

## Review Article

# The Spread of $\beta$ -Lactamases and Extended Spectrum $\beta$ -Lactamase Enzymes among Bacteria: A Threat to Effective Health Care Delivery

Ismail Rabi<sup>1\*</sup>, Isah Ja'afaru Abdullahi<sup>2</sup> and Aminu Abdullahi Mahmoud<sup>3</sup><sup>1</sup>Department of Microbiology, School of Science and Information Technology, Skyline University Nigeria No. 2, Zaria Road, Kano, Nigeria<sup>2</sup>Department of Microbiology, Faculty of Science, Kaduna State University, Kaduna PMB: 2339, Kaduna, Nigeria<sup>3</sup>Department of Microbiology, Faculty of Life Sciences, College of Natural and Pharmaceutical Sciences, Bayero University, P. M. B. 3011, Kano, Nigeria**Article History**

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**Abstract:** Antibiotic discovery continue to play a critical role in disease containment. Misuse and overuse of these drugs are the main drivers in the development of drug resistant pathogens. The World Health Organisation has declared that Antimicrobial resistance is one of the top 10 global public health threats facing humanity. There is the fears that if nothing is done, it might end the antibiotic era soon. In 2017 alone, over 9000 human deaths were caused by ESBL-producing Enterobacteriaceae in the USA. The ability of bacteria to develop newer strategies to acquire and disseminate resistance, can be traced as far back to 1940s when (R-factor) plasmid mediated antibiotic resistance was observed. They become resistant via the production of  $\beta$ -Lactamases and ESBLs enzymes which inactivate or modify antibiotics. Extended Spectrum  $\beta$ -Lactamases are enzymes whose rates of hydrolysis of the extended-spectrum  $\beta$ -Lactam antibiotics are >10 % than that for benzylpenicillin. Some bacteria may produce multiple  $\beta$ -lactamases, which may reduce the effectiveness of  $\beta$ -lactam/  $\beta$ -lactamase inhibitor combinations. These enzymes are susceptible to inhibition by  $\beta$ -Lactam inhibitors such as clavulanic acid, tazobactam, or sulbactam but have no hydrolytic activity against cephamycins and carbapenems. The production of acquired  $\beta$ -Lactamase and ESBL makes the choice of antibiotic treatment of infections caused by Gram-negative bacteria very limited, these have been the major causes of treatment failures, outbreaks of both community and hospital acquired infections, surgical failures, long hospital stay and huge economic losses, which continue to claim uncountable lives, especially in Nigeria and Africa where the health system are weak. The emergence of drug resistant strains may be minimized by maintaining high levels of the drug in the tissues to inhibit mutants, administering two drugs that do not give cross-resistance, and by limiting the use of valuable second line 'reserve drugs' such as the cephalosporins and quinolones.

**Keywords:** Antibiotic, Drug Resistant enzymes, R-factor plasmid,  $\beta$ -Lactam, clavulanic acid, Gram-negative bacteria, cephalosporins and quinolones.

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## INTRODUCTION

The emergence and spread of drug-resistant microbes is far more rapid than the introduction of new medicine into clinical practice (Ling *et al.*, 2015). The introduction of antibiotics around World War II represented a revolution in therapeutic medicine and has saved millions of lives. When penicillin was introduced in the 1940s a "golden age" of antibiotic discovery began and during the next three decades several new classes of antimicrobial agents with

different targets of action were introduced to the market (Peirano *et al.*, 2012).

In 2017, Over 9000 human deaths were caused by ESBL-producing Enterobacteriaceae in the USA (Center for Disease Control, 2013). The same year, World Health Organization (WHO) ranked these resistant bacteria in the first priority tier, under the characterization 'critical', to guide research, discovery and development of new antibiotics (Tacconelli *et al.*, 2015). There reports that isolates that produce ESBL

\*Corresponding Author: Ismail Rabi

Department of Microbiology, School of Science and Information Technology, Skyline University Nigeria No. 2, Zaria Road, Kano, Nigeria

are increasingly resistant to plants extracts which were otherwise known to be effective (Abdulfatai *et al.*, 2018; Adamu *et al.*, 2021; Bale *et al.*, 2021).

The basis for all resistance is the genetic makeup of the bacteria. A bacterium may acquire resistance through changes in gene expression, modification of existing genes or the acquisition of new genes through the process called “horizontal gene transfers”. There are three mechanisms of horizontal gene transfer – transduction, transformation and conjugation. Transduction is DNA transfer mediated by bacteriophages and transformation is direct uptake of genetic material, including plasmids from the environment by “competent” bacteria (Yusha’u *et al.*, 2007; Denisuik, 2013).

The term antimicrobial resistance most often refers to resistance that is acquired by bacteria, as opposed to intrinsic resistance in which some antimicrobials do not affect the large majority of strains from certain bacterial species. The rapid increase in antibiotic resistance is a serious problem in effective health care delivery and may threaten to end the antibiotic era (Nicolas-Chanoine *et al.*, 2012). This has been the topic of recent reports from important stakeholders like the European Centre for Disease Prevention and Control, the American governmental organization, Centre for Disease Control and Prevention, the Swiss Independent Forum and the World Economic Forum (CDC, 2013; Abdulfatai *et al.*, 2018).

With the exceptions of the oxazolidinones and lipopeptides drugs with a Gram-positive antimicrobial spectrum, new antibiotics introduced since 1968 have been chemical modifications of existing drug scaffolds and no new classes of gram-negative drugs have been introduced (Jensen *et al.*, 2008). This is partly a result of diminishing research into new antibiotics. There are several reasons for this including: i) the 1962 "Drug Efficacy Amendment" to the Federal Food, Drug, and Cosmetic Act, in the USA which set stricter rules on new drugs, ii) rules that new drugs should be non-inferior to existing ones, iii) the use of new antibiotics as “last resort” drugs only and iv) the fact that antibiotics are mostly used in short courses (i.e., a lower quantity of drugs are sold compared to lifelong treatment of other drug groups). In parallel with the reduced pipeline of new drugs the use of antibiotics among humans and animals have risen dramatically. Predictably, this has led to an ever increasing problem of antimicrobial resistance in bacteria (Rao, 2015; EUCAST, 2013).

The  $\beta$ -lactams are a group of antibacterial comprising four major groups: penicillins, cephalosporins, monobactams and carbapenems. Structurally, they consisted of a  $\beta$ -lactam ring, which is consist of three carbon atoms and one nitrogen atom

that is linked to a thiazolidine ring. In cephalosporins, the  $\beta$ -lactam ring and dihydrothiazine ring are merged; however, in the carbapenems, the  $\beta$ -lactam ring is joined with a hydroxyethyl side chain, deficient of an oxygen or sulphur atom in the bicyclic nucleus, while monobactam has no additional ring (Yusuf *et al.*, 2011; Yusuf *et al.*, 2011; Sadeeq *et al.*, 2018). The protonation of the  $\beta$ -Lactam, Nitrogen and subsequent cleavage of C-N bond brings about the destruction of the  $\beta$ -Lactam ring, followed by the hydrolysis of bond and drug inactivation (Denisuik, 2013).

ESBLs are enzymes evolved from a narrow spectrum parent ESBL enzyme and thus gained the ability to inactivate the broad spectrum cephalosporins, penicillins, and aztreonam, but not the cephamycins (cefoxitin) or carbapenems by hydrolytic activity and are inhibited by  $\beta$ -lactamase inhibitors, that is, clavulanic acid (Sadeeq *et al.*, 2018).

The cost of AMR to the economy is significant. In addition to death and disability, prolonged illness results in longer hospital stays, the need for more expensive medicines and financial challenges for those impacted. Without effective antimicrobials, the success of modern medicine in treating infections, including during major surgery and cancer chemotherapy, would be at increased risk (European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2013).

Antibacterial Resistance (ABR) occurs when bacteria changes over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result of drug resistance, antibiotics become ineffective and infections become increasingly difficult or impossible to treat. The main drivers of antimicrobial resistance include the misuse and overuse of antimicrobials; lack of access to clean water, sanitation and hygiene (WASH) for both humans and animals; poor infection and disease prevention and control in health-care facilities and farms; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; and lack of enforcement of legislation (Rao, 2015; WHO, 2015).

The emergence and spread of drug-resistant pathogens that have acquired new resistance mechanisms, leading to antimicrobial resistance, continues to threaten our ability to treat common infections. Especially alarming is the rapid global spread of multi- and pan-resistant bacteria (also known as “superbugs”) that cause infections that are not treatable with existing antimicrobial medicines such as antibiotics (Cheesbrough, 2017; EUCAST, 2013).

The clinical pipeline of new antimicrobials is dry. In 2019 WHO identified 32 antibiotics in clinical development that address the WHO list of priority

pathogens, of which only six were classified as innovative. Antibiotics are becoming increasingly ineffective as drug-resistance spreads globally leading to more difficult to treat infections and death (EUCAST, 2013). The cost of AMR to national economies and their health systems is significant as it affects productivity of patients or their caretakers through prolonged hospital stays and the need for more expensive and intensive care. Without effective tools for the prevention and adequate treatment of drug-resistant infections and improved access to existing and new quality-assured antimicrobials, the number of people for whom treatment is failing or who die of infections will increase. Medical procedures, such as surgery, including caesarean sections or hip replacements, cancer chemotherapy, and organ transplantation, will become more risky (Denisuik, 2013; WHO, 2015; Adamu *et al.*, 2021).

### The discovery of $\beta$ -Lactam antibiotics

The  $\beta$ -lactams are a group of antibacterial comprising four major groups: penicillins, cephalosporins, monobactams and carbapenems. Structurally, they consisted of a  $\beta$ -lactam ring, which is consist of three carbon atoms and one nitrogen atom that is linked to a thiazolidine ring (Rao, 2015). In cephalosporins, the  $\beta$ -lactam ring and dihydrothiazine ring are merged; however, in the carbapenems, the  $\beta$ -lactam ring is joined with a hydroxyethyl side chain, deficient of an oxygen or sulphur atom in the bicyclic nucleus, while monobactam has no additional ring (Sadeeq *et al.*, 2018).

Antibiotics were discovered by Alexander Fleming in 1928, when he accidentally discovered that colonies of *Staphylococcus* were inhibited by a contaminating *Penicillium* mould. His further experiments on other bacterial cultures led him to understand that *Penicillium* culture possessed some bacteriostatic and bactericidal effects, against a number of Gram positive cells. For the fact that it was produced from *Penicillium* spp. he named the fungal extracts as Penicillin (Rao, 2015). In 1940, Howard Florey and Ernst Boris Chain continued with the work of Fleming and conducted an experimental analysis to ascertain the validity of Flemings claims. They conducted an in-vivo studies using mice, where they infected them with

*Streptococcus*. This was followed by clinical trials, and following their success the drug was made available for therapeutic use in the year 1941 (Saroj-Kumar and Hemalatha, 2015; Bale *et al.*, 2021).

In the year 1940, Selman Waksman along with his students discovered Streptomycin following his work on *Streptomyces griseus*, and to differentiate them from the continual number of biologically active substance been discovered as at that time, he coined the term “antibiotic” (Rao, 2015). This discoveries, motivated researchers in the search for other biologically active compounds, and in the year 1948, Giuseppe Brotzu following his work on *Acremonium chrysogenum* (now known as *Cephalosporium acremonium*) discovered a new class of antibiotics with extended spectrum of activity (covering both Gram positive and Gram negative bacteria) known as Cephalosporin (D'Andrea *et al.*, 2013).

### 2.6.1 Structure of $\beta$ -Lactam antibiotics

The  $\beta$ -Lactam ring is a four membered cyclic amide and the “ $\beta$ ” represents the position of Nitrogen atom relative to the carbonyl (C=O) group. In penicillin the  $\beta$ -lactam ring is fused to a five membered thiazolidine ring (Vardakas *et al.*, 2012). Penicillin is structurally 6-amino-penicillanic acid, along with a side chain. Cephalosporins too contains a  $\beta$ -lactam ring, which is fused to a six membered dihydrothiazine ring. Cephalosporin is 7-aminocephalosporanic acid with a side chain attached (Cheesbrough, 2017). Through the modification of the side chains attached to the  $\beta$ -Lactam ring, a large number of semi-synthetic penicillins were produced. These modifications were necessitated by the increasing resistance recorded by bacteria to these antibiotics (Tofteland, 2015). Unlike penicillins most Cephalosporins have good antibacterial activity against Gram negative bacteria. These modifications of Cephalosporins side chains have made them the largest group of  $\beta$ -Lactam Baerum antibiotics. They comprise of five generations of antibiotics each with distinct spectrum of activity. Both the naturally and semi-synthetic derived  $\beta$ -Lactam antibiotics are currently the largest family of the antimicrobials presently in used (Baerum, 2014).

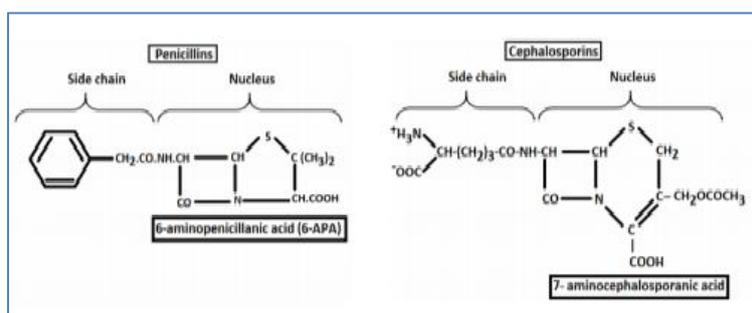


Fig-1: Structure of Penicillin and Cephalosporin antibiotics (Sauvage *et al.*, 2008).

### 2.6.2 Classification of $\beta$ -Lactam antibiotics

The classification of  $\beta$ -Lactam agents was made after the specific type of rings that are attached to the  $\beta$ -Lactam ring (Fisher *et al.*, 2005). The  $\beta$ -Lactam antibiotics groups are named based on the rings that are

attached to the  $\beta$ -Lactam rings. The various groups include monobactams, cephamycins, carbapenems, cephems, oxacephems, penems, carbacephems, clavams, and Penams (Denisuik, 2013).

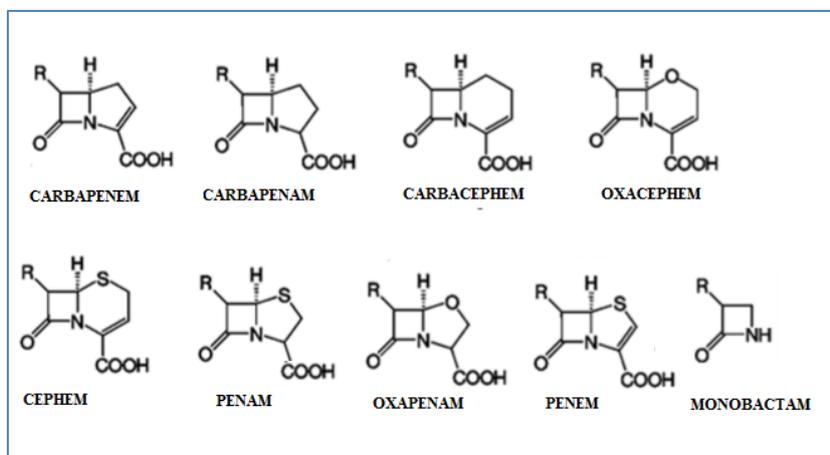


Fig-2:  $\beta$ -Lactam compounds showing their Core structures (Rao, 2015).

Table-1: The various Classifications of  $\beta$ -Lactam antibiotics

Penam		Penem	Carbapene m	Cephem	Monobactam	$\beta$ -Lactamase inhibitors
Narrow spectrum	Extended spectrum	Faropenem	Imipenem, Meropenem, Ertapenem	First generation: Cefalexin, Cefuroxime, Cefalotin	Aztreonam, Tigemonam	Clavulanic acid, tazobactam, Sulbactam
$\beta$ -Lactamase susceptible: Benzyl penicillin	Aminopenicillin:- Ampicillin, Amoxicillin			Second generation: Cefaclor, Cefuroxime, Cefprozil, Cephamycin (Cefoxitin, Cefotetan)		
$\beta$ -Lactamase resistant: Cloxacillin, Oxacillin, Meticillin	Carboxypenicillin: Carbenicillin, Ticarcillin			Third generation: Ceftriaxone, Ceftazidime, Cefotaxime, Cefpodoxime.		
	Ureidopenicillin: Piperacillin, Azlocillin			Fourth generation: Cefepime, Cefpirome		
				Fifth generation: Cefaroline, Cefbiprole		

(Baerum, 2014).

### 2.6.4 Resistance to $\beta$ -Lactam antibiotics

Bacterial resistance to  $\beta$ -lactam antibiotics has evolved in order to counter the detrimental effects of  $\beta$ -lactam antibiotics on them. This is achieved by the bacterial cell in many different ways, this includes;

- The pumping out of the antibiotics before it reaches its cellular target, via efflux pump mechanisms.
- The production of new binding site, which have lower affinity to  $\beta$ -lactam antibiotics.
- Hydrolysis of the  $\beta$ -lactam ring.

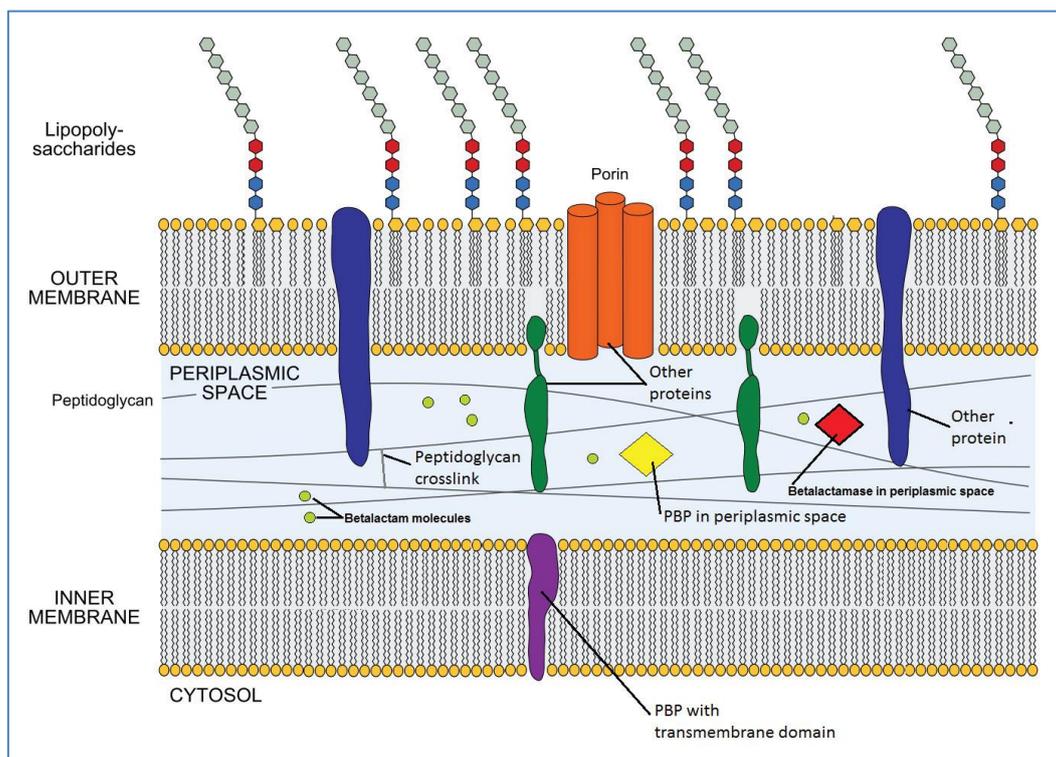
- iv. Mutations of the cellular target which eventually seize the expression of bacterial Porins proteins which allow the entry of  $\beta$ -lactam antibiotics into the cell.

The enzymes,  $\beta$ -Lactamases is a broader name given to bacterial resistant enzymes that hydrolyses the  $\beta$ -lactam ring by the addition of water molecules. Among the Gram negative bacteria, the  $\beta$ -lactamases are present in the periplasmic region of the cell. In the case of Gram positive bacteria, the enzymes are excreted outside the cell (Tofteland, 2015; Denisuik, 2013; Bale *et al.*, 2021).

### 2.7 $\beta$ -Lactamases

So far, more than 500  $\beta$ -lactamases have been reported to date (<https://www.lahey.org/studies/>) produced by diverse bacteria. Beta-lactamases are thought to be the most common resistance mechanism that contributes to widespread resistance among Gram-negative bacteria (Sadeeq *et al.*, 2018).

The  $\beta$ -Lactamases are enzymes which inactivates  $\beta$ -Lactam antibiotics. Resistance to  $\beta$ -lactams is frequently mediated through production of  $\beta$ -lactamase enzymes which break down  $\beta$ -lactam molecules (Baerum, 2014).  $\beta$ -lactamases are thought to have the same origin as the PBPs, and these enzymes are considered to be one molecular superfamily of proteins that are able to bind  $\beta$ -lactams. The inactivation works by acylation and deacylation but the rate of deacylation is up to a million times faster than between a  $\beta$ -lactam and a PBP. They are basically classified in to; Metallo-  $\beta$ -Lactamases (MBLs) and Serine  $\beta$ -Lactamases (Rao, 2015). The acylation deactivates the  $\beta$ -Lactam antibiotics by breaking the  $\beta$ -Lactam ring to form an enzyme-acyl complex, followed by deacylation from serine and then hydrolysis. While the acylation process, it requires nucleophilic serine, deacylation requires hydrolytic water molecule. Beta-lactamases can have different locations in bacteria and may also be excreted. In Gram-negative bacteria they are mostly located in the periplasmic space (Denisuik, 2013; Fisher Fisher *et al.*, 2005).



**Fig-3: The Gram-negative cell wall with location of two different penicillin-binding proteins, one  $\beta$ -Lactamase and  $\beta$ -lactams (Baerum, 2014).**

#### 2.7.1 Mechanism of action of $\beta$ -Lactamases

As the  $\beta$ -Lactam substrate binds to the active site of the  $\beta$ -Lactamase, this leads to the formation of a non-covalent complex. The serine radical in the active site mounts a nucleophilic attack on the carboxyl group leading to their acylation (Tofteland, 2015). The destruction of the  $\beta$ -Lactam ring is due to the

protonation of the  $\beta$ -Lactam, Nitrogen and subsequent cleavage of C-N bond which leads to the formation of acyl-enzyme complex. This is then followed by the hydrolysis of the bond between the  $\beta$ -Lactam carbonyl and oxygen of the serine which regenerates the enzyme and releases the inactive  $\beta$ -Lactam molecule (Denisuik, 2013; Adamu *et al.*, 2021).

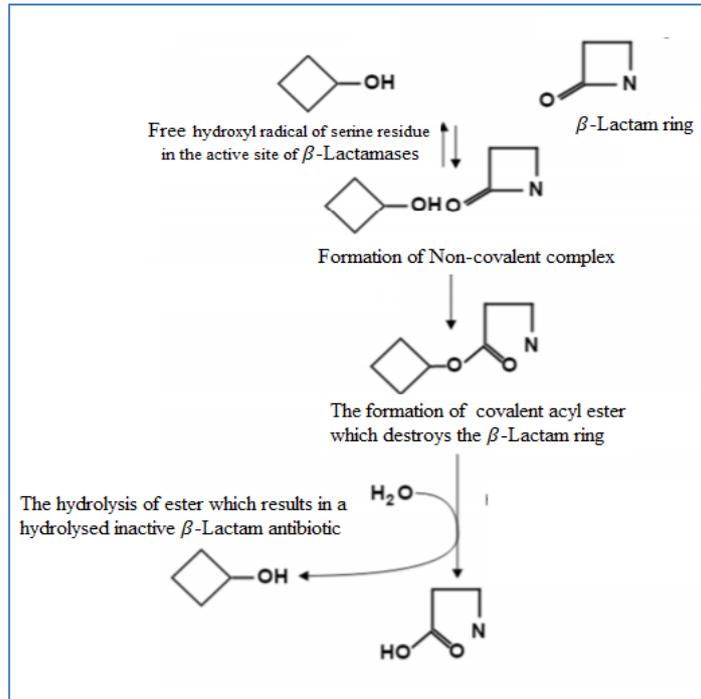


Fig-4: Mechanism of hydrolysis of  $\beta$ -Lactam molecule by  $\beta$ -Lactamase (Manenzhe, 2015).

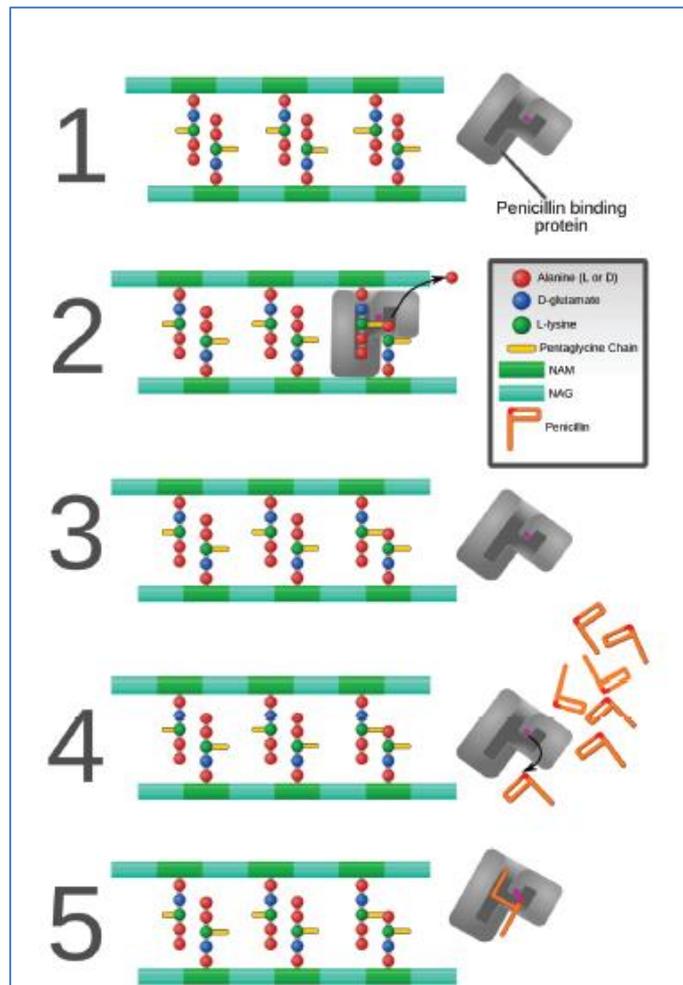


Fig-5: Penicillin and most other  $\beta$ -lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyse cross-linking of bacterial cell walls (Baerum, 2014).

### 2.7.2 $\beta$ -Lactamases Inhibitors

$\beta$ -Lactamase inhibitor was first obtained from the American soil sample in 1971 containing *Streptomyces clavuligerus*. The organism was accidentally discovered while investigating some potential  $\beta$ -Lactam antibiotics producers (Jensen *et al.*, 2008). The isolate was found to produce some antibacterial substances similar to Cephalosporins, but however, it was the discovery of a compound with such anti- $\beta$ -Lactamase property that caught the attention of researchers. Following the isolation and purification, this Cephalosporins similar compounds was named clavulanic acid. Years after, several semisynthetic  $\beta$ -Lactamase inhibitors such as tazobactam, sulbactam and avibactam (A synthetic compound) were produced (Denisuik, 2013). Avibactam is known to inhibit several  $\beta$ -Lactamases as it forms a covalent enzyme substrate complex in the enzymes active site, leading to its deacylation. However, avibactam does not undergo hydrolysis and therefore it is considered a slow reversible  $\beta$ -Lactam inhibitor. Avibactam is being combined with ceftazidime and ceftaroline to form a new fifth generation cephalosporins (Rao, 2015).

The rapid spread of resistance among bacteria is posing a great threat to health care delivery, this is due to the treatment failures, economic loss and prolong hospital stay along with a number of burden it poses on patient care. To counter such effect associated with enzyme mediated resistance to  $\beta$ -Lactam agents an

earnest search was made to find suitable inhibitors (Tofteland, 2015). Certain  $\beta$ -Lactam antibiotics as well as  $\beta$ -Lactamases which mimic the  $\beta$ -Lactam structure inhibits  $\beta$ -Lactamases. Certain  $\beta$ -Lactamases reversible inhibitors such as carbapenems, monobactams, and Extended Spectrum Cephalosporins form acyl enzymes and are able to bind to the active site of  $\beta$ -Lactamases with high affinity there by inhibit it (Jensen *et al.*, 2008). The major setback with these reversible inhibitors is that they get hydrolysed very slowly. Irreversible  $\beta$ -Lactamase inhibitors also known as "suicide inhibitors" acts as substrate for  $\beta$ -Lactamases, just that after hydrolysis they persist in the active sites thereby inactivating the  $\beta$ -Lactamases (Manenzhe, 2015; Fisher *et al.*, 2005).

Like the  $\beta$ -Lactam antibiotics, these  $\beta$ -Lactamase inhibitors work by binding to the active site of the  $\beta$ -Lactamase enzymes and undergo acylation leading to the breaking down of the  $\beta$ -Lactam ring to form a transient imine intermediate (Livermore *et al.*, 2012). These intermediate may rearrange to form enamine intermediate in either cis-or trans-conformation. The clavulanic acid and sulbactam form a mixture of trans-enamine and a less stable cis-enamine intermediate while tazobactam form a stable trans-enamine intermediate (EUCAST, 2013; Birkett *et al.*, 2007).

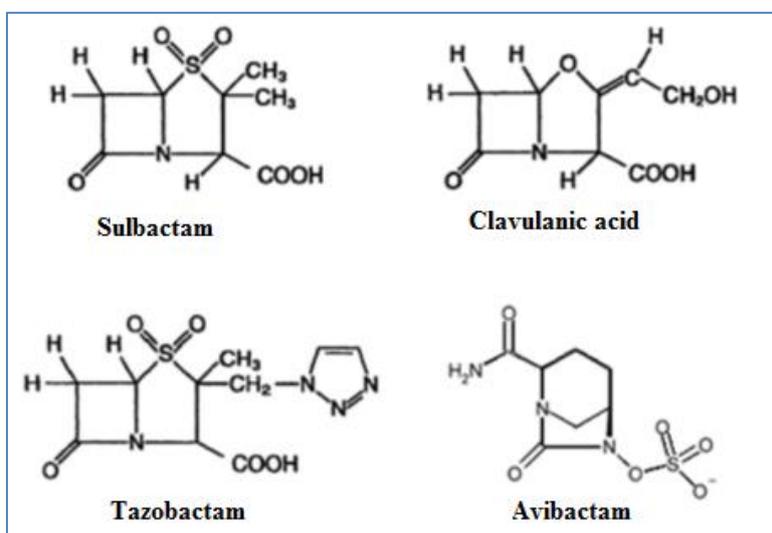


Fig-6: Structure of  $\beta$ -Lactamase inhibitors (Rao, 2015).

Table-2: Comparison of the activities of three  $\beta$ -Lactamases inhibitors

Number of molecules of inhibitor required to inactivate $\beta$ -Lactamases			
	<i>S. aureus</i> PC1	TEM-1	SHV-1
Clavulanic acid	1	160	60
Tazobactam	1	140	5
sulbactam	Data not available	10,000	13,000

(Baerum, 2014).

Effective knowledge of  $\beta$ -Lactamase properties enables clinicians to select appropriate  $\beta$ -Lactamase inhibitor depending on the type of  $\beta$ -Lactamase produced by the infecting organism. However, because  $\beta$ -Lactamases vary in their susceptibility to inhibition by  $\beta$ -Lactamase inhibitors, understanding their activities is an important factor for the functional classification of  $\beta$ -Lactamases (Jensen *et al.*, 2008).

### 2.7.3 Characterization of $\beta$ -Lactamases

Taking a look at various properties,  $\beta$ -Lactamases can be characterized into various groups. This allow scientists to detect new variants along with the identification of existing types. Several methodologies have been used to characterize these enzymes, each with its own advantages and limitations (Rao, 2015). These methods include determination of isoelectric point by isoelectric focusing, immunological reactivity to antisera, determination of substrate profile, determination of gene location, estimation of molecular weight, inducibility of enzyme, determination of MIC, detection of specific sequences by labelled probes, inhibition of enzyme activity and determination of nucleotide and amino acid sequences by molecular techniques (Canton *et al.*, 2012). An enzyme is considered as a cephalosporinase if it hydrolyses cephaloridine at a rate of >30% than that of benzylpenicillin. For penicillinases, benzylpenicillin has been used as the historical reference for hydrolysis, whereas cephaloridine was the chosen reference for cephalosporinases (Tofteland, 2015; Abdulfatai *et al.*, 2018).

### 7.4. Classification of $\beta$ -lactamases

The first attempt for the classification of  $\beta$ -lactamases was in 1968, conducted by Sawai and

Mitshashi. Thereafter, his effort was followed by that of Jack and Richmond, Richmond and Sykes and Sykes and Matthew, who proposed few other schemes (Tofteland, 2015). These schemes were based on physiological properties of the enzymes such as inhibitory profile, isoelectric point, inducibility, molecular weight and hydrolytic prolife (Rao, 2015). Presently, the two popular classification schemes are derived from the works of Ambler RP and Karen Bush. In 1980, Ambler proposed the “phylogenetic” or “molecular” classification based on the amino-acid sequences of the  $\beta$ -lactamases. According to this classification,  $\beta$ -lactamases are divided into two groups: Class A (serine  $\beta$ -lactamases) and Class B (metallo-  $\beta$ -lactamases). The class C, consist of AmpC  $\beta$ -lactamases which was added subsequently by Jaurin and Grundstrom in 1981 oxacillinases (OXA-type) (Canton *et al.*, 2012).

Based on the foundations laid by Richmond and Sykes, Karen Bush proposed another classification based on physiological properties of  $\beta$ -lactamases in 1988. After a minor update in 1989, it was re-launched as the “functional” classification by the team of Bush K, Jacoby GA and Medeiros AA. It was updated again in 2010 (Bush *et al.*, 2010). Furthermore,  $\beta$ -lactamases can be divided into additional three groups. Based on the substrate and inhibitory profiles: 1, 2 and 3. Based on the differences among the enzymes in these groups, they were further divided into several subgroups. Among the three groups, group 2 has the most number of subgroups. Despite being based on physiological properties, this classification is in conformity with Ambler’s molecular classification (Denisuik, 2013).

**Table-3: Functional classification by Bush, Jacoby and Medetros**

Group and subgroup	Molecular class (Ambler)	Preferred substrate	Inhibited by		Representative enzymes
			CA	TZB	
			EDTA		
1	C	Cephalosporins	-	-	MIR-1, ACT-1, CMY-2, FOX-1
1e	C	Cephalosporins	-	-	GC-1, CMY-37
2a	A	Penicillins	+	-	PC
2b	A	Penicillins, early cephalosporins	+	-	TEM-1, TEM-2, SHV-1
2be	A	ESC, monobactams	+	-	TEM-3, SHV-2, CTX-M-15, K1, PER-1, VEB-1
2br	A	Penicillins	-	-	TEM-30, SHV-10
2ber	A	ESC, monobactams	-	-	TEM-50
2c	A	Carbencillin	+	±	PSE-1, CARB-3
2d	D	Cloxacillin	±	-	OX-1, OXA-10
2de	D	ESC	±	-	OXA-11, OXA-15
2df	D	Carbapenems	±	-	OXA-23, OX-48
2e	A	ESC	±	-	CepA
2f	A	Carbapenems	±	-	KPC-2, IMI-1, SME-1
3a	B	Carbapenems	-	+	IMP-1, LI, NDM-1, VIM-1
3b	B	Carbapenems	-	+	CphA, Sfh-1

Keys: CA: clavulanic acid, TZB: tazobactam, ESC: Extended spectrum cephalosporin, (+): Yes, (-): No, (±): Sometimes, A: Serine  $\beta$ -lactamases, B: Metallo- $\beta$ -lactamases, C: AmpC  $\beta$ -lactamases (Rao, 2015).

## 2.8 Extended spectrum $\beta$ -Lactamases (ESBL)

Among the  $\beta$ -lactamases, ESBLs are worthy of the attention of the scientific community over the last decades. Generally, ESBLs are plasmid born and are known for their ability to hydrolyse oxyimino-cephalosporin (3rd- and 4th-generation cephalosporins) and monobactams but not cephamycin such as ceftazidime and carbapenems comprising meropenem, imipenem, ertapenem, and doripenem (Giske *et al.*, 2009). Furthermore, these are generally susceptible to  $\beta$ -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam. Classically, ESBLs are defined as enzymes originally derived or evolved from a narrow spectrum parent ESBL enzyme and thus gained the ability to inactivate the broad spectrum cephalosporins, penicillins, and aztreonam, but not the cephamycins (ceftazidime) or carbapenems by hydrolytic activity and are inhibited by  $\beta$ -lactamase inhibitors, that is, clavulanic acid. (Sadeeq *et al.*, 2018).

The term “extended broad-spectrum  $\beta$ -Lactamases” was coined by Jarlier and co-worker’s in 1988 to describe enzymes conferring (transferable) resistance to Extended spectrum cephalosporins; third generation cephalosporins such as cefotaxime, ceftriaxone and ceftazidime) in opposition to the broad spectrum enzymes – mainly TEM-1 –which could hydrolyse penicillins and broad spectrum penicillins, e.g., ampicillin (Rao, 2015). More so, the term ESBL was used to refer to those enzymes having ‘extended’ activity compared to the ‘broad spectrum activity’ of classical TEM or SHV enzymes. This is followed by stopping the continual use of the old term “broad”. In subsequent publications, the term ‘broad’ was dropped and the name “Extended-Spectrum  $\beta$ -Lactamase” became established (Tofteland, 2015).

The first description of ESBL enzymes was given in 1983 by Knothe and the clinical use of the term was re-defined by Giske *et al.* (2009). The ESBLs as defined by Giske *et al.* include all acquired  $\beta$ -lactamases with activity against extended-spectrum cephalosporins and/or carbapenems. Furthermore, most recent definition divides ESBL into three main groups.

- (i) ESBLA (class A ESBLs) comprises the most frequently found ESBL and the CTX-M, as well as SHV and TEM enzymes. These enzymes are mainly horizontally transferable and can be inactivated or inhibited by clavulanic acid. They are characterized by their ability to hydrolyse oxyimino-cephalosporins and monobactams, but not cephamycins or carbapenems (Baerum, 2014).
- (ii) ESBLM (miscellaneous ESBLs) are sectioned into ESBLM-C (class C, plasmid mediated AmpC) and ESBLM-D (class D). Acquired AmpC are the most frequently found ESBL in this class.
- (iii) ESBLCARBA (ESBLs which degrade carbapenems) are divided into ESBLCARBA-A, ESBLCARBA-B, and ESBLCARBA-D (Sadeeq *et al.*, 2018).

With the exception of ESBLA, the two other groups are ESBLM (for “miscellaneous”), of which transferable AmpC is an example and ESBLCARBA (for “carbapenemase”), of which *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM) and oxacillinase-48 (Oxa-48), Verona integron-encoded metallo- $\beta$ -lactamase (VIM) and imipenem metallo- $\beta$ -lactamase (IMP) are prominent examples (Arne, 2018; Lohr *et al.*, 2008).

**Table-7: Giske Classification of ESBL enzymes**

ESBL			
ESBL Group	ESBL <sub>A</sub>	ESBL <sub>M</sub>	ESBL <sub>CARBA</sub>
Example of enzymes containing carbapenemases with asterics	TEM, SHV, CTX-M	Ampc, some OXA	*NDM, *KPC, *VIM, *IMP, some *OXA

(Arne, 2018; Baerum, 2014).

### 2.8.1 Properties of ESBL

The ESBLs are enzymes whose rates of hydrolysis of the extended-spectrum  $\beta$ -Lactam antibiotics such as ceftazidime, cefotaxime, or aztreonam are >10 % than that for benzylpenicillin. These enzymes are susceptible to inhibition by  $\beta$ -Lactam inhibitors such as clavulanic acid, tazobactam, or sulbactam but have no hydrolytic activity against cephamycins and carbapenems (Bush, 2013). In the light of discovery of newer  $\beta$ -Lactamases and their hydrolytic profiles, the existing definition of ESBL is being strongly contested. Some researchers like “Livermore” are of the view that all  $\beta$ -Lactamases conferring resistance to extended-spectrum cephalosporins should be considered as ESBLs without

taking into account an arbitrary cut-off value of >10% hydrolysis rate (Livermore, 2008). Giske *et al.* (2009), proposed that the definition of ESBLs should include AmpC  $\beta$ -Lactamases and carbapenemases. The debate over the two alternate proposals by Livermore and Giske, respectively, shows that the definition and classification of ESBLs might undergo some changes in future (Bush *et al.*, 2009). Despite the ongoing debate, there is global acceptance of the current definition. Using the current definition, ESBLs have been detected among several bacteria, although members of Enterobacteriaceae remain their chief hosts. The ESBL enzymes have also been encountered among a few non-Enterobacteriaceae, such as *Pseudomonas* spp, *Stenotrophomonas* spp, *Acinetobacter* spp, *Vibrio* spp,

and *Haemophilus* spp, among others (Ny *et al.*, 2017). Despite the diversity in their hosts, the ESBLs predominantly belong to a few limited types. Depending on the general prevalence, ESBLs are broadly grouped into major and minor ESBL types. Major ESBL are commonly expressed by many clinical isolates and are detected in many parts of the world whereas the minor types are rarely encountered and are restricted to certain geographical locations only. As at present, the three major ESBL types are TEM, SHV and CTX-M., and have been found to be in constant spread from one geographical location of the world to the other (Rao, 2015; Tofteland, 2015).

### 2.8.2 Types of ESBLs

When third generation cephalosporins were introduced in the early 1980s, they represented a major breakthrough because they could not be hydrolysed by the broad spectrum penicillinases TEM-1 and SHV-137. This introduction also marked the starting point for a rapid evolution of TEM and SHV, and enzymes that were able to hydrolyse third generation cephalosporins sprung out of both groups (Canton *et al.*, 2012). The various types of ESBLs are;

- i. TEM type ESBLs
- ii. SHV type ESBLs
- iii. CTX-M type ESBLs

### 2.9.1 Risk factor for acquisition of ESBL producing Bacteria

There are a number of risk factors that have been linked with ESBL infections. Quite a lot of studies have been undertaken on the association between several risk factors and colonization or infection by the ESBL producers (Kluytmans *et al.*, 2013). Many of these studies conducted have reported isolation of ESBL producing organisms from food sources, these including fruits, raw vegetables as well as food of animal origins (Geser *et al.*, 2012). It is believed that these animals might have acquired the ESBL producing isolates following human contacts. However, at the same time, origin among these animals cannot be entirely ruled out. Although there are not many reports indicting human acquisition of ESBL producers following consumption of contaminated animal food, but there is the high risk attached to such practices (EFSA Panel on Biological Hazards, 2011; Raphael *et al.*, 2011).

The risk factors that have been linked with the increased colonization or infection by ESBL producing bacteria includes but not limited to; the travel to ESBL endemic regions such as Asian/Middle-East countries, prolong hospital stay, nursing home residence, Asian/African country of birth, the transfer of patients from among different health care facility, prolong and invasive medical procedures, the over use and reckless use of antibiotics (such as; quinolones and third-generation cephalosporins) for more than a week, intra-abdominal surgery, prolong stay in surgical wards, low

birth weight, the processing of central venous catheter, haemodialysis and diabetes mellitus among many others (Demirdag *et al.*, 2010; Saely *et al.*, 2011; Tangden *et al.*, 2010). A number of international collaborative studies such as SENTRY Antimicrobial Surveillance Program, Meropenem yearly susceptibility test Information collection (MYSTIC), and study Monitoring Antimicrobial Resistance Trends (SMART) among others are monitoring the trends and emergence of antibiotic resistance in many part of the world (Falagas and Karveli, 2006).YY.

### Prevention and Control

The infection and spread of ESBL producing bacteria have been linked with un-hygienic practices such as fecal oral contamination of food products, environmental pollution, as well as hand contamination of surfaces (Rawat and Nair, 2010). Proper infection-control practices along with the provision of barriers are equally important to curtail the rapid spread of outbreak caused by ESBL producing bacteria and other multidrug resistant bacteria (CDC, 2019). More so, there is the high need for hospitals to strengthen their infection control measures as many isolates associated with hospital acquired infections have been linked with the production of multidrug resistant enzymes such as  $\beta$ -Lactamase and ESBL enzymes (Ling *et al.*, 2015). At an institutional level, different measures to stop or rather reduce the persistence of resistant bacteria as well as surveillance policies will seriously protect residents from the high risk posed by  $\beta$ -Lactamase and ESBL enterobacteriaceae. Practices such as restrictions, on the empirical use of broad-spectrum antimicrobial agents such as the third- and fourth-generation cephalosporins and quinolones. It is also recommended that the use of  $\beta$ -lactam/  $\beta$ -lactamase inhibitor combinations, rather than cephalosporins, as workhorse empirical therapy for infections suspected as being due to gram-negative bacilli, may facilitate control of ESBL producers (Tacconelli *et al.*, 2015).

## CONCLUSION

The emergence and dissemination of extended-spectrum  $\beta$ -lactamase (ESBL) producing bacteria currently constitutes a major public health concern. ESBLs are enzymes that hydrolyze penicillins, first to third generation cephalosporins as well as aztreonam, at a rate that exceeds 10% of their hydrolysis rate for benzylpenicillin. Resistance to  $\beta$ -lactams is frequently mediated through production of  $\beta$ -lactamase enzymes which break down  $\beta$ -lactam molecules. So far, more than 500  $\beta$ -lactamases have been reported to date. Each of these 500 enzyme poses a serious threat to public health and many were found to be associated with a number of deadly outbreaks which claims thousands of innocent lives globally. The most common type of bacteria that produces ESBL includes *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Salmonella* among many others. The conditions associated with infections

with ESBL producing bacteria includes; diarrhea, skin infections, dysentery and Urinary Tract infections. Hand washings along with other hygienic living conditions have been known to reduce the spreads of ESBL producing bacteria.

## RECOMMENDATION

- i. Different Hospitals in Nigeria should implement and strengthen their Surveillance system, which is to be conducted at a regular basis. This will checkmate for the occurrence of ESBL enzymes as well as the detection of resistant genes, as a particular isolate may harbour many different resistant genes.
- ii. Proper handling of antibiotics as well as dose completion should be encouraged as this is linked with the growing level of microbial multidrug resistance.
- iii. Determination of the antibacterial efficacy of the most commonly used Cephalosporins antibiotics should be conducted regularly

### Conflict of interest

The authors hereby declare no any conflict of interest and have read and agree with the content of the manuscript.

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