated that administration of piperacillin-tazobactam, [7] meropenem [8] and ceftazidime[9] via extended intervals or continuous infusion maximize time of bacteria exposure to adequate drug concentrations and may improve clinical cure rates particularly with pathogens with low susceptibly. Despite clinical trials failing to show a mortality benefit from this strategy [10] there are theoretical arguments and case reports that support the efficacy and safety of prolonged or continuous infusions. In severe infections caused by less susceptible microorganisms in critical ill patients, where the risk of under dosing is higher, continuous or extended infusions of beta-lactams have proven to be safe, with comparable therapeutic efficacy.

The creatinine clearance value greater than130 ml/min/1.73 m^2 in critically ill patients receiving beta-lactams has been associated with sub-therapeutic dosing. Measuring creatinine clearance by use of 24 h urine collection may be used to optimize antibiotic dosing by increasing the total daily dose, shortening the dose interval or use of extended/continuous infusions should be considered [11].

With this background the study was decided to be conducted to find out ongoing prescription pattern of indoor intravenous antibiotic with particular emphasis on dosage regimen in the light of PK/PD variations. This study specially focused on duration of antibiotic infusion during individual dose of the antibiotics, in indoor patients (ICU & General ward).

MATERIAS

Study design and setting

This was Prospective Observational Cohort study. The study was conducted in AMRI hospitals, Kolkata, West Bengal**.** This is a tertiary care hospital. All patients who were admitted in hospital for more than 24 hours and received certain antibiotics were included in this study. Patients were included from intensive care unit and also from indoor admissions.

Patient selection

Inclusion criteria

- Adult patients of more than 18 years age admitted in intensive care unit and indoor beds were included in this study.
- Patients admitted in hospital for more than 24 hours and received intravenous antibiotics were included in this study**.**

Exclusion criteria

- Patients who received single dose of antibiotic were excluded.
- Patients who were receiving antibiotics by other routes like oral and nebulized form were also excluded.

Duration

The study was conducted from July 2014 to March 2015; under Guidance of Dr. Mahuya Bhattacharyya and Dr.T.K.Chatterjee.

Ethical Approval

Informed consent had been waived by institutional ethics committee as it was an observational study.

METHODOLOGY

Data collection

Data was recorded from patients admitted during the study period in intensive care unit (ICU) and general ward. Source documents were bed side patient file, nursing chart (ICU), and medicine record card (general ward bed). Interactions with nursing staffs and resident doctor were done for further clarification of data wherever needed. Data were recorded primarily in the data collection form.

Demographic data

Age, gender, body weight, and diagnosis were recorded in the data sheet for every patient. Diagnosis was recorded during discharge of the patients. The source of sepsis (presumed or known) was recorded according to clinical finding, laboratory report and microbiological report. Creatinine clearance was calculated for each individual with Cockroft gault formula.

Microbiological data

Cultures of different body fluids like urine, blood, sputum, pus, and swab from wound tracheal aspirate were sent during hospital stay of these patients. Reports from these cultures were recorded and appropriateness of the antibiotics was checked.

Antimicrobial data

Following antibiotics were selected, observed and documented in this study. Carbapenem – (Meropenem, Imipenem, Doripenem), Vancomycin, Colistin. Beta-lactum-Beta Lactum Inhibitors (BLBLI) like Piperacillin&Tazobactam, Cefoperazone & Sulbactam. Prescribed antibiotics were noted. The dose including correct dosing as per creatinine clearance were found out and correlated with the actual dosing received by the patient. The prescribed antibiotic was considered appropriate if the patient received those antimicrobial to which the cultured bacteria had in vitro sensitivity. In case of negative cultures, antibiotics were considered appropriate if they were given in accordance with local guidelines and were extended spectrum antibiotics. PK/PD properties of the specified antibiotics were studied and duration of that antibiotic delivery was noted in this study. Duration of antibiotic delivery for each antibiotic, selected for this study was checked from source documents on single occasion. Duration was documented in data collection form and finally analyzed whether they were given following upcoming recommendation as in individual case.

Statistical analysis

Demographic and other variables were described using Mean±S.D values, and percentage values. Data has been demonstrated with tables and diagrams as appropriate.

RESULTS AND DATA ANALYSIS

Sample data sheet (for individual patient)

DEMOGRAPHY	
NAME(Initials)-	Hospital ID -
AGE-	Gender-
DIAGNOSIS-	Source of SEPSIS(presumed or known)-
BODY WEIGHT-	Culture isolates - CREATININE- CREATININE CLEARANCE-

Antibiotic detail		
NAME OF ANTIBIOTIC -1	**NAME OF ANTIBIOTIC -2**	**NAME OF ANTIBIOTIC -3**
Dose & duration-	Dose & duration-	Dose & duration-
Frequency-	Frequency-	Frequency-
Route of administration-	Route of administration -	Route of administration-

Demographic and descriptive data

240 patients were included in the study. Average age of patients in this study was 71±19.27.53% patients were male and 47% were female patients.75% patients were included from ICU Patients and 25% from General ward. Microbiological culture was positive in 53% cases and rest 47% did not show any growth in culture.

Two categories of antibiotics were used for this study, time dependent killing antibiotics, and concentration dependent killing antibiotics. The sources of infections like Lung, Renal, git, Soft tissue, Biliary, Post-surgical Prophylaxis, Hepatic, CNS, Abdomen, Skin, Genital, Throat and other were noted in sepsis. The major sources of infections are lung and Renal, presented in 70 patients in cases. Table 1 depicts the demographic data of study cohort. Fig. 1 and 2 are the pie charts showing percentage gender ratio and ICU/WARD patients ratios respectively.

Table 1: Demographic data of study cohort

Variable	**Mean ± SD or n(%)***
Age	71±19.27
Sex(Male)	127 (53%)
Sex(Female)	113 (47%)
ICU Patients	179 (75%)
General ward Patients	61 (25%)

*Result are expressed as Mean±S.Dor n (%)

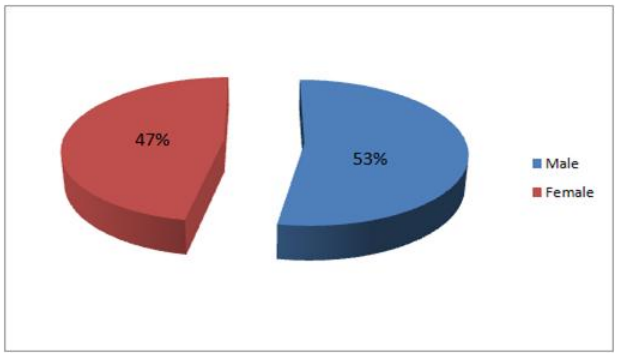

Fig.1: Pie-chart showing percentage gender ratio of total patients

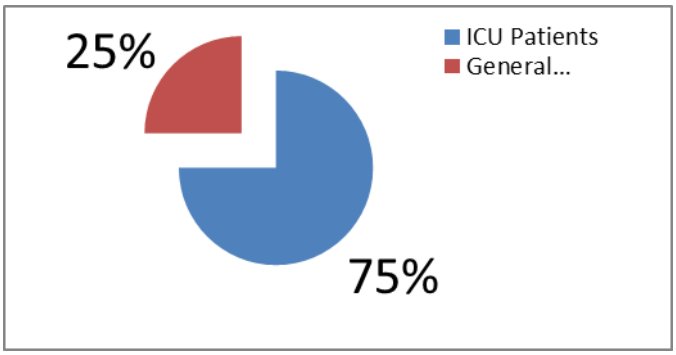

Fig.2: Pie-chart showing Percentage Ratio of ICU and General ward Patients.

Culture isolates

Microbiological culture report was recorded from source file. It was observed that Culture growth occurred in 53% cases and rest 47% showed negative culture. Microbiological culture was not sent in 26 patients. Fig 3.showes culture isolates of total patients, Table 2 represents Culture growth and negative culture. Table 3 depicts the appropriateness of antimicrobial given.

Table 2

Positive Culture	Negative culture
114	100

Table 3

According to culture isolate appropriate anti-microbial given	According to culture isolate in-appropriate anti-microbial given
94.74 %	5.26%

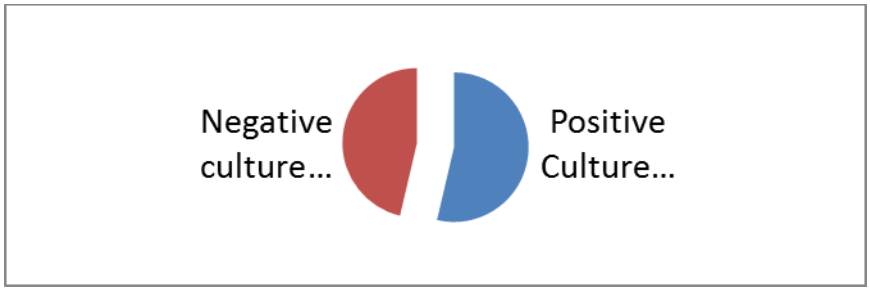

Fig.3: Pie chart shows Culture Isolates of total Patients

Source of sepsis

The sources of sepsis could be lung, renal, GIT, skin and soft tissue, hepato - bilary, post-surgical prophylaxis, CNS, intra-abdominal, genital, and throat or it could be unknown. The major sources of infections in this study were lung and renal (n=70), followed by unknown source (n= 42). Fig. 4 and Table.4 represents different types of source of sepsis among the patient populations.

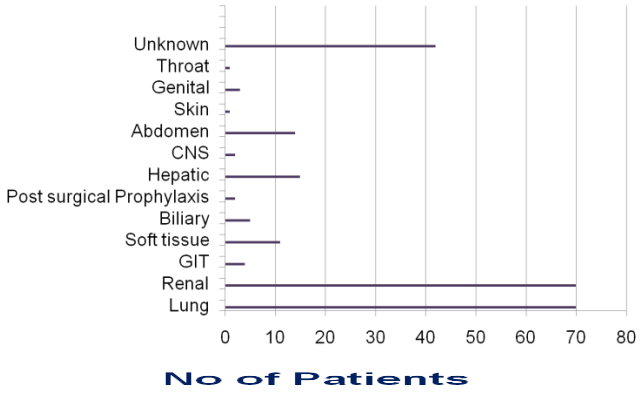

Fig.4 shows different types of source of sepsis among the total patients

Table 4: Shows different types of source of sepsis among the total patients and their percentage.

Source	Percentage of Sepsis
Lung	70 (29%)
Renal	70 (29%)
GIT	4 (1.6%)
Soft tissue	11 (4.5%)
Biliary	5 (2%)
Post-surgical Prophylaxis	2 (0.8%)
Hepatic	15 (6.14%)
CNS	2 (0.8%)
Abdomen	14 (5.73%)
Skin	1 (0.4%)
Genital	3 (1.2%)
Throat	1 (0.4%)
Unknown	42 (17.21%)

Antibiotic administration data of BLBLI

From previous literature following dosage schedule of BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) was taken for this study and compared with prevailing practice in the study cohort.

(A) CrCl> 40mL/min: 4.5g I.V q 6 h infused 4 hours, (B) CrCl 20-40mL/min: 3.375g I.V q 6 h infused 4 hours, (C) CrCl< 20 mL/min use renally adjusted dose with intermittent infusion.

In this study, in ICU eighty four patients (90.32%) received the BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) 4 hours [Mean±S.D (Min) 231.15 ± 31.07] and nine patients (9.67%) received it in less than 4 hours [Mean±S.D(Min)113.33 ± 20].

In ward seven patients (24.13%) received BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) 4 hours [Mean±S.D (Min) 215.71 ± 38.29] and twenty two patients (75.86%) received it in less than 4 hours [Mean±S.D(Min) 62.95 ± 32.24] . Fig.5 and Table5 represents Dose with Duration of Using BLBLI.

Table 5 Duration of BLBLI

	Duration 4 hours Mean±S.D(Min)	Duration < 4 hours Mean±S.D(Min)
ICU	231.15 ± 31.07	113.33 ±20
WARD	215.71 ± 38.29	62.95 ± 32.24

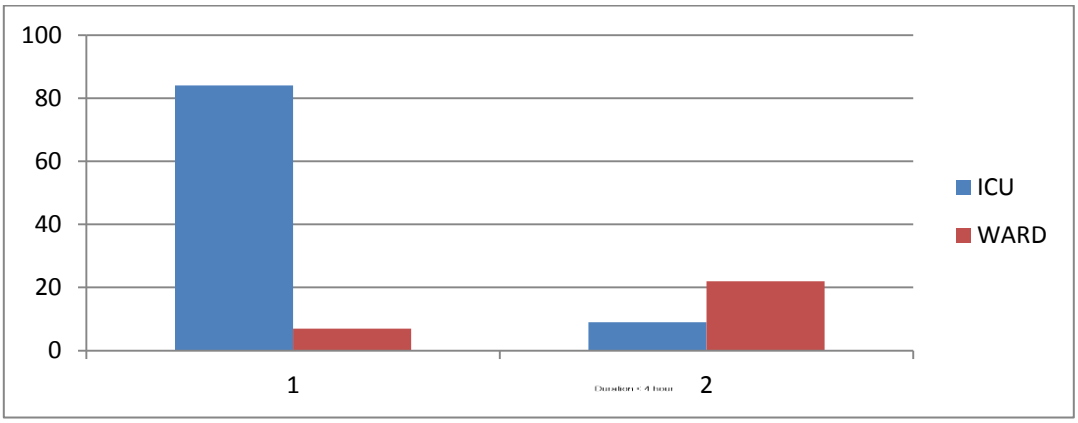

Fig.5: Duration of using BLBLI

Antibiotic administration data of Carbapenem

Meropenem and imipenem are bactericidal against susceptible organisms as demonstrated by time-kill curve studies with *Enterobacteriaceae* [12]

Following dosing schedule has been considered in this study for Carbapenems (Meropenem, Imipenem, Doripenem)

*(*A) CrCl> 51mL/min: 2 g IV q 8 h infused 4 hours, (B) CrCl 26-50mL/min: 1 g IV q 8 h infused 4 hours, (C) CrCl< 26 mL/min use renally adjusted dose with intermittent infusion

Finally after observation study, it was found that, in ICU there were Sixty one patients (80.26%) were received the Carbapenem (Meropenem, Imipenem, Doripenem) in duration 4 hours [Mean±S.D(Min) 222.29 ± 21.91] and fifteen patients (19.73%) were received it in less than 4 hours [Mean±S.D(Min) 120±11.35].

In General ward also nine patients (52.94%) were given Carbapenem (Meropenem, Imipenem, Doripenem) in duration 4 hours [Mean±S.D(Min) 226.66± 26.45] and eight patients (47.05%) received it in less than 4 hours [Mean±S.D(Min) 90 ± 45.35]. Fig.6 and Table 6 represents Dose with Duration of Using Carbapenem.

Table 6 Duration of Carbapenem

	Duration 4 hours Mean±S.D(Min)	Duration < 4 hours Mean±S.D(Min)
ICU	222.29 ± 21.91	120±11.35
WARD	226.66± 26.45	90 ± 45.35

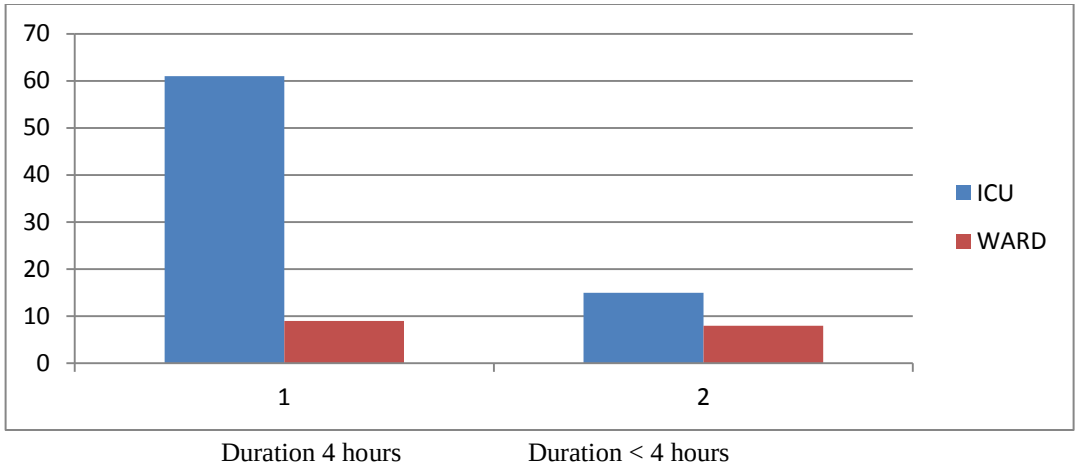

Fig. 6: Dose with duration of Carbapenem

Antibiotic administration data of Vancomycin

In studies examining the penetration of vancomycin into the CSF of patients with un-inflamed meninges, fairly low concentrations have been demonstrated (range, 0–3.45 mg/L), with corresponding CSF-to-serum ratios of 0–0.18 [13]. As expected, inflamed meninges improve penetration of vancomycin into the CNS, with reported concentrations of 6.4–11.1 mg/L and CSF-to-serum ratios of 0.36–0.48 [13]

V Vancomycin should be infused according to Creatinine clearance, at least 60 min.CrC1>50ml/min dose should be between 15-20mg/kg q8-12h, CrC1 30-49 ml/min, dose should be between 15-20mg/kg q 24 h, CrC1between15-29 ml/min dose should be between10-15 mg/kg for 24 hour, CrC1<15 dose between 10-15 mg/kg q 24-48 h.

Finally after observation study, it was found that, in ICU there were four patients received the Vancomycinin duration 1 hour [Mean value (Min)=60]. Here all four patients received vancomycin in same duration so; S.D value could not be calculated.Fig.7 and Table7 represents duration of using Vancomycin.

Table 7 Duration of Vancomycin

	Duration 1 hour Mean±S.D(Min)	**Duration < 1 hour Mean±S.D(Min)**
ICU	60	
WARD		

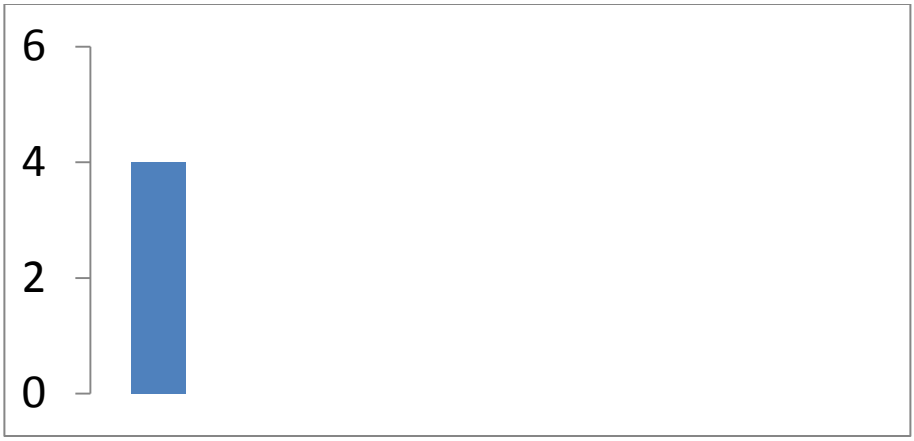

Fig.7: Duration of using Vancomycin

Antibiotic administration data of COLISTIN

The pharmacodynamic (PD) properties of colistin, such as minimal inhibitory concentration (MIC), mutation prevention concentration, population analysis profile, bacterial-killing kinetics, and the post-antibiotic effect (PAE) against multidrug-resistant (MDR) Gram-negative bacteria (GNB), such as *Pseudomonas aeruginosa*, *Acinetobacterbaumannii*, and *Klebsiellapneumoniae*, have been examined in recent studies [14] Based on the study by Owen et al[14]colistin seems to be very active in the initial killing of *A. baumannii*, even with 0.5 × MIC, exhibiting a concentration-dependent bacterial-killing mechanism.

Colistin dosing schedule taken for the study. CrC1>50ml/min,dose should be between 1.25-2.5mg/kg q12 h, CrC1 10-50 ml/min dose should be 1.25 – 1.9 mg/kg q12h,.5mg/kg q24h .CrC1<10ml/min 1.5 mg/kg for 24 hours.

Finally after observation study, it was found that, in ICU there were five patients were received the Colistin (Colistimethate sodium, colistin) in duration more than 1 hour [Mean±S.D (Min) 156 ± 38.49].

In General ward also there were two patients received Colistin (Colistimethate sodium, colistin)in less than 1 hour [Mean value(Min)=45]. Fig.8 and Table 8represents duration of using Colistin (Colistimethate sodium, colistin).

In ward only two patients received colistin in less than 1 hour that is why, S.D value could not be calculated.

Table 8 Duration of Colistin

	Duration > 1 hour Mean±S.D(Min)	**Duration < 1 hour Mean±S.D(Min)**
ICU	156 ± 38.49	
WARD		45

Fig.8: Duration of using Colistin

Table 9: Shows correlation of drug dose adjustment with renal clearance ICU

Carbapenem		BLBLI		Colistin		Vancomycin	
YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
62	19	79	16	4	0	4	0

Table 10: Shows correlation of drug dose adjustment with renal clearance General Ward

Carbapenem		BLBLI		Colistin		Vancomycin	
YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
12	7	13	11	1	1	0	0

Table 9 and 10 depicts the correlation of drug dose adjustment with the renal clearance in ICU and in Ward respectively. Total 19 number of Patients are not taken in analysis due to Renal clearance value is not found.

DISCUSSION

During the ten months of study period 240 patients were included in this study. In the demographic parameter described it was found out that the mean age was in elderly population, it was a male predominant cohort and mostly patients were included from intensive care area. It was observed that culture growth occurred in 53% cases and rest 47% shows negative culture. In majority of cases appropriate antibiotics were given. About 94.74 % were appropriate anti-microbials. Most common bacteria in this study were *Klebsiellapneumoniae, Escherichia coli, Acinetobacterbaumannii, Candida species, Pseudomonas aeruginosa, and Staphylococcus aureus.* The sources of sepsis were lung, and renal in majority however, other sources like GIT, skin and soft tissue, or hepato - bilary, were also there. The major sources of infections in this study were lung and renal (n=70), followed by unknown source (n= 42).

In this study two main categories of antibiotics were selected depending the PK/PD criteria. One category was antibiotic having criteria of time dependent killing and a second category of concentration dependent killing. BLBLI, Carbapenem and Vacomycincome are under the category of time dependent killing antibiotic. Whereas Colistin comes under concentration dependent killing antibiotic.

In this study protocol, duration of using selective antibiotics was mainly focused. The main area of interest was that dose given to the patient in ICU and ward with respect of duration by maintaining the standard protocol/reference. This observational study was done in each and every group of selective antibiotic which were include in the study protocol. The standard dose with duration was also observed on the basis of creatinine clearance value.

From previous literature following dosage schedule of BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) was taken for this study and compared with prevailing practice in the study cohort [15].

It was found that in ICU eighty four patients (90.32%) were received the BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) in duration 4 hour [Mean±S.D(Min) 231.15 ± 31.07] and nine patients (9.67%) were received it in less than 4 hours [Mean±S.D(Min)113.33 ± 20].Even in General ward also, there were seven patients (24.13%) were given BLBLI (Piperacillin & Tazobactam, Cefoperazone & Sulbactam) in duration 4 hour [Mean±S.D(Min) 215.71 ± 38.29] and twenty two patients (75.86%) were received it in less than 4 hours [Mean±S.D(Min) 62.95 ± 32.24](Table 5, Fig 5).

In cases of Carbapenem, it was found that, in ICU there were Sixty one patients (80.26%) were received the Carbapenem (Meropenem, Imipenem, Doripenem) in duration 4 hour [Mean±S.D(Min) 222.29 ± 21.91] and fifteen patients (19.73%) were received it in less than 4 hours [Mean±S.D(Min) 120±11.35].Like ICU, in General ward also there were nine patients (52.94%) given Carbapenem (Meropenem, Imipenem, Doripenem) in duration 4 hour [Mean±S.D(Min) 226.66± 26.45] and eight

patients (47.05%) were received it in less than 4 hours [Mean±S.D(Min) 90 ± 45.35](Table 6, Fig 6).

Finally after observation study, it was found that, in ICU there were four patients who received the Vancomycin in duration 1 hour [Mean value (Min) = 120] (Table 7, Fig 7).

During the observation study, it was found that, in ICU there were five patients who were given the Colistin (Colistimethate sodium, colistin). in duration more than 1 hour [Mean±S.D(Min)156 ± 38.49].In general ward also there were two patients [Mean value (Min)=45] who receividColistin (Colistimethate sodium, colistin) in less than 1 hour(Table 8, Fig 8).

Duration of antibiotic infusion of those with time dependent killing seems most important to achieve adequate therapeutic drug level. In this study it was found that mostly prolong duration was followed as per PK/PD in intensive care area. This could be explained with severity of illness, and ongoing daily surveillance by critical care team. The reason where the drugs were not given following adequate time period could be error while writing prescription, lack of communication with nursing staff, lack of understanding by junior nursing staff.

The correlation of drug dose adjustment with renal clearance was also investigated in this study. Adjustment of drug following creatinine clearance was mostly found in intensive care area as compared to ward. From this study it could be commented that dose adjustment following creatinine clearance is not that prevalent in ward and should be emphasized to get positive clinical outcome and to avoid drug toxicity.

CONCLUSION

From this prospective observational study it was concluded that in ICU area the antibiotics are prescribed more following dosing schedule and PK/PD parameters as compared to ward. There should be more awareness regarding the PK/PD variation to avoid toxicity of drug, for efficient drug delivery and finally patient outcome.

Future direction should be individualize drug therapy, therapeutic drug monitoring in drugs with a narrow therapeutic index, decrease the risk of adverse effects while maximizing pharmacologic response of medications, understanding the mechanism of Drug interaction, to maximise effective antimicrobial treatment.

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