Extended Spectrum Beta-Lactamase: Mode of Action, Classification, Prevalence, Diagnosis and Treatment

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Abstract
Antibiotic resistance among infectious pathogens is emerging world-wide especially in hospitals and community setting causing variety of infections. These bacteria adopt various strategies to counter the effects of antibiotics and their impact on acquisition in all geographical area has enhanced burden in health care units. Hence a thorough investigation of their prevalence with expeditious diagnostic testing and the feasible modification is required for discovery and design of new antimicrobial agents. Beta-lactamases are enzymes produced by bacteria that breakdown the widely used antibiotics called the beta-lactams. Production of Extended-Spectrum β-lactamases (ESBLs) by infections organisms highlights the struggle for new drug development. Clinicians, microbiologists, infection control practitioners, and hospital epidemiologists are concerned about ESBL-producing bacteria because of the increasing incidence of infections, the limitations of effective antimicrobial drug therapy, and adverse patient outcomes. The present review contributes to the increased understanding of the epidemiology of ESBL producing organisms, resistance mechanism, resistance genes/ enzymes involved their types, diagnosis and treatment.

INTRODUCTION

Antibiotic resistance is an inevitable scientific concern both in hospital and community settings. Resistance of pathogenic organisms as a consequence of indiscriminate utilization of antibiotics in human medicine, agriculture and veterinary has contributed to global problem with major penalty on the treatment of infectious diseases. Resistance to antibiotics can occur through a number of mechanisms: I. Permeability changes in the bacterial cell wall. II. Active efflux of the antibiotic from the microbial cell. III. Enzymatic modification of the antibiotic. IV. Degradation of the antimicrobial agent. V. Acquisition of alternative metabolic pathways VI. Modification of antibiotic targets. VII. Overproduction of the target enzyme.

Beginning with the introduction of "penicillin" half a century ago, the beta-lactams are the most widely used and have remained as the largest antibiotic class of clinical relevance representing morethan 60% usage in human and animal medicine. Beta lactam antibiotics are the antibiotics with β-lactam nucleus in their molecular structure. They include penicillins, cephalosporins, carpapenems, monobactam, and β-lactam inhibitors. They are common antibiotics active against wide range of gram positive and negative bacteria with their ability to impede enzymes responsible for peptidoglycon layer synthesis. It binds to penicillin-binding proteins (PBPs) in bacteria and interferes with the structural crosslinking of peptidoglycans and prevents terminal transpeptidation in cell wall, finally resulting in cytolysis or death due to osmotic pressure [1]. The core compound of penicillin, 6-aminopenicillanic acid (6-APA) is used as the main starting point for the preparation of numerous semi-synthetic derivatives. Carbapenems including Imipenem and meropenem are considered as broad spectrum β-lactam antibiotic because they diffuse easily in bacteria. Monobactams do not contain a nucleus with a fused ring attached, but still belong to the group of β-lactam antibiotics by inhibiting cell wall synthesis. The β-lactamase inhibitors, like clavulanic acid, contain the β-lactam ring, but they exhibit negligible antimicrobial activity and are preferred in combination with β-lactam antibiotics to overcome resistance in bacteria that secrete β-lactamase, which otherwise inactivates most penicillins. The β-lactamase inhibitors can be classified as either reversible or irreversible. Irreversible including clavulanic acid, sulbactam, and tazobactam which are more effective causing destruction of enzymatic activity [2].

However, emergence of resistance to these agents in the past two decades has resulted in a major clinical crisis.

Resistance mechanisms against β-lactams

Bacterial resistance against β-lactam antibiotics is increasing at a significant rate and has become a common problem in clinical settings. Continuous exposure to β-lactam antibiotics has resulted in mutation of β-lactamase which has mounted resistance gene even against newly developed β-lactam antibiotic [3]. There are several mechanisms involved in resistance to β- lactam antibiotics. The most common are expression of β-lactamases, as extended-spectrum β-lactamases (ESBLs), plasmid-mediated AmpC enzymes, and carbapenem-hydrolyzing β-lactamases [4,5].

Resistance through extended spectrum β-lactamases

Production of extended-spectrum β-lactamases (ESBLs) is a major mechanism of resistance to β-lactam antibiotics. ESBLs are group of enzymes that can breakdown and thus inactivate a particular group of antibiotics called beta-lactam example cephalosporins, carbapenems and monobactams. They are defined as species with b-lactamase that are generally acquired and are able to confer resistance to oxyimino-cephalosporins (but not carbapenems), as compared with native member of its genetic family. Certain pathogenic strain harbor genes encoding transmissible beta-lactamases that can be exchangeable between bacteria. Bacteria harboring these enzymes not only hydrolyze beta-lactam agents but also display resistance to other unrelated antimicrobial agents and thus often pose a therapeutic dilemma. ESBLs have been isolated from the upper respiratory tract, vaginal swabs, and stools and anal or rectal swabs. Extended spectrum beta lactamase (ESBL) producing Enterobacteriaciae was first described in 1980's in Europe, which has emerged as serious nosocomial pathogens [6]. Although these enzymes occur predominantly in *Klebsiella* species and *Escherichia coli*, they have been encountered in other gram negative bacilli as well [7].

Earlier, b-lactamases were designated by the name of the strain or plasmid that produced them, later they were named after substrates, biochemical properties, sequence, location of their discovery, location of the gene on the chromosome, strains of bacteria, the patient providing a sample, and, the investigators who described them. For example; ABA: derived from *Acinetobacter baumannii*; BES: Brazil extended spectrum; CARB: Active on ceftazidime; CKH: inventors, Chieko Kunuguta and Akio Hyodo; L-1: Labile enzyme from *Stenotrophomonas*; LAT: Named after patient; MIR: found at Miriam Hospital. The β-lactamase family is also classified based on functionality or molecular characteristics. Based on biochemical parameters, β-lactamases are classified into four groups; Groups1, 2, and 4 are serine-β-lactamases, while members of group3 are metallo-β-lactamases [8]. Based on molecular characteristics, i.e., amino acid homology, β-lactamases have been divided into four major groups: Ambler classes A–D, which correlate well with the functional scheme but lack details concerning the enzymatic activity. Ambler classes A, C, and D include the β-lactamases with serine at their active site, whereas Ambler class B β-lactamases are all metallo-enzymes which require zinc as a metal cofactor for their catalytic activities [9].

Resistance gene detected in ESBLS

The first plasmid-mediated β-lactamase, TEM-1, was described in the early 1960s in Gram- negatives. Currently over 1,150 chromosomal, plasmid, and transposon located β-lactamases are well studied [9]. Based on their activity to hydrolyze a small number or a variety of β-lactams the enzymes can be subdivided into narrow, moderate, broad, and ESBLs. The ESBLs are resistance to β-lactam antibiotics penicillins, cephalosporins (first, second, and third generation) and aztreonam, but not to carbapenems and are inhibited by β-lactamase inhibitors. Plasmid- encoded classC β-lactamases or AmpC determinants, like *bla*CMY have also caught people's awareness [5]. Furthermore, in the past decade CTX-M enzymes have become very prevalent ESBLs, both in nosocomial and in community settings [10].

In time course, the parent enzymes *bla*TEM-1, *bla*TEM-2, and *bla*SHV-1 have under gone amino acid substitutions (point mutations) evolving to the ESBLs, starting with *bla*TEM-3 and *bla*SHV-2 [11]. Additional mutations at critical amino acids important for catalysis have resulted in over 140 currently known SHV and TEM ESBL variants. β-lactamase of TEM-type, SHV-type, and CTX-M-type are common in *E. coli* which facilitate in dissemination of resistance in different epidemiological settings [12]. ESBL genes,

including blaCTX-M, blaTEM, and blaSHV, were detected in *E. coli* isolated from chicken farms and live-bird markets located in Northeast China and few strains co-harboring CTX-M-1 group and CTX-M-9 group genes [13]. He et al., [14] have isolated *E. coli* from feces of a diseased pig and chicken which carried blaCTX-M-123 on IncI1 plasmids.

Carbapenem resistance of ESBL-positive *K. pneumoniae* isolates is due to loss of porin channels proteins for antibiotic uptake (OmpK35 and/or OmpK36) along with the expression of AmpC blactamases or expression of carbapenemases [15].

Classification of ESBL

β-lactamase are broadly classified into two classes [8], namely

(1) Amber molecular classification based on protein homology: Class A, C and D which are serine b-lactamase and Class B are metallo-b-lactamases.
(2) Bush-Jacoby-Medeiros functional classification based on function

SHV-type: The SHV-type are the predominant ESBLs type that are found in clinical isolates. SHV refers to *s*ulf*h*ydryl *v*ariable. SHV-1 confer resistance to broad-spectrum penicillins such as ampicillin, tigecycline and piperacillin but not to the oxyimino substituted cephalosporins [16] and are responsible for upto 20% of the plasmid-mediated ampicillin resistance in *K. pneumoniae* species [17]. Various clinical isolates inclusing *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter* spp. are know to harbor SHV-1 type [18,19]. In addition to SHV-1, SHV-2 have also been identified which differ from SHV-1, by replacement of glycine by serine at the 238 position. Within 15 years of the discovery of this enzyme, organisms harboring SHV-2 were found in every inhabited continent, implying that selection pressure from third-generation cephalosporins in the first decade of their use was responsible [20].

TEM-type: TEM-type is capable of hydrolyzing penicillins and first generation cephalosporins but is unable to attack the oxyimino cephalosporin. The TEM-type ESBLs are derivatives of TEM-1 and TEM-2. TEM-1 was first reported in 1965 from *Escherichia coli* isolated from patient in Athens, Greece, named Temoneira [21]. TEM-1 is able to hydrolyze ampicillin at a greater rate than carbenicillin, oxacillin, or cephalothin. It is inhibited by clavulanic acid. Recently, a potential peptidomimetic *Salmonella typhi* β-lactamase TEM1 inhibitor has been identified and according to docking and molecular simulation studies it has been shown that the mimic inhibitor binds more tightly to the active site of receptor than the peptide [22]. TEM-2 has similar hydrolytic profile as TEM-1, but differs from TEM-1 by having native promoter and difference in isoelectric point (5.6 compared to 5.4). *Klebsiella oxytoca* harboring a plasmid carrying ceftazidime resistance gene, was first isolated in Liverpool, England, in 1982 which is termed as TEM-12. Over the years, morethan 100 TEM-type β-lactamases have been described, with their isoelectric points ranging from 5.2 to 6.5. In recent decade, mutants of TEM β-lactamases are being recovered that maintain the ability to hydrolyze third-generation cephalosporins. These are referred to as complex mutants of TEM (CMT-1 to -4) [23,24]. A unique TEM-derived enzyme, TEM-AQ, has been found in Italy [25]. This enzyme has an amino acid deletion not seen in other TEM enzymes plus several amino acid substitutions.

CTX-M and Toho β-Lactamases

The name CTX reflects the potent hydrolytic activity against cefotaxime. They are reported to be originated from *Kluyvera* spp [9]. Additionally, it has been isolated from *Salmonella enterica* serovar, Typhimurium, *E. coli* and some other species of *Enterobacteriaceae* [26]. Organisms producing CTX-M-type β-lactamases typically have cefotaxime MICs in the resistant range of >64 µg/ml. Some CTX-M-type ESBLs may actually hydrolyze ceftazidime and confer resistance to cephalosporin (MICs as high as 256 µg/ml) [27]. In certain cases, the same organism has been found to harbor both CTX-M-type and SHV-type ESBLs or CTX-M-type ESBLs and AmpC-type β-lactamases, which may alter the antibiotic resistance phenotype. A chromosomally encoded β-lactamase gene of *Kluyvera georgiana* with ESBLs, KLUG-1, has been identified which shares 99% amino acid identity with CTX-M-8 [28]. The natural CTX-M enzymes of *Kluyvera ascorbata*, designated as KLUA, are clustered in the CTX-M-2 group [29]. The KLUA-2 enzyme is identical to CTX-M-5 enzyme characterized in a *Salmonella enterica* serovar Typhimurium strain [30]. CTX-M-type β-lactamases have 40% or less identity with TEM and SHV-type ESBLs. The number of CTX-M-type ESBLs is rapidly expanding. Classification of CTX-M type is presented in table 1.

Toho-1 and Toho-2 are structurally related to CTX-M-type β-lactamases. (Toho refers to the Toho University School of Medicine Omori Hospital in Tokyo, where a child was hospitalized who was infected with Toho-1 β-lactamase- producing *Escherichia coli*.) Like most CTX-M-type β-lactamases, the hydrolytic activity of the Toho-1 and Toho-2 enzymes is more potent against cefotaxime than ceftazidime [31].

Table 1: Classification of CTX-M Enzymes based on amino acid sequence similarities

Sl. No	Type	Plasmid-mediated Enzymes	Reference
1	CTX-M-1	CTX-M-1, CTX-M-3, CTX-M-10, CTX-M-12, CTX-M-15, and FEC-1	[32-34]
2	CTX-M-2	CTX-M-2, CTX-M-4, CTX-M-4L, CTXM-5, CTX-M-6, CTX-M-7, CTX-M-20, and Toho-1	[30,35]
3	CTX-M-8	CTX-M-8	[36]
4	CTX-M-9	CTX-M-9, CTX-M-13, CTX-M-14, CTX-M-16, CTX-M-17, CTX-M-19, CTX-M-21, CTX-M-27, and Toho-2	[31, 37-39]
5	CTX-M-25	CTX-M-25 and CTX-M-26	GenBank accession numbers AY157676 and AF518567

The members of each group share >94% identity, whereas ≤90% identity is observed between the members belonging to distinct groups

OXA-type: They are β-lactamases that are able to hydrolyze oxacillin. They are predominant in *Pseudomonas aeruginosa* [40] and about 1-10% of *E. coli* isolates have been known to harbor this gene. These β-lactamases are characterized by hydrolysis rates for cloxacillin and oxacillin greater than 50% that for benzylpenicillin [8]. In general most OXA-type β-lactamases are unable to hydrolyze cephalosporins to a significant degree, however OXA-10 hydrolyzes (weakly) cefotaxime, ceftriaxone, and aztreonam, giving most organisms reduced susceptibility to these antibiotics. Other OXA ESBLS include: OXA-11, -14, -16, -17, -19, -15, -18, -28, -31, -32, -35, and -45. These confer resistance to cefotaxime and sometimes ceftazidime and aztreonam [41,42]. The simultaneous production of a carbapenem-hydrolyzing metalloenzyme and an aztreonam hydrolyzing OXA enzyme can readily lead to resistance to all β-lactam antibiotics [42]. The evolution of ESBL OXA-type β-lactamases from parent enzymes with narrow spectra has many parallels with the evolution of SHV- and TEM-type ESBLs. Unfortunately there are very few epidemiological data on the geographical spread of OXA-type ESBLs.

PER type: PER-1 β-lactamase harbouring strains can hydrolyzes penicillins and cephalosporins but are susceptible to clavulanic acid. It was first reported in *Pseudomonas aeruginosa* and later in *Salmonella enteric* and *Acinetobacter*. PER-2, a variant of PER-1 has been detected in *S. enterica* serovar Typhimurium, *E. coli, K. pneumoniae, Proteus mirabilis,* and *Vibrio cholerae* O1 El Tor [43]. They share only around 25 to 27% homology with known TEM- and SHV-type ESBLs [44]. In Turkey, as many as 46% of nosocomial isolates of *Acinetobacter* spp. and 11% of *Pseudomonas aeruginosa* were found to produce PER-1. Isolates of *Pseudomonas aeruginosa* producing PER-1 have been detected in France, Italy, and Belgium [45, 46]. PER-1 was found in *Proteus mirabilis* and *Alcaligenes faecalis* in Italy [47]. Additionally, a high prevalence of PER-1 in *Acinetobacter* spp. from Korea has been noted [48].

Other ESBLs: A variety of other β-lactamases which are plasmid-mediated or integron-associated class A enzymes have been discovered [49,50]. VEB-1, BES-1, SFO-1 are some of the unusual enzymes having ESBL [11].

VEB-1 (Vietnamese extended spectrum beta-lactamase) was first detected in *E. coli* isolated in a French hospital from the pus of a 4-month old Vietnamese boy in 1996. VEB-1 display high-level resistance to ceftazidime, cefotaxime, and aztreonam, which is reversed by clavulanic acid. The gene encoding *VEB-1* was found to be plasmid mediated; which also confer resistance to non-β-lactam antibiotics and it has 38% homology with PER-1 and PER-2. An identical β-lactamase has also been found in *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter sakazakii*, and *Pseudomonas aeruginosa* isolates in Thailand. In China, it found in 11.4% of *Pseudomonas aeruginosa* isolates [51].

GES-1 (Guiana Extended-Spectrum-β-lactamases) was initially described in *K. pneumoniae* isolated from a neonatal patient from French Guiana. GES types are reported increasingly for Gram negative rods, including *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*. GES-1 possesses a hydrolysis profile similar to that of other clavulanate inhibited Ambler class A ESBLs, including activity against penicillins and broad-spectrum cephalosporins, with higher activity against ceftazidime than against cefotaxime. Also, GES-1 spares cephamycins and carbapenems and is inhibited by clavulanate, tazobactam, and imipenem [49]. However, unlike most ESBLs, GES-1 does not hydrolyze monobactams. GES-2, which differs from GES-1 by a single Gly170Asn substitution located inside the Ω-loop of the catalytic site [37]. A Gly170Ser change was identified in GES-4, GES-5, and GES-6 and resulted in carbapenem and cephamycin hydrolysis. GES-9 differs from GES-1 by a Gly243Ser change, which has an activity against monobactams. GES-11, differs from GES-1 by two amino acid substitutions, including the Gly243Ala change, and possesses increased activity against aztreonam.

Other ESBLs include SFO-1(*Serratia fonticola*), TLA-1 (TLAhucas), BES-1(Brazilian ESBLs) and BEL-1 (Belgium ESBLs). SFO-1 was detected in *Enterobacter cloacae* isolated from Japan in 1988, it hydrolyses cefotaxime very efficiently, ceftazidime poorly, but not cephamycine and cabapenems. It is inhibited by clavulanic acid and imipenem. BES-1 was isolated from *S. marcescens* in a hospital of Brazil in 1996. It confers resistance to aztronem and cefotaxime and its activity is inhibited by clavulanate than by tazobactam. BEL-1 was identified in a *Pseudomonas aruginosa* strain isolated from Belgium in 2004. It significantly hydrolyses most of the extended spectrum cephalosporines and aztronem but not cephamysin or carbapenem. TLA-1 was identified in an *E. coli* strain from patient of Mexico in 1993.

Prevalence of ESBLS

Prevalence of ESBL producing strains varies from one geographical region to another paralleling the indiscriminate utilization of antimicrobial therapy or overuse of beta lactam drugs. Further these bacteria harbor mobile genetic element plasmids that transfer resistance to other bacteria. Until the late 1990s, European surveys on ESBLs found *TEM* and *SHV* enzyme variants while *CTX-M* ESBLs were recorded rarely, although there were large outbreaks of *Salmonella typhimurium* with *CTX-M-4* and *CTX-M-5* enzymes in Latvia [30], Russia and Belarus in the mid-1990 [52]. In France, many types of *CTX-M* enzymes including *CTX-M-1*, *CTX-M-3*, and *CTX-M-14* were detected in six clinical isolates from 1999 to 2000 [53]. In 2003, *CTX-M-15* and *CTX-M-9* were found in *E. coli* isolated from Norway [54], later *CTX-M-15* producing *E. coli* was epidemic in community and hospital infections. The proportion of *CTX-M* producing enterobacteriaceae rose from 0% in 1998 to 58% in 2004 in Austria [55]. There was a large outbreak of ESBL cases in Uppsala involving *K. pneumonia* with CTX-M-15, and in Kristians and caused by a multi resistant CTX-M-15-producing *E. coli* strain [56]. European Antimicrobial Resistance Surveillance System (EARSS) declared 2.6% of *E. coli* and 1.7% of *K. pneumoniae* strains in Sweden were resistant to third-generation cephalosporins in 2010 [57]. Perilli et al [58] have reported *E. coli* and *K. pneumonia* with SHV-12 type in Italy. In Africa, the *CTX-M-15* and *CTX-M-16* producing *E. coli* and *Klebsiella pneumonia* were isolated in Tunisian hospitals between 2000 and 2003 [59]. In United States, the dissemination of ESBL producing *E. coli* rose from 25% to 89% during 2000-2006 and the most common *CTX-M* subtypes were *CTX-M-15*, *CTX-M-16*, *CTX-M-8* and *CTX-M-14* [60].

In Asian countries, the first report on *CTX-M* was from Japan in 1986, when they found a non *TEM* and non *SHV* isolate and it was designated as *FEC-1* under cefotaxime resistant *E. coli* [61]. The prevalence of ESBL producing *E. coli* was 43.2% from clinical samples in Bangladesh [62]. In China, since 1998 several types of *CTX-M* isolated from ESBL producing *E. coli* and *K. pneumonia* were resistant to most antibiotics except for imipenem with *CTX-M-14* genotype being the predominant [63]. Beta lactamases have been isolated from fecal samples in Hong Kong in 2002 with many types including *CTX-M-14*, *CTX-M-24*, *CTX-M-38*, and *CTX-M-9* [64]. According to a report from National public health laboratory, Kathmandu about 31.57% *E. coli* were found to be ESBLs in Nepal [65]. In Thailand many types of *CTX-M* producing *E. coli* including *CTX-M-14*, 15, 27, 40, and 55 have been isolated from health care infections. Beta lactamsase-types including *CTX-M-14*, *CTX-M-27* and *CTX-M-15* producing *E. coli* have been isolated from community acquired urinary tract infection (UTI) in 2004-2005 in Cambodia [66]. The incidence of ESBL producing *E. coli* has increased which include *CTX-M-14*, *CTX-M-15*, *CTX-M-22*, *CTX-M-27* and *CTX-M-57* in Korea during 2007 [67], while in Kuwait the *CTX-M-15* was predominant among hospital and community infections.

In India, the prevalence of ESBL *E. coli* was found to be 14.3% in 2003 and around 63.6% in 2009 [68]. Kumar et al [69] determined the antibiotic susceptibility of respiratory isolates and revealed that sensitivity of pencillin were above the acceptable level. Hafeez et al [70] isolated around 3099 gram negative cultures from different hospitals of Lahore during the period of January 2007 to December 2008, which included samples from urine, wound swabs / pus, sputum, blood, body fluids and bronchial washings. According to the results obtained 1094 (35.5%) bacterial strains were found to be ESBL producers, predominated with *E. coli* (44.8%), and followed by *Klebsiella pneumoniae* (38.6%), *Proteus mirabilis* (31.6%) and *Acinetobacter baumanni*. Rupinder et al [71] observed ESBL production in 48% of *E. coli*, 50% in *P. aeruginosa* and 44% in *K. pneumonia* in the hospital of Patiala, Punjab. According to Perry et al [72] Enterobacteriaceae with NDM-1 type ESBL is prevalent at a rate of 6.9% in hospital of Varanasi and about 18.5% in Rawalpindi, Pakistan. Majda et al [73] noticed 72% of *E. coli* and 65.8% of *K. pneumoniae* were ESBL producers at the Microbiology laboratory of Shalamar Medical College, Lahore. In a study conducted by Shakti et al [74], ICU and NICU isolates were 12.11 and 22.47% ESBL positive respectively. Kaur et al [75] studied the prevalence of AmpC beta lactamase in clinical isolates of *E. coli* isolated from rural hospital wherein 33.78% have been identified as AmpC β-lactamase producers.

Diagnosis of ESBLS

Rapid detection in clinical setup is essential for the authenticated and timely recognition of antimicrobial resistant organisms. The US Clinical and Laboratory Standards Institute (CLSI) and the UK Health Protection Agency (HPA) have published guidelines for ESBL detection in Enterobacteriaceae specifically for *E. coli, Klebsiella* spp., and *Proteus* spp. The HPA guidelines also include other species, such as *Salmonella* spp. They recommend initial screening with either 8 mg/L (CLSI) or 1 mg/L (HPA) of cefpodoxime, 1 mg/L each of cefotaxime, ceftazidime, ceftriaxone, or aztreonam, followed by confirmatory tests (including the E-test ESBL strips) with both cefotaxime and ceftazidime in combination with clavulanate at a concentration of 4 mg/mL. Several recent studies have described various molecular approaches for rapid screening of ESBL positive strain through PCR technique for different genes example blaTEM, blaSHV, blaCTX-M [11, 76]. Duplex PCR, multiplex PCR, real-time PCR have undoubtedly helped in monitoring large number of ESBL producing strains.

Treatment

ESBL producing organisms are responsible for various infections ranging from uncomplicated urinary tract infections (UTIs) to life-threatening sepsis. Therapeutic options available for the treatment of ESBL-associated infections are limited by drug resistance conferred by the ESBLs, along with frequently observed co-resistance to various antibiotic classes including cephamycins, fluoroquinolones, aminoglycosides, tetracyclines and trimethoprim or sulfamethoxazole. Further, the difficulty in diagnosis of ESBL production and inconsistency in reporting has created worst situation on the survey of ESBL producing organisms on a wider geographical scale. ESBL-producing *E. coli* (ESBL-EC) and ESBL-producing *K. pneumoniae* (ESBL-KP) are resistant to penicillins, cephalosporins, and monobactams. The ESBL producers can also confer co-resistance to other classes of antimicrobial agents, such as fluoroquinolones, co-trimoxazole, and aminoglycosides, which are frequently used for UTIs [77]. The carbapenems (imipenem, meropenem, ertapenem, doripenem) are still the first choice of treatment for serious infections with ESBL-producing *E. coli* and *K. pneumoniae*. It has been reported that >98% of the ESBL-producing *E. coli, K. pneumonia* and *P. mirabilis* are still susceptible to these drugs. Fosfomycin could be an alternative treatment option for urinary tract infection (UTI) related to ESBL-producing *E. coli* spp. and community acquired UTI, but not for UTIs related to ESBL producing *Klebsiella* spp [78]. Fosfomycin can inhibit UDP-*N*-acetylflucoamine-3-enol-pyruvyl transferase (MurA), an enzyme catalyzing the early step in bacterial cell wall synthesis. Nitrofurantoin also retains good activity among the multidrug resistant isolates and can be the drug of choice for non-complicated urinary tract infections due to ESBL producing *E. coli* [79].

CONCLUSIONS

In the current situation multidrug resistance has become a worst issue in UTI and has been readily encountered in daily hospital settings. Thus, reasonable measures, such as antimicrobial use and active surveillance programs, should be established to reduce the prevalence and spread of resistant bacteria. The review conclude that medical professionals should be aware of these isolates, should continue strict hygiene procedures and, additionally, should implement an ESBL screening system, in particular for faecal carriage

on haemato-oncological wards with increased use of carbapenems, in order to prevent possible outbreaks caused by these multi-resistant organisms. The review also justifies the need for new drug development to counteract the evolution of resistance in bacteria.

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CONFLIT OF INTEREST
We declare that we have no conflict of interest.

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