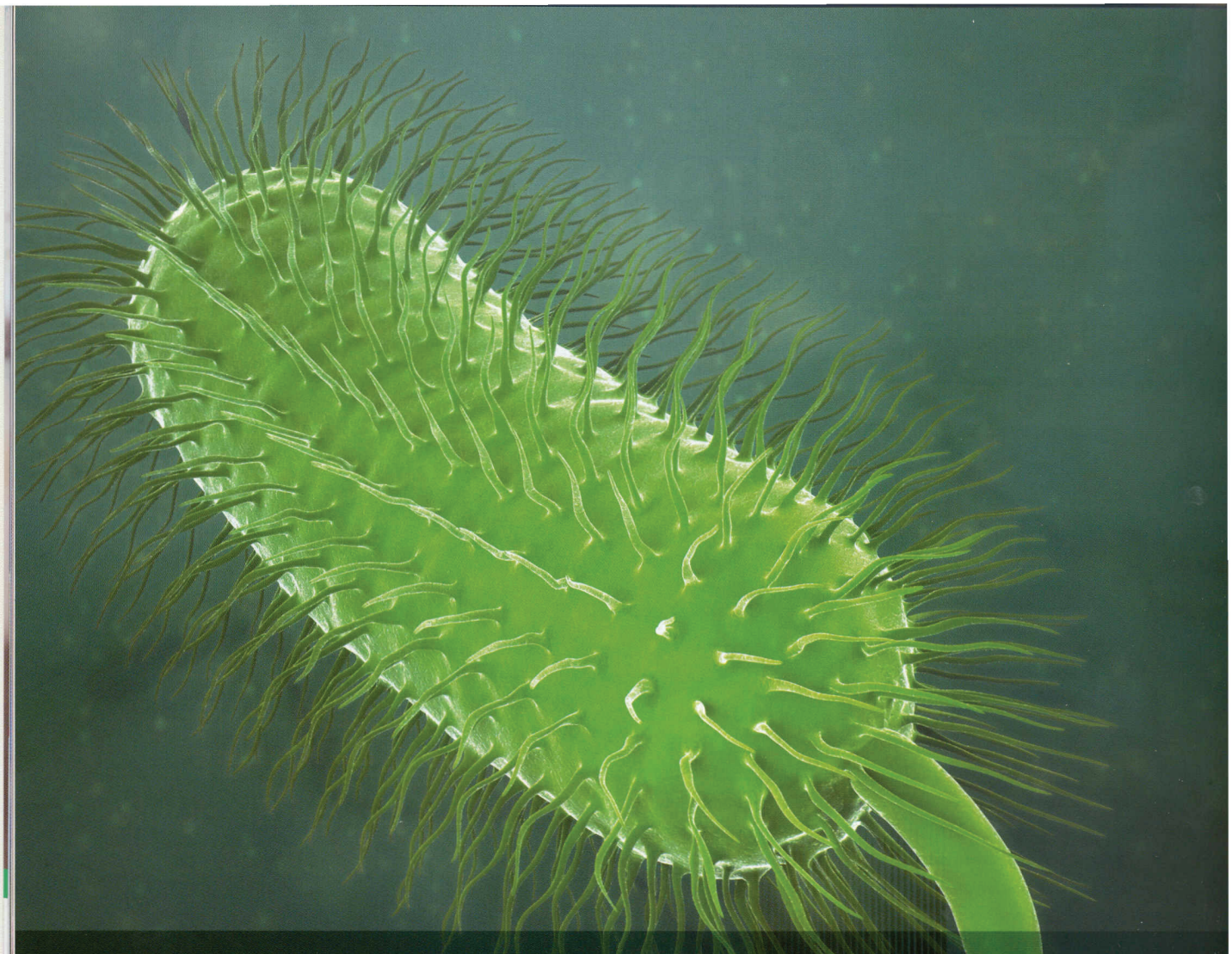

BETA LACTAMASE MEDIATED RESISTANCE IN ENTEROBACTERIAECEAE

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Beta lactam antibiotics form the cornerstone of treatment for a variety of infectious diseases attributed to bacteria. Since β-lactam antibiotics came into clinical use, β-lactamases have coevolved with them. The "new" β-lactamases, include extended spectrum ß-lactamases (ESBLs), plasmid mediated Amp C enzymes and carbapenem hydrolyzing β-lactamases (carbapenemases). With bacteria evolving mechanisms to overcome the effect of these antibiotics chromosomally or through acquisition of plasmids under selective pressure or *de novo*, therapeutic options are declining. The other disturbing feature is the horizontal spread of the resistant genes that can occur between members of the same species and between different species. As a bacterium accumulates varieties of beta lactamases under the 'survival of the fittest' policy, it becomes multi-drug resistant. The recent NDM-1 strain reported in Lancet, is a classic example of how

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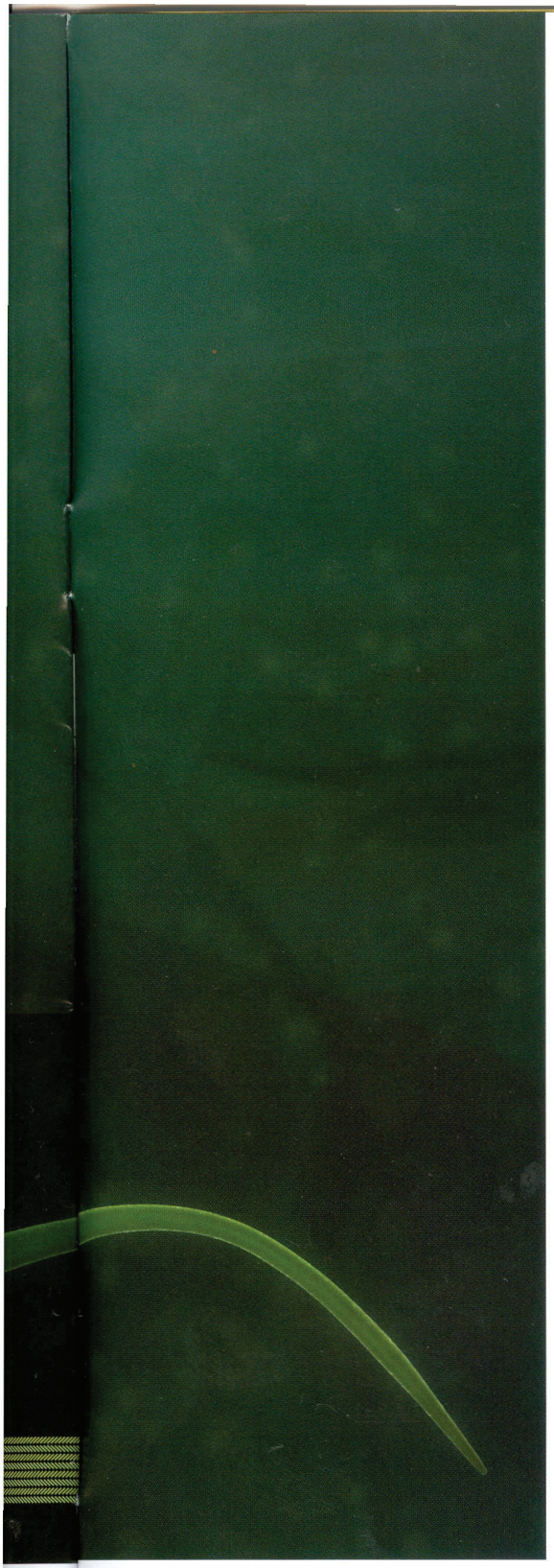

horizontal transfer of resistance gene has rendered Escherichia coli resistant to carbapenems.

One of the major mechanisms by which bacteria render the beta lactam antibiotics ineffective is by the production of beta lactamases. Such enzymes are produced both by gram positive as well as gram negative bacteria. This article focuses on beta lactamases in enterobacteriaeceae. It is to be noted that the same organism can produce more than one type of beta lactamase.

▷ TYPES OF BETA LACTAMASES

Different types of beta lactamases are produced by enterobacteriaeceae.
Each enzyme has a specific substrate (antibiotic) which it renders ineffective.
Chronologically, the serine beta lactamase SHV and TEM arose first in late 1960s, to render ampicillin and similar penicillins ineffective. To increase the spectrum of activity, third generation cephalosporins were introduced in early 1980s. Very soon (1983 - 1988), mutations in SHV and TEM were observed which rendered the organism capable of hydrolysing even the third generation cephalosporins such as cefotaxime, ceftriaxone and ceftazidime. These came to be known as extended spectrum beta lactamases or ESBLs. ESBLs hydrolyse (render ineffective) all third generation cephalosporins and monobactams but have no action on cephamycins. They are susceptible to beta lactamase inhibitors such as clavulanic acid > sulbactum > tazobactam. They are also susceptible to carbapenems. Unless therapy is started early with the right antibiotic, infection with ESBL producing strains are associated with treatment failure and higher rates of morbidity and mortality as compared to the non ESBL producers. Also, ESBL producing strains demonstrate additional resistance to other families of antimicrobials especially fluoroquinolones and varying degree of resistance to aminoglycosides. These strains have currently spread/recognised globally and their prevalence is high and on the rise. Initially recognised in health care settings, such resistance is now being reported even in the community acquired setting making it mandatory for laboratory work up.

The next enzyme to be recognised was CTX-M-1 which specifically hydrolysed Cefotaxime. Subsequently Amp C beta lactamases were recognised. AmpC β-lactamases are cephalosporinases whose preferred substrates are cephalosporins including cephamycins (cefoxitin and cefotetan) and are poorly inhibited by clavulanic acid. Thus, these enzymes have a spectrum similar to ESBL . In addition , they are resistant to beta lactamase inhibitors leaving carbapenems as the only drug of choice for treatment from the beta lactam group. The plasmid encoded Amp C beta lactamases are also being reported from many areas and in many bacterial species. In an organism that carries both ESBL and Amp C enzymes, it has been observed that over production of Amp C Can mask the presence of ESBL during laboratory testing.
For all these resistance mechanisms, risk factors include prior exposure to the same antimicrobial class, prolonged hospital stay, presence of indwelling devices and catheters, and severity of illness.

▷ PREVALENCE OF DIFFERENT STRAINS

The increasing prevalence of ESBL and Amp C producing strains worldwide and the resultant increase in the usage of carbapenems has given rise to carbapenem resistant strains of enterobacteriaeceae especially Klebsiella pneumoniae, Enterobacter cloacae and Escherichia coli, a phenomenon previously restricted only to Pseudomonas and Acinetobacter species. Resistance to carbapenems could be mediated by carbapenemases, metallo beta lactamases, OXA enzymes, through porin loss or increased efflux. Of recent interest are the carbapenemase producing Klebsiella pneumoniae (KPC) and the metallo betalactamase producing Escherichia coli. KPC enzymes are now being recognised in other species as well and being reported from many countries including India. The presence of KPC renders all beta lactams ineffective. Class B Metallo-β-lactamases (MBL) render ineffective carbapenems, penicillins and extended spectrum cephalosporins but not aztreonam.

▷ DRUG RESISTANT STRAINS

Due to the increasing incidence of ESBL producing bacteria, isolation of Multidrug resistant (MDR) strains is becoming a common feature in Intensive care settings. Right selection of antibiotic out of the few available options can be done only by choosing the antibiotic with lowest MIC value, which further would also greatly increase the chances of a successful therapeutic outcome. In this scenario reporting of Antibiotic susceptibility along with the MIC values for the antibiotics becomes extremely important and may be done by highly specialised technologies like using of fully automated ID and susceptibility systems like Vitek and Microscan. These facilities are →

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currently offered by highly specialised and well equipped Microbiology laboratories like Super Religare laboratories which would help the clinician in choosing the right antibiotic with lowest MIC value. Thus reporting of antibiotic susceptibility along with MIC value becomes a superior technique as compared to the traditional Disk diffusion technique.

▷ CONCLUSION

For the clinician, it is imperative to know the effective treatment option for a given patient especially when the patient is seriously ill. The clinical microbiology laboratory has an important role to play in guiding the selection of appropriate antimicrobial for treatment by performing antimicrobial susceptibility tests (AMST) using standard procedures. The recognition of these enzymes is important as each of these hydrolyses different beta lactam substrates leaving few specific therapeutic options. In-vitro testing may reveal an isolate carrying these enzymes as falsely sensitive to the same hydrolysable substrates leading to the choice of erroneous treatment option i.e. an ESBL producing organism can be reported as being sensitive to Cefotaxime if specific tests for detecting these enzymes are not put in routine use. To avoid this, additional antimicrobials need to be tested to detect the presence of these enzymes, thereby inferring resistance to their substrates irrespective of their in-vitro inhibition characteristics. If such an enzyme is detected, irrespective of the in vitro susceptibility test result, the organism should be reported as resistant to all substrates hydrolysed by the enzyme for e.g all cephalosporins upto 3rd generation and monobactams in case of ESBL , all cephalosporins upto 3rd generation and beta lactam beta lactamase inhibitor combinations in case of Amp C and all beta lactams in case of KPC.