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Is 3rd G Cephalosporin & Carbapenam Antibiotic Weaponry at the Verge of Extinction Evidence Based Medicine

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Global proliferation of antibiotic resistance to microbes is attributed to injudicious use of antibiotics at global, national & local levels. Antibiotic usage has to be rationalized for choice, dose & duration in prophylactic, empirical & therapeutic treatment modalities & antibiotic policies need to be formulated based on evidence based medicine.

Resistance is also on the rise as a result of inadequate infection control practices in the hospitals thus making it mandatory to comply with basic components of an effective infection control program. Topic also needs holistic approach on awareness front on mass, print & electronics for both doctor & patient compliance in sticking to antibiotic policy protocols.

Our antibiotic weaponry in the form of resistance inhibitors and combination therapies are proving a failure with the extensive drug resistance scenario leaving the multidrug resistance part far behind. Culture and sensitivity interpretation redefined. Scientific innovations get modified from time to time& so get interpretations. What is logic today may not be applicable tomorrow. We have to change as per the changing times & keep abreast with latest developments& incorporate need based surveillance and research tools in our systems otherwise wrongs would continue to happen.

Our main antibiotic weaponry such as 3rd generation cephalosporins (ceftazidime, ceftriaxone, cefperazone, cefotaxime to name a few) and carbapenams (imipenum, merpenam, doripenametc) are at a stage of extinction due to the onslaught of extended spectram beta lactamase & metallo β-lactamase enzyme inactivation's by way of hydrolysing their beta-lactam ring & resistance originally remaining confined to few germs started disseminating to others irrespective of gram positive, gram negative cocci or bacilli nature and unfortunately resistance was extended to other antibiotic classes also.

Outbreak producing pathogen such as *MRSA*, *E.coli, Klebsiella, Pseudomonas* and *VRE*, are already causing global havoc with their resistance venom. There is every danger that VISA/GISA (Vancomycin & Glycopeptide intermediate resistant *Staphylococcus aureus*) may be a full-fledged futureVRS (vancomycin resistant *Staphylococcus aureus*) entity.

Organisms such as NDM-1 gene (New Delhi metallo-β-lactamase) found on DNA structures, called plasmids can easily be copied and transferred between bacteria, giving the bug "an alarming potential to spread and diversify & thus major threat shifts toward a broad class of bacteria-including those armed with the NDM-1 gene & which are impervious to almost all antibiotics.

Prime physician guidelines under such scenario consists of reducing inappropriate use of antibiotics, reducing the use of broad spectrum antibiotics & using of narrow spectrum antibiotics whenever possible with more emphasis on patient compliance & increased surveillance along with meticulous infection control practices. Important patient guidelines include not insisting on antibiotics when not needed, taking full course when need arises, keeping a diary of antibiotic use & also not sharing antibiotics with others.

Third generation Cephalosporins & Carbapenams are almost at the stage of extinction as a result of irrational use & faulty infection control practices around the globe. Consequent upon the four research studies done at SKIMS, Kashmir India on Esbl & Mbl assays showed an alarming increase in antibiotic resistance. Results depicted 72% & 60% strains of Hospital acquired *K. pneumonae* & *E.coli* as Esbl positive for Esbl respectively. Also 14% of *P. aeruginosa* proved Mbl producing and thus a direct bearing on the use of 3rd generation Cephalosporins & carbapenams in the area. Technologies to diagnose Esbl & Mbl must be incorporated in diagnostic systems routinely to avoid treatment failures & as such these antibiotics need to be prescribed with utmost caution & require strict physician & patient compliance.

Discussion

Salient features of these researches as evidence based medicine and as such given below depict an alarming increase in antibiotic resistance to 3rd generation cephalosporins and carbapenams in Esbl and Mbl producing bacteria respectively.

Prevalence of ESBL producers in Klebseilla pneumoniae was 71.8% and 27.1% were AmpC betalactamase producers (derepressed mutants). While DDST was able to detect 34.8%, PCCDTs detected 78.3% of Esbl producers. Esbl producers mediated very high resistance to both betalactams and non-betalactams. Prolonged hospital stay and prioruse of 3rd generation cephalosporins were identified as important risk factors for ESBL acquisition.

Isolates of E. coli were obtained from patients admitted or attending Out Patient Department (OPD) over a period of 2 years from 1st August, 2005 to 31st July, 2007. 221 E. coli were subjected to screening by using cefotaxime, ceftazidime and ceftriaxone 30 ug discs. Among them, 211 were screen positive for potential ESBL productions which were furthersubjected to confirmatory tests by phenotypic methods: Double Disc Synergy Test (DDST), Phenotypic Confirmatory Disc Diffusion Test (PCDDT) and E-test. 55.9% (118/211) of E. coli isolates were positivefor ESBL production from different clinical specimens, maximum number being from urine (72.9%). Themaximum number of ESBL producing isolates were from inpatients (71.2%) followed by outpatient (28.8%). Resistance pattern of ESBL positive isolates showed resistance to 3rd and 4th generation cephalosporins (97.5 to 99.2%), quinolones (93.1 to 100%) and aminoglycosides (65.2%) in that order respectively. They showed high degree of sensitivity to

imipenam (98.3%), nitrofurantoin (91.5%), gatifloxacin (64.1%) and amikacin (78.2%).

Metallo-beta-lactamases (Mbl) producing *Pseudomonas aeruginosais* strains are responsible for several nosocomial outbreaks in tertiary care centers across the world. It is well known that poor outcome occurs when patients with serious infections due to Mbl producing organisms are treated with antibiotics to which the organism is completely resistant. Therefore, detection of these Mbl producing *P. aeruginosais* crucial for optimal treatment of critically ill patient's and to prevent the spread of resistance.

Another study was undertaken with the aim of optimizing the choice, dose and duration in Mbl producing *P. aeruginosa* infections in a tertiary care center in Kashmir for various types of treatment modalities. Aims and objectives are now specific and not like introduction. Various clinical samples were obtained from patients admitted in hospital or attending the OPD between January 2007 to June 2008. Antimicrobial sensitivity was performed by Kirby-Bauer disk diffusion method. Minimum inhibitory concentration (MIC) of Imipenem resistant isolates was done by agar dilution method. Metallo-beta-lactamase production was detected by combined disk method, MIC reduction of imipenem in presence of EDTA and by Epsilometer test (E-test). The intergroup comparison and risk estimation was performed by using Fisher's exact test and Odd's ratio. Out of 283 *P. aeruginosa* isolates, 38 (13.42%) were resistant to Imipenem. Thirty three (11.66%) were found to be MBL producers by combined disk test and all of them showed reduction in MIC in the presence of imipenem-EDTA in Etest. The number of Mbl positive isolates from ICU was statistically significant (p=0.027). The hospital stay was significantly longer (p=0.000) among patients infected with MBL producers than MBL non producers.

Statistically significant association of antineoplastic chemotherapy, urinary catherization with Mbl production was found. All MBL producers were resistant to commonly used antibiotics. However, they were sensitive to polymyxinB (100%), piperacillin/tazobactum (18.2%), amikacin and ciprofloxacin (9.1%). MIC reduction is a cumbersome, laborious method and given the cost constraints of E-test a simple screening test like combined disk test may be used. In absence of therapeutic MBL inhibitors, polymyxins, aminoglycoside or fluoroquinolone molecule that may have retained some activity against the isolate may be used for the treatment of MDR *P. aeruginosa* infections.

Research study on MRSA assay showed that 35.1% of *Staphylococcus aureus* and 22.5% of coagulase-negative staphylococcal isolates were resistant to methicillin. Highest percentage of MRSA (35.5%) was found in pus specimens (n=151). The multiple drug resistance of all MRSA (n=180) and Methicillin resistant Coagulase-negative *Staphylococcus aureus* (MRCNS) (n=76) isolates was detected. In case of both methicillin-resistant as well as methicillin-sensitive Saphylococcal isolates zero resistance was found to vancomycin whereas highest resistance was found to penicillin G followed by ampicillin. It was shown that the major reservoir of methicillin resistant staphylococci in hospitals are colonized/infected inpatients and colonized hospital workers, with carriers at risk for developing endogenous infection or transmitting infection to health care workers and patients. The results were confirmed by molecular typing using PFGE by SmaI-digestion.

It was shown that the resistant markers G and T got transferred from clinical *S. aureus* (JS-105) to carrier *S. aureus* (JN-49) and the ciprofloxacin (Cf) and erythromycin (E) resistance seemed to be chromosomal mediated. In one of the experiments, plasmid pJMR1O from *Staphylococcus aureus* coding for ampicillin (A), gentamicin (G) and amikacin (Ak) resistance was transformed into *Escherichia coli*. The minimal inhibitory concentrations (MICs) for A and G were lower in *E. coli* thanin *S. aureus*. However, the MIC for Ak was higher in *E. coli* transformants than in *S. aureus*.

All important aspects of Mbl are deliberated upon in an onlinerecent review article of substance on Metallo β-lactamases role in Pseudomonas resistance to carbapenams from Omar Mukhtar university Albeda, Libya (J Pharm Biomed Sci 2014; 04(05): 382-394.May-20141 and in other recent research studies from Kashmir India by the corresponding author [1-6].

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