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A REVIEW ON PENICILLIN: HISTORY, MECHANISMS OF ACTION, BACTERIAL RESISTANT AND PENICILLIN ALLERGY

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ABSTRACT

Penicillin is the first antibiotic drug that was discovered and introduced by Fleming to treat various kinds of diseases. Fleming followed by many scientists carried out experiment to extract material that may have antibiotic properties in order to discover other antibiotics and some scientists also did extensive research on penicillin. Since its discovery, it is the choice of the drug for various infectious diseases and widely used due to its efficacy and stability, however, extensive use also caused bacterial resistance as many microorganisms become resistant to penicillin. To overcome the resistance and enhance the bacterial spectrum, various kinds of semisynthetic penicillin were discovered and introduced to treat those infections caused by resistant microbes and the least effective microbes by penicillin. Penicillin group is well known for its mechanisms of action as it interferes with the synthesis of the bacterial cell wall of growing microbes ultimately killing them so for called bactericidal. Even today, penicillin is being considered as a highly effective and most prescribed drug throughout the world but penicillin allergy is one of the major issues when using penicillin. The aim of the present paper is to review the history, mechanisms of action, bacterial resistance and penicillin allergy.

1. INTRODUCTION

Antimicrobial agents are prepared by using various microbes (including bacteria, fungi, actinomycetes, etc.) that inhibit or kill other microorganisms (Soares *et al.,* 2012). Antibiotic is another term that is most commonly being used nowadays, it was originated from antibiosis that means against life. In the past, the antibiotic was considered as an organic compound taken from one microbe and acted against other microbes (Russell, 2004).

Nowadays, there are more than 60 antibiotics that are produced from different microbes and fight against many bacteria, fungi and other harmful microbes to humans and animals 9 (Pandey *et al.,* 2014). Penicillin and other antimicrobial drugs have been playing an important role in the treatment and control of various infectious diseases in the world (Mandal *et al.,* 2011). However, antibiotics have been misused for a long time due to insufficient knowledge that leads to be the cause of bacterial resistance and decreases its efficacy (Das *et al.,* 2018).

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Penicillin is the first antibiotic to be effective against different bacterial diseases and its medical uses were arguably the most important scientific discovery of the 20th century. It is one of the oldest antibiotics that was discovered by Alexander Fleming which is currently prescribed and used in a large variety of infectious diseases for its wide range of clinical indications (Bush *et al.,* 2016; Tooke *et al.,* 2019). It is a group of closely related compounds that all have the same basic ring structure β-lactam that is derived from cysteine and valine via a tripeptide intermediate. Broadly, there are two main sources of penicillin, one is natural biosynthetic penicillin that is derived from mould through fermentation and the other is semi synthetic that consists of penicillin ring structure include Penicillin V, Ampicillin, Oxacillin, Carbenicillin, Methicillin, etc. These current semi synthetic penicillins can be taken orally because they have resistance to stomach acid and the β-lactamase enzyme that is produced by some bacteria to destroy penicillin. Among the natural source, Penicillin G is the only antibiotic that is currently used in clinics for the treatment of various infectious diseases. The penicillin of natural origin is less effective against gram negative bacteria due to β-lactamases enzyme than semi synthetic penicillin (Walker, 1996)

Discovery

The discovery of penicillin is an accident that started with a mistake, but it played a major role in the treatment and prevention of many human diseases all over the world (Derderian, 2007). A bacteriologist Alexander Fleming was working at Mary's Hospital Laboratory in London on Staphylococcus species. Fleming had set aside many Petri dishes containing bacterial colonies prior to leaving for vacation with his family. In September 1928, when returned from holiday he found that one petri dish was contaminated (Swann, 1983). He observed that a mould was growing along the edge of the plate while affecting the growth of bacterial population. Later, it was identified as a *Penicillium notatum*, an antimicrobial substance produced by the fungus. Flaming named it Penicillin and published his observation in an article in The British Journal of Experimental Pathology in 1929 (Traxler and Kolter, 2012). Furthermore, he followed to test thirteen other fungi species to observe whether they could produce a similar antimicrobial substance or not and concluded that they could not (Fleming, 1929). Following the flaming findings, other scientists started different researches on new substances to check their antimicrobial properties. In 1939, Howard Florey started to work on lysozyme and its antibacterial activity because he was impressed by the Fleming observations for Penicillium and its ability to kill the bacteria. Finally, Flory and a chemist Ernst Chain cultured the fungus in sufficient amount for evaluation of antimicrobial role. A chemist in Flory lab named Norman Heatley played a major role in the purification process of penicillin. They setup a method for the extraction of penicillin in order to obtain enough extract for performing the first trial of the drug in the mid of 1940s. Finally, enough amount of penicillin was extracted and used for a trial to determine its efficacy in mice at the William Dunn School of Pathology in Oxford. On 25th May 1939, an experiment was conducted by Hatley and its Colleagues to check the in-vivo effect of penicillin and concluded that penicillin haven a life-saving drug when they administered against streptococcus induced infection (Lobanovska and Pilla, 2017; Cranston and Sidebottom, 2016).

First trial in human

First time penicillin was administered to a woman with terminal cancer and the patient developed fever and rigor shortly after the drug administration because the penicillin was impure with other pyrogenic substances. Edward Abraham suggested further purification of penicillin to remove all pyrogenic residues before injecting any patient and finally it was further purified. On 12 February 1941, penicillin was administered to a second patient, a policeman suffering from severe staphylococcus and streptococcus infection. After 5 days of repeated intravenous injection, the patient was profound on his recovery and the urine of the patient was collected due to low availability of penicillin and recycled for re-extract more penicillin but the patient relapsed and die in a short time due to overall shortage of penicillin and treatment was terminated (Cranston and Sidebottom, 2016). From 1941 to 1942, more trail (in 170 patients) was conducted by Florey, Chain and Heatley and concluded that penicillin had remarkable effects in combating bacterial infections without any side effect (Ligon, 2004). Flory and his team prepared more penicillin for the treatment of injured soldiers and other civilians during the war. Florey and Heatley

went to the United States in 1941 due to the financial crisis in the UK because the US was not part of War II. Florey and Heatley started entitled "The Penicillin Project" that was focused on main three points: the first point was to enhance the purification of penicillin and the second was to find more effective penicillium strain and last stream was to find pharmaceutical industries that would take on mass production of Penicillin. In 1942, Florey conducted the first trial of penicillin in the war set at military hospital in North Africa and found that penicillin had a good effect on wound healing in the fresh wound as well as infected wound (Fraser *et al.,* 1984). It was proved that penicillin would be instrumental in the war to save the lives of many soldiers. In World War I, the fatal bacterial infection took many lives but after penicillin discovery, diseases become curable. Soon after, the British and American Scientists along with the collaboration of government and industries led to sufficient supplies of penicillin that was prepared by D-Day in 1944. Penicillin was available enough for prescription after the war (Bud, 2007). Fleming, Florey and Chain were awarded the Nobel Prize in 1945 for the Discovery of penicillin and its protective effect in various infections bacterial diseases (Nobel prize, 1945).

Mechanisum of Action

Antibiotics act on bacteria in different ways such as attacking cell wall of bacteria, interfering with bacterial reproduction or inhibiting the protein production in the bacterial cell (Fig 1). It is well known that all penicillin are bactericidal to growing and dividing bacteria, inhibiting the synthesis of the bacterial cell wall by binding to the enzyme responsible for protein crosslinks in the cell wall resulting in structural weakness and activation of the autolytic enzyme as well leads to lysis of the susceptible microorganisms (Miller, 2002). Penicillin work by attacking the bacterial cell wall by binding irreversibly to beta lactam ring at DD-transpeptidase. The bacterial cell contains an essential element, peptidoglycan that preserves its integrity and provides the shape, also impermeable for large molecules (Vollmer *et al.,* 2008). It is one of the most commonly used antibiotics having beta lactam rings that inhibit enzyme transpeptidase in order to prevent the formation of peptidoglycan (Bush and Bradford, 2016). Peptidoglycan is composed of N-acetylglucosamine and N-acetylmuramic acid residues that are covalently cross linked via short peptides. During the cell division and growth of bacterial cells, Peptidoglycan is continuously synthesized and remodelled. These linkages are formed with the help of a specific enzyme named as Transpeptidase. It mimics the last two D-alanine residues of peptide and stops the enzyme from cross linking strands of peptidoglycan to stop the formation of new peptidoglycan and cell becoming lysis due to osmotic stress. It only targets the bacterial cell because eukaryotic cells not have peptidoglycan and enzymes that are necessary for formation of peptidoglycan. Penicillin is considered more effective against gram positive bacteria than gram negative bacteria because gram negative have an outer membrane that restricts the penetration of penicillin (Page, 2012). In addition, some gram-negative bacteria have acquired specific genes that encode for the beta-lactamase enzyme to inactivate penicillin by hydrolysis of the beta-lactam ring of penicillin (Sutherland, 1964). Although, some penicillin as augmentin is used in combination along with non-antibiotic compound that have the ability to inactivate the enzyme penicillinase enzyme (Poirel *et al.,* 2005). The increasing trend to the natural penicillin, semisynthetic penicillin prepared in order to be effective for resistant microorganisms such as methicillin, dicloxacillin and oxacillin etc. They have resistance to Beta lactemase enzyme but due to the narrow spectrum of these drugs third generation of penicillin with broad spectrum was introduced in 1960s which includes amoxicillin and ampicillin, unlike other groups of penicillin they are highly effective against a wide range of bacteria including many gram negatives. The last generation of penicillin has an extended spectrum is included carboxypenicillins and ureidopenicillins (Poirel *et al.,* 2005; Sutherland, 1964).

Penicillin-Resistance

Bacterial resistance develops on the gene level mutation basis. Bacteria have the capability to transfer genetic material from one to another by plasmid (Zaman *et al.,* 2017). Antibiotic resistance to the specific antibiotic may develop in a very short time so that it is the matter of big concern (Levy, 1998). The resistance has been increasing and causing a major issue in recent years (Fig 2). Bacteria develop resistance either natural or acquired. It has been

reported that the resistance to an antibiotic may extend to a similarly structured compound of the same class such resistance to tetracycline may be resistance to all compounds that have a structural resemblance to tetracycline e.g. chlorotetracycline, chlorotetracycline, doxycline and minocycline (Chopra and Roberts, 2001). Bacteria may resist the antibiotic with four different molecular mechanisms; target site modification, antibiotic destruction or modification, efflux of antibiotic and decreased antibiotic influx by alteration of membrane permeability (Munita and Arias, 2016). The resistance mechanisms against antibiotics may be present in bacteria in different combinations by which they can resist multiple antibiotic compounds (Nikaido, 2009). Bacteria may acquire resistance through vertical or horizontal evolution. Vertical evolution may occur spontaneously due to genetic mutation in the bacterial cell resulting in increased resistance against antibiotics. In horizontal evolution, resistance bacteria transfer the resistance gene to susceptible bacterium via conjugation, transformation and transduction (Laws *et al.,* 2019). In Thailand, one experiment was conducted to report that sulfamethoxazole and trimethoprim, ampicillin and tetracycline are ineffective for those infections for which they were most commonly used (Hoge *et al.,* 1998). While in Bangladesh, the same drugs were found effective to same type of infections (Rahman *et al.,* 2017). Aminoglycosides were developed and practiced while just after six years of production bacterial resistance of *Staphylococcus aureus* was reported (Gootz, 1990). Similarly, Methicillin was first introduced in 1961 as semisynthetic penicillinase resistant penicillin to target the *Staphylococcus aureus* and soon after resistance was reported (Zaman *et al.,* 2017). Flourquinolones were developed and introduced for treating gram negative bacterial infection while antibiotic resistance was reported and found that the same antibiotic was also used for gram positive bacterial infection that leads to developing resistance (Rahman *et al.,* 2017). Gram-negative shows the natural resistance as its cell wall are protected by another membrane that prevents the penetration of penicillin. Some microbes produce the enzyme called beta-lactamase that is capable to inactivate penicillin (Lee *et al.,* 2001). The first antibiotic resistance was observed soon after the penicillin discovery. In 1940, it was found that *E. coli* inactivate penicillin by producing an enzyme, penicillinase (Lobanovska and Pilla, 2017). Further, in 1940, staphylococcus aureus was also observed to resist the penicillin antibiotic by producing beta lactamase enzyme that destroys the antibacterial activity of the drug (Foster, 2017). Foster, (2017) further reported that the bifunctional transglycolylase transpeptidase (PBP2) is the major target site of inhibition for beta lactam antibiotics.

Unfortunately, antibiotic resistance has been reported nearly in all antibiotics that have been discovered and used to treat the infection (Table 1) (Ventola, 2015). Different antibiotics were introduced in different years and soon after bacteria developed resistance such as penicillin was introduced in 1928 and resistance in 1940 (*Staphylococcus spp*.) and in 1965 (*Pneumococcus spp*), tetracycline in 1950 and resistance in 1959 (*Shigella spp.*), erythromycin in 1953 and resistance in 1968 (*Streptococcus spp.*), methicillin in 1960 and resistance in 1962 (Staphylococcus spp.), gentamicin in 1967 and soon after resistance reported, vancomycin in 1972 and resistance in 2002 (Staphylococcus spp.), imipenem & ceftazidime in 1984 and resistance in 1998 (*Enterobacteriaceae*), levofloxin in 1996 and resistance in 1996 (Pneumococcus spp.), linezolid in 2000 and resistance in 2001 (*Staphylococcus spp.*), daptomycin in 2003 and resistance observed soon after and ceftaroline in 2010 and resistance in 2011 (*Staphylococcus spp.*), respectively.

For health care, antibiotics are most commonly prescribed throughout the world (Shenoy *et al.,* 2019), however, most of the prescriptions are not appropriate resulting in bacterial resistance and several adverse effects on the patients (Fleming *et al.,* 2016). Penicillin is considered a very useful, effective and important drug but allergy to it causes complications in its uses. It has been reported that hypersensitivity reactions are most commonly caused by penicillin (Zhou *et al.,* 2016). Approximately 0.5 to 2% of penicillin causes adverse reactions on their administrations that could be concerned with the hypersensitive reaction, usually a rash even in nonallergic individuals (Khan and Solensky, 2010). Anaphylaxis because of IgE-mediated allergies is uncommon in most counties (Shenoy *et al.,* 2019). Approximately 1-2% of the administered penicillin may lead to cause an adverse reaction even though in nonallergic persons but the

occurrence of true penicillin anaphylaxis is low (Macy and Vyles, 2018). Following adverse reactions, 38% (rash), 18% (hives), (6%) gastrointestinal abnormalities, (9%) angioedema, 5% (itching) and 5% (anaphylaxis) due to penicillin have been reported by (Blumenthal *et al.,* 2018). Further, they reported increased mortality concerned with penicillin allergy but were unable to know the specific cause of mortality. (MacFadden *et al.,* 2016) also gave a similar type of report as chances of death increased 14% in those patients who were identified for penicillin allergy. When penicillin was administered to patients with penicillin allergy may cause more toxic and less therapeutic effects for subsequent infections (MacFadden *et al.,* 2016). Allergic reactions caused by penicillin, have been categorized on the basis of reaction, clinical syndrome and immune mechanisms such as Type I reaction mediated by IgE antibodies resulting in systemic anaphylactic manifestations (pruritis, angioedema, erythema, urticaria. Laryngeal edema and bronchospasm) (Weissa and Adkinson, 1988). This type of reaction mostly occurs one hour after the exposure of drug. While Type-II and III are concerned with IgG and IgM, however, IV is mediated by T lymphocytes but none of these are associated with the IgE antibodies and these types of reactions usually occur late as 72 hours or more after drug administration (Levine, 1966). Skin testing is considered feasible for the observation of immunological status of the patients with allergy to penicillin, however, have not been approved yet minor determinants by FDA and approximately 16 to 20% of the patients with penicillin skin test positive showed reaction to minor determinants but not major determinants (Adkinson *et al.,* 1971; Macy *et al.,*1997).

2. CONCLUSION

The conclusion is made on the present review as that penicillin is the choice of drug for various kinds of infection. Presently, this group is most commonly used because of its properties such as effectiveness and stabilities in various conditions. Bacterial resistance has been reported by many scientists due to an inappropriate prescription and the most common use of penicillin. Several microorganisms are reported as resistant to penicillin as *staphylococcus spp., salmonella spp.* etc. Semisynthetic penicillins have been developed to overcome the resistance and make it effective against those microbes for which penicillin was least effective. Currently, penicillin allergy is one of the major issues that make its prescription somewhat complicated globally as penicillin allergy patients receive the least therapeutic and most toxic effect of penicillin on their administration. Scientists are extensively working to overcome penicillin resistance and penicillin allergy.

3. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interest regarding the publication of this article.

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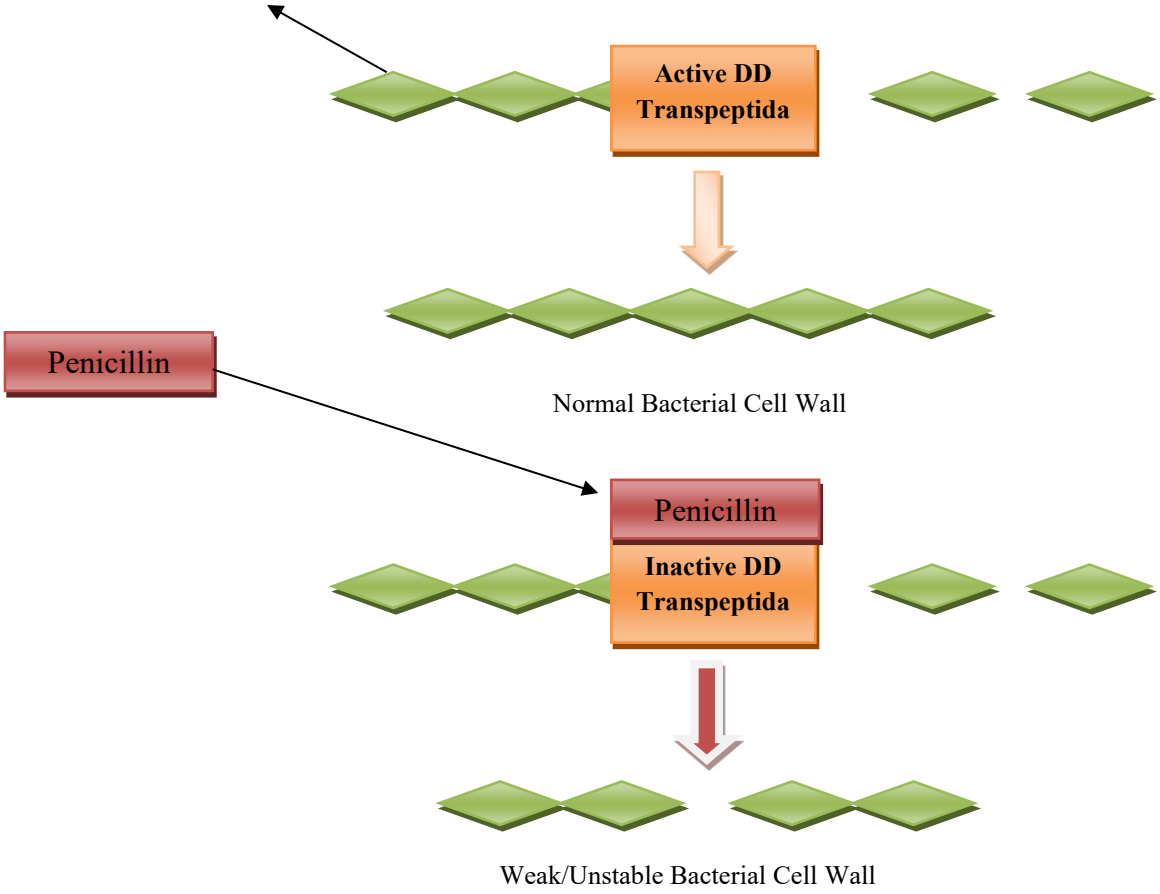

Figure 1. Mechanisms of Action of Penicillin

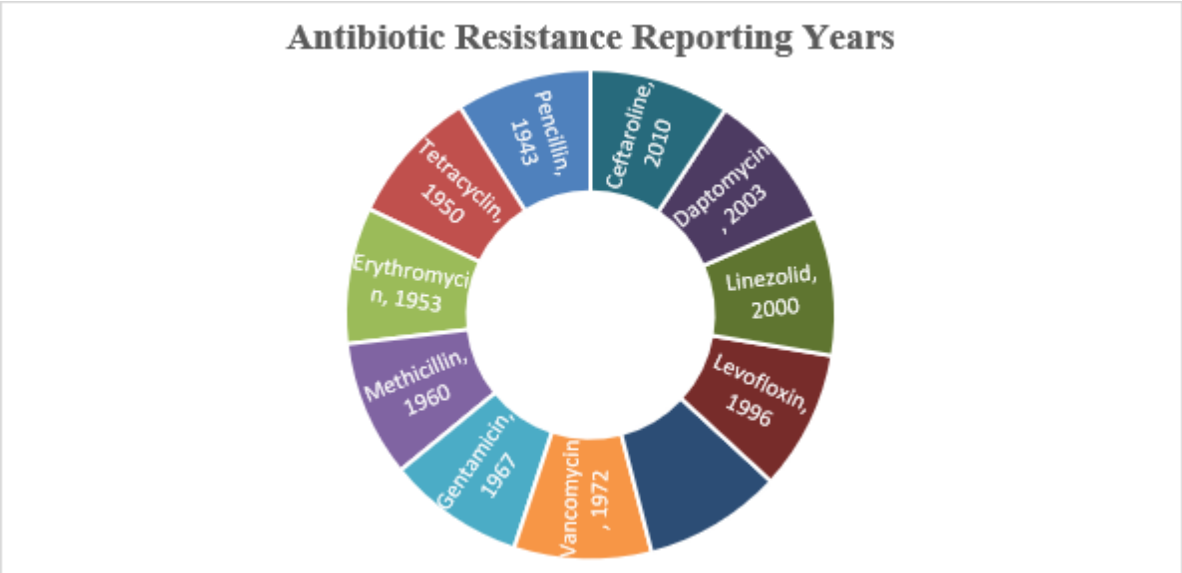

Figure 2. Bacterial resistance against different antibiotics reported in different years

Table 1. Microorganisms are resistant to different antibiotics.

Antibiotics	Resistant microbes	Reference
Chloramphenicol	*Salmonella typhi* *Salmonella paratyphi A*	(Chande *et al.,* 2002)
Multidrug resistant (Ciprofloxacin and norfloxacin)	*Shigella sonnei* *Shigella dysenteriaeserotype 1*	(Dutta *et al.,* 2003)
Multidrug resitant (Nalidixic, furazolidine, co-trimoxazole, tetracycline)	*Vibrio cholera*	(Taneja *et al.,* 2004)
Mutlidrug resistant (Pencillin, gentamicin, vancomycin, aminoglycosides,)	*Enterococcus spp (E. faecalis/faecium)*	(Kapil, 2005)
Multidrug resistant (Penicillin, trimoxazole, chloramphenicol, cefotaxime, erythromycin, trimethoprim sulphamethoxazole)	*Streptococcus pneumoniae*	(Thomas *et al.,* 1999; Fenoll,1991)
Multidrug resistant (Ampicillin, chloramphenicol, erythromycin, trimethoprim sulphamethazole)	*Haemophilu sinfluenza*	(Nag *et al.,* 2001; Jorgensen *et al.,* 1990)
Pencillin	*E.Coli*	(Abraham *et al.,* 1988)
Aminopencillin	*Enterobacteriaceae* (*E. coli*)	(Nordmann, 1998; Paterson, 2006)