Mechanisms of Antibiotics Resistance in Bacteria (Review Article)

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Abstract

One kind of medication resistance that occurs when a microbe can withstand exposure to an antibiotic is known as antibiotic resistance. Antimicrobial drug resistance in bacteria can arise from spontaneous or induced genetic mutations; nevertheless, genes causing resistance can be horizontally transferred between bacteria by conjugation, transduction, or transformation. Therefore, a gene that develops resistance to antibiotics through natural selection might be spread. Antibiotic resistance is subsequently selected for by evolutionary stressors like antibiotic exposure. Plasmids have a large number of antibiotic resistance genes, which aid in their transmission. A bacteria is referred to as multidrug resistant (MDR), superbug, or super bacterium if it possesses several resistance genes. In the modern world, resistance is growing, which has led to a significant public health crisis. The sharp increase in antibiotic use is the main factor causing antibiotic-resistant bacteria to arise and spread. This pattern, which attributes infectious disease causation to microbial pathogens, is a reflection of the global medicalization of society. Antibiotics offer recovery. This, together with the fact that they are generally easy to use, have brief treatment needs, and are freely available without a prescription in many areas of the world, creates a demand that is being filled by a rising number of generic medications made in developing market countries. The animal welfare industry has seen a similar increase in consumption, raising worries about the spread of antibiotic resistance up the food chain. Unpredictable disasters that cause population growth, mass migration, starvation, and contaminated water supplies also pose a hazard to human health and aid in the spread of antibiotic-resistant organisms. State-to-state conflicts, environmental deterioration, and climate change can create conditions that encourage the spread of infectious diseases and perhaps elevate antibiotic resistance.

Keywords: Antibiotics, Multidrug resistance, Mechanism of resistance, Extended-spectrum beta-lactamases genes, Classification of β –lactamase,

Introduction

Even the most dependable and successful antibiotics are in danger of losing their effectiveness due to rising rates of bacterial resistance in both common and dangerous diseases. Multidrug resistant infections are becoming more and more commonplace in our daily lives, making it necessary to discover a strategy to stop their spread before it becomes a major public health issue (1). Up until recently, resistance has mostly been observed in industrialized nations in infections that are transmissible but do not cause illness. They can remain in the body for many periods and only become infectious when they come into contact with areas of the body that are ordinarily free from bacterial colonization—that is, when they are introduced by medical procedures, when they are in children, or when they are in individuals with weakened immune systems. As a result, hospitals and nursing homes are the primary settings where resistant organism problems arise when patients receive acute or

long-term medical care. Conversely, in developing nations, bacteria that are spread through person-to-person contact, contaminated food, tainted drinking water, or insects frequently develop antibiotic resistance. If no other treatment options are available, resistance can mean that individuals infected with such germs do not react to traditional treatments and must rely on their immune system to fight off the illness. Extended spectrum beta-lactamase (ESBL) producing bacteria, particularly gram negative members of the *Enterobacteriaceae* family, are a common resistance that is easily found today and are becoming linked to both clinical and treatment failure. These bacteria are constantly present in both community and hospital environments (2). Similarly, physicians now have fewer treatment options because the development of new antibiotics has not kept up with the increase of resistance. Only five of the 506 new medications under research were antibiotics, according to a recent survey analysis, and reports indicate that the pharmaceutical pipeline for new antibiotics is closing (3). The super bug's concerning characteristics and related issues are quickly growing into a significant worldwide health concern. A 2007 research from the Centers for Disease Control and Prevention estimates that each year, 1.7 million infections related to medical care occur in American hospitals. 99,000 fatalities are linked to these illnesses (4).This is a significant change from former decades, as previously documented. High rates of bacterial resistance are particularly dangerous for tertiary care facilities, teaching hospitals, and institutions that care for critically ill patients in both rural

and urban environments. Numerous bacterial classes have been documented to exhibit such resistances. Hospitals across the United States and the rest of the world have identified multidrug-resistant *Escherichia coli* and *Klebsiella species*. Multiple instances of multidrug resistance to gram negatives have been documented, indicating resistance in various clinical samples, including Nigeria (5, 6 and 7).

Within Enterobacter species (8).An increasing number of cases have been reported in the US and other countries worldwide of methicillin-resistant Staphylococcus aureus (MRSA), a potentially harmful strain of Staphylococcus that is resistant to some antibiotics and can cause skin and other infections in people without access to healthcare systems (9,10). There have also been reports of Salmonella typhimurium-related resistance in Nigeria. There has also been reports of resistance in *Enterococus faecalis* (11).Pseudomonas aeruginosa has also been the subject of several reports. According to (12), there is a bacterial strain that is distinctly more hazardous and resilient, and it has become established in hospitals. Pseudomonas aeruginosa resistance has also been documented in a number of publications (13, 14 and 15). Antibiotic use and misuse in veterinary medicine has also been documented (16, 17). Although they have drastically decreased, infections with Streptococcus pneumoniae resistant to antibiotics still pose a risk to certain populations. A number

of risk factors, such as prolonged hospital stays, advanced age, the use of invasive devices, immunosuppression, hospital staff disregard for infection-control guidelines, and prior antibiotic use, are linked to higher bacterial resistance among patients in the intensive care unit (ICU). Acutely sick, febrile patients often require repeated courses of antibiotic therapy and frequently require endotracheal tubes, urine catheters, and central venous catheters (18, 12).

Dwelling devices can serve as pathways for the colonization and spread of resistant diseases when combined with host variables (1, 12). Prolonged antibiotic usage and insufficient or unsuitable empirical antibiotic therapy, however, seem to be the two main causes of resistance (1, 12). Developing nations face a significant difficulty in protecting the health of their populations against deadly diseases including tuberculosis (TB), typhoid fever, and similar bacterial infections due to rising resistance to current medications. As per the report by (19). For more than ten years, public health professionals have been alerting the public to the impending "post-antibiotic era," in which the rapidly worsening circumstances will result from the growth of antibiotic resistance, rendering effective antibiotic therapy ineffective. Many in the health sector still do not take resistance seriously

enough, despite how dangerous it is. To gather vital information for the creation of containment plans, surveillance is required to track the spread of resistance and determine the scope of the issue.

Mechanism of resistance

Antibiotic resistance in bacteria has been attributed to a number of variables. Among the causes are a few of these: Slow porin channels that restrict access to targets; numerous drug efflux pumps that increase the expulsion of antibiotics; lactamases and aminoglycoside-modifying enzymes that inactivate enzymes; and mutational resistance brought on by regulatory mutations that raise the expression of intrinsic genes and operons, which varies depending on the situation(20). Widespread therapeutic antimicrobial medicines were created to block targets specific to prokaryotic organisms, like the ribosome, DNA gyrase, and bacterial cell wall. The death rate from infectious diseases has decreased as a result of these medications. Antibiotic usage and misuse have accelerated the evolution of bacterial resistance, which frequently leads to treatment failure. According to Fraimow and Abrutyn (21), resistance is an indicator of an organism's capacity to evade the antimicrobial agent's fatal and inhibiting effects.

Microorganisms Demonstrate Resistance in Several Ways

"Intrinsic resistance"

The term "intrinsic resistance" refers to resistance that is innate to a specific species. These organisms may not have the right drug-susceptibility targets or may have natural barriers preventing the agents from reaching the target. Examples of this type of resistance include the intrinsic resistance of penicillin and the natural resistance of gram-negative bacteria to vancomycin, which results from the drug's inability to pass through the gram-negative outer membrane (22, 23).

Circumstantial Resistance

The distinction between an antimicrobial agent's actions in vitro and in vivo is known as circumstantial resistance. Certain agents, like first-generation cephalosporins, which are useless in vivo because they cannot reach the site of infection, may appear active in the lab but be ineffective in vivo. Medication like

aminoglycosides can become inactive; enterococci can defeat trimethoprim-sulfamethoxazole in vivo by not being able to absorb and internalize folate from the corporate environment (21, 24).

Acquired resistance

The main focus of this work is on acquired resistance, which is the result of a genuine alteration in a bacterium's genetic makeup that renders a medication that was previously successful in vivo ineffective (21). The main strategies used by bacteria to evade the effects of antibiotics include limiting the intracellular concentration of the drug by either increasing or decreasing influx or efflux, neutralizing the drug with enzymes that inactivate it either permanently or reversibly, changing the target so that the agents no longer interfere with it, and completely eliminating the target by establishing new metabolic pathways (25, 26 and27). In order to combat a single agent or class of agents, bacteria may use or combine a variety of strategies, or a single alteration may lead to the development of resistance to many agents (25, 26,21and 27).

Mechanism of dissemination of resistance genes

Numerous effective techniques are utilized by bacteria to transfer resistance genes to different organisms and species (28, 29). The two main components of the bacterial genome are plasmids, which are tiny circular DNA elements that encode for additional bacterial functions including resistance genes and virulence factors, and chromosomal DNA, which codes for general cellular features and metabolic repair mechanisms. Although plasmid-mediated traits can swap out for

chromosomal elements, plasmid-mediated traits account for the great majority of resistance genes. Simple recombination processes can transfer genetic material from a plasmid to a chromosome, but transposons substantially speed up this process. Transposons, which comprise integrons, transposons, and insertion sequences, are tiny, mobile DNA elements that can transfer DNA by removing and inserting themselves into host chromosomal and plasmid DNA. The likelihood of these elements spreading to other organisms increases if they are linked to transmissible or mobilizable plasmids. Numerous resistance genes, including those mediated by plasmids, tetracycline-resistant genes, and enzymes that change aminoglycosides, are arranged on transposons, which exhibit wide variations in size and complexity. Transposons may play a significant role in the spread of resistance genes among species and may have a wider host range than their parent

plasmids (30, 29, and 31). Clonal dispersion is the method by which resistance determinants residing on chromosomes are transferred. Additionally, resistance determinants on plasmids are passed vertically; nevertheless, if plasmids lose their specific selection advantage, they may disappear from the bacterial community. Gene transfer in bacteria can result in recombination through three distinct mechanisms: transformation, transduction, and conjugation. (30).

Transformation

The most basic kind of gene transfer is transformation. Genes are transferred into a recipient cell from "free floating" DNA molecules in the surrounding fluid. In the natural world, DNA can originate from deceased cells that undergo lysosomal release. However, in the lab, a suspension of donor bacteria is treated chemically to harvest DNA, which is subsequently given to a recipient bacterial culture. A recipient bacteria can become "transformed" in the lab or in nature when it takes on one or more inheritable traits from a donor bacterium. It is known that only a few species of bacteria can transform, and even these need to be competent—that is, in a growth condition that allows donor DNA to be incorporated. The receiving bacteria are often in the late logarithmic phase of their growth when this scenario arises. A unique protein produced by competent bacterial cells attaches donor DNA fragments to particular locations on the cell surface. While plasmid DNA cannot be easily transferred by a standard transformation process that merely adds DNA to recipient cells, chromosomal DNA may be easily transferred to competent recipient bacteria. However, transformation with plasmid DNA can be achieved by unique methods often utilized in genetic engineering (32). Additionally, plasmids can be introduced into recipient cells.

Conjugation

Bacterial conjugation differs from sexual mating in eukaryotes in that it does not involve the fusion of two gametes to form a single cell. In certain types of conjugation, only a plasmid may be transferred from the donor bacterium to the recipient bacterium. Conjugation is a process of gene transfer that requires cell to cell contact. Plasmids also have the ability to transfer genes horizontally through conjugation, although the efficiency of plasmid transfer both within and between species can vary greatly. In other kinds, a recipient cell may receive a considerable portion—or perhaps the entire—of the chromosome from the donor cell. In contrast, only very tiny chromosomal fragments may be transmitted during transformation and transduction (32). Research on conjugation in E. coli has shown that this bacterium possesses two distinct forms of mating: a donor and a recipient.

The "donor" cells harbor a plasmid known as the F plasmid, where "F" denotes fertility. This F plasmid, like most plasmids, is a tiny, circular fragment of double-stranded DNA that can replicate on its own and is not a component of the bacterial chromosome. It has roughly forty genes that regulate the manufacture and replication of the plasmid, but the host cell has a filamentous appendage known as the sex pilus.

Known as "F" cells, these cells are donors in mating pairs and carry the F plasmid. F-cells are recipient cells devoid of the 'F' plasmid. The end of the F+ sex pilus binds to a nearby F-cell and then retracts, drawing the F+ and F-cells into close contact when F+ and F-cells are combined together in what is known as a F+ x F- cross. One DNA strand from the donor's F plasmid is transmitted to the F-cell through the channel that forms between the two cells. The DNA strand serves as a template for the production of a second, complementary DNA strand once it has entered the recipient's cell. The receiver cell transforms into a F+ cell that is able to donate DNA when the ends of the double-stranded DNA molecule unite to form a circular F plasmid. This allows the conjugation process to go on until every F-cell in the culture has undergone conversion. The cytoplasmic contents of conjugating bacteria do not generally mix, despite the fact that DNA transfer happens easily at the conjugational junction. There is just one DNA strand that is transmitted. When the plasmid is nicked at the particular origin of transfer (oriT) site, a single strand is created. After the duplex is unwound by one or more DNA helicases, a single strand of DNA is gradually exhibited from 5' to 3' and transferred into the recipient. Following completion of transfer, a complementary strand is produced and the F factor is recircularized in the recipient (33). Transfer can continue until the 3' end of (oriT) is reached, a break in the DNA, or cell contact is interrupted. The F genes are transmitted as the single strand moves from 5' to 3'; the recipient does not become

F+. Other conjugative transfer systems in Gram-negative bacteria seem to share the same traits as the F factor transfer system. The F plasmid can transfer chromosomal genes as well, although this is an uncommon occurrence that happens only once per 10 million matings (32).

β-Lactamase and the gram negative bacterial organism

Gram-negative bacteria produce β-lactamase enzymes, especially ESBLs, as a major defense against β-lactam antibiotics; the majority of these β-lactamase enzymes are plasmid encoded. This has made it easier for strains of numerous gram-negative bacterial species to spread among one another.

β-lactamases of Gram Negative Bacteria:

Compared to gram positive bacteria, gram negative bacteria produce a far wider variety. They generated β-lactamase enzymes that were both constitutive and inducible (33). Enzymes are nearly invariably confined to cells. The chromosomalβ-lactamases of gram negative bacteria are activated by an increase in peptidoglycan degradation fragment resulting from β-lactam activity. The enzymes are located in the periplasm and are synthesized at a slower rate than in gram-positive bacteria (34). Here they operate synergistically with outer membrane porins' to successfully guard against susceptible antibiotics (35). Six major classes comprise nearly all of the constitutively generated enzymes.

• Broad spectrum enzymes that hydrolyze cephaloridine and benzyl penicillin at comparable rates.

• Oxacillinases, which quickly hydrolyze oxacillin and related penicillin.
• Those called carbenicillinases that easily break down carbenicillin.
• Extended beta-lactamases, or cefotaxime, ceftazidime, and aztreonam, are examples of enzymes that inactivate β-lactam antibiotics.
•Oxymino β-lactam-breaking enzymes that withstand clavulanate (Cephalosporinases); the genes encoding these enzymes share nucleotide sequence similarities with the chromosomal β-lactamase gene of *Enterobacter*, *Citrobacter*, or *Klebsiella oxytoca*, as well as similar biochemical properties (36, 37, 38 and 39).
• A peculiar β-lactamase that hydrolyzes imipenem (Carbapenemases) is present in *Pseudomonas aeruginosa*. (40).

β -lactamases of Gram-Positive Bacteria

Due to their absence of an outer membrane, gram-positive bacteria like S. aureus overproduce their own class A β -lactamases. Transmembrane spanning penicillin-sensitive receptors trigger these β -lactamases when they detect extracellular

antibiotics (41). Excessive amounts of β-lactamases are released, endowing the host and the surrounding bacterial community with resistance (36). The staphylococcal β-lactamase genes are typically found on transposons or tiny plasmids. Apart from S. aureus strains, larger plasmids encoding β-lactamase and other resistance can also be found and can transmit by conjugation between S. aureus and S. epidermidis (41).

β--Lactamase of Anaerobic Bacteria

The generation of β-lactamase is also a factor in anaerobic bacteria's resistance to β-lactam antibiotics (42). Penicillinase is the main component of fusobacteria and clostridia's β-lactamase. The majority of those produced by Bacteriodes fragilis are cephalosporinases; some of them may be transferable and have been shown to hydrolyze imipenem and cefocitine (43). Sulbactam, tazobactam, and clavulanate block the majority of cephalosporinases. EDTA inhibits the metalo-enzymes carbapenemase, but not clavulanate or sulbactam.

Classification of β -lactamase

Nowadays, there are two well recognized classification schemes: Ameber and Buch-Jacob-Mederios. Initially, the β-lactamases were categorized into classes A or using a scheme created by Ambler (35), based on the amino acid sequence. Following the discovery that the enzymes did not have any sequence homology with classes A or B, class C was created (44). Huovinen and colleagues (45) determined class D. The Bush-Jacoby-Medeiros (46) approach aimed to revise the â-lactamase taxonomy according to characteristics including inhibitor and substrate profiles.

Class A (Group 2) Serine Penicillinases

Both gram-positive and gram-negative bacteria contain them. Class A β-lactamases have a molecular weight of approximately 29 kD and 260–270 amino acid residues (35). At position 70 in the active site, there is a serine residue present in all class A enzymes. They preferentially hydrolyze Penicillin G and ampicillin. Because they have an arginine at position 244 that makes inhibitor action easier, they are typically inhibited by clavulanic acid (46, 36). Many are transposables or plasmids that carry additional resistance genes (36). The two most common families of plasmid-mediated enzymes are TEM and SHV. Among Enterobacteriaceae, TEM â-lactamases are the most prevalent â-lactam resistance mechanism, with TEM-1 being the most frequent in the world (47). The effectiveness of TEM-1 in hydrolyzing therapeutically utilized antibiotics and its positioning on a highly class 2 transposon may be responsible for its success (48). Class enzymes exhibit a wider range of activity against â-lactams due to mutations that raise the entry to the active site (36).

Class B (Group 3) Metallo-β-lactamases

Ambler (35) found that the β -lactamase of Bacillus cereus deviated greatly from the original class A enzyme, so much so that he had to create class B to accommodate it. The class B enzyme was assigned group 3 status by the Bush-

Jacoby-Medeiros system (46). Typically, they have a molecular weight of 23 kD. They can hydrolyze the majority of â-lactam antibiotics, including imipenem, although they lack an active site serine residue and need a metal cofactor, usually zinc (35). Clavulanic acid has no effect on class B â-lactamases; nevertheless, class B β-lactamases can be easily identified by their suppression by EDTA and restoration of activity following the addition of Zn2+ (49). The majority of class B enzymes are found in bacteria that also produce at least one other class of β-lactamase, which leads to a phenotype known as extended-spectrum resistance.

Class C (Group 1) Serine Cephalo-sporinases

Class C was added to the Ambler classification by Jaurin and Grundstrom (50) when researching enzymes with limited sequence to classes A and B. This class is designated as group 1 in the Bush-Jacoby-Medeiros (46) scheme. Clavulanic acid does not inhibit class C β-lactamases, which have a strong substrate affinity for cephalosporins (49). They have basic isoelectric points, molecular weights more than 30 kD, and between 360 and 370 amino acids. The presence of active site serines at position 80 in class C enzymes suggests that they evolved differently from other serine β-lactamases (50). Only Gram-negative bacteria and the Enterobacteriaceae family have them; most species-specific β-lactamases are encoded by chromosomal class C genes (ampC). Cephalosporins can be hydrolyzed by class C enzymes because their active sites are bigger than those of class A enzymes. The primary mechanism for increased β-lactam resistance by class C enzymes is due to mutations in the genes controlling the amount of class C enzymes produced (36). High-copy number plasmids, which are easily spread among Enterobacteriaceae, Escherichia coli, and Klebsiella pneumoniae, are also home to class C β- lactamases.

Class D (Group 2d)

Huovinen et al., (51) expanded the Ambler scheme by introducing class D, which includes enzymes that have minimal structural similarity to classes A or C. While there is an area of homology in the active site with classes A and C, there is no sequence homology with class B, indicating a convergent evolution. Group 2d of the Bush-Jacoby-Medeiros system consists of Class D. Although clavulanic acid normally inhibits Class D enzymes, they are less vulnerable than Class A enzymes.

Class D enzymes have an isoelectric value between 6.1 and 7.7 (49). Class D β-lactamases, which hydrolyze oxacillin and cloxacillin preferentially, are similar in

size to class A enzymes and comprise the plasmid-mediated OXA-1, OXA-2, and PSE-2 enzymes.

β –lactamase

Present Circumstances and Clinical Significance Four categories can be used to categorize β-lactamase:

1. The well-known conventional enzymes mediated by plasmids,

2. The Matrix Proteins

3. β-lactamases that are mediated by chromosomes, and

4. The more recent discovery of extended-spectrum beta-lactamases (ESBLs).

Traditional, Well Known, Plasmid-Mediated

There are more than 50 plasmid-mediated β-lactamases known to exist in Gram-negative bacteria. The majority of β-lactamases encoded by plasmids are constitutively generated, with many of them being encoded by transposons' genes. For instance, TEM-1 enzymes, which were formerly exclusive to the enterobacteriaceae family, have now been found in Neisseria gonorrhoea and Haemophilus influenzae, among other genera and species. Presently, 30-80% of isolates of many enterobacteria, especially in developing nations, have plasmid-mediated β-lactamases (52). When isolates were examined for their ability to produce β lactamases, a significant proportion were found to be doing so. 55–60% of E. coli bacteria in Spain are ampicillin-resistant, and this resistance is mostly caused by these plasmid-mediated β-lactamases (53). Examinations of Neisseria species and Escherichia coli offer remarkable illustrations of the therapeutic significance of plasmid-mediated β-lactamase synthesis as a mechanism of resistance in bacteria. According to a survey conducted in Spain and data from the National Reference Center in Madrid, out of the 2010 isolates of N. gonorrhoea, 23 percent produced TEM-1 β -lactamases, making them resistant to ampicillin. The frequency of gonococci that produce β-lactamases from Pseudomonas aeruginosa varies greatly; in Northern Spain, the percentage of isolates that produced β-lactamases was barely 3%, whereas in Catalonia, the figure was nearly 28%. It has also been demonstrated that Neisseria meningitidis produces β-lactamases. In the Barcelona region, two strains of N. meningitidis that generate β-lactamase have been identified in recent years. Despite their rarity, these organisms serve as a stark reminder of the expanding issue of β-lactamase resistance (53).

Carbapenemase: A Problematic β -Lactamase

A carbapenemase strain originally identified in 1991 in Japan was shown to resemble metallo-enzymes of broad-spectrum chromosomal β-lactamases. This enzyme may hydrolyze a wide variety of distinct β-lactams, including the more recent cephalosporins known as cephamycins. It has only been identified in one strain of Pseudomonas aeruginosa. (40). Meropenem's MIC is 100 μg/ml and imipenem's MIC is 50 μg/ml against these bacteria. Carbapenemase is not inhibited by â-lactam inhibitors that are on the market now. Due to its plasmid origin, this enzyme has the potential to spread, adding to its significance in addition to its wide spectrum of resistance (53).

Chromosomally mediated β –lactamases

Enzymes found in the bacterial chromosome encode β-lactamases, which are mediated by chromosomes. β-lactamases that are chromosomally encoded are frequently found in Gram-negative bacteria and have been reported in enterobacteria. Pseudomonas, Moraxella, Bacteroides, Campylobacter, Acinebacter, Legionella, and Pasteurella spp.; they have not been described in Nesseria or in Haemophilus. Normally, an inducer is required for the creation of class 1 chromosomally mediated β-lactamases in a clinically meaningful amount. When β -lactam inducers are exposed to species including Enterobacter, Citrobacter, Serratia, and Pseudomonas, which are a major cause of nosocomial infections, clinically significant β-lactamase production ensues. The induction process is typically halted if the β-lactam is eliminated or hydrolyzed, allowing the production of β-lactamase to revert to basal levels. Nonetheless, an unintentional mutation in the bacterial genome may lead to a stable downregulated condition where the production of β-lactamase remains excessively high, even in the lack of an external stimulus (53). Differentiating between stronger inducers of β-lactamase, such imipenem, cefamycins, and first-generation cephalosporins, and lesser inducers, like ureido penicillins, mono-bactams, and third-generation cephalosporins, is crucial. The weak inducer activity of a substance has a significant impact on its antibacterial activity. That is to say, rather from being stable to the enzyme, these medicines continue to be active against Gram-negative bacilli species that are inducible for β-lactamase since they are unable to cause the manufacture of β-lactamase. On the other hand, most third-generation cephalosporins, aztreonam, and ureidopenicillins have been shown to select for stably depressed mutants (53). Enterobacter species, Serrantia marcescens, Citrobacter freundii, Morganella morganii, Provindencia species, indole positive Proteus species, and pseudomonas aeruginosa are among the organisms that

generate inducible β-lactamases. Stable derepressed mutants are typically present in any population of these gram-negative bacterial species.

These are seen in E. cloacae most commonly. The evaluation of the rates of resistance emergence in patients treated with newer cephalosporins and infected with organisms containing β-lactamases further highlights the clinical significance of selecting depressed mutants (54). Resistance that develops after cephalosporin medication can range from 14% to 56%, with a mean of roughly 30%; recurrence rates among patients in whom resistance was found ranged from 25% to 75% of cases. The medications, which include nearly all cephalosporins, cephamycins, monobactams, and extended spectrum penicillins, are susceptible to hydrolysis by class 1 β-lactamases. Because of the selection of stably derepressed mutants, the use of these medicines has been linked to the formation of numerous β-lactam resistances. Few induced class 1 β-lactamases are moderately inhibited by tazobactam, and none are inhibited at all by clavulanic acid. Patients with respiratory tract infections, granulocytopenic patients hospitalized to intensive care units, patients with extensive burns, and patients with cystic fibrosis are the most prone to develop this sort of resistance and for it to have clinical significance (55). When establishing an antibiotic policy in a hospital context, it is important to take into account the widespread occurrence of antibiotic resistance linked to these enzymes as well as the clinical implications.

Extended Spectrum Plasmid–Mediated β -lactamases (ESBLs)

A relatively recent class of plasmid-mediated enzymes are the ESBLs. In Frankfurt, Germany, oxyimino β-lactamases, or ESBLs, were first described in 1983 (56). Since that time nearly 40 different ESBLs have been described. Over the past years bacterial have acquired genetic information that permits inactivation of a large group or number of β - lactam antibiotics. Extended-spectrum plasmid-mediated β -lactamases have been identified in enterobacteriaceae particularly on Escherichia coli and Klebsiella pneumoniae. The majority of ESBLs are derived via mutation of TEM-1, TEM- 2 and SHV-1. In general ESBLs are variably capable of hydrolysis second and third generation cephalosporins as well as older β -lactamase inhibitors such as tazobactam, clavulanic acid and sulbactam. The term ESBLs mainly refers to the oxyimino β -lactamases (53).

TEM β –lactamase enzyme

The most prevalent β-lactamase gram-negative bacterium is called TEM-1. The synthesis of TEM-1 is responsible for up to 90% of ampicillin resistance in E. coli (57). This enzyme is also in charge of the penicillin and ampicillin resistance that

is increasingly observed in N. gonorrhoea and Haemophilus influenza. Penicillins and cephalosporins like cephalothin and cephaloridine can be hydrolyzed by TEM-1. The initial TEM-1 derivative, TEM-2, differed from the original β-lactamase by just

one amino acid. The isoelectric point shifted as a result, going from 5.4 to 5.6, but the substrate profile remained unchanged. When TEM-3 was first described in 1989, it was the first TEM-type β lactamase to exhibit the ESBL characteristic. Since the first study, more than ninety more TEM derivatives have been described. There are only a few locations in the TEM enzyme where amino substitution takes place. The combinations of these amino acid modifications produce a variety of mild phenotypic changes, such as a shift in their isoelectric points or the capacity to hydrolyze particular oxyimino-cephalosporins, including ceftazidime and cefotaxime. Several amino acid residues have a crucial role in generating distinct phenotypes when substitution takes place at that specific site. Apart from β-lactamases TEM-1 through TEM-92, a naturally occurring TEM-like enzyme called TEM-AQ has been reported to possess many amino acid substitutions and one delection that have not been observed in other TEM enzymes. TEM type β -lactamases are predominantly detected in enteropathogens such as Klebsiella spp. and E. coli, but they are also increasingly identified in other gram-negative bacterial species. Enterobactriaceae in general have been reported to harbor TEM-type ESBL (58, 59).

Inhibitor-Resistant β -Lactamase enzyme:

Most of the newly discovered TEM derivatives (more than ninety) are ESBLs, albeit a small number of them are suppressed resistance enzymes. Despite not being ESBLs, inhibitor-resistant β-lactamases are frequently addressed alongside ESBLs due to their shared ancestry with classical TEM- or SHV-type enzymes. β-lactamases that were resistant to clavulanic acid suppression were found in the early 1990s. These enzymes were identified by nucleotide sequencing as TEM-1 or TEM2 β-lactamases. Initially designated as inhibition-resistant TEM β-lactamase, these enzymes were later redesignated with numerical TEM designations, all starting with IRT. At least 19 different inhibitor-resistant TEM β-lactamases have been identified (60). Mostly in clinical isolates of E. Coli, inhibitor-resistant β-lactamases have also been detected in certain strains of K. pneumoniae, K. oxytoca, P. mirabilis, and Citrobacter freundii (61, 62).

SHV β -lactamase Enzyme

In contrast to TEM-type β-lactamases, SHV-1 has a comparatively small number of derivatives. Up to 20% of plasmid-mediated ampicillin resistance in E. Coli and K. pneumonia is caused by the SHV-1 β -lactamases, which are mostly prevalent in these two species (63). Numerous E. Coli strains have absorbed bla shv -1 or a similar gene into their bacterial chromosomes (57). There are fewer locations in the structural gene where the bla shv mutations that result in the SHV variants have been

seen. While the ESBL phenotype is present in most derivatives of the SHV type up to this point, one variety, SHV-10, is found to have an inhibitor-resistant phenotype.

CTX-M Enzymes

Although they have also been reported in other Enterobacteriaceacea species, Salmonella enterica serovar Typhimurium and E. coli are the primary hosts of a novel family of plasmid-mediated enzymes known as CTX-M, which selectively hydrolyzes cefotaxime. These comprise the enzymes of the CTX-M type (CTX-M-1, formerly known as MEN-1), as well as CTX-M-2 through CTX-M-10 (64, 65, 55, 66, 67, 5). These enzymes have only about 40% similarity with the two commonly isolated β-lactamases, TEM and SHV, indicating that they are not closely related to these enzymes (68).

OXA Enzymes

Another ESBL family that is expanding is the OXA enzymes. These β-lactamases are classified as members of functional group 2d and molecular class D, which sets them apart from TEM and SHV-enzymes (46). The OXA-type ampicillin is characterized by its high hydrolytic action against oxacillin and cloxacillin, poor inhibition by clavulanic acid, and resistance to both ampicillin and cephalothin (46). Although the majority of ESBLs have been identified mostly in Enterobacteriaceae such as K. pneumoniae and E. coli, OXA-type ESBLs have been identified primarily in Pseudomonas aeruginosa. Numerous OX-type ESBLs have their origins in OXA-10.

Conclusion

Antimicrobial drug resistance is not exclusive to developed countries; it happens all throughout the world. Drug-resistant organisms are being fought by hospitals and other healthcare facilities as they proliferate within these establishments. Infections resistant to drugs can also spread throughout the population. Instances of infections in soft tissues and skin. Resistance development can be slowed down

with tactics until new compounds are found and approved. For instance, we have to be careful not to underdose, as this is a common but sometimes overlooked factor linked to bacterial resistance and treatment failure. A comprehensive comprehension of pharmacokinetic and pharmacodynamic principles can enhance the utilization of antibiotics. For instance, β-lactams can be used to extend the duration above the minimum inhibitory concentration, while fluoroquinolones and aminoglycosides can be used to maximize the peak level or area under the concentration curve. According to Craig (69). To contain resistance, microorganisms that may be resistant must be treated aggressively and empirically as soon as possible. Once the pathogen

has been identified, the antibiotic spectrum must be narrowed and de-escalated. If an infection is suspected but the diagnosis seems unlikely, then empirical therapy should be stopped completely. De-escalation is an important infection-control method and a useful tactic that strikes a compromise between the goal of preventing antibiotic misuse and the requirement to give high-risk patients early, sufficient antibiotic therapy (70). Vaccines do not have the problem of resistance since a vaccine strengthens the body's inherent defenses, while an antibiotic functions separately from the body's usual defenses. Nevertheless, new strains may arise that evade protection conferred by vaccines; for example an updated influenza vaccine is needed each year. Antistaphylococcal vaccinations have demonstrated poor success, despite their theoretical promise. This is due to immunological diversity among Staphylococcus species and the short half-life of the generated antibodies. More potent vaccines are being developed and tested. Acknowledging the need to reduce antibiotic use, the Australian Commonwealth Scientific and Industrial Research Organization (CSIRO) has been developing two alternatives. One possibility is to prevent illnesses by introducing cytokines instead of antibiotics to animal feed. These proteins are created in the animal body "naturally" after an illness and are not medicines, thus they do not contribute to the antibiotic resistance problem. Moreover, research on the usage of cytokines has demonstrated that they have the same growth-promoting effects on animals as currently used antibiotics, but without the negative side effects of nontherapeutic antibiotic use. Phage therapy is a potentially important but as-yet-undeveloped method of treating bacterial diseases. It has been studied thoroughly and utilized as a medicinal agent for more than 60 years, primarily in the Soviet Union (71). Up until the early 1940s, when antibiotics were discovered, phage therapy was a common practice in the US. Viral organisms known as "phages," or bacteriophages, enter bacterial cells and, in the case of lytic phages. The use of lytic bacteriophages therapeutically to treat pathogenic bacterial infections is

known as phage treatment. (72; 73; 74). The reduction of effective drug concentrations at their target site as a result of the increased activity of ABC transporters is one of the main reasons of antibiotic resistance. The potential impact of ABC transporter inhibitors is of tremendous therapeutic interest since they can be used in conjunction with existing medications to boost their effective intracellular concentration. Clinical trials have begun for ABC transporter blockers, which may help improve the effectiveness of existing medications and are accessible for use in treatment regimens (75). With careful preparation, a lot of work, thorough research, illumination, and a persistent dedication to these challenges, we can conquer the issues related to medication resistance in bacteria.

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