International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Extended Spectrum β-Lactamase: Tackling Antibiotic Resistance and Overcoming Treatment Challenges

Leena Muppa[1], Vaishnavi Velmani[2], Nandhani N[2], Vincy Santhana Sophia B[2], Sriram Radhakrishnan[2], Bala Abirami M[2]

[1]Assistant professor, Clinical Pharmacy Department, C.L. Baid Metha College of Pharmacy, Affiliated to "The Tamil Nadu Dr. MGR Medical University," Chennai, India.

[2]Pharm .D. Intern, Department of Pharmacy Practice, C.L. Baid Metha College of Pharmacy, Affiliated to "The Tamil Nadu Dr. MGR Medical University," Chennai, India.

ABSTRACT: Antibiotics, also known as antibacterials, kill or inhibit bacterial growth but are ineffective against viruses, fungi, or parasites, often leading to misuse. They are categorized by molecular structure, mode of action, and spectrum of activity. Antimicrobial Resistance (AMR) occurs when pathogens no longer respond to antimicrobial drugs, arising naturally or through acquisition. Resistance mechanisms include enzymatic (most common), genetic and physical. Bacteria produce various β-lactamases, such as Extended Spectrum β-lactamases (ESBLs), AmpC enzymes, and carbapenemase to exert resistance to Beta-Lactam (βL) class of antibiotics. ESBL families include TEM, SHV, and CTX-M, with E. coli being the most prevalent host. Any Gram-Negative Bacteria (GNB) can be an ESBL producer, but most common ones are the Enterobacteriaceae including Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca and Proteus mirabilis. ESBL-producing Enterobacteriaceae (ESBL-E) resist penicillin, aztreonam, and cephalosporins except cephamycins and carbapenems, posing a significant public health risk. Genetic resistance mechanisms involve random mutations and horizontal gene transfer through either of the following processes namely conjugation, transformation, transduction. Physical mechanisms include efflux pump production and decreased porin channels. In some microbiological laboratories, ESBL production are often not determined, rather resistance based on MIC values to third generation Cephalosporins are considered as resistance due to ESBL production. Antibiotic use in agriculture and medicine has increased Multi-drug resistant (MDR) ESBL-producing E. coli and evidenced in retail meat and among meat shop employees. Community-acquired ESBL-E infections are a growing concern, with hospital transmission primarily occurring among patients sharing rooms with ESBL carriers. Empirical and definitive therapies for ESBL-E infections must be adjusted based on Antibiotic Susceptibility Testing (AST). The MERINO trial identified urinary tract infections as the most common source of ESBL-E bacteremia, with E. coli being predominant. For critically ill patients with non-urinary tract infections, Meropenem or Imipenem-cilastatin are recommended. For uncomplicated UTIs, Nitrofurantoin, Cotrimoxazole, and Piperacillin-Tazobactam (Pip-Taz) are effective, while Cotrimoxazole, Fluoroquinolones, and Ceftolozane-tazobactam are suitable for complicated UTIs. New β-lactamase inhibitors like avibactam, vaborbactam, and relebactam are promising for treatment. Misuse of antibiotics, such as inappropriate dosing and duration, contributes to AMR, a growing global challenge. Deaths from AMR, estimated at 1.27 million in 2019, could reach 10 million by 2050. ESBLs drive the use of broad-spectrum antibiotics, accelerating resistance development. Inadequate therapy exacerbates infections, leading to prolonged hospital stays, complications, and increased mortality. Balancing new drug development with resistance emergence is crucial to combat AMR.

KEYWORDS: Antimicrobial Resistance (AMR), Carbapenemases, Enterobacteriaceae, Treatment, β -lactamase Enzymes.

1. INTRODUCTION TO ANTIBIOTICS AND AMR

Antibiotics are substances that either kill bacteria (bactericidal) by impairing cell wall synthesis or inhibit their growth (bacteriostatic) by disrupting cytoplasmic membrane, nucleic acid, and protein synthesis and function. Their discovery began with Alexander Fleming's identification of penicillin in 1928, derived from the fungus Penicillium notatum. [(1), (2), (3)]. Antibiotics or antibacterials, are effective only against bacteria and not viruses, fungi, or parasites, leading to misuse for infections they cannot treat. [(4)]. Antibiotics are classified based on their molecular structures, mode of action, and spectrum of activity [(2)]. The common classes of antibiotics are depicted in Table.1

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Table.1 Common classes of Antibiotics with their spectrum, mechanism and mode of action [30,54]

Class	Spectrum of action	Mechanism of action	Mode of action
Penicillin	Narrow/ broad	Inhibits cell wall synthesis	Bactericidal
Cephalosporins	Narrow/ broad		Bactericidal
Carbapenems	Broad		Bactericidal
Glycopeptides	Narrow		Bactericidal
Sulphonamides	Broad	Inhibit dihydropteroate synthase	Bacteriostatic
Macrolides	Broad	Inhibit protein synthesis	Bacteriostatic
Tetracyclines	Broad		Bacteriostatic
Chloramphenicol	Broad		Bacteriostatic
Aminoglycosides	Narrow	Alters permeability, inhibit translation of mRNA	Bactericidal
Fluoroquinolones	Broad	Inhibit bacterial DNA gyrase	Concentration dependent Bactericidal

Antimicrobial Resistance (AMR) results when bacteria and other pathogens not any more respond to antimicrobial drugs. AMR is when a microbe evolves to become more or fully resistant to antimicrobials which previously could treat it [5]. Natural resistance includes intrinsic traits universally shared or induced by exposure to antibiotics. Bacteria can also acquire resistance through mutations or intact gene acquisition [6,7]. It occurs over period through genetic changes in pathogens and accelerated by misuse and overuse of antimicrobials [8].

Certain pathogens are capable to neutralize an antibiotic by modifying its component to render it ineffective. Others are capable to export the antibiotics from the pathogens, and some can alter their external structure and receptors to prevent antibiotics attaching to them. These mechanisms might lead to few pathogens surviving the use of the specific antibiotic and developing a resistance that maybe passed to new pathogens as they multiply [9]. A well-known example of a bacterium that is resistant to a number of antibiotics is methicillin-resistant Staphylococcus aureus (MRSA) [5]. The emergence and spread of AMR due to the production of β-lactamases, major defence of Gram-negative bacteria (GNB) against BL antibiotics i.e. penicillins, cephalosporins, carbapenem etc. Bacteria responded with an excess of new β-lactamases including Extended Spectrum βlactamases (ESBLs), plasmid-mediated AmpC enzymes and carbapenem hydrolyzing β-lactamases (carbapenemases) [6].

2. AMR CAUSED BY ESBLs

ESBLs are produced by specific bacteria called ESBL-producing bacteria which enable those bacterial cells to be more resistant to antibiotics and therefore are harder to treat [10]. ESBLs produced by GNB like Enterobacteriaceae, hydrolyze BL antibiotics but are inhibited by β-lactamase inhibitors (BLIs) such as clavulanic acid, sulbactam, and tazobactam. These enzymes, encoded by genes often found on plasmids or transposons, confer resistance to penicillin, aztreonam, and various cephalosporins but not to cephamycins or carbapenems. They also contribute to widespread development of resistance to aminoglycosides, trimethoprim, sulphonamides, tetracyclines, chloramphenicol, and fluoroquinolones. [11]. The ESBL-producing K. pneumoniae that was isolated from nosocomial infection patients in a prior investigation revealed significant rates of resistance to ciprofloxacin (86.2%), tetracycline (80.9%), and nalidixic acid (78.7%) [10,12].

2.1 Current status

A major problem that India is dealing with is the superbugs that are resistant to antibiotics. The increasing prevalence of these infections that are resistant to drugs presents a significant risk to public health.

2.1.1 Global Scenario: A report from the medical publication "The Lancet" highlights a critical issue: in 2019, antibiotic resistance led to 1.27 million deaths globally. The rise of resistant bacteria has diminished the effectiveness of several widely used antibiotics.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Particularly concerning is the emergence of multidrug-resistant infections, such as those caused by Acinetobacter baumannii. This resistance trend is notable even among broad-spectrum antibiotics, which make up 75% of all prescriptions in Indian hospitals [13].

2.1.2 Indian Scenario: India, a major global hub for antibacterial research, faces widespread AMR. With 1.4 billion people, around 18% of the world's population, and many living in poverty, the impact is severe. [14]. Approximately 60,000 infants in India die annually from antibiotic-resistant neonatal illnesses. The Indian Council of Medical Research (ICMR) reports that resistance to carbapenems, essential for treating severe ICU infections like sepsis, has increased by up to 10% in one year [13].

3. ESBL PRODUCERS, CLASSIFICATION, EVOLUTION AND ITS FAMILIES

3.1 ESBL producers

Nosocomial pathogens such as Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species produce Extended-Spectrum Beta-Lactamases (ESBLs) [11]. These enzymes confer resistance to most Beta-Lactam (βL) antibiotics by hydrolyzing them, rendering them ineffective [15]. Among GNB species harboring ESBL genes, E. coli is the most prevalent host, followed by K. pneumoniae. The most dominant variant of ESBL-producing E. coli is the ST131 clone. [11]. Bloodstream infections (BSI) caused by E. coli are found in both community and hospital settings. K. pneumoniae is commonly noted for causing urinary tract infections (UTIs), septicemia, and pneumonia. [10].

3.2 Classification of ESBL enzymes

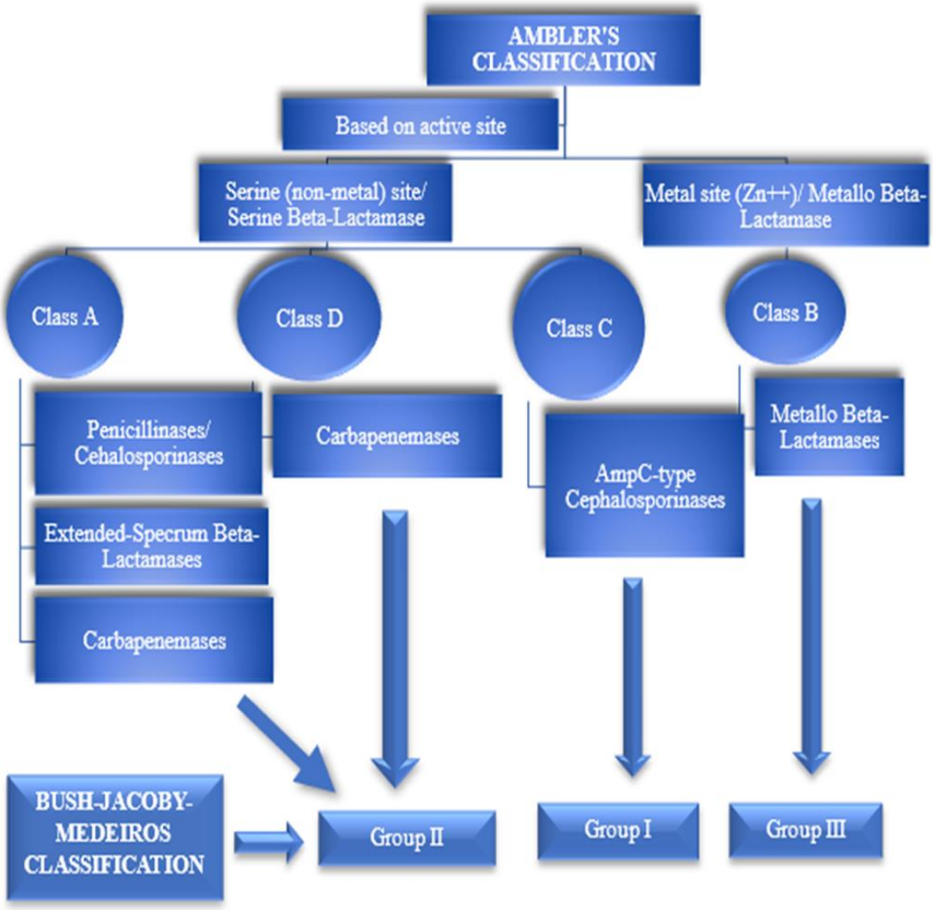

Figure.1 Classification of ESBLs [11]

ESBL are structurally and functionally mutated variants of β-lactamases [11]. β-lactamases are classified by molecular structure using the Ambler system and by function using the Bush–Jacoby–Medeiros system. Among the four Ambler classes (A, B, C, and D),

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

classes A, C and D use serine as the enzyme active center. [16]. According to the Bush–Jacoby–Medeiros system, β-lactamases are classified into groups 1 to 3, along with several subgroups, on the basis of lysis of BL substrates and the effects of inhibitors. [11]. Most ESBL belongs to $ESBL_A$ group, which includes several types of sulfhydryl reagent variable (SHV) β-lactamases, Temoniera (TEM) β-lactamases, and cefotaxime-M (CTX-M) β-lactamases [17].

3.3 Evolution of ESBL enzymes

ESBL evolution involves plasmid-located genes, enabling rapid adaptability and proliferation. Since the first clinical isolates in Germany in 1983, over 100 ESBL variants have emerged across nine structural families. Selective pressure from all antibiotics drives this diversity. The TEM and SHV enzymes, derived from penicillinases TEM-1, TEM-2, and SHV-1, have mutated to enhance their ability to hydrolyze broader spectrum of BL by altering the enzyme's structure to increase the substrate-binding site [11, 18].

3.4 ESBL Families

The various families under ESBL β-Lactamases with their nomenclature names and characteristics are depicted in Figure.2. Based on mutation at different levels, the resistance pattern varies among various ESBL families.

Family	Nomenclature	Characteristics
TEM	Temoneira, the patient infected with the first isolate expressing TEM-1	Point mutation variants of TEM-1 or TEM-2
SHV	Sulfhydryl reagent variable	Point mutation variants of SHV-1
IRT	Inhibitor-resistant TEM	TEM variants that are resistant to inhibition by clavulanate and sulbactam, but do not have ESBL phenotype
CMT	Complex mutant derived from TEM-1	TEM variants that are resistant to inhibition by clavulanate and sulbactam and also have ESBL phenotype
CTX-M	Cefotaxime-hydrolysing β-lactamase isolated in Munich	Derived from the chromosomal β-lactamase from *Kluyvera* spp. Preferentially hydrolyses cefotaxime
GES	Guiana-extended spectrum	More prevalent in *P. aeruginosa* than Enterobacterales Some variants also hydrolyse carbapenems
PER	*Pseudomonas* extended resistant	More prevalent in *P. aeruginosa* and *A. baumannii* than Enterobacterales Inhibition by newer β-lactamase inhibitors is variable
VEB	Vietnam extended-spectrum β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime Inhibition by newer β-lactamase inhibitors is variable
BEL	Belgium extended β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
TLA	Named after the Tlahuica Indians (Mexico), from whom the first isolate was obtained	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
SFO	From *Serratia fonticola*	Inducible
OXY	From *Klebsiella oxytoca*	Chromosomally encoded

Figure.2 ESBL Families with their characteristics [23]

4. MECHANISMS OF RESISTANCE

Resistance to BL is commonly caused by GNB. At a rate of around 1 in 10^8 per chromosomal replication, unlinked point mutations and horizontal gene transfer in the pathogen genome can both lead to antibiotic resistance [19].

4.1 Enzymatic mechanisms of resistance

The primary mode of resistance in GNB is through β-lactamase production. These enzymes cleave the BL ring present in antibiotics, preventing them from binding to bacterial Penicillin Binding Proteins (PBPs) and thus rendering drugs ineffective against Enterobacteriaceae. Example: Resistance of E. coli to BL [20].

B-lactamase enzymes classified under Ambler's classification are produced by GNB, either individually or in combination, to develop resistance against BL antibiotics. These enzymes include ESBLs, penicillinases, cephalosporinases, carbapenemases,

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Metallo-β-Lactamases (MBL), and Amp-C type cephalosporinases. They are located on either the chromosome or plasmid, facilitating rapid spread of resistance. Representative enzymes include TEM-1, SHV-1, IMP, VIM, OXA, and CTX-M [21].

4.2 Genetic mechanisms of resistance

4.2.1 Antibiotic resistance via mutations

Bacterial mutation rate is crucial in resistance development due to their rapid replication and single chromosome structure. Mutations, including point mutations and gene duplication, amplify resistant gene copies. For instance, mutations in DNA-topoisomerase and RpoB genes confer resistance to fluoroquinolones and rifampicin, respectively [22].

4.2.2 Antibiotic resistance via horizontal gene transfer

Horizontal transfer of genetic material is the primary mechanism by which antibiotic resistance spreads. Resistance genes can disseminate through transformation, transduction, and conjugation processes. Transposons, such as Tn1, Tn2, or Tn3, play a key role in carrying and spreading genes encoding TEM-type β-lactamases. Both chromosomes and plasmids facilitate the dissemination of genes encoding SHV-type β-lactamases. CTX-M type β-lactamases are most commonly associated with conjugative transmission [23]. The spread of antibiotic-resistant genes has been discovered to be significantly influenced by five kinds of integrons: intI1, intI2, intI3, intI4, and intI5[24]. Initially, identified in E. coli, CTX-M-15 is now prevalent in other Enterobacteriaceae. It is commonly associated with uropathogenic ST131 lineage. This enzyme is often carried on IncFII plasmids, associated with mobile genetic element (MGE) IS26 [25].

4.3 Physical mechanisms of Resistance

4.3.1 Antibiotic Inactivation

Drugs can be evinced inactive by bacteria in two major ways: by physically breaking down the medication or by adding a chemical group to the drug. Tetracycline is being used as another medication it can be evinced inactive by hydrolyzation through the tetX gene [26][27].

4.3.2 Target Modification

However, since the relationship among an antibiotic and its target is so accurate, even slight alterations to the target structure can have a direct effect on the antibiotic's affinity to bind to it [19].

4.3.3 Efflux Pump

Bacterial transport proteins are also known as efflux pumps and it is involved in the expulsion of substrates from inside cells into the surrounding environment [28]. Bacteria have five different class of efflux pumps: ATP binding cassette (ABC) (*ii*) small multidrug resistance family (*iii*) multidrug and toxin extrusion (MATE) family (*iv*) major facilitator superfamily (MFS) (*v*) resistance nodulation cell division (RND) family. Overproduction of efflux pumps expels drugs from cell interior rapidly [29].

4.3.4 Permeability of Outer Membrane

Drug molecules can enter a cell by three ways: Diffusion via porins, diffusion across the bilayer, and self-uptake. GNB's outer membrane has porin channels. Only porins allow the tiny hydrophilic compounds, such as quinolones and BL, to pass through the outer membrane. Fewer porin channels cause resistance. Example: Pseudomonas aeruginosa resistance to imipenem due to OprD gene [30].

5. RISK FACTORS AND MODE OF TRANSFER OF ESBL VARIANTS

5.1 Risk Factors

One of the main reasons which causes an increasing public health concern is the Community-acquired ESBL-E infections. Possible community sources may include foodstuffs and colonisation resulting from Travelling abroad, may be also related with community-borne illnesses [31]. Patient care may be built up by identifying predicted risk factors. The following are risk factors for ESBL infection: Haemodialysis, intravascular catheter usage, and also extended hospitalization are risk factors for hospital-borne infection and colonization with ESBL producers in the human population [32]. Primary risk factor for the nosocomial transmission of an ESBL-producing infection is that staying in a hospital or room with other patients who have ESBL-producing organisms.

5.2 Mode of Transfer of ESBL Variants

Through contact with contaminated water and dirt, transmission of ESBLs can be done and it mainly occurs in cases when animal or human faeces have polluted water or soil.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Antibiotic Pressure: Antibiotic use in agriculture and medicine affects bacterial populations, promoting the persistence and spread of resistance. CTX-M, a key ESBL type from K. pneumoniae and E. coli, spreads via MGE throughout bacterial communities. Pets and horses are significant reservoirs for CTX-M-15-producing human ST15 and ST101 K. pneumoniae clones [33]. Commonly, E. Coli isolates from humans and animals were found to have the blaCTX-M-1 encoding IncI1 plasmids. There have been observations of ESBL-E obtained from farmers and animals (poultry, pigs) [34] and it shows that there is an increased frequency of MDR ESBL-producing pathogenic E. Coli in retail meat items and among retail meat shop employees [35].

6. TREATMENT

ESBLs are enzymes that inactivate and resist some classes of BL only. But most bacteria often develop co-resistance to other BL and non-BL antibiotics by genetic mutations in the gene responsible for its resistance. So, the drug of choice must depend on several factors. In some microbiological laboratories, ESBL production are often not determined, rather resistance based on MIC values to third generation Cephalosporins are considered as resistance due to ESBL production [36]. But the mechanism of resistance can be either enzymatic or non-enzymatic [37]. There these reports result in false conclusions. Any GNB can be an ESBL producer, but most common ones are the Enterobacteriaceae including Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca and Proteus mirabilis [36]. Not only the definitive therapy after Antibiotic Susceptibility Testing (AST) must be changed in case of ESBL-E but also the empirical therapy in patients suspected to have ESBL producers [38]. Infection source control is the adequate measure in some nosocomial infections [39]. The most common source of ESBL-E bacteremia as per the results of the MERINO trial was found to be Urinary Tract (60.9%) with E. coli being more predominant (86.5%) [40].

Treatment depends on types of bacteria, all the drug hydrolyzing enzymes produced by the bacteria, patient characteristics, site of infection, source, severity, drug availability, physician's perspectives etc [41]. Generally, Piperacillin Tazobactam (Pip-Taz), Aminoglycosides, Quinolones and Cotrimoxazole are effective empirical therapy in Urinary Tract Infections (UTI) caused by ESBL-E [38]. The ESBL bacteria can at times be as a colonizer which doesn't require any treatment. The patient will not be actively infected but are able to transmit the infection to others [42]. For an invasive, active infection, in critically ill patients with source other than E. coli or infection other than in urinary tract, the gold standard drug of choice is Meropenem or Imipenem-cilastatin [36, 40]. In case of uncomplicated UTI or cystitis, Nitrofurantoin, Cotrimoxazole and Pip-Taz have a pivotal role, while in complicated UTI or pyelonephritis, Cotrimoxazole, Fluoroquinolones and Ceftolozane-tazobactam are promising drug of choice [23,36,11].

As ESBL producers are resistant to penicillin and some generations of cephalosporins, the use of Beta-lactam and Beta-lactamase inhibitors (BL-BLI) was widely studied as a carbapenem sparing option, which has evidenced to cause higher 30-days mortality rate when compared with Meropenem. While comparing with cefepime, Meropenem has been again found superior even after adjusting the propensity score as the mortality rates associated with cefepime increases with an increase in MIC. Cefepime is less hydrolyzed by AmpC and ESBL and also has increased MIC values because of high inoculum effect and in patients with severe ESBL-E infection it leads to failure of attaining the desired pharmacodynamic effect. It has been suggested that Cefepime can be used only in patients with non-severe ESBL-E reported with low MIC (≤2 μg/mL) of the drug and where high drug concentrations and pharmacodynamic effects can be achieved [40]. All the ceftriaxone-resistant bacteria are not recommended to be treated with Carbapenems but only in severe and difficult to treat cases are recommended [23]. Newer BLI such as avibactam, vaborbactam, etc are paving way as promising carbapenemase inhibitors [43].

Studies revealed UTI caused by ESBL-E showed better response to Pip-Taz compared to Cefepime with an efficacy rate of 33.3% and 94% for Cefepime and Pip-Taz respectively [38,40]. Cefepime and Pip-Taz both becomes ineffective in case of high bacterial inoculum. Cotrimoxazole and Quinolones are most preferrable in children as they are available in oral formulation. ESBL producers can also be a producer of other enzymes such as carbapenemases rendering carbapenem groups too ineffective. Even in those cases Aminoglycosides and quinolones remain first-line choices, if susceptible [38]. In cases, if ESBL and Carbapenemase coproducer is also resistant to aminoglycosides, quinolones and cotrimoxazole, double disk synergy testing are performed to identify susceptibility to Ceftazidime-Avibactam and Aztreonam synergy or can be given with colistin [38,44,45]. Colistin is nephrotoxic and it has the problem of easy emergence of resistance, hence they're reserved as last resort for patients with MDR bacterial infections [38]. Generally, colistin works efficient against Pseudomonas aeruginosa and Carbapenem resistant Acinetobacter baumannii infections [45].

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 10 October 2024
DOI: 10.47191/ijcsrr/V7-i10-64, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Based on the site of infection and the penetration effects of the drug, the drugs needed to be chosen wisely. For serious infections in patients needing immediate drug effect can be posed to intravenous drug therapy rather than other routes to improve bioavailability, achieve adequate concentration at the site of infection and fasten the onset of action [46]. While choice of antibiotic depends on the AST reports and recent antibiotic consumption, frequency and duration of antibiotic therapy depends on the Pharmacokinetic/ Pharmacodynamic properties of the drug and the site of infection respectively. Severity of illness also determine the duration of therapy and the dose required. Comorbid conditions, age and gender factors, expert's opinion, vulnerable population like pregnancy, geriatrics require unique tailoring of the antibiotic dosing regimen [47,48]. But always prevention is better than cure. Prevention plays a pivotal role in halting the development of resistance and environment is the key part of the solution [49].

7. CHALLENGES AND FUTURE THREATS

The rise of AMR especially by GNB through the production of ESBL enzymes are increasingly high [11]. ESBL-E has led to the use of carbapenems as extended spectrum cephalosporin classes led to high treatment failure rates. The commonly prescribed antibiotics like penicillins, cephalosporins are resistant leading to use of carbapenem groups which is high-end restricted antibiotic [50]. Unaware of the local resistance trend and the institution policy overuse and misuse of high-end restricted antibiotics like carbapenems occurs. Shorter course than required, overtreatment, irrational prophylaxis for surgeries, inadequate doses, inappropriate frequencies, excessive duration of therapy, inappropriate use of broad-spectrum antibiotics may result in development of AMR. Thus, leading to a global challenge in treating those MDR organisms [51].

Leading in this way, there occurs an immediate lack of effective antibiotic against MDR Organisms. This forces to pave way for strict adherence to the protocol, investments in the field of antibiotic discovery and restriction of antibiotic usage in cattle and farms for growth promotion and control of diseases [52]. AMR is listed by WHO as one of the top 10 global health threats. In 2019, AMR directly contributed to approximately 1.27 million deaths worldwide. It is projected that by 2050, deaths due to AMR could reach 10 million annually, surpassing deaths from cancer and other individual infections, becoming one of the leading causes of death globally [49]. Increased length of hospitalization, increased medication costs, lack of therapeutic efficacy, loss of patient's faith in the treatment, strains on medical resources, development of toxicity or complications, loss of workforce productivity, gap in the innovation of new antibiotics, finally, no treatment options. So, AMR directly and indirectly poses a global human health threat [53].

8. CONCLUSION

ESBLs have emerged as a global menace, prompting increased use of broad-spectrum antibiotics and hastening resistance development. Many gram-negative bacteria, once susceptible to cephalosporins, now produce ESBLs at higher rates, nullifying the effectiveness of this antibiotic class. Insufficient treatment can worsen infections, leading to prolonged hospital stays, recurrent infections, complications, and, gravely, organ failure or death. Addressing this global threat of AMR requires a balanced approach to drug development that matches or exceeds the pace of resistance emergence.

REFERENCES

1. Infectious Diseases Society of America (IDSA). Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Available from: https://www.idsociety.org/practice-guideline/amr-guidance/.
2. Etebu, Ebimieowei & Arikekpar, Ibemologi. (2016). Antibiotics: Classification and mechanisms of action with emphasis on molecular perspectives. International Journal of Applied Microbiology and Biotechnology Research. 4. 90-101.
3. Elroy P. Weledji, Elizabeth K. Weledji, Jules C. Assob, Dickson S. Nsagha, Pros, cons and future of antibiotics, New Horizons in Translational Medicine, Volume 4, Issues 1–4,2017, Pages 9-14, ISSN 2307-5023, doi.org/10.1016/j.nhtm.2017.08.001.(https://www.sciencedirect.com/science/article/pii/S2307502317300243)
4. Silva HM. Antibiotics against viruses: Brazilian doctors adrift. Infection Control & Hospital Epidemiology. 2022;43(12):1992–3. doi:10.1017/ice.2021.434
5. Antimicrobial resistance [Internet]. European Medicines Agency. 2021. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/antimicrobial-resistance
6. Yadav, Khushbu & Prakash, Satyam. (2016). Antimicrobial Resistance (AMR): A Global Problem. Global Journal of Public Health and Epidemiology. 03. 120-138.

7. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018 Jun 26;4(3):482-501. doi: 10.3934/microbiol.2018.3.482. PMID: 31294229; PMCID: PMC6604941.
8. World Health Organization: WHO. Antimicrobial resistance. World Health Organization: WHO [Internet]. 2023 Nov 21; Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
9. Habboush Y, Guzman N. Antibiotic Resistance. [Updated 2023 Jun 20]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513277/
10. Sunarno S, Puspandari N, Fitriana F, Nikmah UA, Idrus HH, Panjaitan NSD. Extended spectrum beta lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* in Indonesia and South East Asian countries: GLASS Data 2018. AIMS Microbiol. 2023 Mar 17;9(2):218-227. Doi: 10.3934/microbiol.2023013. PMID: 37091820; PMCID: PMC10113165.
11. Husna A, Rahman MM, Badruzzaman ATM, Sikder MH, Islam MR, Rahman MT, Alam J, Ashour HM. Extended-Spectrum β-Lactamases (ESBL): Challenges and Opportunities. Biomedicines. 2023 Oct 30;11(11):2937. Doi: 10.3390/biomedicines11112937. PMID: 38001938; PMCID: PMC10669213.
12. Mulani M.S., Kamble E.E., Kumkar S.N., Tawre M.S., Pardesi K.R. Emerging Strategies to Combat ESKAPE Pathogens in the Era of Antimicrobial Resistance: A Review. *Front. Microbiol.* 2019; 10:539. Doi: 10.3389/fmicb.2019.00539.
13. Biswas BS. India facing a pandemic of antibiotics-resistant superbugs [Internet]. BBC News. 2022 [cited 2024 May]. Available from: https://www.bbc.com/news/world-asia-india-63059585
14. Nogrady B. The fight against antimicrobial resistance [Internet]. Nature. 2023 [cited 2024 May]. Available from: https://www.nature.com/articles/d41586-023-03912-8
15. Christina Khadka, Manita Shyaula, Gopiram Syangtan, Shrijana Bista, Reshma Tuladhar, Anjana Singh, Dev Raj Joshi, Lok R. Pokhrel, Prabin Dawadi, Extended-spectrum β-lactamases producing Enterobacteriaceae (ESBL-PE) prevalence in Nepal: A systematic review and meta-analysis, Science of The Total Environment, Volume 901,2023,166164, ISSN 0048-9697, (https://www.sciencedirect.com/science/article/pii/S0048969723047897)
16. Aryal S. Beta-Lactamase and Ambler classification [Internet]. Sagar Aryal. 2022 [cited 2024 May]. Available from: https://microbenotes.com/beta-lactamase-and-ambler-classification/
17. Peirano, G., Pitout, J.D.D. Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Update on Molecular Epidemiology and Treatment Options. *Drugs* 79, 1529–1541 (2019). https://doi.org/10.1007/s40265-019-01180-3
18. Gniadkowski M. Evolution and epidemiology of extended-spectrum β-lactamases (ESBLs) and ESBL-producing microorganisms. Clinical Microbiology and Infection. 2001 Nov 1;7(11):597–608.
19. Thenmozhi S, Moorthy K, Sureshkumar BT, Suresh M. Antibiotic resistance mechanism of ESBL producing Enterobacteriaceae in clinical field: A review [Internet]. Ijpab.com. [cited 2024 Jun 11]. Available from: http://www.ijpab.com/form/2014%20volume%202,%20issue%203/ijpab-2014-2-3-207-226.pdf
20. Tankeshwar A. Beta-lactam antibiotics: Mechanism of action, resistance [Internet]. Microbe Online. 2020 [cited 2024 Jun 17]. Available from: https://microbeonline.com/beta-lactam-antibiotics-mechanism-action-resistance/
21. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010 Mar;54(3):969-76. doi: 10.1128/AAC.01009-09. Epub 2009 Dec 7. PMID: 19995920; PMCID: PMC2825993.
22. Ruiz J. Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection. J Antimicrob Chemother [Internet]. 2003;51(5):1109–17. Available from: http://dx.doi.org/10.1093/jac/dkg222
23. Castanheira M, Simner PJ, Bradford P. Extended-spectrum β-lactamases: An update on their characteristics, epidemiology and detection. JAC-Antimicrob Resist. 2021;3:dlab092
24. Cambray G, Guerout A-M, Mazel D. Integrons. Annu Rev Genet [Internet]. 2010;44(1):141–66. Available from: http://dx.doi.org/10.1146/annurev-genet-102209-163504.
25. Bush, K., Jacoby, G.A., Beta-lactamase classification and amino acid sequences for TEM, SHV and OXA extended-spectrum and inhibitor resistant enzymes. Available from: (accessed 27.10.2012).
26. Kumar S, Mukherjee MM, Varela MF. Modulation of bacterial multidrug resistance efflux pumps of the major facilitator superfamily. Int J Bacteriol [Internet]. 2013;2013:1–15. Available from: http://dx.doi.org/10.1155/2013/204141
27. Blair JM, Webber MA, Baylay AJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015;13:42–51.

28. Piddock LJ. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clin Microbiol Rev. 2006;19:382–402.
29. Sharma A, Gupta VK, Pathania R. Efflux pump inhibitors for bacterial pathogens: From bench to bedside. Indian J Med Res. 2019 Feb;149(2):129-145. doi: 10.4103/ijmr.IJMR_2079_17. PMID: 31219077; PMCID: PMC6563736.
30. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: A guide for clinicians. J Anaesthesiol Clin Pharmacol [Internet]. 2017 [cited 2024 Jun 13];33(3):300. Available from: http://dx.doi.org/10.4103/joacp.joacp_349_15
31. Chong Y, Shimoda S, Shimono N. Current epidemiology, genetic evolution and clinical impact of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Infect Genet Evol [Internet]. 2018;61:185–8. Available from: http://dx.doi.org/10.1016/j.meegid.2018.04.005
32. Kang C-I, Wi YM, Lee MY, Ko KS, Chung DR, Peck KR, et al. Epidemiology and risk factors of community onset infections caused by extended-spectrum β-lactamase-producing Escherichia coli strains. J Clin Microbiol [Internet]. 2012;50(2):312–7. Available from: http://dx.doi.org/10.1128/jcm.06002-11
33. Donati V, Feltrin F, Hendriksen RS, Svendsen CA, Cordaro G, García-Fernández A, et al. Extended-spectrum-beta-lactamases, AmpC beta-lactamases and Plasmid mediated quinolone resistance in Klebsiella spp. From companion animals in Italy. PLoS One [Internet]. 2014;9(3):e90564. Available from: http://dx.doi.org/10.1371/journal.pone.0090564
34. Huijbers PM, Van Hoek AH, Graat EA, Haenen AP, Florijn A, Hengeveld PD, et al. Methicillin-resistant Staphylococcus aureus and extended-spectrum and AmpC beta-lactamase-producing Escherichia coli in broilers and in people living and/or working on organic broiler farms. Vet Microbiol. 2015;176:120–5.
35. Ahmed HA, Elsohaby I, Elamin AM, El-Ghafar AEA, Elsaid GA, Elbarbary M, et al. Extended-spectrum β-lactamase-producing E. coli from retail meat and workers: genetic diversity, virulotyping, pathotyping and the antimicrobial effect of silver nanoparticles. BMC Microbiol [Internet]. 2023;23(1). Available from: http://dx.doi.org/10.1186/s12866-023-02948-0
36. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0.
37. Internet A, Maarten. Mechanisms of emerging resistance associated with non-antibiotic antimicrobial agents: a state-of-the-art review [Internet]. AMR Insights. 2023 [cited 2024 Jun 16]. Available from: https://www.amr-insights.eu/mechanisms-of-emerging-resistance-associated-with-non-antibiotic-antimicrobial-agents-a-state-of-the-art-review/
38. Bitsori, Maria MD, PhD; Galanakis, Emmanouil MD, PhD. Treatment of Urinary Tract Infections Caused by ESBL-producing Escherichia coli or Klebsiella pneumoniae. The Pediatric Infectious Disease Journal 38(12):p e332-e335, December 2019. | DOI: 10.1097/INF.0000000000002487
39. Khan HA, Baig FK, Mehboob R. Nosocomial infections: Epidemiology, prevention, control and surveillance. Asian Pacific Journal of Tropical Biomedicine [Internet]. 2017 May;7(5):478–82. Available from: https://www.sciencedirect.com/science/article/pii/S2221169116309509
40. Pana ZD, Zaoutis T. Treatment of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBLs) infections: what have we learned until now? F1000Res. 2018 Aug 29;7:F1000 Faculty Rev-1347. doi: 10.12688/f1000research.14822.1. PMID: 30228863; PMCID: PMC6117850.
41. Patel K, Bunachita S, Agarwal AA, Bhamidipati A, Patel UK. A Comprehensive Overview of Antibiotic Selection and the Factors Affecting It. Cureus. 2021 Mar 16;13(3):e13925. doi: 10.7759/cureus.13925. PMID: 33868859; PMCID: PMC8049037.
42. Jewell T. ESBLs (Extended Spectrum Beta-Lactamases) [Internet]. Healthline. Healthline Media; 2017. Available from: https://www.healthline.com/health/esbl
43. Vázquez-Ucha JC, Arca-Suárez J, Bou G, Beceiro A. New Carbapenemase Inhibitors: Clearing the Way for the β-Lactams. Int J Mol Sci. 2020 Dec 6;21(23):9308. doi: 10.3390/ijms21239308. PMID: 33291334; PMCID: PMC7731173.
44. Wilhelm CM, Inamine E, Martins AF, Barth AL. Evaluation of Aztreonam and Ceftazidime/Avibactam Synergism against *Klebsiella pneumoniae* by MALDI-TOF MS. Antibiotics (Basel). 2023 Jun 16;12(6):1063.

doi: 10.3390/antibiotics12061063. PMID: 37370382; PMCID: PMC10295265.

45. Shaikh S, Fatima J, Shakil S, Rizvi SMohdD, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi Journal of Biological Sciences [Internet]. 2015 Jan;22(1):90–101. Available from: https://www.sciencedirect.com/science/article/pii/S1319562X14000941
46. McCarthy K, Avent M. Oral or intravenous antibiotics? Aust Prescr. 2020 Apr;43(2):45-48. doi: 10.18773/austprescr.2020.008. Epub 2020 Apr 1. PMID: 32346210; PMCID: PMC7186270
47. Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin Ther. 2016 Sep;38(9):1930-47. doi:10.1016/j.clinthera.2016.06.015. Epub 2016 Jul 20. PMID: 27449411; PMCID: PMC5039113.
48. Sime FB, Roberts MS, Roberts JA. Optimization of dosing regimens and dosing in special populations. Clinical Microbiology and Infection. 2015 Oct;21(10):886–93.
49. Environment UN. Antimicrobial resistance: a global threat [Internet]. UNEP - UN Environment Programme. 2020. Available from: https://www.unep.org/topics/chemicals-and-pollution-action/pollution-and-health/antimicrobial-resistance-global-threat#:~:text=According%20to%20recent%20estimates%2C%20in%202019%2C%201.27%20million
50. Antibiotics [Internet]. www.mdpi.com. [cited 2024 Jun 16]. Available from: https://www.mdpi.com/journal/antibiotics/special_issues/epide_ESBL
51. Tarrant C, Colman AM, Jenkins DR, Chattoe-Brown E, Perera N, Mehtar S, Nakkawita WMID, Bolscher M, Krockow EM. Drivers of Broad-Spectrum Antibiotic Overuse across Diverse Hospital Contexts-A Qualitative Study of Prescribers in the UK, Sri Lanka and South Africa. Antibiotics (Basel). 2021 Jan 19;10(1):94. doi: 10.3390/antibiotics10010094. PMID: 33477994; PMCID: PMC7835907.
52. Thakur A, Kumar A, Sharma M, Kumar R, Vanita B. Strategies to Minimize the Impact of Antibiotic Resistance in Livestock Production System. International Journal of Current Microbiology and Applied Sciences. 2019 Mar 10;8(03):2293–310.
53. Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis. The Lancet [Internet]. 2022 Jan 19;399(10325):629–55. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext
54. Sachin M. Patil and Parag Patel. Bactericidal and Bacteriostatic Antibiotics. In Infections and Sepsis Development, Edited by Vincenzo Neri, Lixing Huang and Jie Li, Rijeka. 2021: pp. 1-38

Cite this Article: Leena Muppa, Vaishnavi Velmani, Nandhani N, Vincy Santhana Sophia B, Sriram Radhakrishnan, Bala Abirami M (2024). Extended Spectrum β-Lactamase: Tackling Antibiotic Resistance and Overcoming Treatment Challenges. International Journal of Current Science Research and Review, 7(10), 8038-8047, DOI: https://doi.org/10.47191/ijcsrr/V7-i10-64