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Comparing Doxycycline and Azithromycin in treating cholera

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Abstract. Cholera is a famous bacterial infection that was found in the Indian Ganges Delata during the 19th century. People who were infected suffered a lot from the symptoms like diarrhea and dehydration, which impacted people's living standards. Doxycycline and Azithromycin are the most common drug treatments used for cholera patients. Doxycycline can inhibit the synthesis of bacterial protein by combining with the 30s ribosome and shorten the duration of this disease. Doxycycline is used over a wide range of age groups. Azithromycin can combine with the 50s ribosome to inhibit the synthesis of protein. However, using antibiotics over the given time period will cause the bacteria to grow resistant to them. This essay will discuss the two antibiotics that are used nowadays for Cholera treatment.

Keywords: Cholera, Doxycycline, Azithromycin

1. Overview of disease

1.1. Introduction

Cholera is a global disease that has nearly 4.0 million cases per year and with high mortality. It was first discovered in the 19th century in the Indian Ganges Delata and became a serious public health problem worldwide. The main symptoms of it are diarrhea and dehydration. For developing countries, Cholera may have a higher death rate, because the fewer medical resources. Therefore, effective medical treatments are important for decreasing the severity of Cholera. There are two antibiotics, Doxycycline and Azithromycin, that contribute a lot in treating Cholera.

This essay will be focused on comparing Doxycycline and Azithromycin in treating cholera. First provide the background information on Cholera, including history, symptoms, and influences. After that, introduce two antibiotic synthesis processes, pharmacology, and mode of delivery. Finally, discuss the two drugs' side effects, and drug resistance. The comprehensive research presented in this paper can broaden the understanding of Cholera. Contribute to minimizing the effect of Cholera.

1.2. Introduction of Cholera

The infection known as cholera is caused by *Vibrio cholera* bacteria that is spread through the water and food containing the bacterium *Vibrio cholerae*. Toxin-producing *V. cholerae* causes the disease. It's a highly motile, comma-shaped gram-negative bacterium with many serogroups, including pathogenic and non-pathogenic strains. It exists in the aquatic environment and infects the small intestine. The epidemics caused by cholera are mainly attributed to the two phenotypic variants, monophyletic 'classical' strains and 'El Tor' of *Vibrio cholerae* [1].

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1.3. Symptoms of cholera

The most common symptom of infection is watery diarrhea. The symptoms will show after people ingest the food or water containing the bacterium. However, people won't easily recognize that they are infected because of these two factors. The first is that diarrhea is a common symptom of many illnesses, making it difficult to identify the illness they have. The second is that cholera typically has an incubation period of around 1-2 weeks until the symptoms appear. The vibrio cholera bacterium will spread when the water containing it is digested [2]. The two toxigenic serogroups, *Inaba and Ogawa,* are responsible for the two serotypes, *classical and El Tor*, as well as the two biotypes.

Due to *V. Cholerae*'s motility and adherence characteristics, *V. Cholerae* could colonize efficiently the intestinal wall. However, *Vibrio Cholerae* requires a high infectious dose to produce the cholera toxin. After excretion, which transmission occurs through the contaminated water with the 24-hour-hyper-infectious phase of the bacteria, the two toxin factors will play an important role in the infection: the toxin-coregulated pilus and cholera toxin. They play a crucial role in the host's gut mucosa layer being colonized and the passage of the gastro endothelium wall that results in watery diarrhea [3].

At the same time, Biofilm formation ensures the facilitating colonization in human and aquatic reservoirs of the bacteria.

1.4. Impact and number of mortalities of cholera

Cholera is a disease that has been discovered for a long history. Even though Cholera has impacted 120 countries, it is a disease that took place in developing countries that lack medical resources. Around the time of the fourth era of B.C., Greek Hippocrates; Sushruta Samhita, from India in the fifth century B.C.; and Aretaeus, who is a Cappadocian, are writing in the first century A.D., all reference cases of cholera-like disorders [4].

One of the earliest thorough descriptions of the spread of cholera was given by Portuguese historian Gaspar Correa, author of Legendary India. He addressed a pandemic that plagued both nations in the Ganges Delta in the early spring of 1543. The illness is referred to regionally as "moryxy." It developed quickly, leading to a high death rate that the patient would die within 8 hours of the symptom developing. This outbreak marks the origin of cholera. Then in the 19th century, the first and second cholera pandemics spread from India to Asia, Europe, and the Americas. The third was the deadliest pandemic, which was around 1852–1859 years and impacted multiple continents. (*Cholera*, 2017). Nevertheless, the improvement of public health and infrastructure have helped control pandemics, but cholera is still a significant problem in developing nations, like Africa that outbreak the current seventh pandemic that began in 1961 [5].

Around 1.3 to 4.0 million cases of the present Cholera epidemic in countries that are developing, and there are global-related death cases of cholera that are around 21,000 and 143,000 [6].

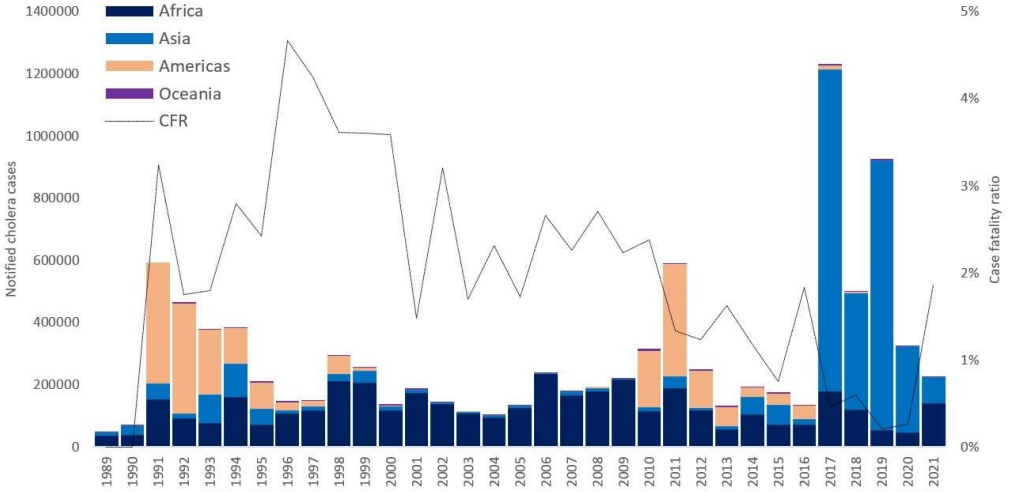

Figure 1. Global cholera cases in 1989-2021 [6]

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Figure 1 demonstrates that cholera epidemics nowadays are primarily found in Asian and African regions. In those areas, people don't have insurance as in nations like America and other countries with high living standards and medical care, which causes a lack of infrastructure and water quality regulation. With the shortages the resources, people are unable to safeguard themselves from the Vibrio cholera. As a result, this area has the highest incidence of cholera and the highest number of cases.

1.5. Significance in China and other countries in the world of cholera

The nations with the greatest cholera risk are Bangladesh, India, Nigeria, China, Ethiopia, and Nigeria (Ali et al., 2015). China has to be taken into account in estimations of worldwide trends of the spread of cholera since it served as both a source and a sink during the seventh pandemic of V. cholerae. Each outbreak in China could be considered the consequence of a different introduction of these bacteria from another country. As a result, China is considered a **"**source**"** or possibly **"**amplified**"** the epidemic's spread to other regions [7].

2. Treatment of cholera

Doxycycline and azithromycin are two drugs that are used to treat cholera nowadays.

2.1. Doxycycline

Doxycycline is synthesized and formed. The effective invention of penicillin during the Second World War, which encouraged others to study antibiotics, may have been the point of departure. As Robert Woodward claimed that these two medicines maintained the same four aromatic rings, scientists have found two broad-spectrum antibiotics. They are tetracyclines as a result. Then, Charlie Stephens' modifications to chemicals resulted in the generation and manufacture of the antibiotic doxycycline, which the FDA approved for use in 1967 [8].

Following the discovery of the first tetracycline group in the 1940s, doxycycline was synthesized as an antibiotic from the soil-dwelling bacteria Streptomyces aureofaciens [9].

2.1.1. Synthesis of doxycycline. Doxycycline, which is among the largest number of partially synthesized tetracycline derivatives. They stand apart from tetracycline by their positioning of a single hydroxyl group that is present.

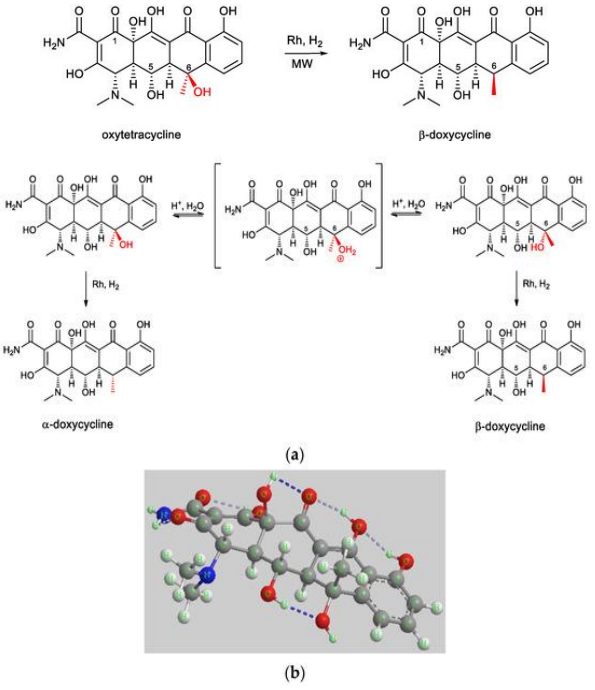

Figure 2. The synthesis of Doxycycline [10]

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Traditionally, doxycycline can be considered as an outcome - a transfer of the hydroxyl group from C6 to C5. Methacycline serves as an intermediary in the modern industrial manufacture of doxycycline. The methods that were used during the synthesis of Doxycycline were conventional and MW-Assisted Methods, Complexation of Oxytetracycline with Cyclodextrins, and Subsequent Hydrogenolysis Reaction. Doxycycline could possibly, in fact, produce two epimers during synthesis: the α and the β forms. The α epimer is the most often used form of doxycycline these days, and it has pharmacological activity. The β epimer would be preferred while using the heterogeneous at the time when it may reach the site of the methyl substituent [10].

2.1.2. Nomenclature of Doxycycline. Doxycycline is a tetracycline in which the 5beta-hydrogen is replaced by a hydroxy group, with molecular formula of C22H24N2O8, and a molar mass of 444.4g/mol. Doxycycline's IUPAC name is (4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide. Vibramycin is the trade name of Doxycycline [11].

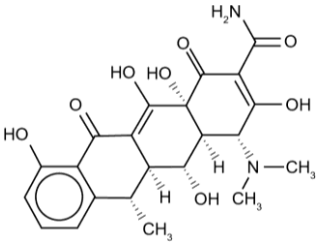

Figure 3. Structure of Doxycycline [12]

2.1.3. Doxycycline's chemical and physical characteristics

Table1. Chemical and physical properties of doxycycline [11].

Drug name	Chemical and Physical properties
Doxycycline	MW: 444.4 g/mol Character: Yellow crystal in rtp. Melting point: 201°C Solubilities: Partially dissociated in ether and chloroform, alcohol, readily soluble in diluted acids, alkali hydroxide, and in water. pKa: 3.09

2.1.4. Drug pharmacology of doxycycline. Doxycycline prevents the synthesis of V. cholerae proteins by irreversibly interacting with the 30S ribosomal subunit. Therefore, it inhibits aminoacyl-tRNA by interacting with the bacterial ribosome [13]. By attaching to the 70S ribosomes, it also affects the synthesis of mitochondrial proteins and functions as an antibacterial agent as a result. In the later stages of the malaria cell cycle, doxycycline combines with apicoplast subunits of ribosomal proteins from Plasmodium falciparum to hinder the synthesis of fatty acids and the generation of heme. Both a pH-sensitive active transport system in the inner cytoplasmic membrane and pores that are hydrophilic in the outer cell membrane which enables doxycycline to enter cells. It additionally reduces angiogenesis and apoptosis, facilitates gum fibroblast attachment, and aids in wound healing, among other things. Specific metalloproteinases, a group of proteolytic enzymes made by inflammatory cells, get similarly affected by doxycycline. Doxycycline's potential for usage in anti-inflammatory and anti-tumor treatments is therefore suggested [12].

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2.2. Azithromycin

Compare to erythromycin, Azithromycin is more easily taken up and has fewer side effects. Azithromycin is produced by a series of process that involves oximation, reduction rearrangement and so on, from erythromycin A. It also has bacteriostatic activity that affect both to the Gram-positive bacteria and Gram-negative bacteria, which include *B. pertussis* and *Legionella* [14]. The reason Azithromycin is a more effective antibacterial is that it is less likely to separate from the ribosome of the gram-negative bacteria [15].

2.2.1. Synthesis of Azithromycin: A sophisticated chain of chemical reactions results in the semi-synthetic form of the 15-membered macrolide antibiotic azithromycin, which is created from erythromycin. Azithromycin is created through an oximation, Beckmann rearrangement, reduction, and N-methylation. In comparison to other antibiotics in its class, azithromycin has higher stability, oral absorption, a longer half-life, and a broader activity. This subsequently improves its antimicrobial properties.

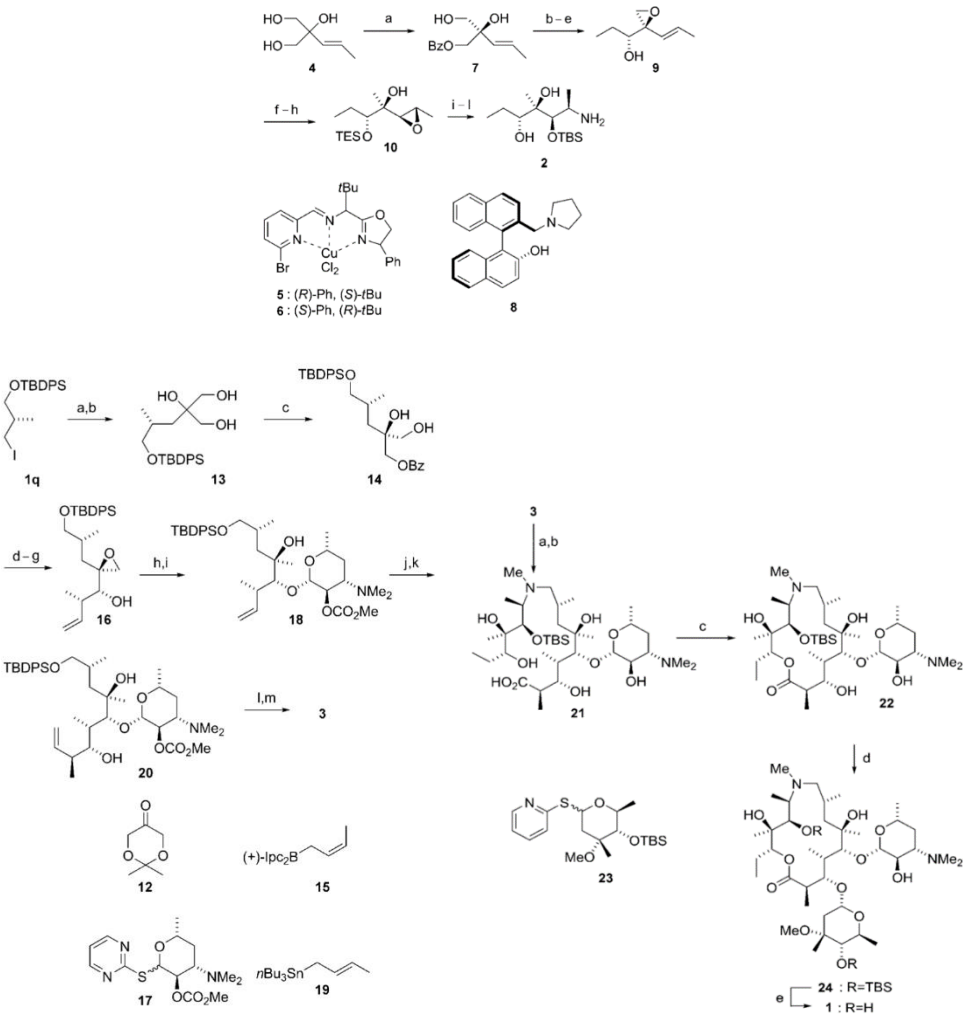

Figure 4. The synthesis of Azithromycin [16].

The synthesis of aminol chain 2 on the west side and hydroxycarboxylic acid chain 3 on the east side is initiated by severing segment 1 at the lactone linkage and C9-N9a bond. The timing of glycosylation stages for efficient macrolactonization, and methods like regioselective epoxide openings, asymmetric ethyl addition, and enantioselective desymmetrization have been used. A triol must first be

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desymmetrized in order to create mono benzoate 7, which is subsequently transformed into epoxy benzoate. The epoxy compounds created R and diastereomeric S alcohols that are required. The western amine segment 2 is created after additional adjustments. Segment 3 is built using a desymmetrization process for a quaternary carbon core and stereogenic centers that are made by crotylation reactions. Then the eastern carboxylic acid chain 3 is created via a number of procedures.

Completion reaction of the synthesis of segments 2 and 3 will take place when they are coupled, by macrolactonization of the carboxylic acid, and a subsequent glycosylation process. Segment 3's main hydroxy group undergoes oxidation and is joined to segment 2 by reductive amination. The 15-membered lactone 22 is produced by macrocyclization, and b-anomer 24 is required by further glycosylation. Therefore, the final product azithromycin, is obtained after purification [16].

2.2.2. Nomenclature of Azithromycin. Azithromycin is a macrolide, which is a natural compound, and is a member of the azalide subclass of macrolides. It consists of a ring with a 15-membered and a nitrogen methyl-substituted group that stands in for of a carbonyl group at position 9a on the aglycone ring, which contributes to simpler the evasion of metabolism. It shares a structural association with erythromycin [14]. The IUPAC name of it is (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3,4,10-trihydroxy-13-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one [17].

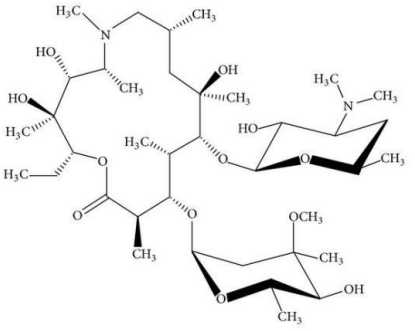

Figure 5. Structure of azithromycin [18].

2.2.3. Chemical and physical properties of azithromycin

Table 2. Chemical and physical properties of azithromycin [17].

Drug name	Chemical and Physical properties
Azithromycin	MW: 749.0 g/mol Character: Amorphous solid Melting point: around 113 to 115 °C Solubility: fully dissociated in ethanol and DSMO, and partially dissociated in water pKa = 8.74

2.2.4. Drug pharmacology of azithromycin. Similar to the azalide subclass of macrolides, azithromycin attaches to the 23S location of 50S bacterial ribosomal subunits. It limits the synthesis of bacterial proteins by obstructing the ribosome's capability to transport aminoacyl-tRNA and the protein-forming process. Azithromycin functions largely as an antibacterial agent, which implies that it inhibits protein

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synthesis instead than aggressively eradicating germs, in contrast to other macrolides and other macrolide antibiotics. In addition, azithromycin may have bactericidal effects, especially at higher doses when used to treat streptococci and H. influenzae. Azithromycin has antibacterial properties and also demonstrates antiviral characteristics in vitro.

In terms of pharmacokinetics, azithromycin could enter quickly into the tissues from the bloodstream, then they could cross the cellular membranes more easily, and fight successfully off intracellular infections. Azithromycin blocks the 50S ribosome found in the apicoplast, which is the non-bacterial organism that has a protein-synthesis mechanism similar to bacteria and is essential for metabolic processes, using apicomplexan parasites including species like; Babesia, Toxoplasma, and Plasmodium to inhibit the protein synthesis [15].

3. Mode of delivery

3.1. Treatment for cholera

The primary treatment for cholera involves oral or intravenous hydration. The patients have extreme symptoms and the special situation will use antibiotics at the same time. the antibiotics would be used based on the patient's tolerance of oral medication and in accordance with regional patterns of antibiotic susceptibility. In the majority of situations, Doxycycline is first recommended to both adults and children; however, if doxycycline resistance is established, alternatives such as azithromycin and ciprofloxacin are available [19].

Azithromycin, which is available in oral and intravenous forms, is typically given once daily for 3 to 5 days. It effectively penetrates tissues undergoes hepatic metabolism, and allows a shorter treatment duration compared to other antimicrobials. The strong tissue penetration, extended half-life, and suitability for patients with renal disease without dosage adjustment make azithromycin a valuable choice in treatment. Its formulations include tablets, packets, suspensions, intravenous solutions, and ophthalmic solutions for bacterial conjunctivitis [15].

For a long time currently, tetracycline has been the first-choice medication used for cholera. Presently, oral tetracycline is the most effective antibiotic medication for treating both cholera patients and carriers, but it must be taken in multiple doses over a period of two or three days. In order to effectively treat this condition, replacement fluid therapy is required. It shortens the time that vibrio excretion lasts and reduces the amount of fluid lost [20]. Doxycycline has been suggested as the treatment of choice for adults, including pregnant women, and children since it has been shown to be similar to treatment with a single 300-mg dose of tetracycline [19].

3.2. Side effects and resistance to doxycycline and azithromycin

3.2.1. Resistance and Side Effects of Doxycycline. The majority of doxycycline resistance is caused by genes like "tet" and "otr," which are always formed by plasmids and transposons. Ribosomal protection proteins and efflux proteins are the main mechanisms of how resistance develops. Since 1953, both Gram-negative and Gram-positive bacteria have shown an increase in resistance to the antibiotic reagent like doxycycline. H. pylori and N. gonorrhoeae are rarely chromosomal mutations but they clinically significant have impact on the resistance of doxycycline [12]. The side effect that is less frequent take place include diarrhea, irritation of the vagina, and being uncomfortable during sexual activity. Severe adverse effects that unusually appear are digestive disorders, visual abnormalities, dermatological issues, etc [21].

3.2.2. Resistance and Side Effects of Azithromycin. Azithromycin increased its resistance by being frequently abused. The 23S rRNA target is mostly modified by methylation, which causes crossover resistance with other antimicrobial agents as a result it makes the bacteria have resistance [22]. Azithromycin is generally regarded as its security, however, 15% of people may have dizzy spells, headaches, and gastrointestinal problems those symptoms. There have been reports concerning

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consequences such as severe cardiac points by rotations and QT prolongation. At the same time an uncommon symptom, liver injury is another issue. Stevens-Johnson syndrome and anaphylaxis are relatively uncommon but they are potentially fatal adverse effects [14]. Nevertheless, the therapeutic efficacy of these medications is constrained by the rise in drug resistance, but at the same time, those adverse effects which vary from moderate to severe need necessitate consideration of treatment [15].

4. Conclusion

To summarize, doxycycline and azithromycin all act as bacterial inhibitors to prevent protein synthesis. cholera treatment comprises hydration and antibiotics such as doxycycline or azithromycin, chosen based on local susceptibility when needed. During outbreaks, it's crucial to monitor antibiotic resistance. Antibiotics should be used alongside aggressive hydration. Azithromycin's characteristics make it an important option for treating cholera (Antibiotic Treatment, 2022). Since cholera possesses a long history of occurrence and treatment with doxycycline and azithromycin, as a result, it makes the V. cholerae bacteria develop the bacterial resistance to those antibacterial agents. Therefore, people are still improving doxycycline and azithromycin continuously by modification. The affordable price, of doxycycline and azithromycin, compared to drugs like fluorouracil and docetaxel, which gives the underprivileged people a chance to treat this illness and aid in the reduction of cholera cases and its effects. Although azithromycin and doxycycline can be produced through chemical synthesis, the biological method is much more effective than the chemical method. Therefore, doxycycline and azithromycin are primarily produced using biological methods. The potential that these two agents have on chemical synthesis and the reasonable price make doxycycline and azithromycin play an important role in treating cholera.

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