

ORIGINAL ARTICLE

SUSCEPTIBILITIES OF ESBL-PRODUCING ENTEROBACTERIAECIAE TO ERTAPENEM, MEROPENEM AND PIPERACILLIN-TAZOBACTAM

Shah Kinal¹, Mulla Summaya A²

¹Consultant Microbiologist, Global Baroda Hospital, Vadodara ²Professor & Head, Department of Microbiology, Government Medical College, Surat

Correspondence:

Dr. Kinal Shah

Email: kvshah81@gmail.com

ABSTRACT

Objectives: The susceptibilities of ESBL-producing *E.coli* and *K. pneumoniae* to ertapenem, meropenem and piperacillin-tazobactam. 53 strains of *E.coli* and *K. pneumoniae* were studied.

Methods: They were originally resistant to ceftazidime. Minimum inhibitory concentration of the strains towards ertapenem, meropenem and piperacillin-tazobactam were determined by Vitek-2 compact system.

Results: The MICs of all ertapenem and meropenem for all isolates were ≤ 0.5 $\mu\text{g/ml}$ and ≤ 0.25 $\mu\text{g/ml}$ respectively and MIC of piperacillin-tazobactam was between 4 to 16 $\mu\text{g/ml}$. ESBL-producing organisms were more susceptible to ertapenem and meropenem. They were susceptible to piperacillin-tazobactam thus in our hospital ertapenem, meropenem and piperacillin-tazobactam are drugs of choice for them.

Keywords: Ertapenem, ESBL, Meropenem, *E.coli*, *K. pneumoniae*.

INTRODUCTION

Production of extended spectrum β -lactamases (ESBL) by gram negative bacteria has become a major issue in the fields of clinical microbiology and infectious disease in past 5 years (1-3). Extensive use of third generation cephalosporins has contributed to the evolution of ESBL (Extended Spectrum β Lactamase). These plasmid mediated group of enzymes are the products of point mutations at the active site of TEM, SHV, OXA enzymes.

Worldwide debate regarding the feasibility of prescribing third and fourth generation cephalosporins for treatment of patients infected with ESBL producing bacteria. Therapeutic options are few and include aminoglycosides, quinolones, piperacillin-tazobactam⁴ and carbapenem⁵.

In order to establish a clinical treatment protocol in our institution we measured the MIC (Minimum Inhibitory Concentration) of Ertapenem & Meropenem and piperacillin tazobactam against ESBL producing strains of enterobacteriaceae.

MATERIALS & METHODS

We compared MIC of Ertapenem, Meropenem and Piperacillin-tazobactam against various ESBL producing gram negative aerobic bacteria.

Laboratory strains of Gram negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) previously shown to produce ESBL were studied. ESBL producer was defined as an organism showing $< 15\text{mm}$ zone of inhibition by disc diffusion towards ceftazidime. Subsequently it was proven to be an ESBL produced by the double disc diffusion method showing an increase of $\geq 5\text{mm}$ in the presence of clavulonic acid. MIC of the laboratory strains were determined by Vitek 2 Compact system against Ertapenem, Meropenem and Piperacillin-tazobactam according to manufacturer's instruction.

RESULT

We studied ESBL producing bacteria isolated from urine, pus, sputum, blood, high vaginal among 53 ESBL producer 26 isolates of *E. coli* and 27 isolates of *Klebsiella pneumoniae*.

Among the antimicrobial agents tested, the three carbapenems: ertapenem, imipenem and meropenem and piperacillin-tazobactam were overall the most consistently active in vitro against *E. coli* and *K. pneumoniae*.

Graph 1 shows susceptibility of *K. pneumoniae* to 18 antimicrobial agents. Graph 2 shows susceptibility of *E. coli* to 18 antimicrobial agents.

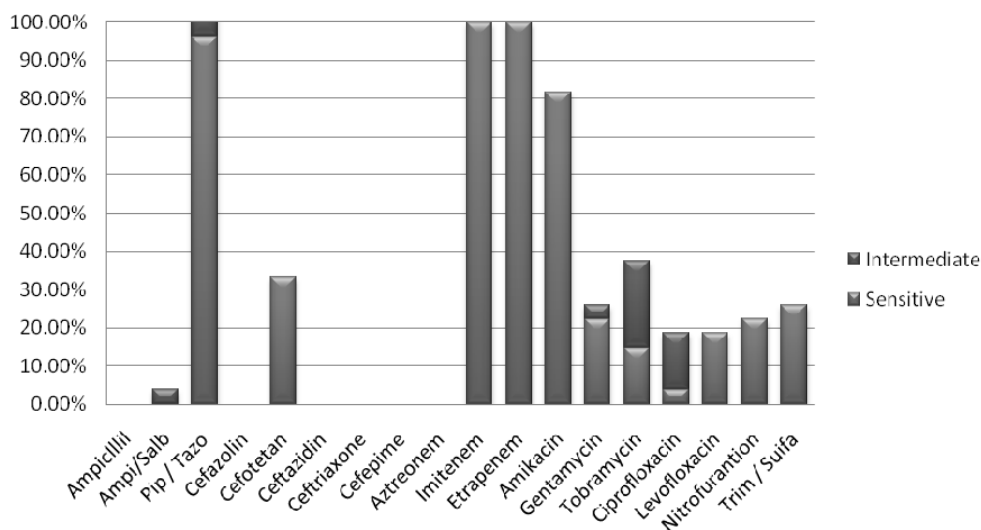


Figure 1: ESBL K. pneumoniae susceptibilities to ertapenem and other antibiotics. (Lighter bar represents percentage of isolates sensitive to antibiotics. Darker bar represents percentage of intermediately sensitive antibiotics.)

The MIC of ertapenem, imipenem and meropenem were ≤ 0.5 , ≤ 1 and $\leq 0.25\mu\text{g/ml}$ and MIC of piperatazabactam was in the range of ≤ 4 to $16 \mu\text{g/ml}$.

In regard susceptibility of ESBL producing organisms to other antibiotic, 3% E.coli and 18.51% K.

pneumoniae are susceptible to quinolone such as levofloxacin, ESBL producing E. coli and K. pneumoniae are 100% and 81.48% sensitive to amikacin (aminoglycoside) respectively. 96.15% and 100% resistance to cefepime respectively and 100% resistant to ceftazidine for all clinical specimens.

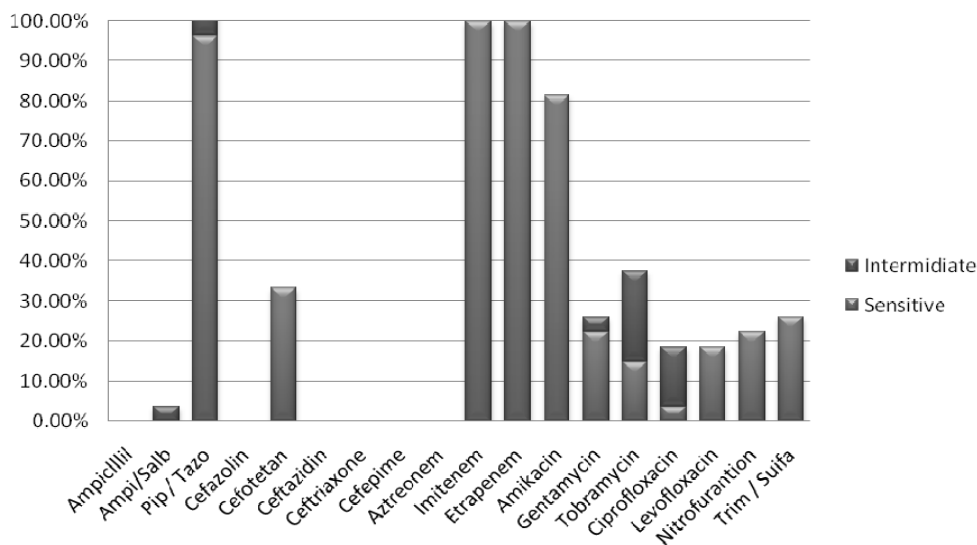


Figure 2: ESBL E.coli susceptibilities to ertapenem and other antibiotics. (Lighter bar represents percentage of isolates sensitive to antibiotics. Darker bar represents percentage of intermediately sensitive antibiotics.)

DISCUSSION

The β -lactamases are a large family of enzymes representing the major mechanism of resistance of bacteria against β -lactam antibiotic. More than 340 β -lactamase enzymes have been detected until 2004 [1,3]. ESBL production by gram negative bacteria has become a major problem in clinical practice in last few years due to extensive use of the β -lactam antibiotic. The chromosomally mediated β -lactamases are

inducible or constitutive non-transferable. The second type of β -lactamases is the plasmid-mediated ESBLs which are constitutively expressed and transferable [3]. Cotransfer of resistance against aminoglycosides, trimethoprim, sulfonamides, tetracyclines, chloramphenicol and quinolones is common on ESBL plasmids.

There is ongoing debate about the optimal treatment of patients infected with ESBL producing bacteria and the

actual in vivo activity of various third and fourth generation cephalosporin antibiotic against these bacteria. A strict recommendation [8] has been published rejecting the use of third and fourth generation cephalosporins against ESBL producing bacteria resulting vastly increased use of carbapenems [2] or non β -lactam agents. Uncomplicated urinary tract infection caused by ESBL producing bacteria could possibly be treated with cephalosporins, as the concentration achieved in urine is very high but this assumption must be clinically evaluated. Cefepime use for systemic infections caused by ESBL producing bacteria may fail [4] due to selection of ESBL producing bacteria during treatment and several studies have documented clinical failures. Therefore cefepime act against ESBL-producing is not recommended unless given in high dose ($\geq 4\text{g/day}$) and combined with aminoglycoside or quinolone [2]. Prospective studies of efficacy of third or fourth generation cephalosporins for such infection will probably never be conducted due to the aforementioned recommendations [8] and would probably even be considered unethical today.

Currently, carbapenems are regarded as the preferred agents for treatment of infection caused by ESBL or AmpC producing bacteria [2,4]. However, chromosomally mediated extended-spectrum serine protease (group 2F) and metallic β -lactamases active against carbapenems are not uncommon. In short, increased utilization of carbapenem against ESBL producing bacteria will possibly lead to improved patient outcome.

In our study, both ertapenem and meropenem showed very low MICs against ESBL producing organisms. We found that piperacillin-tazobactam was also effective against ESBL producers, and its effectiveness is 96.29% for *K. pneumoniae* and 100% for *E. Coli*. These findings correlate to the Asia-Pacific region study [11] reporting that most ESBL strains were still sensitive to piperacillin-tazobactam, but already more resistant to ticarcillin-clavulanate. Thus, in our hospital, tazobactam appears to be much more effective ESBL inhibitor, and piperacillin-tazobactam is becoming drug of choice for infection suspected to be caused by ESBL-producing bacteria. Piperacillin tazobactam is cost effective than carbapenem. So, here in our Hospital it has become a drug of choice. One should consider it as a better option specially for non affordable patients.

There are several limitations to our study. First, only relatively small number of *E. coli* and *K. pneumoniae* isolated were tested. However, we believe that this number is quite representative of the overall studied

phenomena. We did not test the antibiotics with additional β -lactamase inhibitors or combinations.

CONCLUSION

Meropenem and ertapenem remain good choices for the treatment of infections suspected to be due to ESBL producing *E.coli* and *K. pneumoniae*. Piperacillin-tazobactam also has a very good susceptibility in our study and it is not an effective drug. So, piperacillin-tazobactam can be drug of choice for ESBL producing *E. coli* and *K. pneumoniae*.

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