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Bacteriological Isolates and Their Phenotypic Expression of Enzyme Related Resistance Observed From a Tertiary Care Hospital: A Two Year Study

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ABSTRACT

Purpose: This study was designed with the objective of finding the incidence of bacteriological infections over a period of 2 years and to find out their association with enzyme related resistance in our hospital settings.

Methods: This was a retrospective study from Jan 2016 to Dec 2017. Of the total 35,800 specimens; Blood (8770), Urine (14749), Pus (3621), all types of tips (8660) were studied. Aerobic culture followed by automated identification and antimicrobial susceptibility of pathogens were done.

Results: Aerobic culture of blood, pus, urine & all types of tips showed culture positivity of 12.94%, 55.43%, 21.17% & 10.87% respectively. Predominant isolates from these specimens were *Acinetobacter spp, Enterobacter spp, Escherichia coli, Klebsiella spp, Proteae family, Pseudomonas spp, Staphylococcus aureus, Enterococcus spp* accounting for12.31%, 4.07%, 36.61%, 13.99%, 3.63%, 10.48%, 5.52% & 6.66% respectively. *Staphylococcus aureus* was found to be mecA & heteroVISA positive in 45.94% & 18.53% respectively. *Enterococcus spp* expressed Van A like and Van B like resistance in 27.35% and 6.47% respectively.

Conclusions: It is important for every hospital to have a data on prevalent organisms and their antibiotic susceptibility pattern.

Key words: Antimicrobial drug resistance, Carbapenemase, ESBL, heteroVISA, mecA.

INTRODUCTION

The introduction of antimicrobials revolutionized our war against infectious diseases. However, it was subsequently realized that bacterial populations could quickly modify themselves to resist antimicrobials, propagate these resistance traits, and even share resistance genes with other contemporary bacteria within their environment. Such abilities have seriously compromised the usefulness of antibiotics in the war against microbes and warn of a future when antimicrobials may have very limited usefulness to control bacterial infection. Millions of metric tons of newer classes of antibiotics have been produced in last 60 years since its inception. Conversely, the enormous and irresponsible use of the antibiotics, has contributed significantly to the advent of the resistant strains. Resistance to an antibiotic develops in no time and hence, is a big matter of concern. [1, 2]

The impact of antimicrobial agents on public health over the past 50 years is unmatched by any other class. Precise data on current antibiotic use are difficult to ascertain due to a variety of prescriptions and dosage regimens followed. Although resistance is reported among antiviral, antifungal and antiparasitic agents and can have a major impact on the management of infected patients, it is the antibacterial agents, because of the far greater quantity of prescribing and burden of disease, that

attract most attention. Resistance may be either inherent or be acquired by the processes of genetic mutation or gene transfer. The mechanisms of acquired resistance fall into one of the five categories, although bacteria may employ more than one mechanism: (i) enzymatic modification or destruction of the antibiotic (ii) reduced antibiotic uptake into the bacterium (iii) increased efflux of antibiotic from the bacterium (iv) alteration or production of a new target site (v) over-expression of the drug target. [3] Resistance genes may be present naturally, since many antibiotic classes are natural products and bacteria need to protect themselves, or alternatively have evolved from housekeeping genes. [4]

In all cases, in which a comprehensive study has been performed the number of genes involved in the phenotypic expression of resistance is larger than could be predicted if they had evolved as specific elements for counteracting the action of the drugs. Furthermore, several of such genes encode key elements of the bacterial metabolism. Altogether, the results indicate that the specific phenotype of susceptibility to antibiotics is under metabolic control and hence those changes in the bacterial metabolism can consequently alter the susceptibility to antibiotics. [5, 6]

Bacterial infections constitute an important cause of morbidity and mortality in human beings all over the world, but more so in developing countries with poor access to health services. [7] Antibiotic resistant organisms are known as superbugs. These are not only a laboratory concern but have become a global threat responsible for high death tolls and life-threatening infections. [8] Reports of resistance vary, but a general consensus appears to prevail that quinolone and broad-spectrum β-lactam resistance is increasing in members of the family *Enterobacteriaceae* and *Acinetobacter* spp. and that treatment regimes for the eradication of *Pseudomonas aeruginosa* infections are becoming increasingly limited. [9] Data from the Centers for Disease Control and Prevention (CDC) show rapidly increasing rates of infection due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), and fluoroquinolone-resistant *P. aeruginosa.* [10]

Panantibiotic-resistant infections now occur. Several highly resistant gram-negative pathogens- namely *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa*, and carbapenem- resistant *Klebsiella* species and *Escherichia coli*—are emerging as significant pathogens in both the United States and other parts of the world. Our therapeutic options for these pathogens are so extremely limited that clinicians are forced to use older, previously discarded drugs, such as colistin, that are associated with significant toxicity and for which there is a lack of robust data to guide selection of dosage regimen or duration of therapy. [10,11] The growing number of elderly patients and patients undergoing surgery, transplantation, and chemotherapy and dramatic increases in population in neonatal intensive care units produce an even greater number of immunocompromised individuals at risk of these infections. [12]

Equally impressive is the selection by bacteria of antibiotic resistance mechanisms. The re-emergence in recent years of Gram positive bacteria with additional resistance patterns (MRSA, VISA, GRE, PRP), and multi-resistant Gram negative 'superbugs', has been extensively reported, and our concerns are justified. Furthermore, the clinical impact of antibiotic resistance is often poorly defined; it is studied from an *in vitro* perspective and extrapolation is fraught with problems. Antibiotic resistance is a complex, continually evolving problem which is often difficult to put into perspective. [3] Pathogen occurrence and susceptibility profiles show substantial geographic variations as well as significant differences in various populations and environments. [13] Thus, knowledge of the local bacterial etiology

and susceptibility patterns is required to detect on time any changes that might have occurred so that appropriate recommendations for optimal empirical therapy of bacterial infections can be made. The aim of this study was therefore to find out the incidence of bacterial pathogens and their association with enzyme related resistance, reported from microbiology lab of our hospital over a period of 2 years.

MATERIALS & METHODS

The specimens submitted to the Microbiology lab of our hospital in the year 2016 and 2017 were retrospectively studied. The decision to take samples for microbiological culture and the selection of type of samples was made by the physicians. We used commercial blood culture bottles (BacT/ALERT, bioMérieux) to assess bacteremia, and disposable sterile cotton swabs (PW003, Sterile Hiculture device, HiMedia) for superficial infections, urine samples and other specimens were collected in sterile single-use universal containers for microbiological culture. After preliminary tests like Gram staining, motility, oxidase test, catalase test and coagulase test on the growth, standard culture based automated methods were used for species identification and antimicrobial susceptibility testing (Vitek2 Compact, bioMérieux) and reported according to Clinical Laboratory Standards Institute (CLSI) guidelines.

All data was collected from the Laboratory Information System used by Clinical Microbiology Laboratory of our hospital. The data was imported into a Microsoft Excel spreadsheet file and all important patient identifiers were properly and securely discarded. The information regarding organism isolated, phenotypic drug resistance and MIC values against a variety of antibiotics was collected from Vitek 2 Compact database.

Only isolates that underwent susceptibility testing were included in this study. The four specimens with maximum numbers submitted for culture (i.e., blood, pus, urine and all types of tips) were further analysed with respect to the organisms isolated. All types of tips included drain tips, suction tips, endotracheal tips, transtracheal tips, central line tips etc. Foley's catheter tips were not considered as per the rejection criteria of the lab. Due to the enormity of variety of organisms isolated, only commonest organisms were further studied. The organisms included six Gram negative bacilli namely, *Acinetobacter species*, *Enterobacter* spp, *Escherichia coli*, *Klebsiella spp*, members of Proteae family (including *Proteus*, *Morganella* & *Providencia*), and *Pseudomonas* species. *Staphylococcus aureus* and *Enterococcus* species were the two Gram positive cocci which were further studied.

Statistical analysis: Carried out using Chi square test.

RESULTS

A total of 35,800 specimens were submitted to the lab for aerobic culture and sensitivity, of which 16,268 & 20,164 specimens were analyzed in 2016 and 2017 respectively. Four major specimens studied were blood (8770), urine (14749), pus (3621) & all types of tips (8660). Aerobic culture positivity of the commonest specimens is depicted in Table 1.

Table 1: Culture positivity of commonest specimens analyzed

Specimen	Total samples cultured	Culture positive	% positivity
Blood	8770	1127	12.85
Pus	3621	2007	55.43
Urine	14749	3122	21.17
All tips	8660	941	10.87
Total	35800	7197	20.14

The location of specimen when compared against percentage of culture positivity showed that though the number tested from out-patient departments was less, however the percent positivity was high (Figure 1).

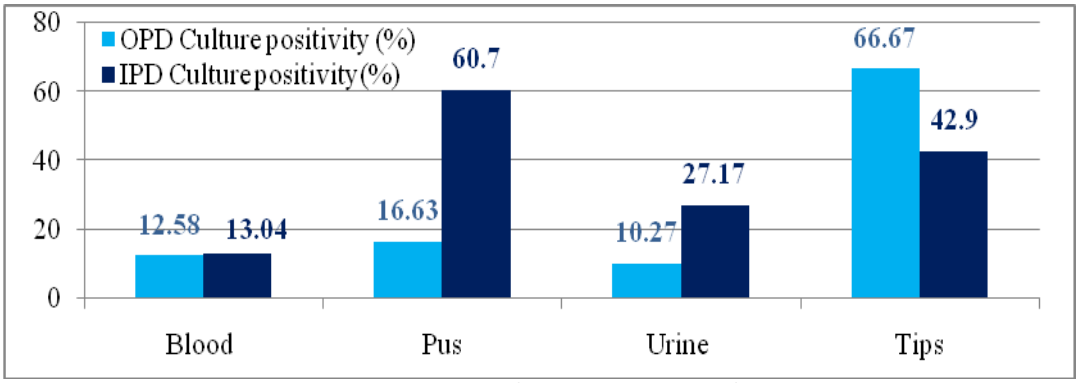

Figure 1: Location wise distribution of percentage positivity of specimens studied

When organisms isolated from various samples were analysed, it was observed that predominant isolates were *Acinetobacter spp, Enterobacter spp, Escherichia coli, Klebsiella spp, Proteae family, Pseudomonas spp, Staphylococcus aureus, Enterococcus spp* accounting for 15.28%, 6.34%, 22.83%, 9.55%, 7.19%, 19.46%, 15.03% & 4.32% respectively (Figure 2).

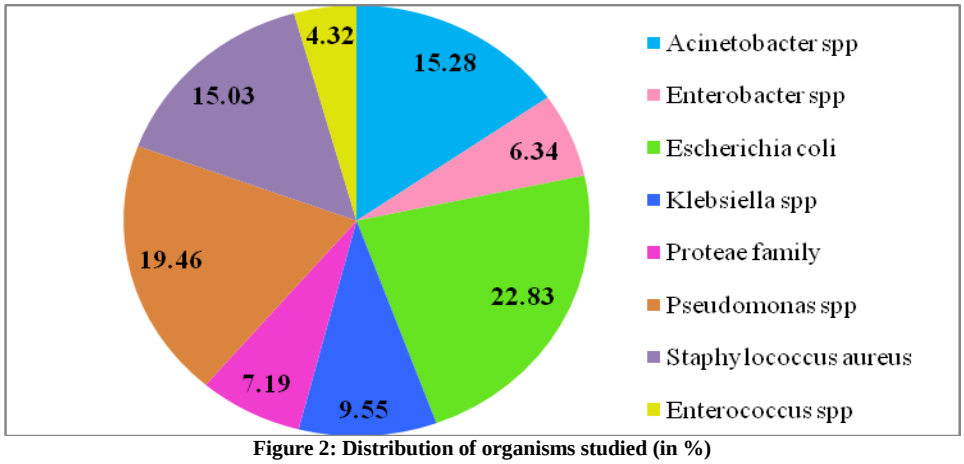

Figure 2: Distribution of organisms studied (in %)

Amongst the non fermenters, distribution of *Acinetobacter* species was found to be 20.85%, 34.82%, 8.13%, 36.20% in blood, pus, urine and all types of tips respectively. While distribution of *Pseudomonas* species revealed 8.49%, 51.33%, 18.57% & 21.62% positivity in blood, pus, urine and all types of tips respectively (Figure 3). With a p value of <0.001, a significant association has been observed between the specimens and *Acinetobacter* spp as well as *Pseudomonas* spp.

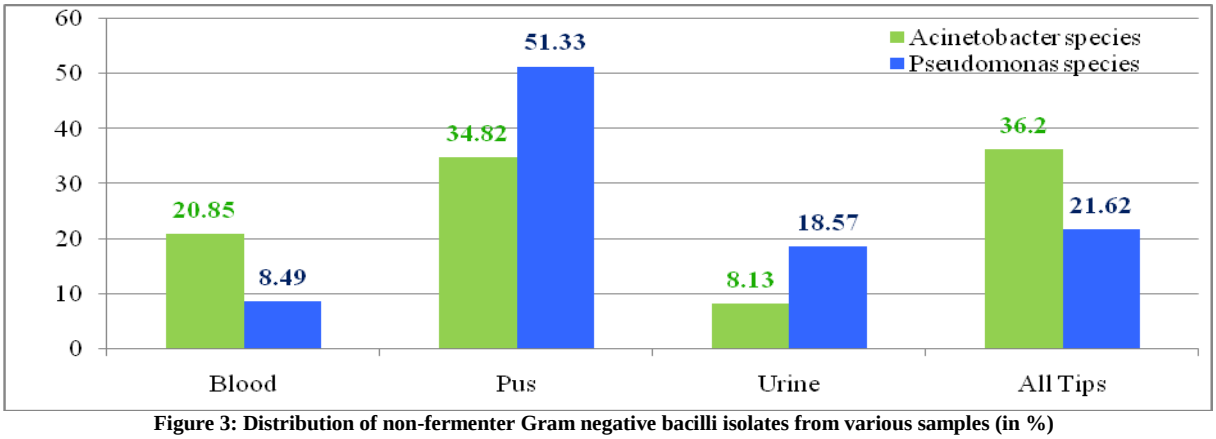

Figure 3: Distribution of non-fermenter Gram negative bacilli isolates from various samples (in %)

Amongst the fermenters analyzed, distribution of *Enterobacter* spp reveals 15.02%, 43%, 34.81% & 7.17% in blood, pus, urine and all types of tips respectively. Presence of *Escherichia coli* was found to be 7.51%, 17.23%, 72.22% & 3.04% in blood, pus, urine and all types of tips respectively. *Klebsiella* spp was found positive in 14.60%, 18.87%, 44.39% & 22.14% of blood, pus, urine and all types of tips respectively. While *Proteae* family was positive in 2.68%, 54.79%, 33.33% & 9.20% in blood, pus, urine and all types of tips respectively (Figure 4). When the distribution of all the organisms was analyzed in relation to the specimens, with a p value of <0.001, a strong association was observed.

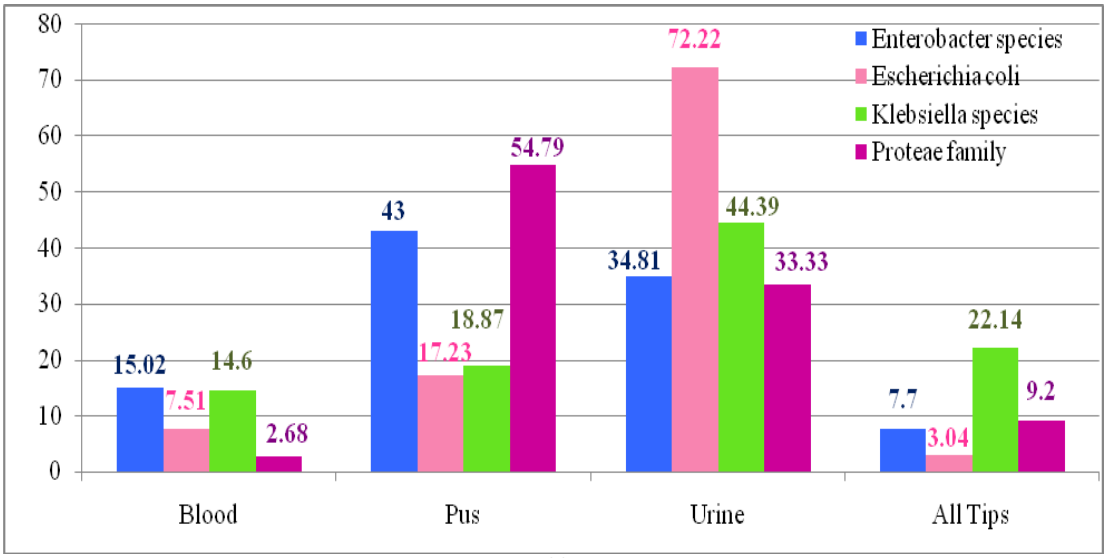

Figure 4: Percentage wise distribution of fermenter Gram negative bacilli isolates

Amongst the Gram positive cocci, *Staphylococcus aureus* was present in 13.45%, 75.89%, 5.08% & 5.58% of blood, pus, urine and all types of tips respectively. While *Enterococcus* spp was found in 16.08%, 17.95%, 62.63% & 3.34% of blood, pus, urine and all types of tips respectively (Figure 5).

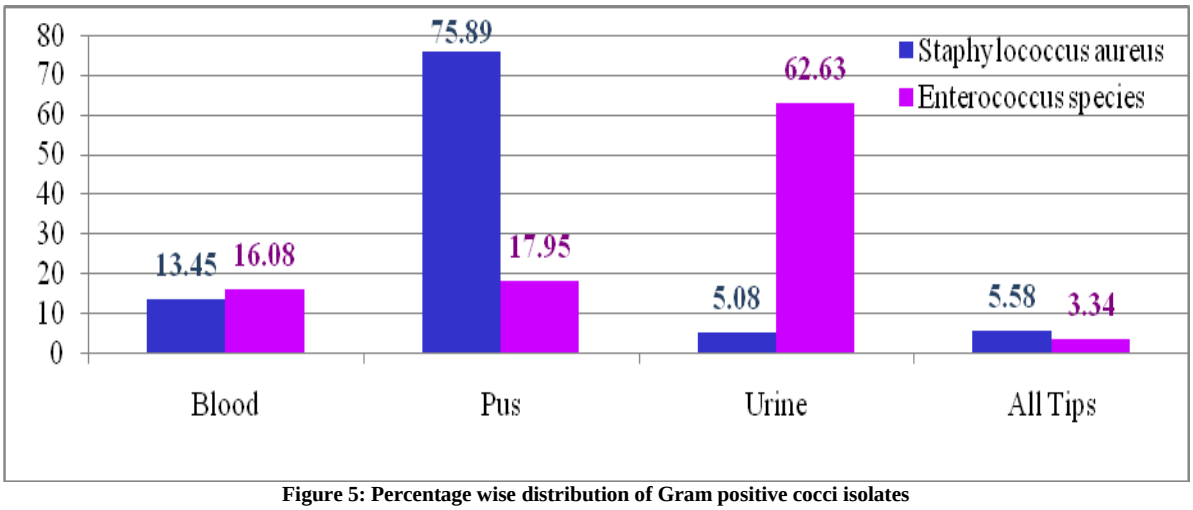

Figure 5: Percentage wise distribution of Gram positive cocci isolates

When the phenotypic expression of acquired penicillinase enzyme by all Gram negative bacilli (fermenters & non fermenters) and *Staphylococcus aureus* were studied. It was observed that overall 17.36% (1079/6217) of the isolates expressed acquired penicillinase enzyme phenotypically (Table 2).

Table 2. Distribution of phenotypic expression of acquired penicillinase (AP) enzyme by the isolates studied

Organism	Total isolates	AP Positive	AP Negative
Escherichia coli	2635	312	2323
Klebsiella species	1007	126	881
Proteae family	261	78	183
Enterobacter species	293	45	248
Acinetobacter spp	873	100	773
Pseudomonas spp	754	190	564
Staph aureus	394	228	166
Total	6217	1079	5138

The presence of Carbapenemase (+ or - ESBL) in Gram negative fermenters was found to be overall 33.87% (1421/4196) as shown in Table 3. While 56.55% (920/1627) of the Gram negative non fermenters i.e., Acinetobacter spp & Pseudomonas spp expressed Carbapenemase (metallo or OXA) phenotypically (Table 4).

Table 3. Distribution of phenotypic expression of Carbapenemase (+ or - ESBL) enzyme by the Gram negative fermenters studied

Organism	Positive	Negative	Total isolates
Escherichia coli	602	2033	2635
Klebsiella species	595	412	1007
Proteae family	65	196	261
Enterobacter species	159	134	293
Total	1421	2775	4196

Table 4. Distribution of phenotypic expression of Carbapenemase (metallo or OXA) enzyme by the Gram negative non-fermenters studied

Organism	Positive	Negative	Total isolates
Acinetobacter spp	745(85.34)	128(14.66)	873
Pseudomonas spp	175(23.21)	579(76.79)	754
Total	920	707	1627

Figures in parentheses indicate percentage

Expression of ESBL in the Gram negative fermenters (*Escherichia coli*, *Klebsiella* spp, *Proteae* family and *Enterobacter* spp) was further studied and the statistical analysis reveals significant results in all with a p value of <0.001 (as shown in Tables 5, 6, 7, 8). This suggests a strong association between the organism and their phenotypic expression of ESBL. Organisms were further analysed regarding their Phenotypic expression of drug resistance as detected by Vitek 2 Compact system.

Table 5. ESBL expression in *Escherichia coli* isolates (n=2635)

		ESBL	
		Positive	Negative
ESBL (CTX-M like)	Positive	414(54.83)	341(45.17)
	Negative	1520(80.85)	360(19.15)

Figures in parentheses indicate percentage
Chi square=<0.001, significant

Table 6. ESBL expression in *Klebsiella* spp isolates (n=1007)

		ESBL	
		Positive	Negative
ESBL (CTX-M like)	Positive	54(51.92)	50(48.08)
	Negative	125(13.84)	778(86.16)

Figures in parentheses indicate percentage
Chi square=<0.001, significant

Table 7. ESBL expression in *Proteae* family isolates (n=261)

		ESBL	
		Positive	Negative
ESBL (CTX-M like)	Positive	14(22.58)	48(77.42)
	Negative	88(44.22)	111(55.78)

Figures in parentheses indicate percentage
Chi square=<0.001, significant

Table 8. ESBL expression in *Enterobacter* spp isolates (n=293)

		ESBL	
		Positive	Negative
ESBL (CTX-M like)	Positive	22(32.84)	45(67.16)
	Negative	55(24.34)	171(75.66)

Figures in parentheses indicate percentage
Chi square=<0.001, significant

On analysis of phenotypic expression of Gram positive cocci studied, it was observed that *Staphylococcus aureus* expressed 57.87% acquired penicillinase, 45.94% expressed mec A and 7.87% were VRSA. (Figure 6) Amongst the *Enterococcus* species 27.35% expressed Van A type of drug resistance. (Figure 7)

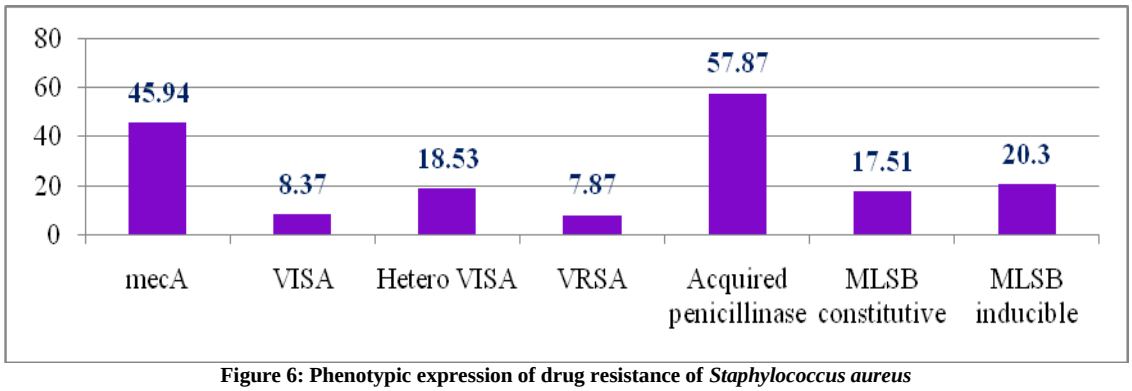

Figure 6: Phenotypic expression of drug resistance of *Staphylococcus aureus*

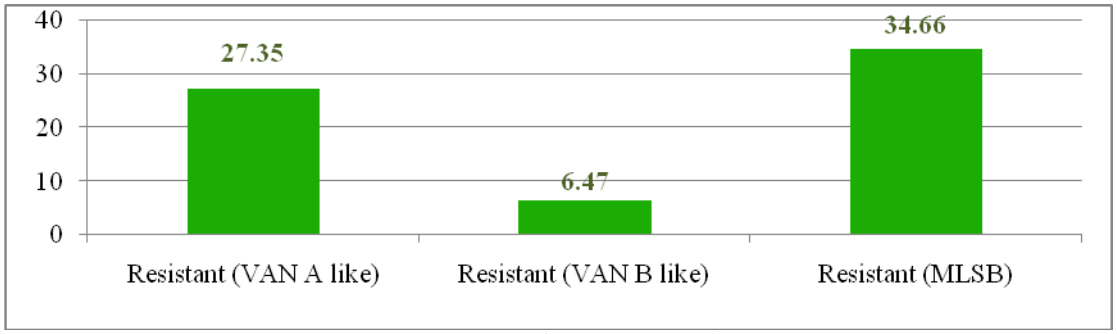

Figure7: Phenotypic expression of drug resistance of *Enterococcus* spp

DISCUSSION

Antibiotics either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defences to eliminate them. [14] Resistance to an antibiotic develops in no time and hence, is a big matter of concern. [2] Extended-spectrum β-lactamases (ESBLs) mediate resistance to all penicillins, third generation cephalosporins (*e.g.* ceftazidime, cefotaxime, ceftriaxone) and aztreonam, but not cephamycins (cefoxitin and cefotetan) and carbapenems. More than 180 different ESBLs have been identified. They are most commonly detected in *Escherichia coli*, *Klebsiella pneumonia* and *Proteus mirabilis*, but have also been found in other *Enterobacteriaceae.* [15,16] The risk of treatment failure with third-generation cephalosporins or with aztreonam is observed in ESBL-producing organisms, even when the strains appear susceptible as per the standard breakpoints. [17]

Enzyme-mediated resistance to carbapenems is due to the production of beta-lactamases that are able to inactivate carbapenems together with other beta-lactam antibiotics and therefore called carbapenemases. [18] This type of resistance is the most important clinically because these enzymes hydrolyze all or almost all beta-lactams, confer high levels of carbapenem minimum inhibitory concentrations (MICs), are encoded by genes that are horizontally transferable by plasmids or transposons and are commonly associated with genes encoding for other resistance determinants. [19] The VanA strains are reported most frequently and exhibit inducible, transferable resistance to vancomycin (MIC 64 −>1000 mg l^{-1}) and teicoplanin (MIC 16–512 mg l^{-1}) associated with a novel 39 kDa cytoplasmic membrane. [3] If *Enterococcus* spp. had not evolved enough strategies to protect them from the action of glycopeptides the emergence of vancomycin-dependence provides a further option. [20]

Resistance rates vary by species; *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas* spp. are invariably more resistant than *Escherichia coli* and *Proteus* spp. Isolates of *Stenotrophomonas maltophilia* and *Acinetobacter* spp. tend to be the most resistant. As with other hospital-acquired infections the resistance data will vary between centre and unit; with patient population and prescribing practices both very relevant. [3]

Though there is no national database on surveillance of use of antimicrobials in the community, there are a few studies in India in this regard. Studies carried out in Delhi and Vellore, with support from World Health Organization during 2003‑2005 suggested a very high use of flouroquinolones in the community as compared to other antimicrobials. Presently there is no national program for prevention of drug resistance and there is inadequacy of quality assured laboratories, insufficient data analysis and dissemination, absence of national guidelines on antimicrobial usage, no control on sale of these drugs for public consumption. [21]

Various strategies can be employed to combat antimicrobial drug resistance such as, establishment of a national alliance against antimicrobial resistance with all key

stake holders as its members. There should be an integrated approach between provider and consumer sides to effectively prevent the antimicrobial resistance. From the provider side policy makers, planners, practitioners and prescribers, pharmacists and dispensers, institution managers, diagnostic and pharmaceutical industries, department of animal husbandry and from the consumer side patients and community is important in this regard. [22]

To control the antimicrobial resistance globally, comprehensive policies on antibiotics use are needed while different countries are at different stages of development of these policies. This could include bringing systematic interventions to educate healthcare professionals about prescribing antibiotics, developing infections control guidelines and keeping a control on the marketing and sales of the antibiotics. Similarly, many hospitals in India have established policies to minimize the surgical infections as patients are directly exposed to the serious antibiotic resistant microbes in health care facilities. [23] Coordinated efforts to implement new policies, renew research efforts & pursue steps to manage the crisis are greatly needed. [24] Another strategy to overcome resistance is to improve the delivery or otherwise enhance the accessibility of antibiotics to their sites of action. [25]

There are three approaches to the problem of bacterial resistance: reduce antibiotic consumption and preserve existing agents, develop new antibiotics, or develop therapeutic strategies for infection that do not involve antibiotics. Where bacterial transmissibility is high the importance of simple infection control measures (e.g. adequate handwashing), rather than antibiotic control, cannot be over-emphasized, although clearly more appropriate to the hospital than community setting. Reducing antibiotic consumption requires first education, then co-operation, of both health care professionals and the public. The development of a new antibiotic may take10 years, will cost several hundred million pounds, and once marketed its commercial success is inevitably compromised with time as target bacteria develop mutations in different genes, each conferring resistance. [3]

CONCLUSION

The study emphasizes on the appropriate knowledge as well as the type of phenotypic expression by bacterial pathogen for anti microbial drug resistance. Such studies when carried out on regular basis could provide data at local and national level, for the rational use of antibiotics and tools for target-oriented infection control-measures. These studies also help in designing antibiotic policies for the hospital especially in ICU settings.

Conflicts Of Interest: None

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