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Short Communication

ROLE OF CHARACTERIZATION AND EXTENDED SPECTRUM BETA LACTAMASE IN INFECTION MANAGEMENT

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Abstract: Antibiotic resistance is a major problem which the clinicians are facing these days while treating their patients. It is mainly due to beta lactamase production by most of the gram negative bacilli. Beta lactamases produced by gram negative bacilli hydrolyzes most of the cephalosporins and even carbapenums. Clinicians are therefore left with very limited choice. It is seen that antibiotic selection differs with different class of Extended Spectrum Beta Lactamase (ESBL). ESBL can be divided into four classes according to substrate profile and molecular sequencing of the genes. These are designated as A, B, C and D. ESBLs can be characterized by using ceftazidime, combination of ceftazidime plus clavulanic acid, cefoxitin, pipracillin and tazobactum and carbapenums. These help in the selection of appropriate antibiotic. By following this practice it is possible to some extent decrease the problem of treatment failure.

Keywords: ESBL, Resistance, Antibiotics

INTRODUCTION

It is well known that the problem of antibiotic resistance has reached a stage where doctors are left with a very limited choice of antibiotics. This is because of production of a variety of beta lactamases by most of the gram negative bacilli.[1-3] Through our study we have tried to suggest a few options regarding selection of antibiotics. Selection of antibiotic is based on the characterization of beta lactamases which further depend on sensitivity of antibiotics like cefoxitin, pipracillin plus tazobactum and amoxicillin plus clavulanic acid. Emergence of resistance to beta lactam antibiotics began long ago. The first beta lactamase was identified in *Escherichia coli* prior to the discovery of penicillin for use in medical practice.[4] Many genera of gram negative bacilli possess a naturally occurring, chromosomally mediated beta lactamase. These enzymes have been thought to have evolved from penicillin binding proteins with which they show some sequence homology. This development was likely due to selective pressure exerted by beta lactamases producing soil organisms found in the environment.[5]

Over the last twenty years many new beta lactam antibiotics have been developed. One of the new classes was oxyimino cephalosporins which were widely used for treatment of serious infections due to gram negative bacteria in 1980s. Resistance to these extended spectrum beta lactam antibiotic due to beta lactamases developed very quickly. Because of their increased spectrum of activity against oxyimino cephalosporins, these enzymes were called extended spectrum beta lactamase.[6]

Characterization of ESBL:

The majority of ESBLs contains a serine at the extreme site and belongs to Ambler's class A. Class A enzymes are characterized by active site serine and the preferential hydrolysis of penicillin[7]. More recently a classification was devised by Bush, Jacoby and Medeiros that uses biochemical properties of the enzymes plus the molecular structure and molecular sequencing of the genes to place beta lactamases into functional groups.[8] According to this classification ESBLs can be divided into 4 groups and many subgroups. To a large extent it has been possible to find out as to which class particular ESBL belongs. Treatment options are different for different classes of ESBL.

Detection of new beta lactamases:

Detection of extended spectrum beta lactamases is less straight forward than earlier because of heterogeneity of enzyme, presence of multiple beta lactamases in a single organism and their variable

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activity against same substrate. The procedure currently recommended by clinical and laboratory standard institute (CLSI) guidelines, involves an initial disc diffusion screening test with one or more oxyimino beta lactam. It is then followed by a confirmatory test that involves a disc of extended spectrum cephalosporin (ceftazidime or cefotaxime) and its combination with clavulanic acid. A difference in zone of inhibition of 5 mm or more is considered as beta lactamase producing organism.[9-10] So far as detection of different classes of beta lactamases is concerned; there are no specific CLSI guidelines. But it is assumed that ESBLs belonging to class A can be found easily by difference in zones of ceftazidime and ceftazidime plus clavulanic acid.[11] Organisms which show resistance to carbapenums (imipenum and meropenum) are supposed to produce carbapenases and thus belong to group B. The method used for detection of Amp C is to apply cefoxitin disc on sensitivity plate. Any organism that shows resistance to cefoxitin, first, second and third generations of caphalosporins and is sensitive to carbapenums is considered to produce Amp C.[12] Oxa D that belongs to group D can be detected by PCR only but few surrogate markers can be used to identify them. Combination of pipracillin plus tazobactum and ticarcillin plus clavulanic acid are surrogate markers for identification of Oxa D type of ESBL. Organisms showing resistance to these markers are supposed to produce ESBL belonging to class D.

Risk factors for ESBL production:

Risk factors for colonization or infection by ESBL producing organisms are little different from risk factors for other nosocomial infections. Few of them are central venous catheter, emergency abdominal surgery, prolonged hospital and ICU stay, low birth weight, prior use of any antibiotic especially extended spectrum cephalosporin, severity of illness, urinary catheter and ventilator assistance.[13-18] Patients on hemodialysis, diabetes, age more than 65 years, low immunity status, patient on anti-cancer drugs are also under the risk of developing ESBL producing organism. Prescription of undesired, under dose or under scheduled antibiotics by patient's family doctor or private practitioners is also important risk factor of ESBL production and development of resistance. Doctors and paramedics also contribute to development of this resistance by not maintaining the required hygiene. Another common reason is that doctor and nursing staff do not wash their hands while examining different patients. Moreover self-medication by patients and interruption of treatment plays crucial role in development of resistance.

Treatment options:

By analyzing the criteria of identification of beta lactamase using sensitivity disc of cefotaxime, ceftazidime , ceftazidime plus clavulanic acid, cefoxitin, imipenum, meropenum etc. We can have an idea, to which class beta lactamase belongs. In case it belongs to class A, the best option for the treatment will be one of the combination of beta lactam plus beta lactamase inhibitor e. g. cefperazone plus sulbactum , pipracillin plus tazobactum, cefotaxime plus sulbactum and amoxicillin plus clavulanate. [19]Among these combination drugs, the drug having tazobactum as beta lactamase inhibitor is considered the best.

If it belongs to class B which is indicated by resistance to carbapenums, the best treatment option would be tigecycline and colistin, although there are some limitations for the use of tigecycline. It is not effective against *Pseudomonas* and also not recommended for blood infections and lung infections as its concentration is very poor at such places. Colistin belongs to polymyxin group. It is always given with meropenum. Its main function is to increase the permeability of the cell wall and thus facilitates the entry of meropenum.

The best line of treatment for beta lactamases belonging to Amp C is carbapenums. For patients suffering from community acquired infections, ertapenum is the best choice but it is not effective against *Pseudomonas*. For mild hospital acquired infections cefepime plus tazobactum is a good choice while for serious hospital acquired infections, meropenum or imipenum are the best choice[20]. The choice of drug for the treatment of group D class of beta lactamases is only carbapenums. Organisms producing variety of beta lactamases are generally multidrug resistant or pan drug resistant. Infections with such highly resistant organisms can be treated with polymyxin-B.

Outbreak control:

The production of beta lactamase may be of chromosomal or plasmid origin. Plasmid mediated production is often acquired by transfer of genetic information from one organism to another. Such transferable plasmids also codes for resistant determinants to other antimicrobial agents. Hence they are multidrug resistant. Following points should be followed to control ESBL production.

a) An antibiotic policy should be formulated and followed by all hospitals in which after certain time one class of antibiotic should be replaced by other.
b) Infected patients should be isolated to prevent spread of beta lactamase producing organisms.
c) Right and full course of antibiotics should be administered.
d) Patients should be kept in the hospital for a minimum possible period to avoid colonization of ESBL production.
e) Catheterization should be for as less time as possible.

CONCLUSION

ESBLs are now a big problem for public health that threatens the life in hospitalized patients all over the world and also increases the cost of health care. Gram negative bacteria have adapted to broad spectrum beta lactam antibiotics with help of these enzymes. Their prevalence is often underestimated because detection in clinical laboratories is inadequate.

There are no beta lactams in development that can treat infections with organisms producing some of the new beta lactamases. Antibiotics need to be used judicially. The guidelines regarding the use of antibiotics have emerged as a potentially effective means of both, avoiding unnecessary antibiotic administration and increasing the effectiveness of prescribed antibiotics. If antibiotics are given according to different classes of ESBL, risk of treatment failure can be reduced to a substantial extent which in turn will reduce the cost of treatment and development of resistance.

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