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INCREASE IN ANTIBIOTIC RESISTANCE: ARE BACTERIA GROWING WITH PAN RESISTANCE?

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ABSTRACT

Introduction: Pan Drug Resistant (PDR) bacteria are currently the leading cause of concern to the clinicians as they pose serious therapeutic challenges. A bacteria that is non-susceptible to all agents in all antimicrobial categories has been defined as PDR. This retrospective study has been undertaken to determine the prevalence of PDR –GNRs (Gram negative rods) and to assess the risk factors associated with that in hospitalized patients of our rural hospital.

Material & Method: A total of 1748 GNRs isolated and identified by standard phenotypic methods from various clinical specimens received in this laboratory between 1st June 2011 to 31st May 2012 from IPD patients were enrolled in this study. Antibiotic susceptibility of these isolates was done using Kirby-Bauer disk diffusion method as per CLSI guidelines. Predisposing factors for acquisition of PDR isolates were also studied.

Results: A total of 32 (1.8%) of the 1748 GNRs studied were found to be PDR and these were recovered predominantly from surgical units (31.3%). Among these 45.5% were *Acinetobacter species*, 24.2% *Klebsiella species,* 15.2% *Pseudomonas aeruginosa* and 12.1% *E.coli.* 53.1% isolates were from pus & wound swabs followed by 21.9% from tracheal swabs. Prolonged hospital stay and patients with surgical interventions were found to be important predisposing factors.

Conclusions: PDR-GNRs are originating in our rural hospital and particularly in patients with having prolonged stay in the hospital.

Key Words: PAN drug, PDR-GNR, Acinetobacter

INTRODUCTION

The fight between a mankind and microorganism is going on since ages. Microorganisms keep on acquiring new methods of resistance to the existing antibiotics and to cope up with these phenomenon human beings keep on discovering new antibiotics. It is constantly observed that microorganisms are slowly getting supremacy in their method of acquiring resistance and mankind is lagging behind at times with the discovery of new antibiotics and both them are trying to discover new defence to tackle with each other.

Patients who are admitted in the hospital, having suppressed immune system have a greater risk of acquiring bacteria from environment of hospitals. Most of the nosocomial infections arise due to improper hand washings, improper sterilization of instruments and cross infections through patients wearing, IV stand, beddings, leading to surgical wound infections.

In the hospital environment amongst many resistant bacteria, Gram negative bacilli are increasingly prevailing[1-3]. Amongst the Gram Negative bacilli considerable resistance are observed in Enterobacteriaceae and Nonfermenters[4].One of the common mechanism by which these Gram negative bacilli acquires resistance is via production of enzymes "betalactamases". These betalactamases include ESBLs, AmpC & MBLs. In Indian hospitals, ESBL producing Klebsiella spp are predominant organism responsible for high morbidity.

As per the definitions published in the article of Journal European Society of Clinical Microbiology and Infectious diseases 2012. Definition of MDR means "resistant to more than one antimicrobial agent" but no standardized definitions for MDR have been agreed upon yet by the medical community.

XDR means: Bacteria, which are epidemiologically significant due to not only to their resistance to multiple

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antimicrobial agents but also to their ominous likelihood of being resistant to all. Extensively resistant Bacteria (XDR) are resistant to all but 1 or 2 classes of antibacterial agents and Pan drug resistant (PDR) means resistant to all antibiotic classes available for empirical treatment" [5]. Amongst the all Gram negative bacilli *Acinetobacter, Pseudomonas* and *Klebsiella* are the predominantly important cause of nosocomial infections due to pneumonia, bactereamia wound infections, nosocomial infections which shows PDR pattern.

Globally,prevalent Pan drug resistant-Gram Negative (PDR-GNRs) are *Acinetobacter, Pseudomonas & Klebsiella sp.*[6] The prevalence of PDR-*Acinetobacter* worldwide is about 0-20% of all Acinetobacter *sp.*infection.[7, 8]

In India, prevalence of MDR-GNR vary from 9-90% & PDR- GNR from 2-5%.[9,10] The risk factors found to be associated with PDR –GNR infection depends on severity of the illness, admission to ICU, use of invasive interventions, duration of hospital and previous antibiotic use[7,8].

MATERIAL AND METHODS:

This observational study was carried out on isolates to study the prevalence of PDR in E.coli, *Klebsiella, Pseudomonas & Acinetobacter species* isolated from hospitalised patients and to assess the risk factors associated with these organisms from 1st June 2011 to 31st May 2012 in tertiary care rural hospital of central India.

Data was collected from case records of all patients from whom PDR-GNR isolates were isolated. Details were included as date of admission, demographic information (sex and age), medical history (underlying diseases, previous use of antibiotic(s), medical devices and corticosteroids), admission to Intensive Care Unit (ICU), site of infection or colonization, laboratory data (the pathogenic organism isolated and their antibiotic susceptibility pattern), mortality, treatment and outcome.

E. coli, Klebsiella, Pseudomonas & Acinetobacter isolates from the clinical samples viz: pus & wound swab, endotracheal tube secretions, urine, blood, different body fluids, catheter tips, sputum, vaginal swab, from patients admitted in hospital.

Isolates were identified & confirmed by using Standard laboratory techniques,and antibiotics were tested as per CLSI guidelines. Interpretation of zone diameter was done as per CLSI guidelines.[11]As per the reading of antibiotics, isolate were placed into categories of MDR, XDR and PDR (MDR as: one agent in three or more antimicrobial categories, XDR: resistant to at least one agent in all but two or fewer antimicrobial, PDR: Resistant to all available antibiotics in all antimicrobial groups).

Information regarding associated risk factors in patients was retrieved from patient's Case records.

RESULTS

During the study period a total of 1,748 Gram Negative Bacilli were isolated. Amongst 1748, 1616 (92.44) were E.coli, Klebsiella, Pseudomonas and Acinetobacter while 132(7.55) were Salmonella-(3.03), Proteus-(28.03), Shigellaflexnerii-(10.60), Citrobacter-(50.75), Enterobacter-(5.30), Serratia-.(75), Vibrio cholerae –(1.51) and Gram positive positive ( ) organisms. (Table 1) 16.2% isolates were sensitive to all the antibiotics to which isolate was subjected for testing.11.1% isolates were resistant to 2 and > 2 drugs.(Table 2) 26.9% were MDR, 7.4% were XDR & 1.9% were PDR Gram negative bacilli.

In E.coli 31.40% were MDR and .5% were PDR while in Klebsiella 26.3% were MDR and 2.10% were PDR. In Pseudomonas and Acinetobacter maximum resistance was seen to drugs of all the categories. In these two organisms 10.20% and 10.30% were XDR while PDR was noted in 2.30% and 6.30%. Acinetobacter showing 10.30% PDR was isolated from Pus, wound swab, tracheal swab and urine samples. PDR from blood sample was isolated from E.coli and pseudomonas .53.1% PDR& 28.3% XDR was isolated from pus and wound swab. Maximum number of MDR was isolated from urine (60%) and *E.coli* (31.4%). Maximum number of XDR was isolated from tracheal swabs (24.2%).

Table 1: Distribution of resistance to drugs amongst Gram negative Bacilli

Isolates analysed in study(GNR)	Sensitive to all categories		Resistant to < 2 Categories		Resistant to > 2 categories					
					MDR- GNR		XDR- GNR		PDR- GNR	
	No.	%	No.	%	No.	%	No.	%	No.	%
1616	261	16.2	1176	72.7	435	26.9	120	7.4	32	1.9

Table 2: Organism wise distribution of resistance category

Total no. of GNRs Under study	Resistant isolates					
	MDR- GNR		XDR- GNR		PDR- GNR	
	No.	%	No.	%	No.	%
E.coli (n=799)	251	31.4	26	3.3	4	0.5
Klebsiella sp.(n=381)	100	26.2	47	12.3	8	2.1
Pseudomonas sp. (n=214)	50	23.3	23	10.7	5	2.3
Acinetobacter sp.(n=222)	34	15.3	24	10.8	15	6.8
1616	435	26.9	120	7.4	32	1.9

Table 3: Associated risk factors with isolation of PDR isolates

Risk Factors	PDR –Acinetobacter (n=30)	PDR-Klebsiella (n=8)	PDR-Pseudomonas (n=5)	PDR-E.Coli (n=4)
Hospital stay (15 days to 3 months)	12(80)	4	4	3
Diabetes	2 (13.34)	0	1	0
Malignancy	1 (6.67)	0	0	0
Surgery	6 (40)	3	3	3
ICU stay for more than 5 days	3 (20)	0	1	1
Burn units	0	0	1	0
sepsis	1 (6.67)	1	0	1
Pneumonia	2 (13.34)	2	1	0
Shock	3	2	0	1
Mortality	-	2	1	1

Amongst the organisms PDR Acinetobacter was Prolonged hospital stay, surgical interventions and admission to ICU are the factors found to be associated with PDR- GNRs

DISCUSSION

The medical community has been witnessing growing outbreaks of infections due to Gram-negative bacteria resistant to many classes of antibiotics in most countries of the world (Sharma et al., 2005; Canton et al., 2003; Hsueh et al., 2002; Landman et al., 2002).

The control of nosocomial infections due to antibiotic-resistant organisms is a public health priority worldwide. It has been documented that bloodstream infection caused by Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin- resistant enterococci (VRE), extended-spectrum lactamase- producing *Enterobacteriaceae*, and multidrug-resistant *Acinetobacter baumannii* are associated significantly with mortality.Numerous papers have demonstrated that prior antimicrobial drug exposure is a strong risk factor for colonization and infection due to a drug-resistant pathogen.[12]

Studies have identified the risk factors for acquiring infection or colonization with PDR isolates which include the severity of the illness, admission to ICU, use of invasive interventions, duration of hospital stay before specimen collection, previous antibiotic use of especially third-generation cephalosporins, fluoroquinolones, amikacin and carbapenems and use of mechanical ventilator, central venous catheter, Foley catheter and total parenteral nutrition invasive interventions can lead to environmental contamination [13-20].

However, the association between antibiotic therapy and the acquisition of antibiotic-resistant bacteria is still unclear and is often confounded by insufficient data on antibiotic usage.

We could demonstrate that patients with PDR infection or colonization had a significantly longer length of hospital stay, compared to those infected or colonized with non-PDR. However, the mortality was not significantly different between the two groups.

In our study, it was observed that Acinetobactor sp., Pseudomonas, *E. Coli* and *Klebsiella* were the organisms showing the resistance to many classes of antibiotics and similar pattern of resistance were observed in other studies done with similar objectives. These organisms are commonly associated with various nosocomial infections including septicaemia, pneumonia, bacteriemia, wound infections; hence, their isolation is more in majority of the studies done with the similar objectives.

India currently produces at least 30% of the world's oral & inject able antibiotics, and could rightly argue they are supporting the WHO agenda of supplying the world with affordable medicines. However, overuse of antibiotics that are excreted by the patients and find their way into hospital and community waste-water systems provides an environmental selection pressure for the emergence and persistence of multi-drug-resistant (MDR) and pan-drug-resistance (PDR) bacteria.

Thus, at a time when PDR-GNRs are fast becoming a global reality, both academia and pharmaceutical industry are ill equipped to respond. PDR GNRs is an emerging nosocomial pathogen especially in tertiary care settings. Risk factor for PDR-GNR acquisition includes those associated with the patients such as severity of the illness, inappropriate use of antibiotics, surgical interventions, prolonged hospitalization.

The prevalence of PDR-Acinetobacter baumanii worldwide is about 0-20 percent of all *A. baumannii* infections. In Thailand, a report from Siriraj Hospital in Bangkok revealed the prevalence of MDR-AB to be 57.6 percentduring1996 and 1997. No PDR-AB was described during that period.[14] The incidence of PDR-AB has been increasing in Maharaj Nakorn Chiang Mai Hospital. From 1998 to 2002, *Acinetobacter* spp. were either the fifth or sixth most common cause of nosocomial nfections at Maharaj Nakorn Chiang Mai Hospital. However, in 2003 *Acinetobacter* spp. had become the leading cause of nosocomial infections, followed by Pseudomonas *aeruginosa, Klebsiella pneumoniae* and *E. coli.*

CONCLUSION

In our study, the proportion of of PDR- and MDR-*Acinetobacter* was 6.8% and 15.3%. PDR Acinetobacter mostly isolated from pus and wound swab 7(21.9%) followed by from tracheal swab 5(15.6%).

Prolonged hospital stay, surgical interventions and admission to ICU are the factors found to be associated with PDR- GNRs.To know the details regarding prior antibiotic use is very essential.

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