Penicillin: The Beginning of Antibiotic Resistance

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Abstract

Penicillin is a natural antibiotic (bactericidal agent) produced from the fungi *Penicillium* species, specifically the strains of *Penicillium chrysogenum*. It is the first antibiotic drug known to man, and since its discovery in 1928, several derivatives of penicillin have been synthesized. It prevents the growth of bacteria by inhibiting cell wall synthesis. Although penicillin was once seen as the "wonder drug," the abuse and improper use of this drug have led to the increase of antibiotic resistance bacterial strains. To prevent the possibility of going back to the pre-antibiotic era, the use of all antibiotics, not just penicillin, must be heavily regulated.

Background

The antimicrobial ability of *Penicillium spp.* was first described in 1928 by Alexander Fleming, a microbiologist at St. Mary's Hospital in London[1]. Fleming discovered that one of his petri dishes, plated with *Staphylococcus aureus*, was contaminated by a mold which he later identified as *Penicillium spp*[1]. To his surprise, the area surrounding the mold showed no signs of bacterial growth, indicating that the mold may be secreting a substance that inhibits growth. Fleming published his findings on the antimicrobial ability but he was unable to isolate penicillin. It wasn't until the 1940s that scientists Howard Florey and Ernst Chain from Oxford University isolated and purified penicillin via fermentation[1]. Even with the successful isolation of penicillin, one more problem still remained: the small yield of penicillin from each fermentation process. This problem was solved when Florey and his research team found a more productive strain of *Penicillium* from a moldy cantaloupe. With the tremendous increase of yield resulting from the use of a different strain and nutrient medium, penicillin was ready to be mass produced. Pfizer became the first pharmaceutical company involved in large-scale production of penicillin[1].

Synthesis

Penicillin and penicillin-derived drugs all have one general structure: the beta-lactam ring. These drugs are often referred to as beta-lactam antibiotics because the

ability to kill microorganisms lies in the beta-lactam ring. The beta lactam structure can also be seen as the combination of amino acids cysteine and valine[4]. The bicyclic structure of the lactam ring and the thiazolidine ring creates a strain and the greater this strain is, the more active and unstable the molecule becomes[5]. The types of penicillin we have are defined by the acylamino acid side chain (R group). When penicillin was first discovered, we were only able to obtain the product completely through fermentation, but in 1957, the organic chemist John C. Sheehan was able to achieve a complete synthesis of penicillin V. A major problem that previous researchers encountered was the closing of the ring to form the beta-lactam ring. Sheehan solved this issue by using a new reagent DCC, N,N`-dicyclohexylcarbodiimide, that coupled carboxylic acids with amines to yield amides[6]. Today, it is possible to synthesize more effective semi-synthetic penicillin using the same intermediates from Sheehan's experimentation.

Mechanism of Action & Application

Penicillin's main mechanism of action is to inhibit bacterial cell wall synthesis. It interferes with the linking of peptidoglycan, a structural molecule that keeps the cell wall intact and allows the bacteria to develop[3]. The synthesis of the peptidoglycan involves three steps: 1) precursor formation, 2) the accumulation of uridine diphosphate (UDP)-acetylmuramyl-pentapeptide, and 3) the bonding of D-alanyl-D-alanine with transpeptidase to complete the cross- link[7]. The intervention of penicillin happens at the third step. Penicillin is structurally similar to D-alanyl-D-alanine so it is able to bind to the active site of transpeptidase irreversibly and disrupt cell wall synthesis[7]. With a fragile and incomplete cell wall, water can enter the cell, which will eventually lead to the cell bursting or lysis.

Penicillin and its derivatives are still used for different clinical implications. It is more effective on gram positive bacteria like *staphylococcus* infections because 90% of the bacteria's cell wall is composed of peptidoglycan. Gram negative bacteria, on the other hand, should not be treated with penicillin because they have very little peptidoglycan in their cell walls. Today, penicillin and its derivatives are used to treat a variety of disease such as otitis media (ear infections), streptococcus pharyngitis (strep throat), sinusitis, and bacterial endocarditis prophylaxis[8].

Antibiotic Resistance

Penicillin was once considered the "miracle drug" because of the impact it had on the world during World War II. People were no longer dying from the now easily treated conditions such as strep A throat infections. Amputations were no longer

common among soldiers because penicillin was applied on open wounds to prevent the spread of infection. However, according to the article "Origins and Evolution of Antibiotic Resistance," several years after penicillin was discovered, researchers identified penicillinase (beta-lactamases).[2] Beta- lactamase is an enzyme that actively cleaves the beta-lactam ring, which holds the antimicrobial ability of this miracle drug, rendering penicillin useless. As the antibiotic became more widely accessible, new strains of penicillin-resistant bacteria became more prevalent like the penicillin-resistant *streptococcus pneumoniae* and the more serious penicillin resistance *staphylococcus aureus.*

As a way of controlling the increase of antibiotic resistance towards not only penicillin, but other market drugs, health organizations have proposed the following: strictly control use of antibiotics and sharing of antibiotics between people; an accurate prescription for the correct diagnosis; and controlling the use of antibiotics in the agricultural industry[2].

Conclusion

Overall, the health community has recognized the dangers that can arise from the abuse of antibiotics. More and more strains of nosocomial and community-acquired infections are becoming resistant and harder to treat. If this continues, the world will fall back to the pre-antibiotic era where lives will be lost to easily treatable diseases. The development of resistance is something that will eventually happen over the years, but the goal is to slow this progression. People need to be more educated about both the risk of not finishing their antibiotic therapy and the over-use of antibiotics. Prevention of antibiotic resistance has now become everyone's responsibility.

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Cite as: Chan, S. (2015). Penicillin: The beginning of antibiotic resistance. *City Tech Writer, 10,* 30-32. Online at https://openlab.citytech.cuny.edu/city-tech-writer-sampler/