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Treatments for Syphilis: Penicillin G and Linezolid

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Abstract:

Syphilis is a common sexual disease that is transported by body fluid and caused by a spirochete bacterium *Treponema pallidum*. With the development of antibiotics that are applied to treating syphilis, the number of patients suffering from syphilis has decreased rapidly since 1943, when penicillin antibiotics were started to be introduced as clinical pharmaceuticals to treat syphilis. However, in recent years, the number of patients of syphilis has increased again, 95% of the patients are infected by sexual intercourse. The World Health Organization (WHO) reported that in 2022, nearly 8 million adults who are between 15 and 49 years old acquired syphilis. Because most infections are asymptomatic and unrecognizable during the long incubation period, many people are unconscious of syphilis infection, and they do thus not go to hospitals to check whether they are infected. Penicillin G is a traditional and commonly used antibiotic to treat syphilis by inhibition of production of the complete peptidoglycan cell wall, *T.pallidum* cells thus burst and die due to osmotic pressure in a hypotonic environment. But penicillin G has been approved for nearly one hundred years to treat syphilis and other diseases bacteria, including *T.pallidum* has developed the antibiotic-resistance to penicillin G by producing β-lactamase to inactivate penicillin G by opening its β-lactam ring irreversibly. As a result, it is quite urgent and necessary to introduce a new antibiotic to confront syphilis. In 2021, scientific experiments revealed that linezolid, which has been used to treat other Gram-positive bacterial infections for a long time, has impressive effects on treatment for syphilis, indicating that this artificially developed antibiotic could be used clinically to control syphilis by blocking bacterial protein synthesis. In this paper, the symptoms of syphilis and the treatment for syphilis, including penicillin G and linezolid, will be briefly introduced.

Keywords:-Syphilis; Penicillin G; Linezolid; Antibiotics; Transpeptidase; β-Lactam ring

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1 Introduction

Syphilis, which can be transmitted sexually through lesions and is inheritable by Treponema pallidum, which is a Gram-negative bacterium, is a chronic infection that is divided into several stages. The earliest record of syphilis is in the early 16th century in Europe [1]. The long-time development of pharmaceuticals to treat syphilis demonstrates that penicillin G is the major and ubiquitous antibiotic [2]. As syphilis is still spreading currently, and the rate of spread of syphilis has been increasing in recent years in the world due to sexual intercourse after the abuse of drugs. Syphilis has now become a global health issue. It is necessary and urgent to find or develop a new antibiotic to confront syphilis when penicillin G fails to kill *T.pallidum* as *T.pallidum* has demonstrated its penicillin-resistance to penicillin G[3,4,5].

Venereal syphilis could be sexually transported by spirochete *T.pallidum* subsp. *pallidum*. Bacteria from *Treponema* genus are barrel-shaped and motile. *Treponema pallidum* cannot survive outside of the human body for a long time; it could enter the human body through the skin or mucous membranes by lesions, arrive at the lymph nodes within several hours, and then spread rapidly throughout the body[5,6]. *T.pallidum* has a cell wall with a thin layer of peptidoglycan; this feature helps *T.pallidum* to penetrate the tissues of the hosts by lowering the volume of *T.pallidum*. The spiral structure of *T.pallidum* will be damaged if the thick cell walls exist[7,8,9,10,11,12]. The other features of the biological structure of *T.pallidum* are the paucity of lipopolysaccharides on the outer membrane and the lower density of outer membrane-spanning protein molecules than that of other Gram-negative bacteria. These features indicate that although *T.pallidum* is classified into Gram-negative bacteria, its features do not entirely accord with the common features of Gram-negative bacteria. The lack of pathogen-associated outer membrane proteins enables *T.pallidum* to get the capacity of immune invasion; T.pallidum is therefore described as a "stealth pathogen"[9]. The time period for every turn of reproduction of *T.pallidum* is 30 to 33 hours[1,13,14,15,16,17]. The simple version of the structure of T.pallidum is shown in Figure 1.

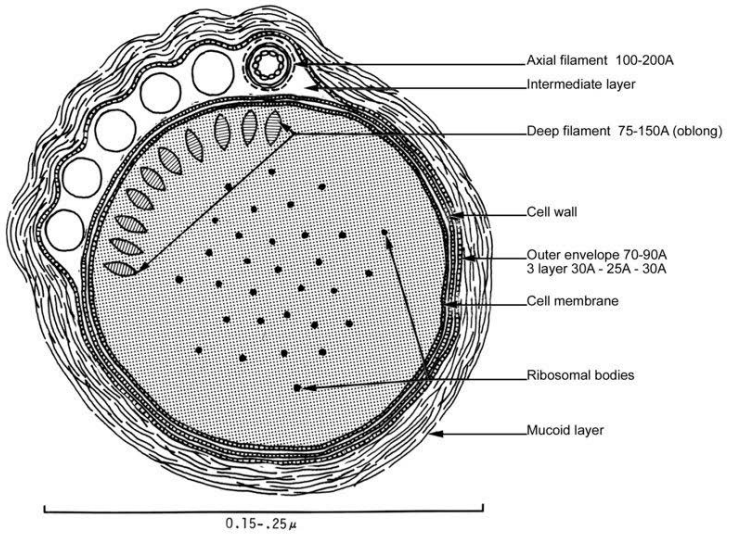

Fig.1 The schematic illustration of the cross section of *T.pallidum*[18].

The symptoms of syphilis are noticeable and easy to be observed. Syphilis is a multi-stage disease. In the primary stage after several weeks of incubation period, the red papulae develop into genital chancres that are present around or on the genitals, lips or mouth as *T.pallidum* adhere to the mucopolysaccharides that are used to combine cells together and breaks down the mucopolysaccharides. The MOSP^{N} and MOSP^{C} domains on the cell membrane surface of *T.pallidum* engage in this process[7,8,12]. In this regard, chancres are usually the painless ulcers with hard surface. The fluid composed of *T. pallidum* will be released when chancres are damaged. The nearby lymph nodes will be larger and no longer tender[6,13,14,19,20,21]. During the secondary stage, when is nearly six weeks after the presences of hard chancres, the *T.pallidum* spirochetes are spread through the whole human body by the blood flow, the widespread mucocutaneous lesions are being produced everywhere[22,23].

Lymph nodes become swollen. These symptoms will persist for several months, then all chancres will be healed without scars. Due to the superficial recovery, many patients will consider that their syphilis is totally overcome, they may thus stop getting treated. Actually, syphilis is still existing and exacerbating as the reproduction of *T.pallidum* is continuing. The tertiary stage is usually addressed as the late syphilis, it is always present in decades after the secondary stage. This interval is the incubation period, which is also called as the latent syphilis. In this period, the patients often have no symptoms. The tertiary syphilis is the most dangerous and fatal stage. This stage could be classified into different groups in accordance with different symptoms. Gummatous syphilis, which is the most common tertiary syphilis, usually develops on skins, organs and even bones to form gummas, that are large and soft lesions like holes. The gummas will continue developing on the organs and bones, causing external organs such as nose or eyes to drop off from the body. Gumma syphilis usually develop with nearly ten years after the infection. Cardiovascular syphilis usually incubates for nearly twenty years after the infection and demonstrates aneurysmal dilation of aorta and narrows the coronary arteries, number of functional aortic valves therefor decreases. As the result, cough and hoarseness will be caused when pulsations of the enlarged aorta compresses adjacent organs in the chest. The other main tertiary syphilis is neurosyphilis, that includes meningitis or Argyll Robertson pupils. Argyll Robertson pupils do not respond to light[5,6,15,24,25].

In order to treat syphilis, scientists and doctors firstly introduce penicillin G, also called as benzylpenicillin[2,13,15]. Penicillin G is the major antibiotic used to confront with *T.pallidum*, it is bacterially produced by *Penicillium chrysogenum* and found by Alexander Fleming (1881-1955) in 1928[26,27,28,29]. The other new choice is linezolid. This antibiotic is produced artificially and used to treat Gram-positive infections, such as the infections caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*[30]. In 2021, the scientists had done some relative experiments to explore the effects of some antibiotics on syphilis, the result shows that the ability of linezolid to kill or inhibit the growth of *T.pallidum* is much better than that of moxifloxacin and clofazimine, indicating that linezolid could also be used to treat syphilis[3].

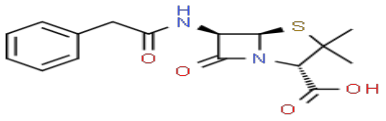

Fig.2 Skeletal structure of penicillin G[26,31].

2 Penicillin G (Benzylpenicillin)

Penicillin G is a β-lactam antibiotic as the nitrogen atom in the lactam ring is connected to the β-carbon atom. To explain the position of the lactam nitrogen atom, the carbon atom connected to the carbonyl carbon in lactam is the α-carbon, the next carbon atom that is attached to the α-carbon is called β-carbon. Penicillin G has a thiazolidine ring that is attached to the β-lactam ring. To distinguish penicillin G from other penicillin antibiotics, the R group connected to carbonyl carbon on side chain of penicillin G by a CH_2 group is a phenyl group, penicillin G has thus another name, benzylpenicillin. The Figures 2 above and 3 below have shown the skeletal chemical structure of penicillin G[26,32,33,34].

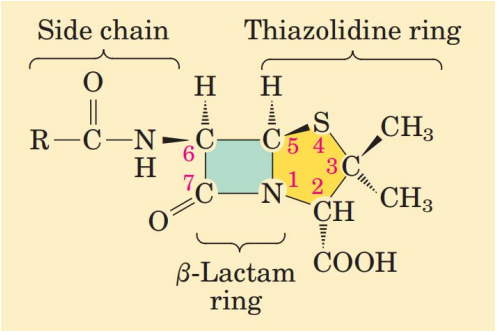

Fig.3 General structure of penicillins[33].

The fungus *Penicillium chrysogenum* could produce penicillin G within its cell[28]. In 1928, Alexander Fleming had found the presence of penicillin when he noticed that the growth of bacterium *Staphylococcus aureus* in a Petri dish was inhibited by the green fungus *Penicillium notatum*. This phenomenon indicates that the fungus is producing a specific substance as the surrounding culture of *S.aureus* could not grow normally. Alexander Fleming therefor named this substance penicillin and did some in-depth experiments using penicillin, the experimental results all infer the anti-microbial effect of penicillin against a wide range of bacteria including *Treponema pallidum*, *Bacillus anthracis*. Penicillin G is mainly used to kill Gram-positive bacteria that have thick cell walls made of peptidoglycan. Peptidoglycan is connected by transpeptidase that is the target of penicillin G and even all penicillins[28,35,36,37].

Cell wall that protects bacterial cells from osmotic lysis is a common feature among bacterial organisms. The main substance constituting bacterial cell walls is peptidoglycan, it strengthens bacterial envelopes and provides bacteria rigidity of their structures. Peptidoglycan is an alternating copolymer with linear shape. To describe the details of peptidoglycan, *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc) are two major

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components of peptidoglycan, they are responsible for forming oligosaccharides through being linked by β (1 to 4) glycosidic bonds, and cross-linked by short lengths of peptides attached to the *N*-acetylmuramic acid molecules in the peptide chains. Those short peptides chains are often composed by both non-proteinogenic amino acids with L-configuration structures and proteinogenic amino acids with D-configuration structures[33,38]. During the reproduction of bacteria, the work of connecting oligosaccharides with peptides is done by DD-transpeptidase[35]. The mechanisms of reactions are shown in the Figures 4 and 5.

In June of 1943, the scientists J.F. Mahoney, R.C. Arnold and A. Harris started to use penicillin for the treatment for syphilis for the first time. The good initial results of treatment of four patients indicate that penicillin is an effective and non-toxic treatment[18]. Because the effectiveness of penicillin derives from the inhibition of synthesis of cross-linkages in peptidoglycan that constitutes bacterial cell walls, and human body cells are not adversely attacked by penicillin antibiotics as they are without cell walls[33,36].

Because bio-availability of penicillin G is limited for oral pharmaceuticals, penicillin G is generally taken as an injection into veins in the forms of sodium, potassium, procaine or benzathine forms[39,40]. If penicillin G is injected into muscles, penicillin G should be maintained in the two long-acting forms of procaine or benzathine salts[41]. To elaborate the principals of treatment, a treponemacidal level of penicillin G of 0.03 U. per milliliter is supposed to be maintained in the blood of the patient who is suffering from syphilis for an adequate time period. The treponomacial time period of penicillin G should continue for 7 to 10 days, the suppression of divisions of *T.pallidum* could thus be effective. The dosage of penicillin G used to cure syphilis should be increased with the number of *T.pallidum* existing[18].

In the clinical treatment of syphilis, penicillin G is always the major option to kill *T.pallidum*. Even though *T.pallidum* is a Gram-negative bacterium, its thin layer of outer membrane and lack of lipopolysaccharides enable penicillin G to inhibit the synthesis of cell wall during the reproduction of *T.pallidum*[7,37]. Penicillin G blocks formation of the peptide cross-linkages in peptidoglycan structures. The structure of penicillin G resembles the some parts of peptidoglycan cell wall[35]. Penicillin G combines with DD-transpeptidase by entering its active site during the reproduction of *T.pallidum*. The proton on the hydroxyl group of the serine hydroxyl group attacks the carbonyl carbon atom in β-lactam ring of penicillin G. The lactam ring is therefor unraveled when the covalent bond between the carbonyl carbon atom and the nitrogen atom is broken down, and the carbonyl carbon is connected with the DD-tranpeptidase. A stable and inactive penicilloyl-enzyme derivative complex that inactivates the DD-transpeptidase is formed[33]. The DD-transpeptidase is therefore inactivated by penicillin G through mechanism-based inhibition, the shape of active site is changed irreversibly. As the result, the further formation of cross-links between polysaccharides is thus blocked[35,36,37].

Due to the lack of transpeptidation, the cell walls are not cross-linked as peptidoglycan is not formed, which means that cell wall synthesis does not occur because cross-woven peptide chains have been blocked by penicillin G[28]. The cell walls of *T.pallidum* are weakened and even disappear. As the result, a *T.pallidum* cell is liable to be killed by movement of water by osmosis from higher water potential to lower water potential. The *T.pallidum* cell membrane bursts in a hypotonic environment when the water pressure inside the cell increases[33,35,36].

Widespread utilization of penicillin antibiotics plays a role as a natural selection pressure to sift out of the bacteria which are antibiotic-resistant to penicillin, which means that, the evolution of bacteria for antibiotic-resistance has taken place. To confront the antibiotics, the mechanism of enzymatic hydrolysis to inactivate antibiotics is commonly imposed. In this regard, β-lactamase catalyzes the inactivation of penicillin G, providing *T.pallidum* with a chance to escape from being destroyed by penicillin G[33,34].

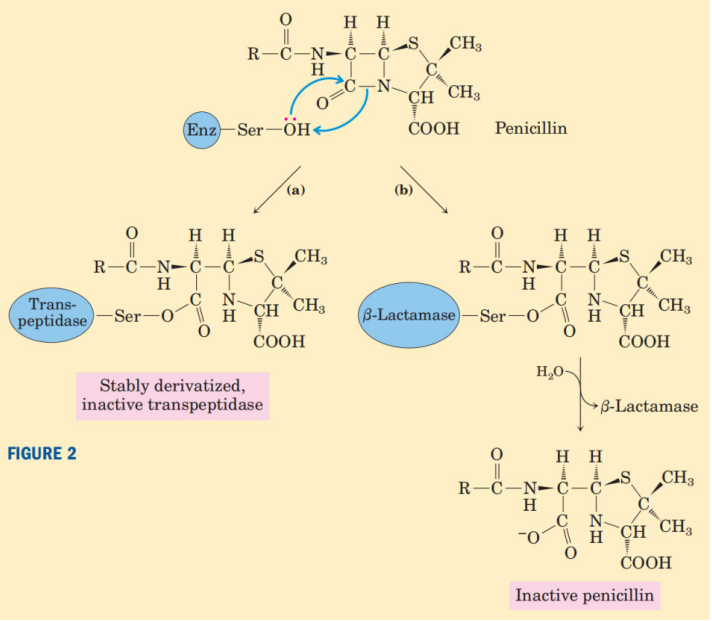

Fig.4 The chemical reactions of penicillin antibiotics in bacterial cells. The pathway (a) demonstrates the mechanism of penicillin to inactivate DD-transpeptidase, the pathway (b) demonstrates the mechanism of β-lactamase to inactivate penicillin antibiotics[33].

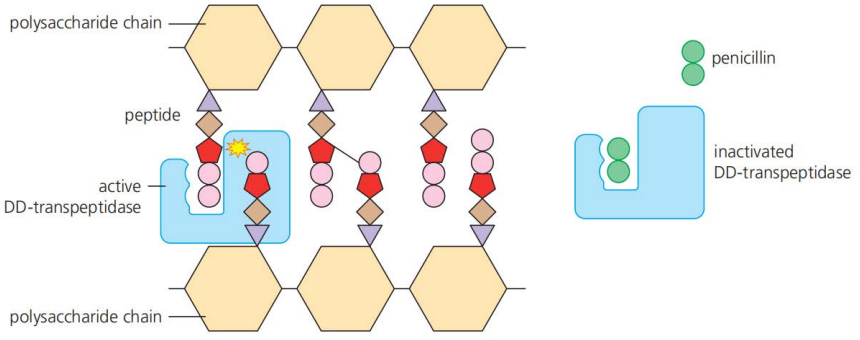

Fig.5 The mechanism of penicillin G to inhibit the formation of cross-linkages of peptides between polysaccharide chains of peptidoglycan[35].

The β-lactamase forms a temporary covalent complex with the carboxyl group of the β-lactam ring that has already been opened, this process is similar to the reaction between the β-lactam ring of penicillin G and hydroxyl group on serine of DD-transpeptidase. However, the enzyme-substrate complex is immediately hydrolyzed by water, the covalent bond between the carbonyl carbon atom of the β-lactam ring and the hydroxyl oxygen atom on serine of β-lactamase is broken down. An active β-lactamase is regenerated, leaving an inactive penicillin G molecule with an opened β-lactam ring[33,34].

To circumvent this antibiotic resistance to penicillin G, other penicillin analogs, such as methicillin, are theoretically supposed to be applied because methicillin is a poor substrate for β-lactamases[33]. Other methods are to administer the antibiotics which cannot be limited by β-lactamases, such as linezolid, it will further be discussed.

In order to synthesize penicillin G, *Penicillium chrysogenum* is required to produce penicillin G enzymatically *in vivo*. The biosynthetic pathway of penicillin G is carried out by the combination of some intermediates that are enzymatically synthesized, such as L-cysteine, L-valine and α-aminoadipate. In 2019, R. Nawfa, A.S. Purnomo, H.S. Putro had calls[28]. The results indicate that, the antibiotic production time period of penicillin G is 6 days, using diffusion method. On the sixth day, the treatment of *P.chrysogenum* cell membrane permeability to increase the membrane permeability in order to increase the antibiotic concentration should be imposed by using the mixture of ethanol and toluene at the ratio of 1:4. Under the optimum experimental conditions, the final result of enzymatic formation of penicillin G is at 130.60 mg/L[28].

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3 Linezolid

Linezolid is an antibiotic that belongs to the class of oxazolidinone[25]. Interestingly, linezolid is the first approved and commercially available member of oxazolidinone antibiotics, its brand name is Zyvox[30,42,43]. The symbol structure of oxazolidinone is its 2-oxazolidinone ring which is a 5-membered heterocyclic ring containing nitrogen atom and oxygen atom[44,45]. The Figure 6 demonstrates chemical structure of linezolid.

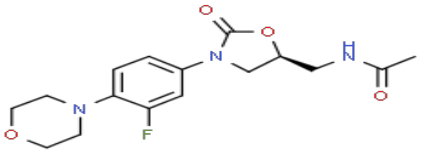

Fig.6 Skeletal structure of linezolid[45].

Oxazolidinones are mainly used as antibiotics. They were firstly introduced in 1978 due to their outstanding effectiveness in controlling plant diseases. In 1984, their anti-bacterial properties were documented, as the result, oxazolidinones began to be used as antibiotics. In 1996, linezolid as an improved oxazolidinone was firstly produced by Pharmacia, and it was approved by the US Food and Drug Administration (FDA) in 2000[30,34,35].

Linezolid is usually applied to treating Gram-positive infections, such as pneumonia caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*, skin and soft tissue infections (SSSIs) caused by *Streptococcus pyogenes*[30].

In 2021, some scientists had done an experiment using linezolid, clofazimine and moxifloxacin to test their effects on treatment for syphilis by comparing their impacts on growth of *T.pallidum*. The experimental results show that the effect of linezolid on inhibition of growth of *T.pallidum* is the most obviously outstanding among the antibiotics used, indicating the potential ability against *T.pallidum* of linezolid. This research also promote the utilization of linezolid in the clinical treatment for syphilis[3]. This research presented that the minimum inhibitory concentration (MIC) of linezolid for *T.pallidum* cells is 0.5 μg/mL, the time taken for healing of lesions by linezolid is similar to that by penicillin G. After 3 days of treatment for syphilis by linezolid *in vivo*, dark-field microscopy and qPCR assessments showed absence of *T.pallidum* cells in the lesions[3].

Linezolid is able to inhibit the synthesis of bacterial protein through binding to tRNA molecules that are responsible for translation of mRNA into peptide chains. Linezolid can also inhibit the formation of initiation complex during genetic transcription, the mRNA generated is thus shorter. This step could reduce the length of peptide chain, decreasing the rate of translation elongation[30]. In *T.pallidum* cells, linezolid works as a protein synthesis inhibitor, targeting the step of translation that involves the binding of *N*-formylmethionyl-tRNA to the ribosome. The analysis of linezolid by high-resolution microscopy revealed that linezolid will bind to the deep cleft of the 50S ribosomal subunit which is surrounded by 23S rRNA nucleotide molecules[3,30]. As the result, production of *N*-formylmethionine molecule is blocked, this amino acid is essential to bacterial protein synthesis because *N*-formylmethionine initiates all bacterial proteins and even the mitochondrial proteins in mammalian cells, which means that *N*-formylmethionine corresponds to the starting codon of bacterial protein synthesis[35]. Due to the lack of protein synthesis, *T.pallidum* cells malfunction when reproduction and other cellular functions are carried out. Besides, bacterial proteins with abnormal structures are unable to perform their biological functions properly, which will affect the survival and reproduction of *T.pallidum* cells[3,30,46].

This resistance of *T.pallidum* to linezolid derives from the mutation taking place in the 23S rRNA gene. Besides, genetic mutations in ribosomal proteins uL3 and uL4 are also associated with the resistance to linezolid[3,30]. In this regard, linezolid is no longer able to connect with the 50S ribosomal subunit because the rRNA molecules could not bind to linezolid[30].

To artificially synthesize linezolid, the most efficient method requires 7 steps[47,48], which is circumstantially demonstrated in the Figure 7. In the first region, 1,2-difluoro-4-nitrobenzene and morpholine are required to prepare aniline by the nucleophilic aromatic substitution (S_NAR) reaction, followed by hydrogenation under palladium catalyst. In the second stream, (+)-epichlorohydrin whose ring is opened by Lewis acid is reacted with acetonitrile to start the epoxide synthesis. The aniline and epoxide intermediates are then composed to form the amino alcohol intermediate which is sensitive to oxidation. By adding the oxidant catalysts, the amino alcohol intermediate will rapidly form the product, linezolid. The entire process requires only 1 hour to produce 1g of linezolid in 73% yield rate, the average yield rate in every step is 95%[47,48,49].

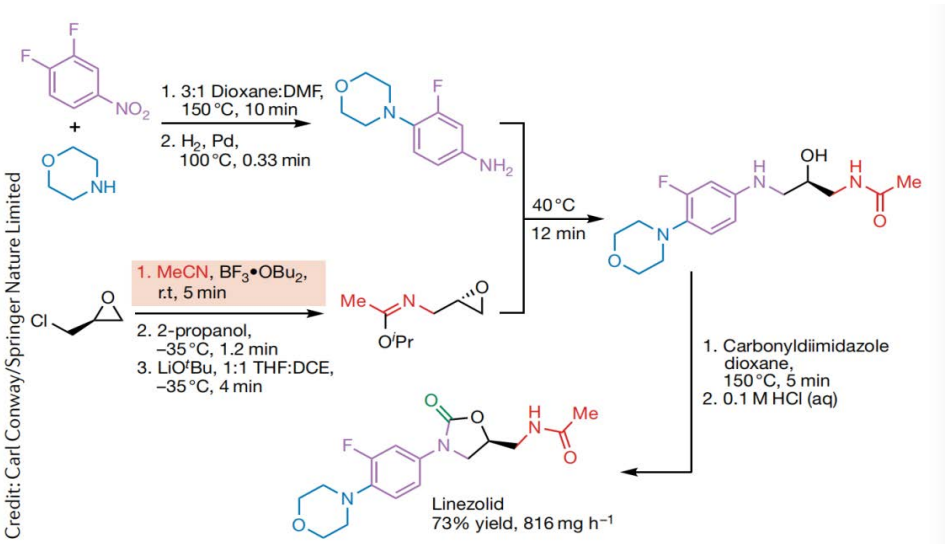

Fig.7 The 7 steps required to synthesize linezolid[48].

4 Conclusion

Syphilis is a chronic and multi-stage disease caused by *T.pallidum*, which is a particular Gram-negative bacterium that can be killed by penicillin G and linezolid (Zyvox). In the treatment for syphilis, penicillin G works as an inhibitor of synthesis of bacterial cell wall, binding with DD-transpeptidase to block the production of peptide chains that form the whole peptidoglycan structure, then *T.pallidum* cells are killed by osmotic pressure under hypotonic conditions. The artificial developed antibiotic linezolid performs the characteristic as a bacterial protein synthesis inhibitor, connecting with the 50S ribosomal subunit to block or disfavour the bacterial protein production when *N-formylmethionine* is not added, the survival and reproduction of *T.pallidum* are affected and malfunction, as the result, *T.pallidum* cells die as they could not perform their biological functions appropriately.

This paper has concluded two types of antibiotics, penicillin G and linezolid, and their properties of killing *T.pallidum* and treat syphilis. The methods to produce those two antibiotics are also interpreted. However, due to the lack of clinical statistics of treatment for syphilis by linezolid and the detailed date of number of patients who suffered from syphilis and were healed by penicillin G, this paper does not present sufficient data as the evidence to support that penicillin G and linezolid are useful antibiotics and major choices to treat syphilis, especially linezolid, it lacks enough time to perform clinically. Because of the developing antibiotic-resistance of *T.pallidum* to penicillin G and linezolid, the potential substitute should be developed as the secondary option when penicillin G and linezolid cannot totally perform their functions. Besides, due to the lack of proper technology, the pictures about the structure of T.*pallidum* cells, the structures of antibiotics and their reactions are all from other essays, books and professional websites. Thanks for their contributions.

References

[1] Tudor, M.E., Al, A.M. and Gossman, W.G. (2023). *Syphilis.* [online] Nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK534780/.

[2] STAMM, L.V. (2014). Syphilis: antibiotic treatment and resistance. *Epidemiology and Infection*, 143(8), pp.1567–1574. doi: https://doi.org/10.1017/s0950268814002830.

[3] Efficacy of linezolid on *Treponema pallidum*, the syphilis agent: A preclinical study. (2021). *EBioMedicine*, [online] 65, p.103281. doi: https://doi.org/10.1016/j.ebiom.2021.103281.

[4] www.niid.go.jp. (n.d.). *About Syphilis*. [online] Available at: https://www.niid.go.jp/niid/ja/diseases/ha/syphilis/392-encyclopedia/465-syphilis-info.html [Accessed 25 Jul. 2024].

[5] Tantalo, L.C., Lieberman, N.A.P., Pérez-Mañá, C., Suñer, C., Vall Mayans, M., Ubals, M., González-Beiras, C., Rodríguez-Gascón, A., Canut, A., González-Candelas, F., Mueller, J., Tapia, K., Greninger, A.L., Giacani, L. and Mitjà, O. (2023). Antimicrobial susceptibility of *Treponema pallidum* subspecies *pallidum*: an in-vitro study. *The Lancet Microbe*, [online] 4(12), pp.e994–e1004. doi: https://doi.org/10.1016/S2666-5247(23)00219-7.

[6] Merck Manuals Professional Edition. (n.d.). *Syphilis - Infectious Diseases*. [online] Available at: https://www.

ISSN 2959-409X

merckmanuals.com/professional/infectious-diseases/sexually-transmitted-infections-stis/syphilis.

[7] Hawley, K.L., Montezuma-Rusca, J.M., Delgado, K.N., Singh, N., Uversky, V.N., Caimano, M.J., Radolf, J.D. and Luthra, A. (2021). Structural Modeling of the *Treponema pallidum* Outer Membrane Protein Repertoire: a Road Map for Deconvolution of Syphilis Pathogenesis and Development of a Syphilis Vaccine. *Journal of Bacteriology*, 203(15). doi: https://doi.org/10.1128/jb.00082-21.

[8] Liu, J., Howell, J.K., Bradley, S.D., Zheng, Y., Zhou, Z.H. and Norris, S.J. (2010). Cellular Architecture of *Treponema pallidum*: Novel Flagellum, Periplasmic Cone, and Cell Envelope as Revealed by Cryo-Electron Tomography. *Journal of molecular biology*, [online] 403(4), pp.546–561. doi: https://doi.org/10.1016/j.jmb.2010.09.020.

[9] Radolf, J.D., Deka, R.K., Anand, A., Šmajs, D., Norgard, M.V. and X. Frank Yang (2016). *Treponema pallidum*, the syphilis spirochete: making a living as a stealth pathogen. *PMC*.

[10] Fitzgerald, T.J. and Johnson, R.C. (1979). S*urface Mucopolysaccharides of Treponema pallidum. Infection and immunity*, 24(1), pp.244–251. doi: https://doi.org/10.1128/iai.24.1.244-251.1979

[11] www.publicdomainfiles.com. (n.d.). *Public Domain Picture | A schematic illustration of a cross section of a Treponema pallidum bacterium. | ID: 13530399616091 | PublicDomainFiles.com*. [online] Available at: http://www.publicdomainfiles.com/show_file.php?id=13530399616091.

[12] Augustyn, A. (2018). Penicillin | Discovery, Mechanism of Action, & Uses. In: *Encyclopædia Britannica*. [online] Available at: https://www.britannica.com/science/penicillin.

[13] Mayo Clinic (2019). *Syphilis - Diagnosis and treatment - Mayo Clinic*. [online] Mayoclinic.org. Available at: https://www.mayoclinic.org/diseases-conditions/syphilis/diagnosis-treatment/drc-20351762.

[14] STAMM, L.V. (2014). Syphilis: antibiotic treatment and resistance. *Epidemiology and Infection*, 143(8), pp.1567–1574. doi: https://doi.org/10.1017/s0950268814002830.

[15] World Health Organization (2023). *Syphilis*. [online] www.who.int. Available at: https://www.who.int/news-room/fact-sheets/detail/syphilis.

[16] The Modern Epidemic of Syphilis. (2020). *New England Journal of Medicine*, 382(24), pp.2379–2380. doi: https://doi.org/10.1056/nejmc2006129.

[17] Peeling, R.W., Mabey, D., Kamb, M.L., Chen, X.-S., Radolf, J.D. and Benzaken, A.S. (2018). Syphilis. *Nature Reviews Disease Primers*, [online] 3(1). doi: https://doi.org/10.1038/nrdp.2017.73.

[18] www.publicdomainfiles.com. (n.d.). *Public Domain Picture | A schematic illustration of a cross section of a Treponema pallidum bacterium. | ID: 13530399616091 | PublicDomainFiles.com*. [online] Available at:

[19] Dunlop, E.M.C. (1974). Penicillin and the control of syphilis. *American Heart Journal*, 88(4), pp.395–400. doi: https://doi.org/10.1016/0002-8703(74)90198-7.

[20] Golden, M.R., Marra, C.M. and Holmes, K.K. (2003). Update on Syphilis. *JAMA*, 290(11), p.1510. doi: https://doi.org/10.1001/jama.290.11.1510.

[21] Jefferiss, F.J.G. and Willcox, R.R. (1963). Treatment of Early Syphilis with Penicillin Alone. *Sexually Transmitted Infections*, 39(3), pp.143–148. doi: https://doi.org/10.1136/sti.39.3.143.

[22] Smith, C.A., Kamp, M., Olansky, S. and Price, E.V. (1956). Benzathine penicillin G in the treatment of syphilis. *PubMed*, 15(6), pp.1087–96.

[23] LEIFER, W. (1945). THE TREATMENT OF EARLY SYPHILIS WITH PENICILLIN. *Journal of the American Medical Association*, 129(18), p.1247. doi: https://doi.org/10.1001/jama.1945.02860520015004.

http://www.publicdomainfiles.com/show_file.php?id=13530399616091.

[24] www.osmosis.org. (n.d.). *Argyll Robertson Pupil: What Is It, Causes, and More | Osmosis*. [online] Available at: https://www.osmosis.org/answers/argyll-robertson-pupil.

[25] Dichter, S.L. and Shubert, G.S. (2020). *Argyll Robertson Pupil*. [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537179/.

[26] PubChem (2019). *Penicillin g*. [online] Nih.gov. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Penicillin-g.

[27] Gurarie, M. (2023). *What to Know About Penicillin G*. [online] Verywell Health. Available at: https://www.verywellhealth.com/penicillin-g-5075834.

[28] Nawfa, R., Purnomo, A.S. and Putro, H.S. (2019). Synthesis of Antibiotic Penicillin-G Enzymatically by *Penicillium chrysogenum*. *Asian Journal of Chemistry*, 31(10), pp.2367–2369. doi: https://doi.org/10.14233/ajchem.2019.21766.

[29] Rosenberg, J. (2005). *How Alexander Fleming Discovered Penicillin*. [online] ThoughtCo. Available at: https://www.thoughtco.com/alexander-fleming-discovers-penicillin-1779782.

[30] Hashemian, S.M., Farhadi, T. and Ganjparvar, M. (2018). Linezolid: a review of its properties, function, and use in critical care. *Drug Design, Development and Therapy*, [online] Volume 12, pp.1759–1767. doi: https://doi.org/10.2147/dddt.s164515.

[31] www.chemspider.com. (n.d.). *Benzylpenicillin | C16H18N2O4S | ChemSpider*. [online] Available at: https://www.chemspider.com/Chemical-Structure.5693.html.

[32] BioTechnology Notes. (2018). *Penicillin: Biosynthesis, Structure, Fermentation Process and Uses*. [online] Available at: https://www.biotechnologynotes.com/antibiotics/penicillin/penicillin-biosynthesis-structure-fermentation-process-and-uses/13843.

[33] Lehninger, A.L., Nelson, D.L. and Cox, M.M. (2005). *Lehninger principles of biochemistry*. 4th ed. New York: W.H. Freeman.

[34] Martin, J.F., Alvarez-Alvarez, R. and Liras, P. (2022).

Penicillin-Binding Proteins, β-Lactamases, and β-Lactamase Inhibitors in β-Lactam-Producing Actinobacteria: Self-Resistance Mechanisms. *International Journal of Molecular Sciences*, 23(10), p.5662. doi: https://doi.org/10.3390/ijms23105662.

[35] Clegg, C.J. and Davis, A. (2023). *Biology for the IB Diploma Third edition*. Hodder Education.

[36] Reece, J.B., Urry, L.A., Cain, M.L., Alexander, S., Minorsky, P.V., Jackson, R.B. and Campbell, N.A. (2014). *Campbell biology*. 10th ed. Boston: Pearson.

[37] Clement, M.E., Okeke, N.L. and Hicks, C.B. (2014). Treatment of syphilis: a systematic review. *JAMA*, [online] 312(18), pp.1905–17. doi: https://doi.org/10.1001/jama.2014.13259.

[38] Chemistry LibreTexts. (2016). *25.2: Structure and Stereochemistry of the Amino Acids*. [online] Available at: https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Map%3A_Organic_Chemistry_(Wade)_Complete_and_Semesters_I_and_II/Map%3A_Organic_Chemistry_(Wade)/25%3A_Amino_Acids_Peptides_and_Proteins/25.02%3A_Structure_and_Stereochemistry_of_the_Amino_Acids.

[39] https://www.facebook.com/Drugscom (2017). *Penicillin G Injection*. [online] Drugs.com. Available at: https://www.drugs.com/pro/penicillin-g-injection.html.

[40] Enna, S.J. and Bylund, D.B. (2008). *XPharm : the comprehensive pharmacology reference*. Amsterdam: Elsevier, pp.1–6.

[41] Stuart, M.C. and World Health Organization (2009). *WHO model formulary 2008*. Geneva: Who.

[42] Ford, C., Zurenko, G. and Barbachyn, M. (2001). The Discovery of Linezolid, the First Oxazolidinone Antibacterial Agent. *Current Drug Target -Infectious Disorders*, 1(2), pp.181–199. doi: https://doi.org/10.2174/1568005014606099.

[43] www.webmd.com. (n.d.). *Linezolid Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD*. [online] Available at: https://www.webmd.com/drugs/2/drug-18168-6154/linezolid-oral/linezolid-oral/details.

[44] PubChem (n.d.). *Linezolid*. [online] pubchem.ncbi.nlm.nih.gov. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Linezolid#section=2D-Structure.

[45] www.chemspider.com. (n.d.). *Linezolid | C16H20FN3O4 | ChemSpider*. [online] Available at: https://www.chemspider.com/Chemical-Structure.390139.html?rid=091d92e4-1936-4aeb-a901-662dde278204&page_num=0.

[46] Liu, A.H. (2008). Innate microbial sensors and their relevance to allergy. 122(5), pp.846–858. doi: https://doi.org/10.1016/j.jaci.2008.10.002.

[47] Russell, M.G. and Jamison, T.F. (2019). Seven-Step Continuous Flow Synthesis of Linezolid Without Intermediate Purification. *Angewandte Chemie International Edition*, 58(23), pp.7678–7681. doi: https://doi.org/10.1002/anie.201901814.

[48] Davey, S.G. (2019). Seven steps, no stops. Nature Reviews Chemistry, 3(5), pp.289–289. doi: https://doi.org/10.1038/s41570-019-0102-6.

[49] Zhang, X., Chen, W., Li, C. and Wu, X. (2009). An efficient and practical synthesis of antibacterial linezolid. *Journal of Chemical Research*, 2009(12), pp.739–740. doi: https://doi.org/10.3184/030823409x125905758886078.