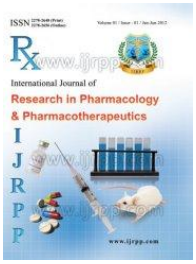
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.6 | Issue 1 | Jan - Mar - 2017***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

ISOLATION OF MULTIDRUG RESISTANT (MDR) BACTERIA & HEMODYNAMIC STABILITY ON THE DAY OF STARTING OF ANTIBIOTICS

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ABSTRACT

There is a generalized assumption among clinicians that the hemodynamically unstable patients are mostly infected with the multidrug resistant organisms compared to the hemodynamically stable patients, and that is why the patients who are considered to be hemodynamically less stable, are empirically prescribed with the broad spectrum antibiotics. This hypothesis has not been supported by any valid evidence yet .So the aim of our study was to find the association of the hemodynamic status of patients with the drug resistance pattern of organisms and the prescribing pattern of antibiotics. In the present study it has been found that the MDR organisms were isolated more frequently from hemodynamically unstable patients compared to the stable patients (70% Vs 63.25%). However the difference is not statistically significant. Interestingly in case of bacteremia, significantly higher no. (p=0.001) of hemodynamically unstable patients have been infected with MDR organisms. Moreover another significant finding of the study is that the hemodynamically unstable patients have been mostly prescribed with broad spectrum antibiotics like Colistin (p=0.031) and combination of multiple groups of antibiotics (p=0.004) than the stable ones. So the study may provide an important indication for the correlation of hemodynamic stability with multidrug resistance and antibiotic prescription pattern.

Key words: Multidrug resistance, Hemodynamic stability, Bacteremia,Antibiotic.

INTRODUCTION

Antimicrobial resistance is a major challenge to clinicians for the treatment of patients as it leads to high mortality and morbidity rates, prolonged illness and hospital stay, economic loss to the patient due to the decreased effectiveness of drugs and for being easy target to the immunocompromised condition. Both the Gram-positive and Gram- negative bacteria are affected by the emergence of antimicrobial

resistance [1]. According to European Centre for Disease Control (ECDC) and Centre for Disease Control & Prevention (CDC), the Multidrug resistance (MDR) can be defined as acquired non susceptibility to at least one agent in three or more antimicrobial categories [2].The clinical isolates such as *Pseudomonas aeruginosa*, Methicillin Resistant *Staphylococcus aureus* (MRSA), *Enterococci* especially Vancomycin Resistant *Enterococci* (VRE), and members of Family *Enterobacteriaceae*, for example, *Klebsiella pneumoniae*, *E. coli*, and *Proteus sp*, rapidly develop antibiotic resistance and spread in the hospital environment.

Clinically isolated Multidrug Resistant Organisms

Extended spectrum beta-lactamase (ESBL)

In Indian hospitals ESBL- producing *Klebsiella sp* are predominant organisms responsible for high morbidity [3]. ESBLs are β-lactamases capable of conferring bacterial resistance to the Penicillins, first, second and third-generation Cephalosporins; and Aztreonam (but not the Cephamycins or Carbapenems) by hydrolysis of these antibiotics, and which are inhibited by β-lactamase inhibitors such as Clavulanic acid. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms [4]. ESBL producers might be susceptible to β-lactam-β-lactamase inhibitor (BLBLI) combination antibiotics such as Piperacillin–tazobactam or Amoxicillin– clavulanate [5] .

AmpC

AmpC β lactamases are resistant to 3 generation Cephalosporin including BLBLI (in contrast to ESBL) but retain sensitivity to 4 generation Cephalosporin (Cefepime/Cefpirome). These are Cephalosporinases that are found on the chromosomes of *Enterobacter* sp, *Serratia sp*, *Citrobacter freundii*, *Proteus vulgaris*, *Providencia sp* and *Morganella morganii* [3].

Carbapenem resistant

Carbapenems, such as Imipenem and Meropenem are often used to treat infections caused by extended-spectrum beta lactamase (ESBL) producing Gram-negative bacteria & other MDR organisms. Carbapenemases are the enzymes which can hydrolyze all Penicillins, Cephalosporins, and Carbapenems. Another Carbapenem, called Ertapenem also show high resistance in *Klebseilla sp* and *E.coli*. . Tigecycline, is another alternative drug for multi drug resistant organisms. Colistin should always be used in combination with other antimicrobials to have adequate activity and prevent resistance [3].

Enterococcal resistance

High-level aminoglycoside resistance (HLAR) in Enterococci is mediated generally by aminoglycoside-modifying enzymes, which eliminate the synergistic bactericidal effect usually seen when a cell wall–active agent is combined with an aminoglycoside [6]. Since the vancomycin resistant *Enterococci* has the resistance to ampicillin and HLAR also so they are more difficult to treat [7]. ß-lactam (if sensitive) or Vancomycin/Teicoplanin in combination with an aminoglycoside, is recommended as a drug of choice in patients with serious Enterococcal infections [3].

Methicillin-resistant *S. aureus* (MRSA)

This high prevalence of MRSA is because of persistent high usage of Cephalosporins and quinolones that predisposes to selection of MRSA [3].

Hemodynamics

Infection with multidrug resistant organisms can cause sepsis and septic shock which ultimately leads to hemodynamic instability. At this condition, the body does not receive enough oxygen to properly function and drugs called vasopressors are used to raise the blood pressure. Hemodynamic status of patients infected with multidrug resistant organisms is our choice of interest.

Hemodynamic instability is most commonly associated with an abnormal or unstable blood pressure, especially hypotension, but in a broad sense it is defined as global or regional perfusion that is not adequate to support normal organ function [8]. Besides hypotension, the classic signs and symptoms of Hemodynamic shock are tachycardia, relative hypotension (a decrease in baseline BP of 40 mmHg), tachypnea, cool and clammy extremities, oliguria, dysglycemia, and delirium [9].The evaluation of whether a patient has hemodynamic stability or not

can be assessed clinically by some vital signs such as heart rate, respiratory rate, blood pressure, body temperature and assessment of pain.

AIMS AND OBJECTIVES

The Study was conducted to assess the hemodynamic status of the patients, infected with MDR organisms, compared to those patients infected with non MDR organisms and also to find out the correlation of hemodynamic stability and prescription pattern of antibiotics.

MATERIALS AND METHODS

An observational, comparative study has been conducted based on the data set collected from 314 indoor patients of AMRI Hospital, Dhakuria, Kolkata (West Bengal , India) during the time period of 7 months (September 2015 to March 2016). Only Indoor patients, with positive specimen culture report, and who were prescribed with antibiotics within 24 hours of sample collection, have been considered for data collection. Outdoor patients are not included in this study. Patients who are not prescribed with any antibiotic were also excluded. Then required data like demographic information, culture report, antibiotic history, drug resistance profile (multidrug resistant or not), hemodynamic parameters (mean arterial pressure and requirement of vasopressors) etc of those patients have been collected from culture reports, patients' file, medicine charts and medical records. Based on the data set the subjects are classified into two groups- MDR organisms (Microorganisms which are resistant to at least 3 or more than 3 classes of antibiotics) infected group and non MDR organisms infected group. Among these two groups, hemdynamically unstable (if the mean arterial pressure is below 60 mmHg or application of vasopressor is required) and hemodynamically stable (if the mean arterial pressure>= 60 mmHg or no requirement of vasopressors) patients were also considered. Finally the data set has been analyzed to compare the hemodynamic status and prescription pattern of antibiotics between the two groups (MDR vs non MDR).

Statistical methods

Categorical variables (Drug resistance pattern & hemodynamic status) are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square (χ^2) test for Independence of Attributes. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05, it has been considered as significant.

Approval of Ethics Committee

The study had been approved by the Independent Ethics Committee (IEC) of AMRI Hospital ,Dhakuria, Kolkata (Ref : AMRI-EC/AP/CRCH-01/2015-16).

RESULTS

In our study total 314 indoor patients have been included during September '15- March '16, considering both the ICU and Non ICU patients. Among them majority are male patients (60.5%) and most predominant age group is 61-80 yrs followed by the young adults of age group 18-60 yrs. Patients are classified into different groups like ICU, General ward, Bacteremic and non bacteremic. The demographic details of patients are given in Table 1.

Table 1: Demographic details & classification of patients

Variable	Number (n=314)	Percentage
Gender		
Male	190	60.5
Female	124	39.5
Age Group(Yrs)		
18-60	108	34.39
61-80	155	49.36
>80	51	16.24

In-Patient Department		
ICU	126	40.12
General Ward	188	59.87
Bacteremic sepsis		
Bacteremia	56	17.83
Non Bacteremia	292	92.99

Types of MDR and non MDR isolates

Organisms isolated from patients' specimen culture (e.g. sputum, urine, blood, swab, ET suction etc.) include *Enterobacteriacae, Pseudomonas, Acinetobactor, Enterococcus* (HLAR), MRSA. *Enterobacteriacae* group includes *E.coli, Klebsiella pneumonia, Proteus mirabilis, Morganella morganii, Enterobacter sp, Citrobacter sp, Serratia marcescens*. *Enterobacteriacae* group is also subdivided into Carbapenem producing group and ESBL producing group. Besides these organisms some other strains like *Candida sp, Stenotrophomonas sp. ,Chryseobacterium sp , Elizabethkingia sp , Providencia sp.* etc. have been also isolated from few no. of patients.

The no. of patients infected with various MDR and non MDR organisms have been included in Table 2

Table 2: MDR & Non MDR isolates from patients

Organisms	**No of patients**	
	MDR	Non MDR
Enterobacteriacae	76(CR) 80(ESBL)	61
Pseudomonas	33(CR)	33
Acinetobactor	46(CR)	4
Enterococcus	23(HLAR)	7
Staphylococcus	1(MRSA)	1
Others	10	14

CR- Carbapenem resistant, ESBL- Extended spectrum β lactamase producer, HLAR- High-level aminoglycoside resistance, MRSA- Methicillin resistant *Staphylococcus aureus*

HEMODYNAMIC STATUS

We found total 215 patients, who were infected with MDR organisms whereas 117 patients were infected with Non MDR organisms. The no. of hemodynamically stable patients is 253 and no. of hemodynamically unstable patients is 79. Among the stable patients 63.25% are infected with MDR organisms and 36.75 % are infected with non MDR organisms. On the other hand 70% of unstable patients are infected with MDR organisms and rest of the patients (30%) are infected with non MDR organisms (p=0.288) (Fig:1).The hemodynamic status of different groups of patients (ICU, Ward, Bacteremic, Non Bacteremic) have been shown in Table 3

Table 3 : Hemodynamic profile of patients

Hemodynamic status	**Drug resistance pattern of different groups of patients**							
	ICU (n=126)		**WARD (n=188)**		**BACTEREMIA (n=56)**		**NON BACTEREMIA (n=292)**	
	MDR	**Non MDR**	**MDR**	**Non MDR**	**MDR**	**Non MDR**	**MDR**	**Non MDR**

Stable	58.75%	41.25%	65%	35%	32%	68%	69%	31%
Unstable	71%	29%	77%	23%	73%	27%	77%	23%
P value	0.124		0.304		0.001		0.174	

Hemodynamic status did not vary significantly with Multidrug resistance pattern in case of ICU as well as Ward patients (p=0.124 & 0.304 respectively) but when we considered only bacteremic patients (positive blood culture), then it was found that significantly higher no. of unstable patients (73%) had been infected with MDR organisms and most of the stable patients (68%) had been infected with Non MDR organisms (p=0.001) (Fig: 2). In case of non bacteremic patients no significant difference has been observed between these two groups

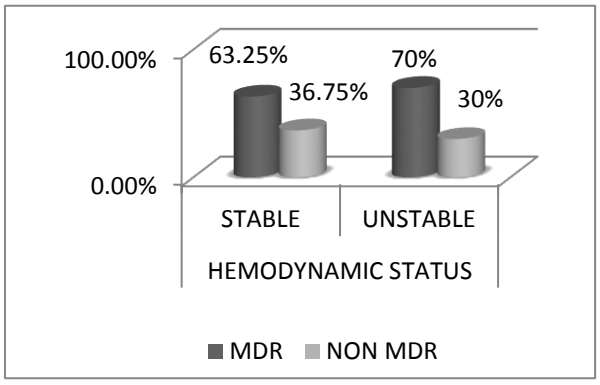

Fig 1: Hemodynamic status of total patients

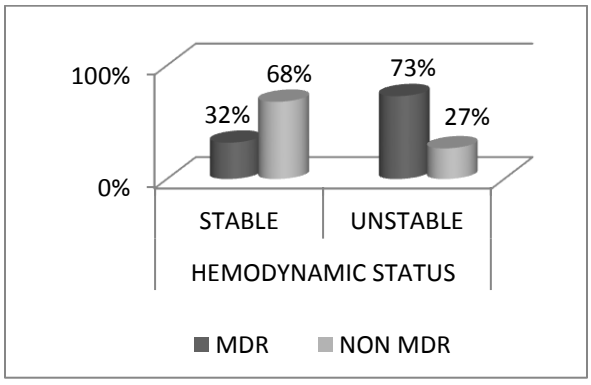

Fig 2: Hemodynamic status of bacteremic Patients

When we compared the hemodynamic status of patients infected with different sub groups of MDR and non MDR microorganisms (table: 4) then no significant difference was observed among these 2 groups, but only exception is in case of *Enterococussp* where significantly (p=0.028) higher no. of patients were hemodynamically stable in both groups.

Table: 4 Hemodynamic status according to different subgroups of organisms

	MDR			**NON MDR**			
ORGANISMS	**TOTAL NO. OF PATIENTS**	**NO. OF STABLE PATIENTS**	**NO. OF UNSTABLE PATIENTS**	**TOTAL NO. OF PATIENTS**	**NO. OF STABLE PATIENTS**	**NO. OF UNSTABLE PATIENTS**	**P Value**
Enterobacteriacae	156	119 (76%)	37 (24%)	61	51(84%)	10 (16%)	0.210
Pseudomonas	33	26 (76%)	7 (21%)	33	26 (76%)	7 (21%)	1.000
Acinetobacter	46	29 (63%)	17 (37%)	4	3 (75%)	1 (25%)	0.600
Enterococcus	23	19 (83%)	4 (17%)	7	7	0	0.028
Staphylococcus	1	1	0	1	0	1	NA
OTHER STRAINS	10	7(70%)	3 (30%)	14	10 (71%)	4 (29%)	0.940

Prescription pattern of antibiotics

In the present study, we have also tried to correlate the prescription pattern of antibiotics with hemodynamic status. Patients have been mostly prescribed with Colistin, Carbapenem, BLBLI, Tigecycline/ Minocycline groups of antibiotics. Colistin and Carbapenem are relatively broad

spectrum antibiotics, compared to BLBLI and Tigecycline/ Minocycline groups.

The prescription pattern of antibiotics in total patients (Table 5& Figure 3) and bacteremic patients (Table 6 & Figure 4) have been mentioned below. Hemodynamically unstable patients have been prescribed mostly with broad spectrum antibiotics like Colistin (p=0.031) and combination of multiple groups of antibiotics (0.004) than the stable ones.

Table 5 : Antibiotic prescription pattern for all in-patients

HEMODYNAMIC STATUS	**PRESCRIPTION PATTERN OF ANTIBIOTICS**				
	Colistin	Carbapenem	BLBLI	Tigecycline/ Minocycline	Combination
Stable	4.6%	23%	36%	5.3%	2.7%
Unstable	14%	31.5%	17.8%	11%	15%
P Value	0.031	0.158	0.001	0.153	0.004

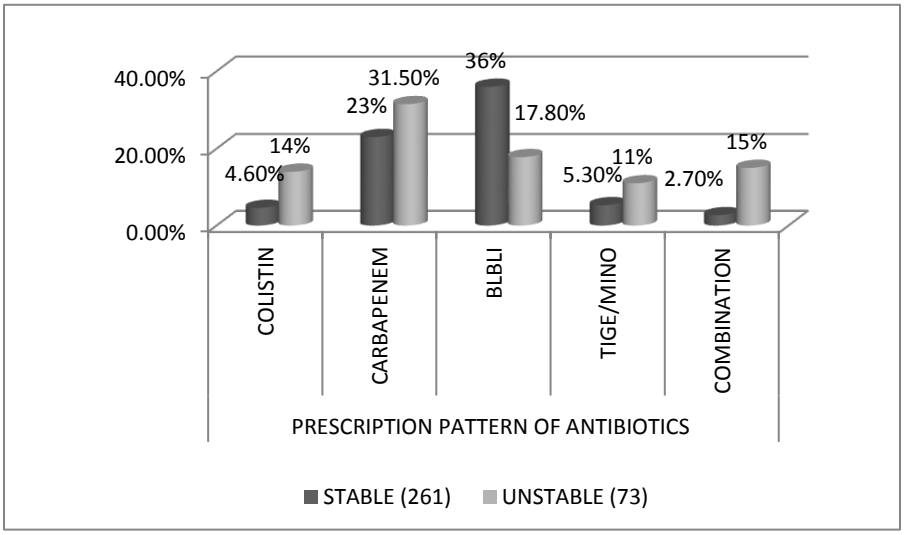

Fig 3: Antibiotic prescription pattern for all in-patients

Table 6: Antibiotic prescription pattern for bacteremic patients

	PRESCRIPTION PATTERN OF ANTIBIOTICS				
HEMODYNAMIC STATUS	Colistin	Carbapenem	BLBLI	Tigecycline/ Minocycline	Combination
Stable	9%	20%	32.35%	6%	3%
Unstable	9%	23%	23%	4.5%	14%
P Value	0.973	0.850	0.423	0.824	0.174

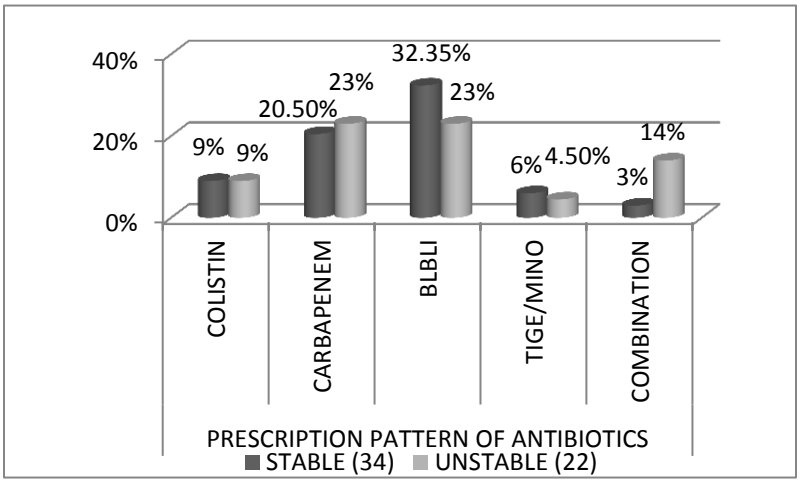

Fig 4: Antibiotic prescription pattern for bacteremic patients

The data set has been further analyzed to find the antibiotic prescription pattern of patients infected with several groups of MDR and non MDR organisms.

Table 7: Antibiotic prescription pattern of patients infected with several groups of MDR organisms

			CLASSES OF ANTIBIOTICS				
GROUPS OF MDR ORGANISMS	MDR STRAINS	HEMODYNAMIC STATUS	COLISTIN	CARBAPENEM	BLBLI	TETRACYCLINE/MINOCYCLINE	COMBINATION
	Enterobacteriacae (Carbapenem Resistant)	Stable-55	5	12	13	7	1
		Unstable-21	1	6	3	0	8
		P Value	0.474	0.551	0.327	0.005	0.001
	Enterobacteriacae (ESBL producer)	Stable-64	1	21	23	3	1
		Unstable-16	3	5	2	2	1
		P Value	0.082	0.904	0.022	0.368	0.453
	Pseudomonas (Carbapenem Resistant)	Stable-26	3	5	7	2	0
		Unstable-7	1	3	1	1	1
		P Value	0.851	0.243	0.426	0.643	0.280
	Acinetobactor (Carbapenem Resistant)	Stable-29	4	7	3	4	3
		Unstable-17	3	2	1	3	3
		P Value	0.732	0.267	0.579	0.732	0.500
	Enterococcus (HLAR)	Stable-19	0	7	6	0	0
		Unstable-4	0	2	1	0	0
		P Value	NA	0.630	0.785	NA	NA
	MRSA	Stable-1	0	0	1	0	0
		Unstable-0	0	0	0	0	0
		P Value	NA	NA	NA	NA	NA
	Other MDR Strains	Stable-7	1	0	1	1	1
		Unstable-3	0	1	1	0	0
		P Value	0.280	0.221	0.529	0.280	0.280

Table 8: Antibiotic prescription pattern of patients infected with several groups of non MDR organisms

		CLASSES OF ANTIBIOTICS					
	NON MDR STRAINS	HEMODYNAMIC STATUS	COLISTIN	CARBAPENEM	BLBLI	TIGECYCLINE/MINOCYCLINE	COMBINATION
NON MDR ORGANISMS	*Enterobacteriacae*	Stable-51	0	6	28	0	3
		Unstable-10	1	4	3	0	0
	P Value		0.292	0.080	0.121	NA	0.074
	Pseudomonas	Stable-26	1	5	13	2	0
		Unstable-7	0	1	1	1	1
	P Value		0.308	0.747	0.030	0.643	0.280
	Acinetobactor	Stable-3	0	0	1	0	0
		Unstable-1	0	0	0	0	0
	P Value		NA	NA	0.221	NA	NA
	Enterococcus	Stable-7	0	0	3	0	0
		Unstable-0	0	0	0	0	0
	P Value		NA	NA	NA	NA	NA
	Staphylococcus	Stable-0	0	0	0	0	0
		Unstable-1	0	0	0	0	0
	P Value		NA	NA	NA	NA	NA
	Other Non MDR Strains	Stable-10	1	2	1	0	0
		Unstable-4	0	0	1	3	0
	P Value		0.292	0.114	0.526	0.001	NA

DISCUSSION

Till now very few studies have been conducted to correlate the hemodynamic stability and multidrug resistance along with the antibiotic prescription pattern. Our study may be a clinically important evidence in this regard.

Total 314 patients have been included in the study population and it has been found that 60.5% of the populations are male patients. In another study, *Proda A. et al (2013)* showed that the highest percentage of isolates corresponded to males (53.6 %)[10] . The prevalence of MDR organisms has also been observed in this study. High percentages of both hemodynamically stable and unstable groups of patients were infected with MDR organisms (63.25% and 70% respectively). This findings have been supported by *Basak S et al* (2016), who showed that a large no of patients were infected with MDR organisms, and a few more percentage of patients are infected with extensively drug resistant organisms [1].

In our study most commonly isolated MDR organism was ESBL producer *Enterobacteriacae* followed by Carbapenem resistant *Enterobacteriacae* and after that most frequently isolated group is Carbapenem resistant *Acinetobacter* sp and in case of non MDR organisms *Enterobacteriacae* and *Pseudomonas* were mostly prevalent. *Wattal C et al (2010)* also showed that in Indian hospitals ESBL-producing *Klebsiella sp* are predominant organisms and are responsible for high morbidity. ESBL-producing organisms exhibit co resistance to many other classes of antibiotics, resulting in limitation of therapeutic option. Carbapenems are the treatment of choice for serious infections due to ESBLproducing organisms [3]. We have also found that patients infected with MDR and non MDR *Enterococcus* are mostly hemodynamically stable (p=0.028), but in case of other subgroups of MDR and non MDR organisms the hemodynamic stability of patients did not vary significantly. One of the most interesting findings of our study is that in case of bacteremia, the hemodynamically unstable patients are mostly infected with MDR organisms and stable patients are infected with non MDR organisms (p=0.001).In case of other groups of patients (ICU, Ward, non Bacteremic) the difference is not statistically significant. Antibiotic prescription pattern according to the hemodynamic status and severity of infection is another important issue. Colistin and Carbapenems are the presumptive treatment of choice to prevent drug resistance. Kara B et al also showed

that BLBI can also be alternative drug of choice for carbapenemase producing *Enterobacreria* [11].In this regard in 2012 Rodreguez et al described the efficacy of Amoxicillin-Clavulanic acid and Piperacillin-Tazobactam as suitable alternatives to Carbapenems for treating patients with bloodstream infections due to ESBL producing *E.coli* [12].Kara B et al (2008) studied the use of Tigecycline as initial treatment for serious infection caused by MDR gram-negative Bacilli. In our study Tigecycline/ Minocycline antibiotic were mostly prescribed to the hemodynamically stable patients. The reason might be the bacteristatic nature of the drug. The hemodynamically unstable patients had been prescribed mostly with broad spectrum antibiotics like Colistin (p=0.031) and combination of multiple groups of antibiotics (0.004) than the stable ones. On the other hand stable patients had been significantly prescribed with relatively narrow spectrum group antibiotics like BLBLI (p=0.001) (Table 5).

So, the hemodynamic status may be a useful guide for physicians to initiate empiric antibiotic therapy during sepsis, which will help to avoid the initial treatment with inappropriate antibiotics.

CONCLUSION

In conclusion, our study reveals that majority of the patients (considering both ICU & Ward) included in the study are hemodynamically stable (76.2%).MDR organisms have been isolated more frequently from hemodynamically unstable patients compared to the hemodynamically stable patients (70% Vs 63.25%) . However the difference is not statistically significant. In case of patients with bacteremia, significantly higher no. (p=0.001) of MDR organisms have been isolated from unstable cases than the stable ones (73% Vs 32%), which supports the preliminary assumption of clinicians (Table 3 & Fig 2).

Hemodynamically unstable patients were mostly prescribed with broad spectrum antibiotics like Colistin (p=0.031) and combination of multiple groups of antibiotics (0.004) than the stable ones (Table 5). In case of Carbapenem resistant *Enterobacteriacae* isolates, significantly higher no. of hemodynamically unstable patients (including both ICU & Ward) have received combination of multiple broad spectrum antibiotics compared to the stable patients (Table 7) of the same group (p=0.001). In most of the cases BLBLI & Bacteriostatic agents like Tigecycline/ Minocycline have been prescribed to the hemodynamically stable patients (p=0.030 & 0.005 respectively, table 7,8).

Further study including larger no. of patients is required to elucidate the absolute clinical impact based on the findings.

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