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Increasing Prevalence of Extended Spectrum Beta Lactamase Producing Microorganisms: A review

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ABSTRACT

The development of antibiotic resistance in various species of bacteria following introduction of antimicrobial agents has emerged as an important medical problem everywhere in the world including India. Extended spectrum beta lactamases (ESBLs) are rapidly evolving group of beta lactamase enzymes produced by the Gram negative bacteria. Beta-lactam antibiotics are the largest and most commonly used group of antimicrobial agents world-wide. They show very good tolerability and many of the drugs can be administrated orally. Bacteria expressing extended-spectrum beta-lactamases (ESBLs), enzymes hydrolyzing penicillins and cephalosporins, may not respond to therapy using some of these antibiotics. These enzymes are found most commonly in the *Enterobacteriaceae* family, and organisms that produce ESBLs are often resistant to non-beta lactam antibiotics, such as fluoroquinolones and aminoglycosides, by additional mechanisms, thus further limiting treatment options. At present, ESBLs has been increasing as a serious nosocomial and community pathogen having the property multidrug resistance. It is a great challenge for clinician to treat these bacterial infections. There was a limited number of drugs sensitive for these bacteria, the only drug of choice is imipenem, followed by amikacin in injectable form. But most probably in near future, if this irrational use is not stopped, infection with that Gram negative bacteria increase the rate of resistant to drugs that are now sensitive, resulting increase morbidity and mortality. Infection-control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria specially ESBLs efficiently to minimize the spread of these bacteria and help to select more appropriate antibiotics.

Key words: Antimicrobial agents, Prevalence, Resistance pattern

INTRODUCTION

Antimicrobial agents are one of the most commonly prescribed groups of drugs for treating various infectious diseases. Bacterial resistance to antimicrobial treatment is emerging as one of the global public health treats at the beginning of the 21st century. The wide spread use and in sometimes the misuse of antibiotics in all healthcare facilities over the past several decades has been regarded as the contributing factor in the development of resistance.

Extended Spectrum Beta Lactamase (ESBLs) are enzymes produced by certain bacteria that can make them resistant to certain antibiotics. The main mechanism of bacterial resistance to Beta lactam class of antibiotics is the production of Beta lactamase, which can hydrolyze these antibiotics before they reach the penicillin binding protein located at the cytoplasmic membrane. These enzymes produce resistance to a variety of ß-lactam antibiotics including extended spectrum penicillins, 3rd generation cephalosporins and monobactams. They are often shows cross resistance to many other classes of antibiotics such as fluoroquinolones and aminoglycosides by additional mechanisms.

Resistance pattern vary internationally, and even locally, from one institution to the other. The frequency of ESBL producing organisms differs significantly in accordance with geographic location. It is important to know the national and also the local institutional prevalence in order to adjust antimicrobial therapies and try to avoid a further increase in rate. [1]

HISTORY

The most common plasmid-mediated ß lactamase is TEM-1, which has been reported in about 75-80% of plasmid mediated ß lactamase resistance. The TEM enzyme was originally isolated from a single strain of *Escherichia coli* from the blood culture of a patient, in Greece in 1965. Following this, the TEM-1 ß lactamase spread worldwide throughout the family *Enterobacteraceae.*

Over the last 20 years, many new ß lactam antibiotics have been developed that are specifically designed to be resistant to the hydrolytic action of beta lactamases. However, increasing use of these agents has been associated with the emergence of resistant bacterial strains with mutated beta lactamase. The first mutated form of beta

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lactamase, SHV-2 was isolated from a clinical strain of *Klebsiella ozaenae* in Germany in 1983. At present, over 150 different ESBLs have been described. [3]

TYPES OF ESBL:

Most ESBL derivatives are TEM and SHV enzyme types and are mostly found in *Klebsiella pneumoniae* and *Escherichia coli*. A total of more than one fifty different enzymes are included in both groups together. Recently other types of ESBLs are detected in *Klebsiella oxytoca, Proteus mirabilis* and other genera of *Enterobacteriaceae.* There is a considerable geographic difference in the prevalence of ESBL in different countries. CTX-M type, a new family of plasmid mediated ESBLs with increased activity against cefotaxime, has been widely spread over many parts of the world including Europe and other continents in the last few years. [3]

OXA type enzymes are another growing family of ESBLs. They have been predominantly found in *Pseudomonas aeruginosa* isolates from Turkey and France. Another type PER type beta lactamase was first discovered in strains of *Pseudomonas aeroginosa* isolated from patients in Turkey. In addition to the above mentioned groups, newer enzyme groups have been isolated. Recently, VEB, GES and KPC series of enzymes have been described in multi-resistant organisms such as *P. aeruginosa* and *A. baumanii*. Different enzymes differ in their ability to hydrolyze different antibiotic substrates and present different behaviors in terms of laboratory detection.[4]

EPIDEMIOLOGY:

Epidemiology of ESBLs genes are rapidly changing and shows marked geographic differences in distribution. The prevalence of ESBLs in Europe is higher than in the USA but lower than in Asia and South America.

A study performed in Turkey showed and prevalence of 21% ESBL producers among *E coli* causing community acquired urinary tract infection during 2004-2005. In Italy, the prevalence of ESBL producers among clinical isolates has also increased over the past ten years. The prevalence of ESBL over 10% in Hungry, Poland, Russia and Turkey. Asia probably has a long history of the occurrence of extended spectrum beta lactamase producing bacteria. Both India and Pakistan have reported high rates of ESBLs since the 1990s. There were several studies in India in 2002, 2007, 2008 were 60%, 46.5, and 51.4% in *E coli* respectively. [3, 5]

RISK FACTORS FOR ACQUIREMENT:

Several case control studies have evaluated the risk factors colonization or infection with ESBL producing organisms in hospitalized patient. Various risk factors have been implicated in the selection and spread of ESBL producing strains.

Reported risk factors include advanced age, patient's previous comorbidities (such as neoplasia, renal failure, immunosuppression, etc), presence of central venous or arterial catheter, gastrostomy or jejunostomy tube, urinary catheter, emergency intra-abdominal surgery, GI colonization, prolonged ICU or hospital stay, prior antibiotics, number and duration of antibiotic therapy probably most important factor, prior nursing home stay, severity of illness and ventilator assistance. In general it is well accepted that 3rd generation cephalosporins are strong inducers for the appearance of ESBL outbreaks in hospital and long term care facilities. [3, 6]

LABORATORY DETECTION:

The methods for detection of ESBLs can be broadly divided into two groups. Phenotypic methods that use non molecular techniques, which detect the ability of the ESBL enzymes to hydrolyze different cephalosporins; and genotypic methods, which use molecular techniques to detect the gene responsible for the production of ESBL.

The phenotypic tests for ESBL detection involve screening and confirmatory steps. The screening step consists of testing for resistance to cefpodoxime, cefotaxime, ceftazidime, ceftriaxone or aztreonam. The confirmatory step is based on the demonstration of synergy between the above agents and clavulanic acid. Several methods including the double disc synergy test, the combination disc method, or specific ESBL E test can be used in this regard.

The genotypic for the detection of ESBL consists of polymerase chain reaction. Additional molecular techniques, such as sequencing or restriction fragment polymorphism, are required for the identification of specific point mutation. The genotypic methods have advantage of identification of the specific type of ESBL present in the micro-organisms, which may be useful for epidemiological purposes. They can be performed without prior culture of microorganism, so that they can detect low level resistance. [5]

CLINICAL SIGNIFICANCE OF DETECTING ESBLs:

It is increasingly being recognized that the production of ESBLs is becoming an important public health issue with regards to the community and healthcare setting. These resistant organisms are clinically important because it will results in increased morbidity and mortality. ESBL producing bacteria are frequently resistant to many classes of antibiotics, resulting in difficult to treat infections. Other problem due to ESBL producing bacteria include the difficulty in detecting the presence of ESBLs, limited treatment options, and a deleterious impact on clinical outcome. Clinicians should be familiar with the clinical significance of these enzymes and potential strategies for leading with this growing problem. Unfortunately, the laboratory detection of ESBLs can be complex and sometimes misleading. The antibacterial choices are often complicated by multi drug resistance. [5, 9]

TREATMENT:

ESBLs are enzymes capable of hydrolyzing penicillins, broad-spectrum cephalosporins and monobactams. The presence of ESBLs complicates the selection of antibiotics, particularly in patients with serious infections such as bacteremia. The reason for this is that ESBL producing bacteria are often multi drug resistant to various antibiotics, and CTX-M producing isolates are co-resistant to the

fluoroquinolones.[7] Antibiotics that are regularly used for empirical therapy of serious community-onset infections, such as the third-generation cephalosporins (eg, cefotaxime and ceftriaxone), are often not effective against ESBL-producing bacteria. Empirical therapy is prescribed at the time when an infection is clinically diagnosed, while the results of cultures and antimicrobial susceptibility profiles are awaited. Infections caused by ESBL-producing organisms faces a challenge while selecting an empirical regimen to treat the infection; these agent should have adequate activity against the infecting organisms. Empirical antibiotic choices should be individualized based on institutional antibiograms.[8]

Beta lactam /Beta lactamase inhibitor combinations

As ESBL producing Enterobacteriaceae are frequently susceptible in vitro to Beta lactam/ Beta lactamase inhibitor combinations, it is logical to assume these combinations would also be clinically effective.[10]

Carbanepem

Carbapenems (e.g., imipenem, meropenem, ertapenem) are considered as the drug of choice for treating the ESBL producing bacteria. [11]

Fluoroquinolones

If there is in vitro susceptible to ciprofloxacin, a satisfactory clinical response can be achieved by using quinolones. [11]

Tigecycline

Tigecycline, a derivative of minocycline, first member of the glycycline class of antibiotics available for clinical use and it is a potent broad spectrum antibiotic. Detailed data on the antimicrobial activity of Tigecycline against ESBL-producing Enterobacteriaceae are reported in the literature studies. *In vitro* data supports the notion that tigecycline can be considered an alternative to Carbapenems for treatment of infections due to ESBL-producing *Enterobacteriaceae*. However, clinical experience with Tigecycline is still evolving. [12]

Fosfomycin

Fosfomycin tromethamine is a soluble salt of fosfomycin with improved bioavailability over fosfomycin. It inactivates the enzyme pyruvyl transferase, which is required for the synthesis of the bacterial cell wall peptidoglycan. [12] The excellent *in vitro* activity of fosfomycin against ESBL-producing *E. coli* and *K. pneumoniae* strains has been recently reported. Further studies are required to assess the efficacy of fosfomycin for the treatment of UTIs caused by ESBL producing enterobacteria.

Colistin

Although once considered a toxic antibiotic, clinicians have now turned to colistin as a last resort agent for the treatment of infections caused by multidrug resistant gram negative bacteria. The antimicrobial target of colistin is the bacterial cell membrane, where the polycationic peptide ring interacts with the lipid A of Lipopolysaccharides, allowing penetration through the outer membrane by displacing Ca + and Mg + . Insertion between the phospholipids of the cytoplasmic membrane leads to loss of membrane integrity and to bacterial cell death. [12] The cephamycins, including cefoxitin and cefotetan, are stable to hydrolysis by ESBL producing *Enterobacteriaceae*. However, there is a general reluctance to use these agents because of the relative ease by which some isolates may decrease the expression of outer membrane proteins, thus creating resistance to these agents during therapy. [12]

CONCLUSION:

The increasing prevalence of ESBL producing organism, particularly the *E coli and K. pneumoniae*, make the infections caused by these pathogenic microorganism an important public health concern. ESBL producing organisms pose challenges to treating clinicians, clinical microbiologist, infection control professionals and also to scientist who engaged in finding new antibacterial agents. Antibiotic resistance is predominantly caused by the over use or improper use of antibiotics. The development and spread of ESBL is most likely caused by over use of expanded spectrum cephalosporins in hospital setting. The regular introduction of newer antibiotic classes over the years has partly masked the problem of increasing resistance. However now the pipeline of newer antibiotics is nearly empty, therefore we need to preserve the currently available antibiotics for use by future generations. With this in mind, the early detection of ESBL strains and judicious use of antibiotics and proper implementation of infection control strategies are essential to prevent the spread of this thread in the community. Infection control practices should focus on preventing the main modes of patient to patient transmission via colonization of inanimate environment, the hands of healthcare personals and medical equipments.

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