The Penicillin Evolution- A Ray of hope in the World of Beta-Lactam Antibiotics

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Abstract

A diverse range of microorganisms, including some gram-positive *streptomycetes*, a few gram-negative unicellular bacteria, and certain filamentous fungus, produce penicillins and cephalosporins. These beta-lactam antibiotics are produced by substantially the same biosynthesis mechanism in all. The majority of the genes that produce penicillin and cephalosporins have recently been cloned, sequenced, and expressed. In addition to being arranged in chromosomal gene clusters and exhibiting coordinated expression, the biosynthetic genes code for enzymes with multifunctional peptide synthetase, cyclase, epimerase, expandase, hydroxylase, lysine aminotransferase, and acetyltransferase capabilities. Beta-lactam biosynthesis genes may be more common in nature than traditional antibiotic screens suggest, according to streptomycetes' DNA hybridization screens. They present the chance to broaden the search for organisms that could produce novel beta-lactam antibiotics. There has been some success in trying to increase the yields of beta-lactams in production strains by adding more copies of biosynthetic genes to them. The beta-lactam biosynthesis genes of bacteria and fungi share a relatively high degree of sequence identity, according to comparative sequence analysis. Horizontal gene transfer between the two groups of species is assumed in an evolutionary scenario that explains the similarities in biosynthetic genes. There is indirect evidence that the bacteria and fungus were transferred.

Keywords: Penicillin, Beta Lactamases, Beta Lactams Determinants, Antimicrobial resistance, Public health.

Cite this Article as: Khalid A, Naseeb N, Bibi S, Bilal M, Asrar R, Manan M and Umar M, 2025. The penicillin Evolution- A ray of hope in the world of beta-lactam antibiotics. In: Farooqi SH, Kholik K and Zaman MA (eds), One Health Horizons: Integrating Biodiversity, Biosecurity, and Sustainable Practices. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 227-232. https://doi.org/10.47278/book.HH/2025.314

A Publication of Unique Scientific Publishers

Chapter No: 25-031

Received: 04-Feb-2025
Revised: 21-Apr-2025
Accepted: 23-May-2025

Introduction

Antimicrobial resistance (AMR) is a natural process, the exploitation of antibiotics is the main reason of the public health disaster caused by the unchecked expansion of this phenomena. Its prevalence has increased, but other reasons are also largely to blame. These elements are often called "socioeconomic determinants" and include things like hazardous food, insufficient infection controller in clinics and hospitals, environmental antibiotic buildup, and the use of antibiotics in the food and livestock industries. The majority of *S. aureus* isolates had become resistant to penicillin, which was once the most common antibiotic used to treat them (Mancuso et al., 2021).

The World Health Organization (WHO) first issued a list of 12 families of bacteria that pose the greatest threat to human health in 2017. However, for a long time, antibiotic resistance was not a serious concern worldwide because new drug classes, like vancomycin and methicillin, were developed in the 1960s, suggesting that the problem of resistance might be easily resolved through the manufacture of new molecules. Unfortunately, bacteria developed many different mechanisms of antibiotic resistance that have shielded them from the effects of these drugs, and as a result, antibiotic resistance has proceeded (Urban-Chmiel et al., 2022).

Animal illnesses and multidrug-resistant bacteria that endanger individuals in hospitals and assisted living facilities are among the pathogens that fall under the most critical category. *Acinetobacter, Pseudomonas, and K. pneumoniae, E. coli, and Enterobacter* species, are considered critical-priority bacteria. Bacteria that are resistant to different antibiotics, including vancomycin and fluoroquinolones, such as *Staphylococcus aureus and Enterococcus feacium*, fall under the high priority group. *Shigella and Streptococcus pneumonia*e are among the microorganisms in the medium priority category; despite their potential for resistance, they can still be killed with effective antibiotics (Vrancianu et al., 2020).

Physiotherapists can help people improve their quality of life at any stage of life where their mobility and function are impaired by age, disease, accident, ailments, or environmental factors. In certain situations, such as musculoskeletal disorders, respiratory conditions, and sports

injuries, physiotherapy by itself might not be sufficient to address the problem; in these cases, adjunct medication may be required. Pharmacotherapy may help with functional movement or airway clearance, increase breathing, encourage integumentary repair and protection, or lessen discomfort or inflammation (analgesics and anti-inflammatory medicines), depending on the ailment. The advantages of granting prescribing privileges to patients, the physiotherapy profession, and the healthcare industry as a whole were emphasized by the participants. Furthermore, those who are interested show a definite preference for medications that help treat conditions that are frequently observed in physiotherapy (Lalchhandama, 2021).

Since more than two-thirds of hospital prescriptions today contain antibiotics, particularly those of the β-lactam class, these drugs are critical to 21st-century medical rehearsal. The four main chemical groups that include the most common β-lactam-containing drugs are monobactams, carbapenems, cephalosporins, and penicillins. Because these agents are so precious, the medical community is very concerned about the continuous increase of medicine resistance around the world. Even though resistance patterns may vary geographically, there is still a chance that any new resistance mechanism could spread swiftly to neighboring areas (Hutchings et al., 2019). As early as 2006, for instance, the gene encoding the New Delhi metallo-β-lactamase-1 (blaNDM-1), which causes resistance to the majority of β-lactam antibiotics, was discovered; at first, its occurrence was limited to the Indian subcontinent. Nevertheless, the gene extent around the world within five years of the first recorded occurrence, in part due to sick or populated individuals going to North America, Europe, and the Middle East. Monitoring resistance as a function of time and place is essential to limiting emergent resistance determinants to certain geographic areas (Prevention & Control, 2018).

Even in modern isolates, certain β-lactamases are common, including the TEM-, SHV-, and OXA-type enzymes expressed by plasmids. The SPM-1 metallo-β-lactamase for example, has only been found in one particular niche and has little to no spread outside of Brazil, with the exclusion of a Swiss patient who was first admitted to the hospital there. In order to direct the most efficient use of antibiotics in different geographic places, it is vital to take note of the sources and distribution of the most common and harmful medicines (Prevention & Control, 2017).

Mechanisms of Penicillin

There are several ways that resistance to β-lactams might arise, all of which are connected to how these agents work. β-Lactams operate as stand-in substrates for penicillin-binding proteins, or PBPs, which are essential bacterial cell wall-synthesizing proteins that cross-link cell wall fragments prior to cell division. The acylation of an active-site serine in the PBP's trans peptidase domain is the defining feature of its inhibitory activity, despite the structural differences between PBPs in different bacterial species. Gram-positive pathogens were the first germs to show outbreak-level resistance to penicillins, which constituted a vital part of the hospital arsenal (Bush, 2018).

The development of resistant infections in both groups of organisms has been significantly influenced by PBP alterations, particularly those that require an active serine for catalysis. It can attach to a PBP fastened on the cell's inner membrane to halt cell growth and division unless it is caught and rendered inactive by a β-lactamase in the periplasmic space. In both cases, the β-lactam undergoes a reaction to create a reactive intermediate that can be broken down (Bush & Bradford, 2019).

Penicillin Resistance

Gram-negative bacteria's main determinant of β-lactam resistance. In short, by uniting the drug, shattering the amide bond of the four-membered azetidinone ring that is found in all β-lactams, and adjoining a water molecule to the ring-opened molecule, these enzymes stop the killing activity of β-lactams. Enzymes that require at least one divalent zinc atom for hydrolysis and β-lactamases that use an active-site serine for hydrolysis have different processes. In MBLs, Zn2+ facilitates the development of a noncovalent reactive complex with the β-lactam, while the serine β-lactamases first create a covalent acylated enzyme. Interestingly, the same microbiologically inactive molecule that cannot form an enzymatically productive compound with a PBP is the end product of both reactions (Eichenberger & Thaden, 2019).

B-Lactam Antibiotics Classes

The most common, clinically significant, and often most effective bacterial defense against the deadly effects of b-lactam antibiotics is the production of one or more b-lactamases. Thus, the creation of novel compounds that can withstand inactivation by a growing variety of b-lactamases has been a constant struggle in the development of b-lactam antibiotics (Das & Banik, 2024).

Penicillin

The first penicillin to be used in therapeutic settings was benzyl-penicillin, a biosynthetic antibiotic. As nosocomial pathogens, it significantly reduced the prevalence of streptococci, which posed the biggest risk to hospital patients prior to 1941. However, as early as 1942, Staphylococcus aureus that was resistant to penicillin was discovered. By the end of the 1940s, their nosocomial infection prevalence had skyrocketed to pandemic levels. Clonal transmission of strains is the mechanism by which resistance is spread. The hunt for penicillinases stable b-lactam antibiotics was prompted by the fact that staphylococcal penicillinases could inactivate benzyl-penicillin and its congeners (De Rosa et al., 2021). Certain side chains were added to the 6-APA nucleus to produce acid-stable compounds like cloxacillin, oxacillin, and flucloxacillin, which are still widely used, and isoxazolyl-penicillins like methicillin, which is only used parenterally due to its acid instability. The main purpose of these substances is to treat staphylococcal infections (Durão et al., 2018).

Penicillins with an expanded antibacterial spectrum are known as broad-spectrum aminopenicillins. Shortly after the isoxazolyl penicillins, ampicillin, the first semi-synthetic penicillin having action against Gram-negative bacteria, was brought to the market. Transferable plasmids containing b-lactamase genes expressing enzymes that hydrolyzed ampicillin and other b-lactam antibiotics were quickly acquired by species that were naturally susceptible to the antibiotic, such as *Escherichia coli*. The first known producer of TEM-1 was a strain of *E. coli* that was discovered in Athens in 1963 (Lalchhandama, 2021). TEM-1 gene-carrying transposons proliferated all over the planet. Since then, a variety of

plasmid-mediated b-lactamases with varying specificities against aminopenicillins have spread among clinical isolates of Pseudomonas and Enterobacteriaceae, especially in hospitals. While PSE-1 is more common in Pseudomonas aeruginosa, the most common of these enzymes are TEM-1 and SHV-1, which are seen more often in Enterobacteriaceae (MacLean & San Millan, 2019).

Ureidopenicillins such as Heterocyclic groups have been substituted on the a-amino group of azlocillin, mezlocillin, and piperacillin, the piperazine penicillin. This mostly enhances affinity for PBP-3, which increases activity against Gram-negative bacteria. Additionally, the chemical structure lessens the likelihood that organisms including *Enterobacter* species, *C. freundii*, *Serratia* species, indole-positive *Proteus* species, and *P. aeruginosa* would produce class C b-lactamases. When evaluated with high inoculum, Ureidopenicillins lose their effectiveness against *Klebsiella spp.* (San Millan, 2018).

The addition of a carboxylic (carboxypenicillins), sulfamic, or sulphonic acid makes these antibiotics much more active against *P. aeruginosa* by sustaining them against the chromosomal AmpC b-lactamase that the organisms express. While Klebsiella species are often resistant to ampicillin, carbenicillin exhibits some efficacy against ampicillin-resistant indole-positive Proteus and *Enterobacter* species. Alkyl groups are present on the amidino nitrogen atom of amidino penicillins. While practically all fast growing fermentative Gram-negative bacilli are susceptible, mecillinam and its oral ester pivmecil linam have no effect on Gram-positive bacteria. *B. fragilis, H. influenza,* and *Pseudomonas* species are resistant (Stanton et al., 2020).

Temocillin, a non-classical 6-a-methoxypenicillin, is the only penicillin that is completely resistant to being hydrolyzed by the AmpC chromosome enzymes (Windels et al., 2019).

Cephalosporins

The initial member of the cephalosporin class of b-lactam antibiotics, cephalosporin C, is resistant to staphylococcal penicillinases because it has a side chain made of D-a-aminoadipic acid condensed with a dihydrothiazine b-lactam ring system (7-aminocephalosporanic acid). When the first-generation cephalosporins entered clinical use in the middle of the 1960s, they remained stable against the then-current b-lactamases. Compared to penicillins, they penetrated Gram-negative bacilli's outer membrane more quickly. However, Gram-negative bacilli became more common, clinical isolates with reduced permeability appeared, and these organisms replaced *S. aureus* as the most common nosocomial pathogen. In hospitals, *K. pneumonia* that carried plasmids encoding TEM-1 together with many genes resistant to antibiotics became widespread. The overabundance of class C cephalosporinases led to the emergence of isolates that are rarely linked to clinical resistance, including *S. marcescens* and *Acinetobacter* specimens (Das et al., 2019).

Cefamandole and cefuroxime, two second-generation cephalosporins, are more effective against Gram-negative bacteria. In clinical use, they were resistant to break down by plasmid-mediated b-lactamases and more constant than cefoxitin against the chromosomal cephalosporinases of numerous *Enterobacteriaceae*. The overproduction of b-lactamases in *Enterobacteriaceae* as a result of regulator gene mutations, the invention of inducible chromosomal b-lactamases by *Pseudomonas spp.,* and the overproduction of class C b-lactamases (Lin & Kück, 2022).

While third-generation cephalosporins are significantly more effective against *Enterobacteriaceae*, especially strains that produce b-lactamases, they are typically less effective against Gram-positive cocci than first-generation cephalosporins. Third-generation cephalosporins have substituent aminothiazolyl and iminomethoxy groups, which give chromosomal class C b-lactamases more stability and a wider range of action. In an effort to improve pharmacokinetic and pharmacodynamics properties and broaden the antibacterial range, several derivatives were added to the classes. The capacity of third-generation cephalosporins to generate b-lactamases varies, although none of them can do so as well as cephamycins, clavams, or carbapenems (Karunarathna et al., 2024).

Their affinity for third-generation cephalosporins and monobactams was increased, albeit to differing degrees, by transmutations in the structural genes of plasmid-mediated enzymes (Chaudhry et al., 2019).

Since fourth-generation cephalosporins include a positively charged quaternary nitrogen atom at position C-3, they are more active against P. aeruginosa and other intestinal bacteria that have b-lactamase derepressed mutations than third-generation cephalosporins. The 7-amino-thiazolyl groups are present in cefepime and cefpirome, two fourth-generation cephalosporins. Cefepime has a low affinity for inducible chromosomally mediated cephalosporinases and is stable against hydrolysis by the more prevalent chromosomal and plasmid-mediated b-lactamases. While cefepime was discovered to have efficacy against Gram-negative bacteria resistant to ceftazidime, ESBLs hydrolyze it less than third-generation cephalosporins such as *E. aerogenes* and K. pneumoniae, it is markedly disposed to an inoculum effect (Macy et al., 2021).

Cephamycins

The methoxy group at C-7 of the b-lactam ring of 7-aminocephalosporanic acid gives cephamycins, also known as a-methoxy cephalosporins, their structural similarity to cephalosporins. Because of the 7-a-methoxy group, cefoxitin, a semisynthetic product, has a wide range of activity and is very resistant to being hydrolyzed by b-lactamases. The b-lactam ring is shielded from harm by the methoxy group and other substituents on the 7-a position. Following the discovery of cephamycins, substances like cefoxitin, cefotetan, latamoxef, cefbuperazone, and cefmetazole were created. Particularly among *E. cloacae* and *C. freundii*, compounds with 7-a-methoxy groups are good inducers of chromosomally mediated b-lactamases and lead to the selection of derepressed mutants (Srikhanta et al., 2019).

Genes that determine class C b-lactamases with cephamycinase activity have been obtained using plasmids. This has made it easier for Gram-negative bacteria to spread. Because of its 7-a-methoxy group, the oxacephem latamoxef is extremely resistant to b-lactamases and works well against Gram-negative aerobes and anaerobes. However, it has no effect on staphylococci. Both Gram-positive and Gram-negative microorganisms can be inhibited by flomoxef, an oxacephem that is derived from latamoxef and has a difluoromethylthio-acetamide group at C-7. Both substances are labile to cephamycinases but stable against ESBLs (Fu et al., 2019).

Monobactams

One b-lactam ring structure characterizes monobactams. Although norcardins were the original members of this class, aztreonam is the only monocyclic b-lactam that is utilized in therapeutic settings. Aztreonam's b-lactam ring is activated by a sulfonic acid substituent at position C-1, and its C-3 side chain is the same as ceftazidime. The monobactams nucleus needs molecular replacement surrounding it to reach its full antibacterial potential because it has poor antibacterial action. Compounds with mostly Gram-positive, primarily Gram-negative, or broad-spectrum action are produced by side-chain substitution. The main action of aztreonam is Gram-negative. Monobactams are susceptible to ESBLs, class C enzymes, including *K. oxytoca*'s class A chromosomal b-lactamase. Monophospham can be produced by substituting a phosphonate for the 1-sulfonic residue in monobactams, whereas monocarbams can be produced by substituting N-sulphonylated carbonyl amino moieties. Monophosphams are more durable against b-lactamases but have less inherent antibacterial action (Prescott & Hardefeldt, 2024).

Carbapenems

Carboxylic acids containing substituents at the C-2 and C-6 positions are known as carbapenems. In contrast to the cis-configured aminoacyl groups seen in the majority of other b-lactam antibiotics, the two carbapenems that are now in clinical use, imipenem and meropenem, contain a straightforward trans-configured 6-hydroxy ethyl group that confers significant b-lactamase stability. The compounds' C-2 substituents vary; meropenem is slightly less potent against Gram-positive organisms but four to eight times more effective against Gram-negative bacteria. Of all the b-lactam antibiotics, carbapenems exhibit the widest range of action. Ipenem's high affinity for PBP-2, a protein necessary for the formation of cell walls in G-negative bacteria, its high empathy for important PBPs of G-positive species, and its exceptional b-lactamase strength all contribute to its exceptional activity (Aurilio et al., 2022).

Meropenem and imipenem are also potent b-lactamase inhibitors. Despite being strong inducers of AmpC b-lactamases, their stability guarantees that clinically beneficial action is maintained. Biapenem, a more recent carbapenems, exhibit strong stability to serine b-lactamases and outstanding activity against a variety of bacterial infections. Biapenem hydrolyzes less quickly than imipenem and meropenem for Bacteroides fragilis and Stenotrophomonas maltophilia enzymes, despite being labile to metallo b-lactamases. After being discovered in Japan, plasmid-mediated carbapenem-hydrolyzing metallo b-lactamases have spread to *K. pneumoniae* (Liang et al., 2020).

Carboxypenams

Both the alteration at C-6 and the addition of carboxyl substituents at C-2 in Carboxypenams T-5575 and T-5578 give b-lactamases increased stability and antibacterial activity. Although T-5575 is more effective against the majority of Gram-negative bacteria, it shares a spectrum of activity with aztreonam. Additionally, it has demonstrated strong effects against *P. aeruginosa, C. freundii*, and *Enterobacter cloacae* that are resistant to ceftazidime. Both substances don't work well against bacteria that are Gram-positive. They have strong affinity for PBP-3 of *P. aeruginosa* and *E. coli* and are stable against a variety of b-lactamases (Bouza, 2021).

Trinems

A tricyclic nucleus is the primary structural characteristic of the novel class of b-lactam antibiotics known as Trinems. Because of its stability to the b-lactamases it produces, sanfetrinem—the first trinem to be fully developed—is a very powerful agent with a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria (with the exception of *Pseudomonas spp.*), aerobes, and anaerobes. With its broad range action, high potency, and stability against the most prevalent clinically significant b-lactamases, GV 129606 is a novel parenteral trinem. It is superior to all other penicillins and cephalosporins, has a very broad antibacterial range (including *Pseudomonas spp.*), and is on par with meropenem (Decuyper et al., 2018).

B-Lactamase Determinants

Clavulanic acid and the penicillanic acid sulphones, sulbactam and tazobactam, are two significant classes of therapeutically significant b-lactamase inhibitors. Commercial combinations of clavulanic acid with antibiotics and, in certain countries, cefoperazone, and tazobactam and piperacillin have all been made (Osborn et al., 2019).

Clavulanic Acid

S. clavuligerus is the source of the naturally occurring b-lactamase inhibitor clavulanic acid. It exhibits little activity against chromosomal b-lactamases of class C. Although it is typically a more powerful inhibitor of cell-free enzymes, clavulanic acid can inactivate both extracellular and intracellular b-lactamases because it can pass through bacterial cell walls. Depending on the specific b-lactamase inhibited, its mode of action varies, but in general, it functions as a competitive and frequently irreversible inhibitor. Clavulanic acid has the ability to produce cephalosporinases (Peng et al., 2021).

Sulbactam

Sulbactam is a sulphone of penicillanic acid that inhibits similarly to clavulanic acid. It is a weak antibacterial agent that is generally ineffective against most other bacteria, including *E. coli*, but it is somewhat active against *N. gonorrhoea* and the majority of isolates of Acinetobacter and Bacteroides species. Though less effective than clavulanic acid, sulbactam inhibits penicillinases and ESBLs. According to reports, it has a poor inhibitory capacity for TEM-1, especially when the b-lactamase is overproduced. Except for those in a specific strain of *P. vulgaris*, sulbactam has been shown to be a poor inducer of the majority of cephalosporinases (Wang et al., 2021).

Tazobactam

An irreversible b-lactamase inhibitor, tazobactam is a penicillanic acid sulphone that inhibits a variety of b-lactamases, including several

of *Providencia stuartii*'s chromosomal cephalosporinases. Tazobactam and clavulanic acid are equipotent. Its effectiveness against ESBL manufacturers originating from SHV is debatable, nevertheless. While Livermore cited another study that showed good susceptibility to the combination, other investigations have indicated that microbe expressing SHV were generally resistant to inhibition by tazobactam (Gnanasekaran et al., 2021).

Numerous novel penicillanic acid sulphones are now being studied, including the sodium salt and Ro 48-1220, a 2-b alkenyl penicillanic acid sulphone. All of these substances have good comparisons to the inhibitors now in clinical use. Since 1991, it has been noted that inhibitor-resistant b-lactamases have emerged and become more common. Another resistance mechanism that has been suggested is the overproduction of traditional plasmid-mediated b-lactamases that overwhelm the inhibitor (Lal et al., 2023).

Gram-positive and Gram-negative bacteria produce b-lactamases, which are effectively inhibited by brobactam 6-b-bromopenicillanic acid. With 6-b-aminopenicillanic acid, a potent reversible b-lactamase inhibitor is created. The more prevalent plasmid-mediated enzymes, including TEM-1, TEM-2, and SHV-1, are strongly inhibited by it. The broad spectrum chromosomally-mediated enzymes present in Klebsiella aerogenes, the chromosomal cephalosporinases of *P. vulgaris* and *P. rettgeri,* and the OXA-type enzymes are all vulnerable to suppression by brobactam. Ampicillin and brobactam have been used together in clinical settings. When compared to other oral b-lactam antibiotics currently used in clinical practice, this combination performs well (Lal et al., 2023).

Additional Inhibitors Despite being strong b-lactamase inhibitors, penems like BRL42715 and SYN-1012 were not developed for clinical usage due to specific pharmacokinetic characteristics. Although it inhibits class C b-lactamases, the bridging monobactams inhibitor Ro 48-1256 has no discernible antibacterial action of its own. Free mercapto-acetic acid acts as a competitive inhibitor, and several thiol esters of mercapto-acetic acid have been found to be metallo b-lactamase inhibitors (Dorairajan et al., 2025).

Conclusion

First-generation cephalosporins and penicillinase-resistant penicillins were the first line of defense against bacterial infections for more than 20 years before G-negative bacteria developed a significant issue. The pharmaceutical industry responded by introducing new families of b-lactam antibiotics, including carbapenems, monobactams, clavam, penicillanic acid sulfone inhibitors, cephalosporins and cephamycins. However, because of their therapeutic application, a variety of b-lactamases with ever-increasing antibiotic substrate spectra have been selected. The development of a plasmid-mediated AmpC b-lactamase would be the presumed resistance mechanism if the isolate was also resistant to cefoxitin and cefotaxime. In this scenario, testing b-lactamase inhibitor combinations would not be necessary. To aid in the selection of treatment approaches, a specific resistance phenotype was identified, and consequently, the probable b-lactamase implicated. The appearance of such intricate organisms with a wide variety of b-lactamases, however, has a number of ramifications. First, the production of several b-lactamases enhances the probability of b-lactamase inhibitors being overwhelmed, regardless of the presence of AmpC enzymes. Second, the intricacy limits the usefulness of "interpretative reading," which forms the foundation of the guidelines established to analyze anti-biogram data. Third, the possibility that some of the resistance mechanisms found in an isolate would be obscured by others makes monitoring the molecular basis of antimicrobial resistance increasingly challenging. Given the emphasis on the necessity of high-quality surveillance of resistance and its causes, these are serious concerns.

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