

Penicillins: An Updated Review on its Therapeutic Potential and Resistance Trends

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Abstract

Penicillin, discovered in 1928, is becoming increasingly resistant due to beta-lactamase synthesis, changed binding proteins, and decreased permeability. Ampicillin resistance approaches 80% in Asian region, complicating therapy. Penicillin allergies affect fewer than 5% of people, but can complicate matters. Metal nanoparticles are being investigated as an alternative therapy to combat antibiotic resistance. Antimicrobial resistance (AMR) must be addressed continuously through monitoring and innovation. The current review focus on therapeutic potential along with resistance trends of Penicillins.

Introduction:

Penicillin was first discovered in 1928 and is now the most widely used antibiotic (2). Fleming was experimenting

with the influenza virus in the Laboratory of the Inoculation Department at St. Mary's Hospital in London, and he was often described as a careless lab technician. Fleming returned from a two-week vacation to find that a mold had developed on an accidentally contaminated staphylococcus culture plate. Upon examination of the mold, he noticed that the culture prevented the growth of staphylococci. An article published by Fleming in the British Journal of Experimental Pathology in 1929 reads, "The staphylococcus colonies became transparent and were obviously undergoing lysis... the broth in which the mold had been grown at room temperature for one to two weeks had. acquired

marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria. Fleming described the colony as a "fluffy white mass which rapidly increases in size and after a few days sporulates" and changes color from dark green to black to bright yellow. Even in the early experimentation stages, penicillin had no effect against gram-negative organisms but was effective against gram-positive bacteria (3, 4).

Chemistry of penicillin:

The penicillin class of antibiotics comprises a large group of bicyclic penam compounds differing in the acyl side chain attached to the fused B-lactam-thiazolidine ring system (5). Most are semisynthetic derivatives of the penicillin nucleus, 6-aminopenicillanic acid (6-APA), prepared synthetically by the addition of acyl side chains at the 6-amino group. The penicillins are also called beta-lactam antibiotics (6). The presence of the lactam ring is essential for biological activity and is usually the site of cleavage by bacterial penicillinase or by an acid. The nature of the R (variable) group determines the drug's stability to enzymatic and acidic hydrolysis and its activity against different bacteria. Alteration of the R group, such as the addition of bulky side chains or functional groups, gives different variants of penicillins that are known to enhance activity, show resistance to penicillinase, and are more resistant to acid (3).

Types of penicillin:

Two of the major differences between the types of penicillin are the way they're made and what kind of bacteria they're effective against. Types of penicillin include:

Natural penicillins:

Natural penicillins are found in the world around us (they aren't made by people). Scientists isolate (purify) just the penicillin from where it's found to make it into medications (7). **Examples:** Penicillin G and penicillin V (also known as penicillin V potassium) are natural penicillins (8). Healthcare providers use natural penicillins to treat a range of infections, including strep throat, syphilis and Lyme disease (9). Penicillin G comes in IV form. Penicillin V can be taken by mouth.

Semi-synthetic penicillins:

Scientists alter penicillin's natural form to make more effective antibiotics (10). These are called semi-synthetic penicillins. They include penicillinase-resistant penicillins, aminopenicillins and extended-spectrum penicillins. **Examples:** Penicillinase-resistant penicillins. Nafcillin, oxacillin and dicloxacillin are penicillinase-resistant penicillins (11). They come in both IV and pill form and are often used to treat staph infections. Methicillin, which is rarely used anymore, is also a penicillinase-resistant penicillin (12).

Aminopenicillins:

Amoxicillin and ampicillin are aminopenicillins. Amoxicillin is one of the most commonly used penicillins (13). Healthcare professionals use it to treat ear infections, UTIs, pneumonia and other common infections. It comes in a pill or liquid you can swallow. Ampicillin comes in pill or IV form.

Combination medications:

Penicillins are often combined with other medications into one drug to help them work better. The following examples include: Penicillin can be combined with other drugs, called beta-lactamase inhibitors, to help them work better(14). Beta-lactamase inhibitors work by preventing bacterial enzymes (beta-lactamases) from destroying the

antibiotic (15). Some penicillin/beta-lactamase inhibitor combinations include: Augmentin® (amoxicillin and clavulanic acid), Unasyn® (ampicillin and sulbactam). And Zosyn® (piperacillin and tazobactam).

Objectives:

Examine the patterns of penicillin resistance in Pakistan and around the world.

Compile case studies on penicillin-resistant bacteria from ScienceDirect, PubMed, and Google Scholar.

Examine epidemiological research on the distribution and prevalence of penicillin resistance.

Examine how bacteria become resistant to penicillin.

Determine which bacterial species are susceptible to penicillin.

Using available data and resistance-influencing variables, forecast future trends in penicillin resistance.

Epidemiology:

In Pakistan:

Only 28 studies (30.11%) have identified the resistance gene at the molecular level. The most commonly reported resistance genes are blaTEM (78.94% in *Shigella* spp.) and blaNDM-1 (32.75% in *Klebsiella* spp.), followed by VanA (45.53% in *Enterococcus* spp.), mcr-1 (1.61% in *Acinetobacter* spp.), and blaKPC-2 (31.67% in *E. coli*). Sindh has the most studies (40.86%), followed by Punjab (35.48%), while no AMR data was provided for Balochistan. Only 28 studies (30.11%) have identified the resistance gene at the molecular level. The most frequently reported resistance genes are blaTEM (78.94% in *Shigella* spp) and blaNDM-1 (32.75% in *Klebsiella* spp), followed by VanA (45.53% in *Enterococcus* spp), mcr-1 (1.61% in *Acinetobacter* spp), and blaKPC-2 (31.67% in *E. coli*). The majority of the studies (40.86%) were from Sindh, followed by Punjab (35.48%), with no AMR data available for Balochistan. A high percentage of resistance was observed against some antibiotics, including trimethoprim, co-trimoxazole, amoxicillin/clavulanate, ciprofloxacin, piperacillin/tazobactam, cefotaxime and ceftazidime (1).

According to a multicenter surveillance study by the Pakistan Antimicrobial Resistance Network (Pak-ARIN), the percentage of *Streptococcus pneumoniae* isolates that were non-susceptible to penicillin varied by region, ranging from 28% to 42%. Over 68% of *Escherichia coli* urinary isolates in Karachi were ampicillin-resistant, according to a hospital-based study, indicating widespread β -lactam resistance (1). Furthermore, it was discovered that the prevalence of MRSA (methicillin-resistant *Staphylococcus aureus*) in Pakistani healthcare settings ranged from 42% to 65%, particularly in intensive care units (ICUs). One of the contributing factors in Pakistan is the availability of antibiotics over the counter without a prescription and inadequate methods for controlling infections (1).

In the World:

Penicillin resistance varies greatly throughout the world: The European Centre for Disease Prevention and Control (ECDC) reports that between 10% and 25% of invasive *S. pneumoniae* isolates in Europe were penicillin non-susceptible, with higher percentages seen in southern European countries like Spain, Italy, and Greece (16). The Centres for Disease Control and Prevention (CDC) discovered that 30% of *S. pneumoniae* isolates that caused invasive infections in the US had decreased penicillin susceptibility (17). Over 50% of Gram-negative organisms in Southeast Asia and Sub-Saharan Africa have β -lactam resistance due to uncontrolled antibiotic use (17). High levels of penicillin resistance are especially prevalent in low- and middle-income

countries (LMICs), according to the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) report (18).

Global trends suggest:

- Declining MRSA rates in developed countries (e.g., the U.S., Europe)
- Rising penicillin and ampicillin resistance in developing nations
- Increasing emergence of multidrug-resistant (MDR) strains globally.

Mode of Action of Penicillin:

Most bacteria feature a peptidoglycan cell wall encasing the bacterial plasma membrane, which prevents osmotic lysis and offers structural integrity (19). This peptidoglycan wall undergoes continuous remodeling during replication and growth. Penicillin functions by inhibiting the cross-linking of peptidoglycan within the cell wall (20). The catalyst for this reaction is penicillin-binding proteins, such as the enzyme DD-transpeptidase. Penicillin's 4-membered β -lactam ring can bind to cell walls.

As the bacteria enter into the cell and kill fragments β -lactamas β -lactamas can occur

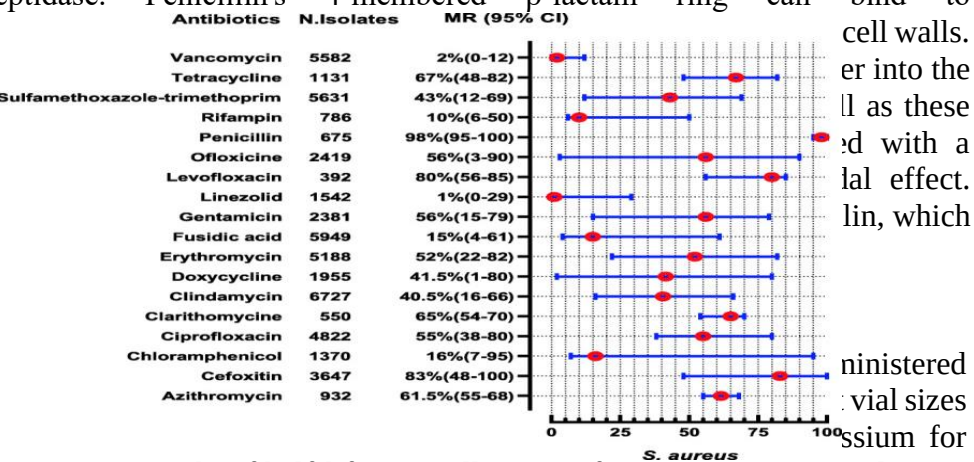
Administration:
Strengths, intramuscularly available:

injection USP. Due to its brief half-life, penicillin G is often given intravenously (IV) or intramuscularly (IM) in divided doses spaced 4–6 hours apart. The injection of penicillin G benzathine guarantees a consistent low dose of penicillin G for two to four weeks. A procaine penicillin G combination of antibiotics and local anaesthetics has also received FDA approval. Orally administered versions of penicillin V and its potassium salt derivative, penicillin VK, include reconstitution solutions (125 mg/5 mL and 250 mg/5 mL) and tablets (250mg and 500mg) (22). To avoid bacterial resistance, patients should be counselled to complete the course of treatment, just like with any antibiotic. Penicillin exhibits restricted blood-brain barrier penetration. For bacterial meningitis brought on by susceptible organisms like *Propionibacterium acnes*, penicillin G is advised by the Infectious Diseases Society of America (IDSA). The Centres for Disease Control and Prevention (CDC) advise against using penicillin as a first-line treatment for anthrax or as a postexposure prophylaxis unless susceptibility is established (23).

Resistance:

Penicillin:

Penicillin, discovered by Alexander Fleming in 1928, faces bacterial resistance through three main mechanisms: 1) **Reduced permeability** – In Gram-positive bacteria, this involves cell wall thickening (e.g., in *S. aureus*). In Gram-negative bacteria, it involves mutations or reduced numbers of porins (e.g., in *P. aeruginosa*, *E. coli*, *Enterobacter*, *Klebsiella*) (19). 2) **Altered penicillin-binding proteins (PBPs)** – Mutations reduce antibiotic binding. For example, *S. pneumoniae* and *S. aureus* produce mutant PBPs with low affinity for penicillin. MRSA produces PBP2a via the *mec* gene system, which resists most antibiotics (24). 3) **Enzymatic degradation** – β -lactamases hydrolyse the



β -lactam ring of penicillin, rendering it ineffective. Over 2,000 types exist, each with a distinct activity. Additionally, *P. aeruginosa* can resist antibiotics through biofilms and persisting cells. Gram-positive bacteria can protect nearby Gram-negative bacteria by secreting large amounts of β -lactamases (25). Penicillin G (benzylpenicillin) and penicillin V (phenoxymethyl penicillin) are the most frequently used natural penicillins. Penicillin G is preferred in serious infections, especially when parenteral administration of large doses is required (5). The disadvantages of penicillin G are that (1) it is degraded by gastric acid, (2) it is destroyed by the enzyme penicillinase, and (3) its use is associated with an allergic reaction in approximately 10% of patients, a problem shared by all penicillins (26).

First Signs, Progression and the Global Problem:

The first sign of antibiotic resistance became apparent soon after the discovery of penicillin. In 1940, Abraham and Chain reported that an *E. coli* strain was able to inactivate penicillin by producing penicillinase (27). The spread of penicillin resistance was already documented by 1942, when four *Staphylococcus aureus* strains were found to resist the action of penicillin in hospitalized patients (28). During the next few years, the proportion of infections caused by penicillin-resistant *S. aureus* rapidly rose, spreading quickly from hospitals to communities. By the late 1960s, more than 80 percent of both community and hospital-acquired strains of *S. aureus* were penicillin-resistant (29). The rapid spread of penicillin resistance temporarily came to a halt after the introduction of the second-generation, semisynthetic methicillin in the 1960s (30). However, methicillin-resistant strains soon emerged, and only in 1981 was this mechanism of resistance unraveled. These strains harbored an altered PBP, designated PBP-2a, which showed a reduced affinity for penicillin, thereby conferring resistance to penicillin (31). PBP-2a is encoded by *mecA*, a gene located on the *S. aureus* chromosome (32). This resides within the mobile genomic island SCCmec (staphylococcal cassette chromosome mec) (33). In approximately 20 years, methicillin resistance became endemic in the U.S., reaching 29 percent of hospitalized *S. aureus*-infected patients (34). By 1999, the percentage of cases associated with antibiotic-resistant pneumococcus had tripled compared to 1979, reaching 14.4 percent in South Africa (35). In 1967, strains of *S. pneumoniae* also became resistant to penicillin. In addition, the rapid spread of gonococcus resistance followed. In 1976, beta-lactamase-producing gonococci were isolated in England and the U.S. (36). Furthermore, in 1983, a large outbreak of resistant non-beta-lactamase-producing gonococci affected Durham city in North Carolina (U.S.) (37).

Cases reported:

S. aureus was reported in 20 studies, in which 13 studies also report MRSA. *S. aureus* shows high resistance to penicillin, followed by cefoxitin and levofloxacin, i.e. (MR 98, 95%CI: 95–100), (MR 83, 95%CI: 48–100%) and (MR 80, 95%CI: 56–85), respectively, as shown in Figure 1 (38).

FIGURE 1 ANTIBIOTIC RESISTANCE IN PAKISTAN (1)

A study conducted in Iran looked into how pharmaceutical workers' exposure to penicillin dust at work affected the emergence of bacteria resistant to the antibiotic. The results emphasized the occupational health hazards connected to antibiotic manufacturing environments by indicating a greater frequency of resistant strains in workers exposed to penicillin dust as compared to a control group (1).

An examination of *Neisseria gonorrhoeae* isolates from 1992 to 2009 in Pakistan showed a marked rise in ofloxacin, tetracycline, and penicillin resistance (39). The study underlined that tetracycline, ciprofloxacin, and penicillin should no longer be used empirically to treat gonorrhea in Pakistan. As first-line treatments, ceftriaxone and cefixime were advised, with recurring monitoring to identify any new resistance (40).

Methicillins:

Methicillin, a β -lactam antibiotic, inhibits penicillin-binding proteins (PBPs) that synthesise peptidoglycan, a crucial mesh-like polymer that surrounds cells (41). *S. aureus* can develop resistance to methicillin and other β -lactam antibiotics by expressing a foreign PBP, PBP2a, which is resistant to methicillin but can still execute host PBP functions. Methicillin-resistant (42). *S. aureus* isolates are frequently resistant to other antibiotic classes (by distinct mechanisms), limiting treatment options, and this has prompted the hunt for novel drugs efficacious against these infections (43). Understanding the mechanism of methicillin resistance has resulted in the discovery of accessory variables that control the level and character of the resistance (43). Research into how MRSA resists methicillin has also resulted in the discovery of accessory factors like Fem proteins, which aid the bacteria's survival and may serve as novel therapeutic targets (44). Furthermore, natural substances such as epicatechin gallate (from green tea) and corilagin have shown promise in decreasing MRSA resistance, bringing new hope for future therapies (45).

Oxacillin:

Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) is a poorly known variant of methicillin resistance (46). BORSA strains have modest, borderline resistance to penicillinase-resistant penicillins (PRPs), with oxacillin MICs typically equivalent to 1–8 $\mu\text{g ml}^{-1}$ (47). Unlike MRSA, they do not contain a changed penicillin-binding protein, PBP2a, expressed by the *mecA* or *mecC* genes (48). Their resistance is often linked to hyperproduction of beta-lactamases or, in certain cases, specific mutations in PBP genes (49). BORSA strains are neither truly resistant nor truly susceptible to methicillin (50). However, they are commonly misinterpreted, posing a clear epidemiological and therapeutic risk. BORSA strains are routinely isolated from humans and animals, and they can be found in both hospitals and the community. BORSA cannot be classed as fully methicillin-resistant or really methicillin-susceptible. They are, nevertheless, commonly misinterpreted, posing a clear epidemiological and therapeutic concern. BORSA strains are frequently isolated from humans and animals and can be found in hospitals as well as in the community (47). BORSA infections appear to have the same epidemiology and clinical presentation as MRSA infections; however, these infections are typically more severe than those produced by methicillin-sensitive *S. aureus* (MSSA) (51). Even with higher dosages of oxacillin, treatment for severe BORSA infections may be futile. The existing research suggests that BORSA constitute a frequently neglected problem. The existing research reveals that BORSA are an often overlooked concern, and their proliferation in new contexts recommends that they must be monitored and accurately differentiated from MSSA and MRSA (51).

Cases Reported:

Enterococcus spp. were reported in 4 studies showing high resistance to oxacillin (MR 100%), and erythromycin (MR 96, 95%CI: 79–100), while linezolid showed 100% susceptibility against 240 tested isolates, as illustrated in the figure below (1).

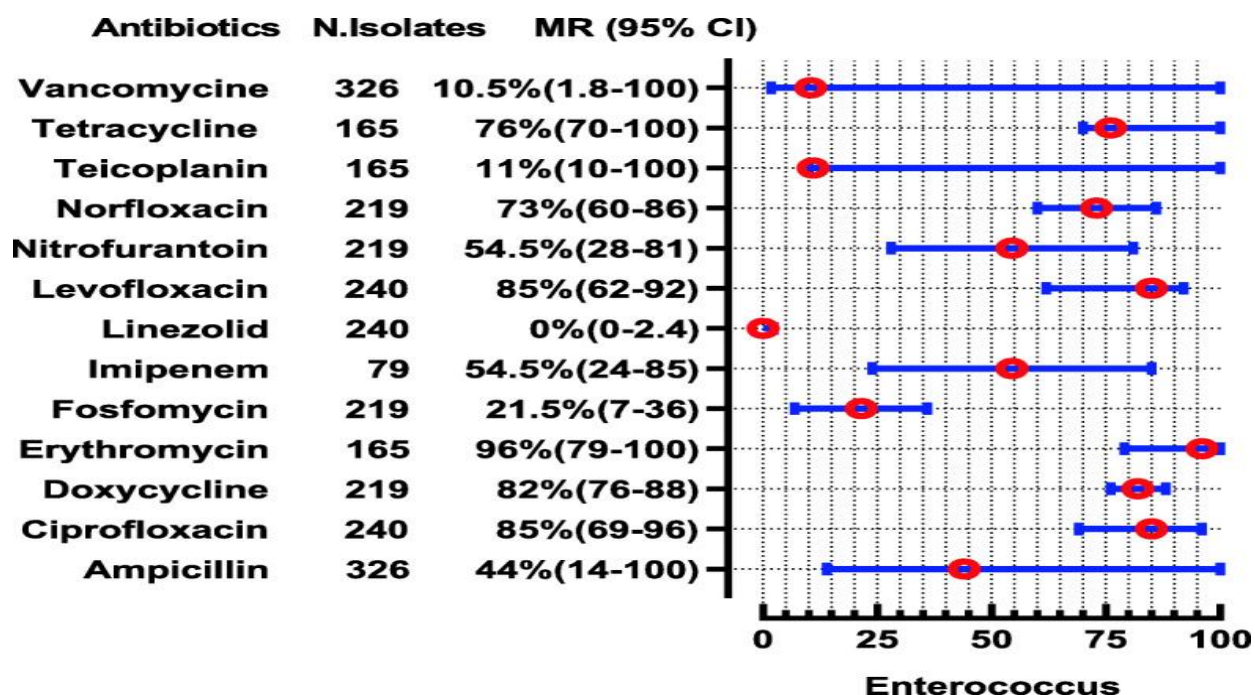


FIGURE 2 METHICILLIN-RESISTANT *S. AUREUS* (1)

Mechanisms of Amoxicillin Resistance in *Helicobacter pylori*:

Resistance to amoxicillin in *Helicobacter pylori* has become a major issue in the treatment of gastric infection (52). Early rates of resistance were low, from 0.8% to 1.4% (53). Current data, however, show a disturbing increase in resistance in many regions, such as Italy, Brazil, El Salvador, India, and Taiwan (54). It is important to identify the major mechanisms of this resistance in order to develop effective treatment strategies.

Production of beta-lactamase:

One of the main mechanisms of resistance is beta-lactamase production. Resistant *H. pylori* strains produce beta-lactamases, enzymes that can hydrolyze the beta-lactam ring of amoxicillin (55). Hydrolysis inactivates the antibiotic, making it unable to effectively bind to penicillin-binding proteins (PBPs) and interfere with bacterial cell wall synthesis. Recent research has found beta-lactamase-like genes in the *H. pylori* genome, specifically the gene that encodes HcpA (*H. pylori* cysteine-rich protein A). Even though HcpA slowly hydrolyzes some beta-lactam antibiotics, substantial beta-lactamase activity connected to amoxicillin resistance at a high level was described for clinical isolates.

Structural alterations of penicillin-binding proteins:

Penicillin-binding protein changes are also essential for drug resistance. The penicillin-binding proteins of bacteria play critical roles in synthesizing cell walls, with the amoxicillin effect targeting largely PBP1. Genetic alterations within *pbp1A* encoding for PBP1 enable resistance of *H. pylori* to beta-lactam compounds. These mutations reduce the amoxicillin binding affinity and hence its antibacterial activity. Studies have demonstrated that changes in the *pbp1A* gene are highly correlated with elevated minimum inhibitory concentrations (MICs) of beta-lactam antibiotics, substantiating its central role in resistance (56). The development of these resistance mechanisms poses considerable treatment challenges. The combination of beta-lactamase production and alterations in PBPs is responsible for the failure of eradication regimens involving amoxicillin (57). As patterns of resistance change, monitoring these mechanisms in clinical practice becomes increasingly important. The increasing incidence of resistance

emphasizes the need for routine susceptibility testing and the possible utilization of alternative antibiotics or combination regimens to treat *H. pylori* infections effectively. High-level resistance to amoxicillin is linked with the production of beta-lactamase, whereas low-level resistance is caused by point mutations in the *pbp1A* gene (58). *H. pylori* is also capable of exchanging DNA via natural transformation, enabling the transfer of the *bla*TEM-1 amoxicillin resistance gene between strains. This is a potential risk during treatment (59). The countries that already have increased rates of resistance can see further increases, with some areas potentially reaching levels above 30% (60). This increased resistance will tend to lead to more treatment failure in eradication treatments, stressing the need for the creation of new treatment methodologies(61).

Ampicillin Resistance in Gram-Negative Bacteria:

Gram-negative bacterial resistance to ampicillin is a serious public health issue, driven by the extensive application of the antibiotic as a beta-lactam (55). Resistance stems primarily from expression of plasmid-mediated beta-lactamases, which are enzymes that hydrolyze the beta-lactam ring of ampicillin, thereby inactivating it (62). Among all the various beta-lactamases, TEM-1 has been most prevalent, accounting for over 50% of all the plasmid-mediated ampicillin resistance throughout the globe (63). Its ability to confer resistance in diverse forms of bacterial species, particularly where transferable ampicillin resistance is predominant, places it as a prominent research area in antibiotic resistance.

Mechanisms of Ampicillin Resistance:

The most common mechanism of resistance to ampicillin in Gram-negative bacteria is through the production of plasmid-coded beta-lactamases. These are enzymes that are capable of hydrolyzing the beta-lactam ring of the antibiotic with great efficiency, an integral part of its therapeutic action. While more than 30 different plasmid-encoded beta-lactamases are found, TEM-1 is the most prevalent type and occurs in such species as *Escherichia coli* and *Haemophilus influenzae*. The incidence of resistance to ampicillin has increased to alarming proportions in India, to about 82%. Significantly, a large proportion of *E. coli* strains found in this nation have mechanisms of resistance that differ from those found in the United Kingdom. In addition to beta-lactamase production, resistance has been found to be a result of mutations in penicillin-binding proteins (PBPs), particularly PBP3. These lower the binding energy of ampicillin, which is responsible for resistance patterns in some bacterial strains. Although this is not as prevalent as beta-lactamase production, it is of equal significance in the larger resistance landscape.

Comparison to Amoxicillin Resistance:

While ampicillin and its analogue, amoxicillin, share similar resistance mechanisms, there are considerable variations between the two. Both antibiotics are susceptible to hydrolysis by beta-lactamases, but certain enzymes may hydrolyze one antibiotic more than the other. As an instance, TEM-1 beta-lactamase has been known to confer resistance to both ampicillin and amoxicillin; however, their prevalence and effectiveness may be strain-dependent as well as depending on environmental factors. Also, amoxicillin has a broader spectrum of activity than ampicillin, particularly against certain Gram-positive bacteria. This enhanced activity could have an effect on resistance patterns because bacteria evolve different mechanisms of resistance based on the kind of antibiotic pressure to which they are subjected.

Prevalence and Future Trends:

Resistance to ampicillin is being increasingly detected, particularly in the developing world, like India, where resistance rates are above 80%. Also, resistance among *H. influenzae* strains among some groups is approximately 40%. The ongoing generation of new beta-lactamases and the genetic versatility of the bacteria mean that resistance to ampicillin will continue to increase. This trend underlines the necessity of close monitoring of resistance and the development of new types of therapy for combating resistant infections (64, 65).

Alternative approaches to treating infectious diseases

Investigating alternatives to antibiotic therapy is an alternative strategy because of the existing temporal constraints in the fight against AMR. Some metals are known to have antibacterial capabilities; thus, investigating metal nanoparticles as a potential antimicrobial therapy could remove antibiotic-resistant bacteria. Metal nanoparticles can alter bacterial survival in a variety of ways. Antimicrobials containing silver, for example, can cause physical stress on bacterial cells. Other research suggests that gallium can interfere with bacterial metabolic pathways by disrupting bacterial metal ion intake, which inhibits biofilm-forming *P. aeruginosa* in vitro. Gallium is already in clinical studies as an antibacterial treatment for cystic fibrosis patients; nonetheless, metal nanoparticles' overall toxicity and narrow spectrum activity remain a barrier (66). Rapid diagnostic instruments are necessary for the alternative treatments in order to promptly and effectively detect bacterial infections. By identifying the type of bacteria causing the illness, this will enable more specialised treatment methods. In addition to reducing the empirical administration of current antibiotics, rapid screening and effective diagnostic methods should also lessen the selective advantage for germs that are resistant to antibiotics. It is still crucial to comprehend the processes underlying resistance because the development and acquisition of resistance differ depending on the species and infection stage. The creation of beta-lactamase inhibitors, for example, has demonstrated great success in the past at subverting resistance processes themselves and may increase the useful life of our current antibiotics supply (67).

Conclusion:

Although penicillin transformed medicine, its limited effectiveness against Gram-negative bacteria, β -lactamase synthesis, and changed PBPs have led to rising resistance. Treatment is made more difficult by resistance to related drugs such as ampicillin, amoxicillin, and methicillin. Careful usage, precise diagnosis, and the creation of alternative treatments like metal nanoparticles and β -lactamase inhibitors are important to combat antibiotic resistance.

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