International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 7, Issue 2, pp: (243-257), Month: October 2019 - March 2020, Available at: www.researchpublish.com

A review on β-lactam antibiotic drug resistance

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Abstract: **β-lactam antibiotics constitutes a extensive magnificence of antibiotic marketers that comprise β-lactam ring in their molecular shape these agents includes cephalosporins, monobactams, penicillins and carbapenems. these are the most extensively used antibiotics which act by inhibiting the synthesis of the bacterial mobile wall such interest ends in the lysis and demise of the micro organism. The declining effectiveness of antibiotics imposes potentially big fitness and financial burdens on societies. Quantifying the financial results of antibiotic resistance efficiently can help policy-makers and healthcare experts to set priorities, but figuring out the actual impact of antibiotic resistance on scientific consequences is a vital first step. In this newsletter, we overview and talk the contributions and obstacles of studies that estimate the ailment burden on account of antibiotic resistance and research that estimate the monetary burden of resistance. We additionally remember other elements which might be essential in a comprehensive technique to evaluating the economic burden of antibiotic resistance. because of the wide packages of those antibiotics bacteria have developed resistance mechanism in opposition to these antibiotics which is usually mediated via the enzymes β-lactamases, it hydrolyses β-lactam ring of the β-lactam antibiotics rendering it inactive. latest research have revealed that the combination of β-lactam antibiotics with β-lactamase inhibitors may be used to correctly triumph over the impact of β-lactamases. This overview mentioned the mechanism of β-lactam antibiotic hobby, the mechanisms of β-lactam antibiotic resistance and the way to triumph over the effect of the β-lactamases.**

Keywords: **Antibiotic resistance, attributable morbidity, mortality, economics, Beta-lactum, Beta-lactamases, Penicillin- Binding, protein, penicillin, Amp-gents.**

1. INTRODUCTION

B-Lactams are the most widely used class of antibiotics. Since the discovery of benzylpenicillin in the 1920s, thousands of new penicillin derivatives and related b-lactam classes of cephalosporins, cephamycins, monobactams, and carbapenems have been discovered. Each new class of b-lactam has been developed either to increase the spectrum of activity to include additional bacterial species or to address specific resistance mechanisms that have arisen in the targeted bacterial population. Resistance to b-lactams is primarily because of bacterially produced b-lactamase enzymes that hydrolyze the b-lactam ring, thereby inactivating the drug. The newest effort to circumvent resistance is the development of novel broad-spectrum b-lactamase inhibitors that work against many problematic b-lactamases, including cephalosporinases and serine-based carbapenemases, which severely limit therapeutic options. This work provides a comprehensive overview of b-lactam antibiotics that are currently in use, as well as a look ahead to several new compounds that are in the development pipeline.

When **Alexander Fleming** was searching for aconsortium of scientists from England and the an antistaphylococcal bacteriophage in United States were able to optimize the isolation his laboratory in the 1920s, he deliberately left plates out on the bench to capture airborne agents that might also serve to kill staphylococci (Fleming 1929). His success was greater than he must have hoped for. His initial publication on benzylpenicillin described a substance that was unstable in aqueous solution but that might serve as an antiseptic or as a selective agent for isolation of Gram-negative bacteria that were present in mixed cultures of staphylococci and streptococci. Asthepotentialutility of penicillin G as a parenteral therapeutic agent became more obvious, Fleming, Abraham, Florey, and and identification of benzylpenicillin to assist in the treatment of Allied soldiers in World War II (Macfarlane 1979). These activities set the stage for the launch of the most successful class of antibiotics in history.

b-Lactam antibiotics are currently the most used class of antibacterial agents in the infectious disease armamentarium. As shown in Figure 1, b-lactams account for 65% of all prescriptions for injectable antibiotics in the United States. Of the b-lactams, cephalosporins comprise nearly half of the prescriptions (Table 1).

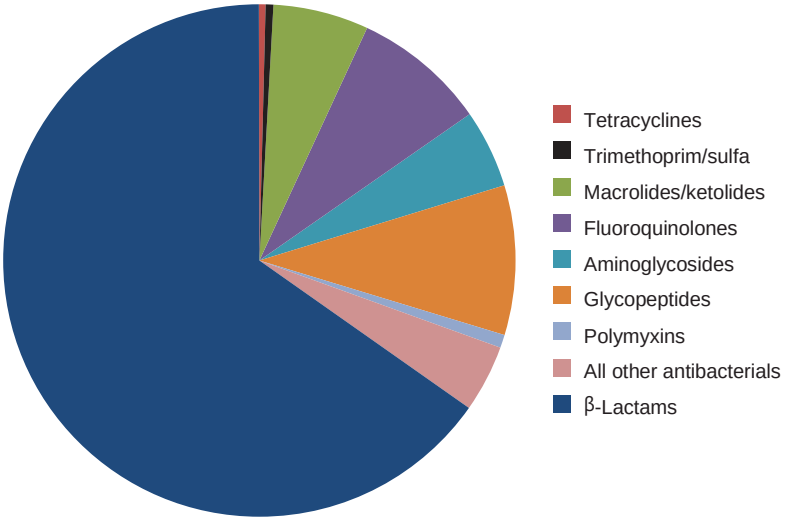


Figure 1. Proportion of prescriptions in the United States for injectable antibiotics by class for years 2004–2014. The percentage of standard units foreach injectable antibiotic prescribed in the United States from 2004 to 2014 is shown as follows: b-lactams, 65.24%; glycopeptides, 9%; fluoroquinolones, 8%; macrolides/ketolides, 6%; aminoglycosides, 5%; polymyxins, 1%; trimethoprim/sulfamethoxazole, 0.5%; tetracyclines (excluding tigecycline), 0.4%; all otherantibiotics (including daptomycin, linezolid, and tigecycline), 4.21%. (Datafrom the IMS MDART Quarterly Database on file at tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam. AstraZeneca.)

The b-lactams are well tolerated, efficacious and widely prescribed. Their major toxicity is related to an allergic response in a small percentage of patients who react to related side chain determinants; notably, these reactions are most common with penicillins and cephalosporins with minimal reactivity caused by monobactams (Saxon et al. 1984; Moss et al. 1991). The bactericidal mechanism of killing by b-lactams is perceived to be a major advantage in the treatment of serious infections. When these agents were threatened by the rapid emergence of b-lactamases, b-lactamase-stable agents were developed, as well as potent b-lactamase inhibitors (BLIs). In this introductory description of the b-lactams, the most commonly available b-lactams and BLIs will be presented, with a brief summary of their general characteristics. Occasional agents have been included for their historical or scientific importance. Note that resistance mechanisms will be discussed in detail in other articles in this collection.

Table 1. Usage of parenteral b-lactams by class from 2004–2104 in the United States

Class of b-lactam	Percentage of prescriptions[a]
Narrow spectrum penicillins	3.12
Broad spectrum penicillins[b]	36.54
Cephalosporins	47.49
Monobactams	1.66
Carbapenems	11.20

The percentage for each injectable antibiotic class prescribed in the United States from 2004 to 2014. (Data from the IMS MDART Quarterly Database on file at tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam.

AstraZeneca.) b Broad-spectrum penicillins include the b-lactam/ b-lactam-inhibitor combinations piperacillin-

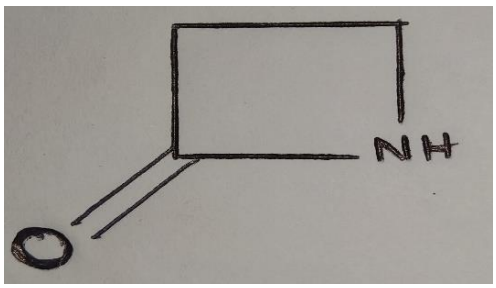
The concept that involves the use of chemicals to alleviate disease date back to the ancient Egypt One of the major significant advances in medicine is the development of antibiotics.[1] Antibiotics have saved many lives and continue to be the main therapy for infections related to bacteria. Penicillin G was the first of beta-lactam developed which lead the search for the synthesis of additional derivatives. The quest gave result to the beta-lactam antibiotics in clinical

application today.[2] the class of broad-spectrum antibiotics that consist of all antibiotic agents with beta-lactam ring in their structures is called β-lactam antibiotics. It includes penicillin derivatives, monobactams, cephalosporin and carbapenems.[3]

β-lactam antibiotics act by inhibiting the bacterial cell wall biosynthesis; they are the most available antibiotics which treat a number of bacterial infections. For having a global positive impact on health by treating bacterial infections, penicillin and other β-lactam antibiotics are arguably considered the most important drugs ever.[4] A broad spectrum of bacteria can be killed by β-lactams and its toxicity to humans is very low this implies that, the resistance to β-lactam antibiotics is severe threat,[5] bacteria and other infection causing microbes are remarkably developed several ways to become resistant to antibiotics and other antimicrobial drugs. This is as a result mainly of increase use and misuse of the antibiotics in different medical illnesses.[6] nowadays, about. It was reported that 70% of the bacteria causing infections in hospitals are resistant to at one or more of the commonly used drug, some bacteria are found to be resistant to almost all antibiotics that are approved and can be treated only by some drugs that are potentially toxic. There have been reports which are documented about the alarming increase in bacterial antibiotic resistance which cause community acquired infections, examples include the *staphylococci* and *pneumococci* which are major causes of disease and mortality.[7] high prevalence of bacterial resistance to various pathogens such as *Acinetobacter*, *Proteus*, *E.coli*, *Klebsiella* and *Pseudomonas*.[8]

Accumulate evidence also proved that bacteria could pass resistance genes between strains and species. *Staphylococci* genes of antibiotic-resistance are carried on plasmids which will be exchanged with enterococcus, bacillus and Streptococcus making it possible for acquiring additional genes and gene combinations. Organisms that are resistant to treatment with many drugs are known as multiple drug resistant.[9] Examples of multiple drug resistant organisms include: Extended-spectrum beta-lactamases (ESBLs) which show resistance to monobactams and cephalosporins. Penicillin-resistant *Streptococcus pneumonia* (PRSP) the enzymes of ESBL are plasmid mediated enzymes that have the capability to hydrolyze and inactivate a wide variety of beta lactams, including, third generation aztreonam, cephalosporins and penicillins.[10]

β-lactam antibiotic resistance however has become a major health care issue. The reactions that involve the cleavage of the β-lactam ring of the antibiotic by β-lactamases of bacteria is the primary mechanism of β-lactam resistance.[11] the cell wall of bacteria consists of Peptidoglycan which is a giant polymer of repeated chains of disaccharides joined by peptide bridges. The joining results from a transpeptidation reaction catalysed by enzymes which are inhibited by β-lactams. The enzymes responsible for the assembly of peptidoglycan are known as PBPs2 or penicillin-binding proteins. They consist of penicillin-binding domain which generally catalyses the transpeptidation reaction, but can also act as a endopeptidase or carboxypeptidase in some cases Figure 1.[12]



Beta Lactam Ring

Figure 1: Some clinically important β-lactams.

2. BETA-LACTAM ANTIBIOTICS

The structures of penicillin consist of a thiazolidine ring connected to a beta-lactam ring, which is attached to a side chain. All penicillins are derived from 6-Amino-penecillinic acid; the various penicillins differ in their side chain structure. Penicillins are divided into natural and semi-synthetic ones. Natural penicillins are extracted from the cultural solution of penicillia. Prototype is penicillin G which is PH sensitive and effective against Gram- positive cells susceptible to penicillinase.

Semi-synthetic penicillins are produced by growing penicillium in culture so that only the nucleus is synthesised. R group are attached in lab or grow penicillium, extract natural penicillin, remove the R group and attach wanted R group. This

group of penicillins have broader spectrum they are effective against Gram- negative cells and they are not resistant to Penicillinase. The cephalosporins are a class of β-lactam antibiotics originally derived from the *fungus Acremonium*, which was previously known as "*Cephalosporium*".

Cephalosporins are derivatives of 7-amino-cephalosporanic acids and are closely related in structure to Penicillin. They have betalactam ring. They are relatively stable in dilute acid and are highly resistant to penicillinase. All cephalosporins are active against most Gram-positive cocci, the first generation include cephalothin, cefazolin, cephalexin est. they have stronger effect against Grampositive bacteria than Gram-negative bacteria, the second generation antimicrobial acation against Gram-negative bacteria is increased. The third generation has broadest effect against gram-negative and lowest activity against Gram-positive bacteria. The fourth generations are extended-spectrum agents with similar activity against Gram-positive organisms as first-generation cephalosporins, Fourth-generation cephalosporins are zwitterions that can penetrate the outer membrane of Gram-negative bacteria.[13] They also have a greater resistance to β-lactamases than the third-generation cephalosporins Figure 2 and Figure 3.

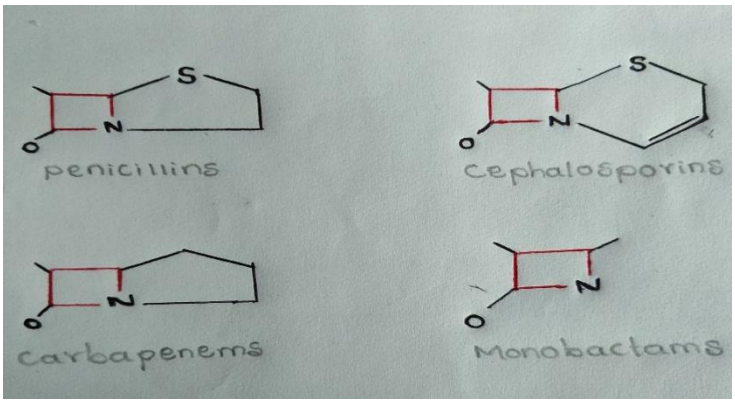


Figure 2: Mechanisms of action of β-lactam antibiotics.

The mechanism of action of beta-lactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis.[13] the stability of cell wall is essential for the shape and protection of the cell in hostile and hypertonic environment the cell wall is comprised of two alternating units which are the N-acetylmuramic acid (NAM) and N-acetyl glucosamine (NAG), these two units are linked together by enzyme transglycosidase. Pentapeptide is attached to each NAM unit which includes D-alaine-D-alanine. The cross-link between the two Dalanine of two NAM is catalysed by PBP. The cross-linked between the adjacent glycans gives the rigidity of the cell wall.[14,15] The ring of beta-lactams antibiotics is similar to the pentapeptide's D-alaineD-alanine of N-acetylmuramic acid, because of this similarity the penicillin binding proteins uses beta-lactam as building blocks for the synthesis of cell wall instead of NAM Pentapeptide.[16] This result in the acylation of the enzyme PBP subsequently rendering the enzyme incapable of catalyzing further transpeptidation reactions.[17] when this reaction comes to a halt, Peptidoglycans autolysis commence which result to the compromises of the integrity of the cell wall and increase its permeability .thus the beta-lactam mediated activity (inhibition) causes the lyses of the cell and the death of the bacteria.[18]

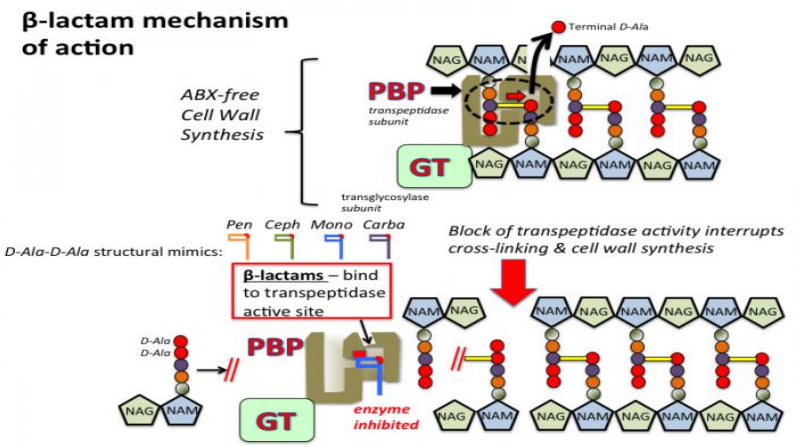


Figure 3: Mechanism of action of β-lactam.

PHYSIOLOGICAL ANALYSIS OF B-LACTAM EFFECT:

It was discovered by Gardner that bacteria forms filaments when treated with low concentration of penicillin.[19] this discovery support early investigation which indicated that penicillin interferes with the maintenance of the cell shape of the cell. Results from subsequent studies by Duguid using different concentration of penicillin proved the interference of penicillin in cell division and maintenance of the integrity of the bacterial cell.[20]

BIOCHEMICAL ANALYSIS OF B-LACTAM EFFECT:

Park and Johnson gave the first biochemical clue about the penicillin action site.[21,22] they observed the accumulation of novel uridine peptides in the cytoplasm of *S. aureus* after being treated with penicillin. Subsequent investigation by Park and Stominger revealed that the amino acids and sugars of the accumulated peptides were similar to those of the cell wall of bacteria. This observation suggested that the accumulated uridine peptides in the cytoplasm were the precursors of cell wall accumulated as a result of inhibition of cell wall biosynthesis by penicillin.[23]

BIOPHYSICAL ANALYSIS OF B-LACTAM EFFECT:

In 1949, radioactive penicillin was used to study the specific site of action on the cell wall of bacteria.[24–27] it was observed that penicillin bind to a target which was termed penicillin binding component PBC and the complex formed was penicillin-PBC complex.[25] penicillin binds to its target via covalent bond. The complex was subjected to SDS-PAGE and the PBC resolved into various proteins of molecular weight that ranges between 40-90 KDa.[28] these proteins were termed PBPs and were given numbers according to their descending molecular weight. The concentration of the proteins, their numbers, molecular weight and sensitivity to β-lactam antibiotics varies from one specie to another.[29]

3. GENETIC ANALYSIS

PBP1 functions involve the elongation of the cell wall. PBP1cephaloridine is an agent that act against PBP1 resulting in the inhibition of cell wall elongation.[30] There are two distinct components of PBP1 which are PBP1a and PBP1b. PBP1a gene was mapped to MrcA or ponA. Mutant strain lacking ponA/MrcA appeared to grow normally but show slow rate of β-lactam induced lysis.[31] PBP1a catalysis the polymerization of glycan subunits.[32] while PBP1b is responsible for transglycosylase and DD-transpeptidase enzymatic reaction.33,34

PBP2 was the first to be discovered due to its ability to specifically bind with mecillinam.[35] its binding with mecillinam causes changes in *E.coli* shape from rod to ovoid.[36] PBP2 is the major protein involves in the maintenance of cell shape; its inhibition by β-lactams can cause destruction of the cell shape and inhibition of division.[37–38]

PBP3 – mutant *E.coli* strains lacking PBP3 proteins when isolated and cultured at temperature of 30°C.[35] appeared slightly longer than the parental strain. At an increase restrictive temperature to 42°C cell division ceased but, there was continuous increase in cell density. This suggested that DNA replication and cell growth were not affected in the absence of PBP3 at restrictive temperature. It also proves that PBP3 it is essential cell division protein.[39] Other Supporting evidence for its vital role in cell division came from the use of piperacillin, PBP3- specific β-lactam antibiotics and, furazlocillin.[40]

PBP4–strains of *E.coli* lacking the penicillin- sensitive activities of DD-endopeptidase and DD-carboxypeptidase1b showed a loss of PBP4.[41,42] This mutation was mapped and the gene was located at 68min on the E. coli map which is dacB gene.[42] However, the PBP4 overexpression showed an increase in DD-endopeptidase and DDcarboxypeptidase, which has no effect transpeptidation reaction.[43] PBP4 was demonstrated as the only PBP of E. coli that possessed DD-endopeptidase activity.[44]

PBP5 membrane-bound proteins which catalyzes a transpeptidase reaction and have a weak penicillinase activity.[45] the gene which is encoding PBP5 was mapped to dacA.[46]

PBP6–the gene that encode for this protein is the dacC shares up to 62% sequence with PBP5.[47] PBP6 and PBP5 catalyze identical reactions but, PBP5 shows higher specific activity than PBP6 toward uncross-linked peptidoglycan.[48] Deletion of dacC had no effect on cell morphology and growth rate.[49] However, strains lacking PBP6 showed a very slight increase in antibiotic sensitivity.[49]

PBP7 and PBP8 these are characterized more recently than the other PBPs. PBP8 is a product of PBP7 as result of OmpT proteolytic reaction.[50] PBP8 increased expression is usually associated with the increased ceftazidime and cephaloridine resistance.[51] Both PBP7 and PBP8 are soluble periplasmic proteins that are peripherally associated with the membrane. Encoding gene of was narrowed to 47.8 and 48min on the *E. coli* chromosome and pbpG encode for PBP7.[52]

RESISTANCE TO B-LACTAM ACTIVITY:

There are four major ways bacteria avoid the bactericidal effect of beta-lactams:-

Altered Penicillin-binding proteins that showcase pretty low affinity closer to beta-lactam antibiotics a few examples are the PBP 2_(PBP2a) of Staphylococcus aureus and PBP 2x of Streptococcus pneumoniae.fifty three penicillins are unable to inactivate those PBPs due to the fact they're exceedingly resistant to it and they can expect the features of different PBPs after their deactivation. diminished or completely lack of expression of outer membrane proteins (OMP) in gram-terrible bacteria. to be able to gather get right of entry to to PBPs, beta-lactam have circulate thru porin channels inside the outer membrane, lower expression of OMPs limits the of certain beta-lactams from entry into the periplasmic area of gram-poor micro therefore restriction its access to PBPs at the internal membrane. Resistance to Imipenem in Klebsiella pneumoniae and Pseudomonas aeruginosa can stand up from the loss of OmpK36 and OMP D2, respectively. fifty four–56 It became stated that the resistance to meropenem and Imipenem in a few isolate of multidrug resistant Acinetobacter baumannii to is associated with the loss of the CarO OMP. fifty seven,fifty eight insertion of a few collection to porin encoding genes or its mutation can lead to the manufacturing of proteins with lessen features and in the end lower the diffusion of beta-lactam into the cell.fifty nine it's far believed that the destruction of porin alone isn't always sufficient enough for acquiring resistance phenotype. This mechanism is usually coupled with the expression of beta-lactamases. 59,60

Efflux pumps it is a part of intrinsic resistance or acquired resistance phenotype. Efflux pumps have the capability to export various substrates from the periplasmic part of the cell to the surrounding environment.[61] these pumps are the determinant of multidrug resistance in various Gram-negative bacteria especially *P. aeruginosa*. The decrease in the organism outer membrane permeability in combination with the upregulation of the mexAmexB-OprD can contribute to decreased susceptibility to various betalactam antibiotics including Cephalosporin, penicillin, tetracycline, quinolones and Chloramphenicol.[62–65]

Beta-lactamases Production Bacteria produce enzymes known as Beta-lactamases that hydrolyze the beta-lactam ring subsequently the beta-lactam antibiotic is rendered inactive before it get to the PBP target. because of the structural relation that beta-lactamases shares with PBP, it bind, acylate and also use water molecules to hydrolyze and inactivate beta-lactam share with PBPs allows these enzymes to bind, acylate, and use a strategically located water molecule to hydrolyze and thereby inactivate the beta-lactam.[66] in gram-negative bacteria the most important resistance mechanism is the inactivation of beta-lactams by beta-lactamases. It has been reported that there are over 530 beta-lactamase enzymes (K. Bush, 9th International Congress on beta-Lactamases, Leonessa, Italy). beta-lactamases contains either serine residue or metal ion In their active site, betalactamases with a serine residue (Ambler classes A, C, D) and metal ion Zn^{2+} (Ambler class B) that attack beta-lactam ring and break the amide bond in the ring Figure 4.[67–69]

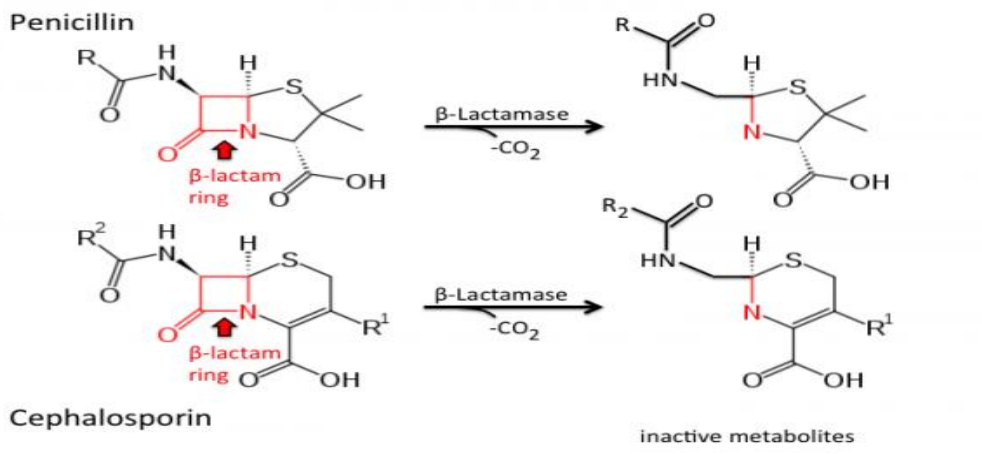


Figure 4: Mechanism of beta-lactam resistance.

Serine β-lactamases have serine as an active-site which is used to hydrolyze the ring of β-lactam in β-lactam antibiotics. The serine β-lactamases are classified based on sequence similarity into three classes, A, C, and D.[70–72] which are all related to the DD peptidases.[73]

Amber class A:

This class was first observed in *E.coli* in 1963 and was termed TEM; it was named after the person from whom it was isolated. This class of enzyme exhibit a level of susceptibility to many commercially available β-lactamase inhibitors like Clavulante, Sulbactam and Tazobactam.[74,75] other members of this class including VH5, PER and SHV were also reported.[76] SHV-1 and TEM-1 have almost 68% sequence homology and can be found in *E.coli*, K. Pneumoniae and other pathogens responsible for various infections. TEM-t and SHV-1 confers resistance to Ampicillin and Piperacillin.[77]

Ambler class B:

These enzymes contain an enzymes a small number Zn^{2+} this class one of the atoms of Zinc in inactivation cephalosporins and penicillins of are MBLs that use one of two zinc (Zn^{2+}) atoms for inactivating penicillins and cephalosporins. However, their activity can be inhibited by chelating agents (EDTA) but not by sulfones or clavulanic acid. IMP-1 was the first to be discovered in this class form *P. aeruginosa*. Varieties of genetic element such as plasmid, integron were found to have the bla genes encoding.[78]

Ambler class C:

Enzymes in this class are active against cephalosporins, therefore sometimes called cephalosporinases.[79] their genes are encoded in the chromosome and are mostly synthesized by Gram-negative bacteria. The sequences of these enzymes that are known are highly conserved.[80] The cephalosporin-hydrolyzing chromosomal β-lactamase of his class in *P. aeruginosa* are encoded by ampC (PA4110), which was cloned and sequenced.[81]

Amber class D:

The enzymes in this class are capable of degrading isoxazolyl β-lactams like methnicillin and oxacillin. Thus they are also called oxacillinases.[82] however their activity is inhibited by clavulanic acid.[83]

4. OVERCOMING B-LACTAMASES

There are basically two ways to overcome the effect of hydrolytic activity of beta-lactamases. The first principle involves getting molecules that inactivate or inhibit beta-lactamases. Sulbactam, clavulanic acid and tazobactam-lactamase are the three inhibitors that are used in the clinical application. All of these three compounds share similar structures with penicillin. Some of the features of these compounds include high affinity for β-lactamases, each of these compounds occupies the active site relatively longer than β-lactams and undergoes different reaction chemistry and they are also poorly hydrolyzed by the enzyme.[84–86] therefore, β-lactamase inhibitors are also called "suicide inhibitors" because they get trapped by the beta-lactamase. This phenomenon has been the subject of research by academic laboratories and some pharmaceutical companies.[87–93] synthesis of compounds by substituted sulfones, cephem and penem gives optimism that new inhibitors of β-lactamase will be found.[94] The Recent research studies that are being carried out to elucidate the mechanistic details of beta-lactamase inhibition of deacylationdeficient beta-lactamases will surely advance the knowledge of the chemistry of inactivation.[95]

The second principle involves getting a new beta-lactam antibiotic that possesses great affinity for the β-lactamases and cannot be hydrolyzed by the PBP, or poorly hydrolyzed by it. This has been the original rationale behind extended-spectrum carbapenems or cephalosporins. Common example of this principle is the development of compounds such as doripenem and ceftobiprol**.** Ceftobiprole is an "anti-MRSA cephalosporin" which demonstrates very high affinity for PBP2, it is active against gram-negative bacteria possessing betalactamases and resistant to penicillinase of *S. aureus* and is.[96] Doripenem is a modified carbapenem with sulfamoylaminomethyl substituted pyrrolidylthio group at the C2 position and 1-beta-methyl group, which shows very high activity against *Acinetobacter* spp, *P. aeruginosa* and Burkholderia cepacia. [97]

Sulbactam:-

Sulbactam known as a semi synthetic substance capable of inactivating β-lactamases though it is not as potent as Clavulanic acid it shows high activity against class ii-iv and displays relatively low action against class1β-lactamase. The combination of sulbactam with some antibiotics tends to increase their activity against antibiotic resistant bacteria for example; the antibacterial activity of ampicillin will be extended and becomes more effective when it is combining with sulbactam. A compound was developed containing sulbactamampicillin known as sultamicillin was found clinically effective in treatment of various infections such as those of skin and soft tissues as well as many other infections. it was

also reported that a single dose of ampicillin-sulbactam administered intra-muscularly with probenecid had therapeutic effect against infections of neisseria gonorrhae which is an ampicillin resistant.[98]

Tazobactam:-

Piperacillin combined with tazobactam was first prepared in 1993 in the United state. piperacillin is known to have antibiotic activity against gram-negative and gram-positive as well as aerobes and anaerobes.[99] piperacillin-tazobactam combination act as a good β-lactamase inhibitor with broad spectrum of antibacterial activity in both gram-negative and gram-positive bacteria. But such combination has no inhibition effect against isolates of gram-negative bacillus having AmpC β-lactamase. Piperacillin-tazobactam combination is reported to be effective for treatment of various infections including intra-abdominal infections.[100]

Clavulanic acid:-

Ticarcillin-clavulanate was the first combination β-lactam β-lactamase inhibitor developed in 1985 for parenteral administration. It increases the inhibitory activity against -lactamase-producing *staphylococci*, *Proteus* spp, H. influenzae, *Pseudomonas* spp, *Klebsiella* spp *Providencia*, and *E. coli*.[101] the combination of amoxicillin to clavulanic acid increases the organism susceptibility to amoxicillin like amoxicillin resistant *Haemoehilus influenza* and *Neisseria gonorrhea*.[102]

ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE: HOW MUCH DO WE REALLY KNOW?

The introduction of antibiotics, along with public health improvements in sanitation, hygiene, and safe drinking water, was associated with an accelerated decline in infectious disease-related mortality in the USA during the 20th century [103,104]. Clinical studies have shown that the mortality reduction with antibiotics ranges from 10% for skin infections to 75% for bacterial endocarditis [105]. Antibiotics have been pivotal in treating and preventing common infections, but their overuse and misuse have contributed to an alarming increase in antibiotic resistance worldwide. With a declining choice of antibiotics, we have entered a 'post-antibiotic' era [106,107].

Several studies have shown that antibiotic-resistant infections are associated with increased morbidity and mortality as compared with antibiotic-susceptible infections; however, quantifying the disease burden with any degree of accuracy has proven difficult, and existing studies have major methodological limitations and biases [108–110]. Accurately quantifying the effect of antibiotic resistance on clinical outcomes is essential for estimating the associated economic burden. In this article, we review the existing estimates of disease and economic burdens attributable to antibiotic-resistant bacterial infections (excluding tuberculosis). We summarize the limitations of these studies, and discuss ways to more accurately quantify the disease and economic burdens attributable to antibiotic resistance.

BROADER APPROACHES TO ESTIMATING THE ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE:

maximum research considering the costs of antibiotic-resistant infections take a microeconomic approach that consists of fitness area expenses. however, Smith et al. [111] argue for a macroeconomic technique that consists of larger monetary indicators, inclusive of country wide earnings, labour supply, gross home product (GDP), and monetary increase.

At least one take a look at has hypothesized that an increase in resistant infections has the capability to lower the excellent and amount of the labour deliver, as fewer individuals would make contributions to the labour market, hampering manufacturing sports [112]. in step with this argument, as country wide output depends on these labour inputs, country wide output—and ultimately countrywide income—might fall. similarly, decreased productiveness can bring about an increase in the price of productiveness, and, as a end result, the charges of products and offerings can upward push, which then can decrease general GDP. With a reduction in call for for goods and services, producers will lessen the usage of labour inputs, inflicting unemployment and lowering family earnings and typical monetary growth.

the usage of a computable widespread equilibrium (CGE) approach, Smith et al. [111] proven the macroeconomic effects of MRSA for the UK. A CGE model is a quantitative approach for evaluating the effects of economic and coverage 'shocks' at the financial system as an entire. The model makes use of three monetary sellers to explain the financial system: consumers, producers, and the government. Equilibrium represents the fees at which the extent of manufacturing and consumption inside every man or woman zone confirms that the quantity furnished equals the amount demanded throughout all sectors. Antibiotic resistance is added into the model as a shock that alters labour deliver and enter productivity. Assuming that forty% of S. aureus isolates are methicillin-resistant, primarily based on previous estimates inside the united kingdom, a CGE technique suggests that this shock could reduce the labour supply by using zero.1% and decrease GDP by means of zero.4%, equal to losses of £3 billion and £eleven billion, respectively.

5. CONCLUSION

Estimating the economic burden of antibiotic-resistant bacterial infections remains a challenge. Quantifying the disease burden attributable to antibiotic resistance is an important prerequisite. Although resistance has been shown to be associated with adverse health outcomes, existing studies quantifying the disease burden have methodological limitations. Recent studies using multistate models accounting for the time-varying nature of antibiotic-resistant infections have reported more conservative estimates of morbidity and mortality; however, these studies did not address all methodological limitations, leaving the true disease burden still largely unknown. Future studies estimating clinical outcomes of antibiotic-resistant infections should address the methodological limitations by using multistate models with large patient populations in multicentre settings or by using large administrative datasets. {112}

Similarly, current economic estimates of antibiotic resistance are limited in scope and do not take into account the wider societal value of antibiotics, thereby likely misestimating the true economic effects of antibiotic resistance. To better quantify the economic repercussions of antibiotic resistance, future studies must use macroeconomic approaches that consider the broader consequences of increasing resistance, including the loss of antibiotic efficacy in modern medicine. Until we overcome these challenges, the true disease and economic burden of antibiotic resistance will remain poorly quantified.

Since b-lactam antibiotics introduction into clinical field more than 60years ago, beta-lactam antibiotics have been the major source of antimicrobial therapy. The mechanism of action of betalactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis subsequently resulting in the lysis and death of the bacteria. Unfortunately, bacteria have developed resistance to β-lactam antibiotics through a defense mechanisms to protect themselves against the effect of the antibiotics by Altered Penicillin-binding proteins that exhibit relatively low affinity toward beta-lactam antibiotics, diminished or completely lack of expression of outer membrane proteins (OMP) in gram-negative bacteria, Efflux pumps it is a part of intrinsic resistance or acquired resistance phenotype and by beta-lactamases Production which plays the major role in resistance mechanism by hydrolyzing the beta-lactam ring subsequently the beta-lactam antibiotic is rendered inactive before it get to the PBP target. This review have shown how the β-lactamase activity can be overcome which is by two principles, the first involves getting molecules that inactivate or inhibit beta-lactamases. molecules like sulbactam, clavulanic acid and tazobactam .the second principles involves getting a new beta-lactam antibiotic that possesses great affinity for the β-lactamases and cannot be hydrolyzed by or poorly hydrolyzed by β-lactamases.

6. B-LACTAM RESISTANCE: CONCLUDING REMARKS

Resistance to the b-lactams continues to increase, especially in Gram-negative organisms (Vasoo et al. 2015), because of the widespread therapeutic dependence on these efficacious and safeantibiotics (see Fig. 1).Major resistance mechanisms will be expanded on in other articles in this collection. PBP acquisition or mutation is the major b-lactam-resistance mechanism in Gram-positive bacteria (see Fisher and Mobashery 2016). The most prevalent and most damaging resistance mechanisms among Gram-negative pathogens are represented by the b-lactamases (Babic et al. 2006; Livermore 2012), both chromosomally encoded enzymes that may be produced at high levels and transferable enzymes that travel on mobile elements among species (Bush 2013). When these targeted mechanisms are combined with decreased uptake or increased efflux of the blactam, high-level resistance becomes a major clinical problem (see Bonomo 2016). Perhaps the most encouraging prospect in counteracting resistance is the emergence of new classes of blactamase inhibitors that will provide protection for some of the most valuable antibiotics in clinical practice, at least for the present time.

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