



Azithromycin Use As Broad Spectrum Antibiotic

Battu Rakesh^{*1}, Jaladi Himaja¹

1. Department of Pharmacy Practice, Bharathi College of Pharmacy, Bharathinagara, K.M.Doddi, Mandya, Karnataka, India-571422.

ABSTRACT

Azithromycin is a semi-synthetic 15-membered azalide antibiotics derived from erythromycin. Azithromycin is a macrolide antibiotic suitable for the management of a number of bacterial infections. This comprises respiratory tract infections, skin infections, chlamydia infections, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the new-born. It can be given intravenously and by mouth. Azithromycin displays bacteriostatic activity or inhibits growth of bacteria, principally at higher concentration, however the mechanism is not completely understood. By binding to the 50s subunit of the bacterial rRNA complex, protein synthesis and subsequent structure and function processes critical for life or replication are inhibited. Azithromycin is very rapidly absorbed, and diffuses into most tissues and phagocytes. Usual dosage range: -Oral: 500 mg once daily. Azithromycin has pharmacokinetics that allows shorter dosing schedules because of prolonged tissue levels. The bioavailability of azithromycin is approximately 37 % in humans. Tissue concentrations exceed serum concentrations by as far as 100-fold after a single 500 mg oral dose. Macrophages and polymorphonuclear leucocytes concentrate azithromycin at levels greater than those found in tissues themselves. High concentrations of drug are found in tissues such as tonsil, lung, prostate, liver and lymph nodes with relatively low concentrations in fat and muscle. As with all antimicrobial agents, pseudomembranous colitis can occur during and up to several weeks after azithromycin therapy. However, it has a few side effects like mild diarrhoea, nausea, vomiting, abdominal pain. Azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Evidence indicates that azithromycin is largely excreted in the faeces unchanged, with a small percentage appearing in the urine. Exacerbations of myasthenia gravis have also been reported with the use of azithromycin. Azithromycin's pharmacokinetics and tolerability make it particularly useful in the treatment of sexually transmitted infections, intracellular enteric pathogens and for prophylaxis of mycobacterial infection. It is furthermore beneficial for treating a variety of respiratory diseases. Unfettered use of azithromycin, particularly for its immunomodulatory properties, is of concern in light of macrolide resistance.

Keywords: Azithromycin, Macrolide Antibiotic, Chlamydia Infections, Syphilis, Bacteriostatic, Phagocytes, Pseudomembranous colitis and Myasthenia Gravis.

*Corresponding Author Email: rakeshjaanu143@gmail.com

Received 10 January 2017, Accepted 18 January 2017

INTRODUCTION

Macrolides are antibiotics which entails of a large macrocyclic lactone ring (normally comprising of 12-17 atoms in the ring) to which are attached deoxy sugars. The attached sugars are desosamine and cladinose. The lactone rings are usually 14-, 15-, or 16-membered¹. Macrolides are natural products which belong to the class of polyketides. Macrolides (such as erythromycin, clarithromycin, azithromycin, dirithromycin, troleandomycin, etc.) are valuable in management of infections triggered by gram-positive bacteria. The macrolides are considered to be slightly broad-spectrum antibiotics when compared to penicillin's and are commonly used in place of penicillin in patients which demonstrate allergic symptoms to penicillin. Clinically macrolides are the most important class of antibiotics².

Azithromycin is a semi-synthetic derived from erythromycin, prepared by Beckman rearrangement of the corresponding 6-oxime, followed by N-methylation and reduction of the resulting ring-expanded lactam. It is a prototype of a series of nitrogen-containing, 15-membered ring macrolides known as azalides³. Removal of the 9-keto group coupled with incorporation of a feebly basic tertiary amine nitrogen function into the macrolide ring surges the constancy of azithromycin to acid-catalysed degradation. These changes also increase the lipid solubility of the molecule, thereby conferring unique pharmacokinetic and microbiological properties⁴.

Azithromycin, 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin a dihydrate, is a semi-synthetic 15-membered azalide antibiotics derived from erythromycin. Its chemical arrangement diverges from that of erythromycin by the attachment of methyl-substituted nitrogen at position 9a in the lactone ring. This modification results in the enhanced acid steadiness accompanying with more unswerving and greater oral bioavailability, more extensive tissue penetration, and significantly longer elimination half-life, which exhibits an extensive spectrum of activity compared with erythromycin. Azithromycin is active against gram-positive and gram-negative pathogens. Owing to its widespread tissue permeation and dispersal, Azithromycin appears to be appropriate antibiotic for the management and prophylaxis of respiratory tract infection, skin and soft tissue infection, and sexually transmitted diseases^{5,6}.

Azithromycin is an antibiotic suitable for the management of numeral bacterial infection. This embraces strep throat, pneumonia, traveller's diarrhea, middle ear infections, and certain other intestinal infections. It may also be used for a number of sexually transmitted infections including chlamydia and gonorrhoea infections. Beside with extra medications, it can also be used for malaria. It can be taken by mouth or intravenously with doses once per day⁷.

Azithromycin is a broad-spectrum macrolide antibiotic with bacteriostatic activity against many Gram-positive and Gram-negative microorganisms counting *Bordetella pertussis* and *Legionella* species. It also has activity against *Mycoplasma pneumoniae*, *Treponema palladium*, *Chlamydia* species and *Mycobacterium avium* complex⁸.

Azithromycin is a macrolide antibiotic useful for the treatment of a number of bacterial infections¹. This includes respiratory tract infections, skin infections, chlamydia infections, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the new-born. It can be given intravenously and by mouth⁹.

New macrolides are further chemically constant and better accepted than erythromycin, besides they have a broader antimicrobial spectrum than erythromycin against *Mycobacterium avium* complex (MAC), *Haemophilus influenzae*, non-tuberculous mycobacteria, and *Chlamydia trachomatis*. All three macrolides have excellent activity against the atypical respiratory pathogens -*C. pneumoniae* and *Mycoplasma* class and the *Legionella* species. Azithromycin and clarithromycin have pharmacokinetics that permits smaller dosing schedules because of sustained tissue levels. Both azithromycin and clarithromycin are vigorous agents for *Mycobacterium avium* complex (MAC) prophylaxis in patients with late-stage attained acquired immunodeficiency syndrome (AIDS), although azithromycin may be the preferable agent because of fewer drug-drug interactions. Azithromycin has the advantage of shorter treatment regimens and improved tolerance, potentially improving compliance in the treatment of respiratory tract and skin or soft tissue infections. Parenterally administered azithromycin has been accepted for management of adults with mild to moderate community-acquired pneumonia or pelvic inflammatory diseases¹⁰.

Azithromycin is specified for lung, urogenital, dermatological and additional bacterial infections, and exerts immunomodulatory effects in chronic inflammatory disorders, including diffuse panbronchiolitis, post-transplant bronchiolitis and rosacea. Variation of host reactions aids its long-standing therapeutic advantage in cystic fibrosis, non-cystic fibrosis bronchiectasis, exacerbations of chronic obstructive pulmonary disease (COPD) and non-eosinophilia asthma. Initial, stimulatory properties of azithromycin on immune and epithelial cells, involving connections with phospholipids and Erk1/2, are followed by far along intonation of transcription factors AP-1, NFκB, inflammatory cytokine and mucin release. Delayed inhibitory effects on cell function and high lysosomal build-up supplement disruption of protein and intracellular lipid transportation, regulation of superficial receptor expression, of macrophage phenotype and autophagy. These later changes generate many immunomodulatory effects of azithromycin,

contributing to resolution of acute infections and decrease of exacerbations in chronic airway diseases. A sub-group of post-transplant bronchiolitis patients appears to be sensitive to azithromycin, as may be patients with severe sepsis¹¹.

Its safety during breastfeeding is not confirmed, but it is likely safe. Azithromycin is an azalide, a kind of macrolide antibiotic. It works by decreasing the manufacture of protein, thus preventing bacterial growth¹². Azithromycin was first made in 1980¹³. It is on the World Health Organization's List of Essential Medicines, the utmost essential medications required in elementary health system¹⁴. It is available as a generic medication¹⁵ and is sold under many trade names worldwide¹⁶. The wholesale cost in the developing world is about 0.18 to 2.98 USD per dose¹⁷. In the United States it is about 33 USD for a course of treatment¹².

Mechanism of action:

Clinically macrolides are the utmost significant class of antibiotics. Even though the precise mechanism of action of macrolides is not clear, it has been assumed that macrolides show their action by blocking protein synthesis in bacteria in the succeeding ways:

1. Preventing the Transfer of the Peptidyl tRNA from the A-site to the P-site.
2. Promotion of Peptidal tRNA Dissociation
3. Blocking Peptidyl Transferase.
4. Preventing Ribosomal Assembly.

The extent to which each of these mechanisms is followed varies from macrolide to macrolide and it is believed to be dependent on the size of the ring and the sugars attached².

Preventing the Transfer of the Peptidyl tRNA from the A-site to the P-site and Promotion of Peptidal tRNA Dissociation:

The macrolide antibiotics appear to bind at the P-site of the 50S ribosomal subunit. As a consequence of which, during translation, the P-site is engaged by the macrolide. When the t-RNA attached with the peptide chain tries to travel to the P-site, it cannot go there due to the existence of the macrolide, thus getting thrown away. This inhibits the transfer of the peptidyl tRNA from the A-site to the P-site and blocks the protein synthesis due to the inhibition of the translocation of the nascent peptide chain (Figure 1, 2). The macrolides also promote the premature dissociation of the peptidal tRNA from the A-site².

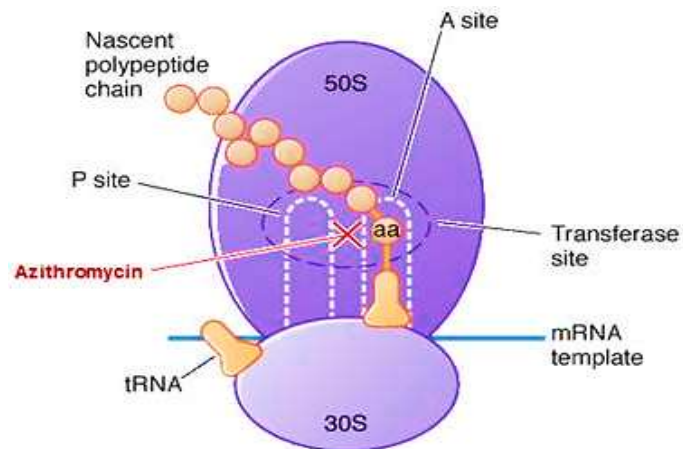


Figure 1: Mechanism of Action of Azithromycin

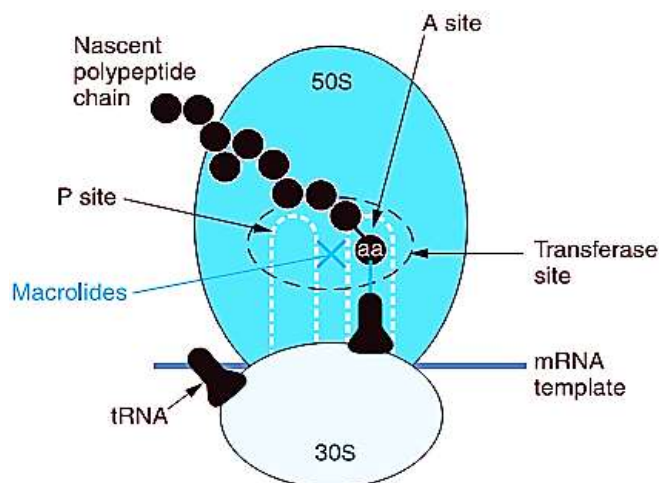


Figure 2: Inhibition of bacterial protein synthesis by the macrolide antibiotics

Blocking Peptidyl Transferase:

Macrolides fix to the P-site of the 50S ribosomal RNA and also chunk the action of the enzyme peptidyl transferase. This enzyme is in authority for the creation of the peptide bonds among the amino acids located on the A-site and the P-site in the ribosome. By blocking this enzyme, the macrolides are capable of inhibiting protein biosynthesis and thus kill the bacteria (Figure 1, 2).

Preventing Ribosomal Assembly:

Research has shown that in the presence of macrolides, the amount of free 50S ribosomal subunits increases in the interior bacterial cells, which lead to the hypothesis that macrolides prohibited the assemblage of the ribosomes in bacterial cells and also caused bacterial cell death².

PHARMACOKINETICS:

Azithromycin is an acid-stable antibiotic, so it can be taken orally with no necessity of safety from gastric acids. It is freely absorbed, but absorption is superior on an empty stomach¹⁸. The

medication has a total oral bioavailability of 35–42% in healthy volunteers and people with cystic fibrosis^{19,20}. Time to peak concentration (T_{max}) in adults is 2.1 to 3.2 hours for oral dosage forms. Due to its great concentration in phagocytes, azithromycin is dynamically transported to the site of infection. During active phagocytosis, large concentrations are released. The concentration of azithromycin in the tissues can be over 50 times greater than in plasma due to ion trapping and its great lipid solubility. Azithromycin's half-life permits a large single dose to be administered and yet sustain bacteriostatic levels in the infected tissue for quite a few days¹⁸. Tissue concentrations exceed the minimum inhibitory concentration that would constrain 90% of likely pathogens (MIC90) after a single 500 mg oral dose. Mean concentrations in tissue are 10–100-fold higher than those reached in serum and persist for several days²¹.

Following a single dose of 500 mg, the apparent terminal elimination half-life of azithromycin is 68 hours. Biliary excretion of azithromycin, predominantly unchanged, is a chief way of elimination. Above the course of a week, about 6% of the administered dose appears as unchanged drug in urine¹⁸. The oral bioavailability of azithromycin is good, nearly 40%, provided the antibiotic is administered at least 1 hour before or 2 hours after a meal. Food decreases its absorption by as much as 50%. Azithromycin administered orally is absorbed rapidly and distributed widely throughout the body, except to the brain and CSF. Protein binding is 50% at low plasma concentrations and less at higher concentrations. Azithromycin undergoes some hepatic metabolism to inactive metabolites, but biliary excretion is the major route of elimination²².

Extensive enterohepatic recycling of the drug occurs. Azithromycin apparently is not metabolized to any significant extent. In contrast to the 14-membered ring macrolides, azithromycin does not significantly inhibit cytochrome P450 enzymes to create potential drug interactions²³. Azithromycin is quickly absorbed by neutrophils, macrophages and fibroblasts. This aids in the fast conveyance of the drug in infected tissues. The concentration of AZM is 10–100 times higher in tissues than in serum. In addition, it has a lengthy half-life which permits it to be suggested for a tiny period of time^{24,25}.

Frequency, dosage and route of administration:

Azithromycin is normally administered in film-coated tablet, capsule, oral suspension, intravenous injection, granules for suspension in sachet, and ophthalmic solution. Dose: 500 mg once daily one hour earlier or two hours after food (food decreases bioavailability); (children above 6 month 10 mg/kg/day) for 3 days is adequate for most infections. AZITHRAL 250, 500 mg cap and 250 mg per 5 ml dry syrup; AZIWOK 250 mg cap,

100 mg kid tablet, 100 mg/5 ml and 200 mg/5 ml suspension. AZIWIN 100, 250, 500 mg tab, 200 mg/5 ml liquid. Also AZITHRAL 500 mg inj²⁶.

For outpatient treatment of community-acquired pneumonia, pharyngitis, or skin and skin-structure infections, a loading dose of 500 mg is given on the first day, followed by 250 mg/day for 4 additional days. Treatment or prophylaxis of *M. avium-intracellulare* infection in AIDS patients requires 500 mg daily in combination with other agents for treatment, or 1200 mg once weekly for primary prevention. Azithromycin is useful in management of sexually transmitted diseases, particularly during pregnancy when tetracyclines are contraindicated. Uncomplicated nongonococcal urethritis presumed to be due to *C. trachomatis* is treated with a single 1-g dose of azithromycin, which also is effective for chancroid. Azithromycin (1 g/week for 3 weeks) is an alternative drug for granuloma inguinale or lymphogranuloma venereum.

In kids, the suggested dose of azithromycin oral suspension for acute otitis media and pneumonia is 10 mg/kg on the first day (maximum 500 mg) and 5 mg/kg (maximum 250 mg/day) on days 2–5. The dose for tonsillitis or pharyngitis is 12 mg/kg/day, up to 500 mg total, for 5 days²².

Chlamydial Infections:

Chlamydial infections can be cured efficiently with any of the macrolides. A single 1-g dose of azithromycin is recommended for patients with uncomplicated urethral, endocervical, rectal, or epididymal infections because of the ease of compliance²².

The greater activity of azithromycin against *H. influenzae*, *M. catarrhalis*, and *M. pneumoniae* coupled with its extended half-life permits a 5-day dosing schedule for the treatment of respiratory tract infections caused by these pathogens. The clinical efficacy of azithromycin in the treatment of urogenital and other sexually transmitted infections caused by *Chlamydia trachomatis*, *N. gonorrhoeae*, *H. ducreyi*, and *Ureaplasma urealyticum* suggests that single dose therapy with it for uncomplicated urethritis or cervicitis may have advantages over use of other antibiotics²⁷.

Because of higher efficacy, better gastric tolerance and convenient once a day dosing, azithromycin is now preferred over erythromycin as first choice drug for infections such as:

(a) Legionnaires' pneumonia:

500 mg OD oral/ i.v. for 2 weeks. Erythromycin or a FQ are the alternatives.

(b) Chlamydia trachomatis:

Non-specific urethritis and genital infections in both men and women 1 g single dose is curative, while 3 weekly doses are required for lymphogranuloma venereum. It is also the drug of choice for chlamydial pneumonia and is being preferred over tetracycline for trachoma in the eye.

(c) Donovanosis caused by *Calymmatobacterium granulomatis*:

500 mg OD for 7 days or 1.0 g weekly for 4 weeks is as effective as doxycycline.

(d) Chancroid and PPNG urethritis: Single 1.0 g dose is highly curative²⁸.

The other indications of azithromycin are pharyngitis, tonsillitis, sinusitis, otitis media, pneumonias, acute exacerbations of chronic bronchitis, streptococcal and some staphylococcal skin and soft tissue infections. In combination with at least one additional drug it is effective in the prophylaxis and treatment of MAC in AIDS patients. Other potential uses are in multidrug resistant typhoid fever in patients allergic to cephalosporins; and in toxoplasmosis.

Adverse effects:

Azithromycin is usually well tolerated, but has fairly common adverse effects (1–5% of patients) include gastrointestinal upset, headache and dizziness. Transient increases in transaminases have also been reported in 1.5% of patients²⁹. Hearing loss or impairment has also been reported with azithromycin, including in patients with COPD and normal hearing at baseline, and appeared to be irreversible in some patients^{30,31}. Case reports of hearing loss after short-term use have also been published³².

Nervousness, dermatologic reactions, and anaphylaxis have been reported. As with all antimicrobial agents, pseudomembranous colitis can happen during and up to a number of weeks after azithromycin therapy. An allergic reaction or a type of diarrhea triggered by *Clostridium difficile* is possible³³. Serious adverse effects include QT prolongation and torsade's de pointes resulting in death. The US Food and Drug Administration issued a warning in 2012 to consider the hazard of fatal heart rhythms in those:

- With a prolonged QT interval (including congenital long QT syndrome).
- Taking medicines that are likely to prolong the QT interval.
- With a history of torsade's de pointes, arrhythmias or uncompensated heart failure.

This advice was primarily based on a large retrospective cohort study that suggested an escalation in cardiovascular deaths, and demise from any reason, in individuals treated with a 5 days course of azithromycin compared to amoxicillin, ciprofloxacin, or no drug³⁴.

Clinically significant drug interactions:

Azithromycin has a number of clinically relevant drug interactions²³⁻²⁹. Due to its long half-life, interactions may continue for several days after it has been stopped.

- Azithromycin should be used with abundant carefulness if co-administered with other drugs that prolong the QT interval³⁵.

- There are a number of published reports suggesting that azithromycin might potentiate the action of warfarin, however medical events due to extreme anticoagulation attributable to warfarin are controversial due to patient factors and study design. Some retrospective series have failed to find interactions^{36,37} or found an interaction but no adverse events³⁸. Given the current uncertainty about interactions, it is prudent to monitor INR carefully in patients on warfarin who necessitate azithromycin.
- Pharmacokinetic modelling proposes reduced clearance of everolimus³⁹.
- Macrolides, including azithromycin, may potentiate digoxin toxicity. This relates to P-glycoprotein. A case report defines a 31-month-old who developed symptoms of digoxin toxicity after starting azithromycin⁴⁰.
- Azithromycin may increase colchicine concentrations, with consequent toxicity³⁹.
- Concomitant use of statins and azithromycin may increase the risk of rhabdomyolysis⁴¹.
- Co-ingestion of antacids (aluminium, magnesium) may reduce the peak concentration of azithromycin.
- Azithromycin has been found not to affect hepatic CYP3A4 enzyme. Interaction with theophylline, carbamazepine, warfarin, terfenadine and cisapride is not likely, but caution may be exercised.
- Aluminium and Magnesium antacids do not alter bioavailability but retard absorption and decreases peak serum concentrations of azithromycin; hence it should be given 1 hour before or 2 hours after antacid.
- Nelfinavir can increase plasma levels of azithromycin⁴⁴.

Pregnancy and breast feeding:

No harm has been found with use during pregnancy⁷. However, there are no adequate well-controlled studies in pregnant women⁴². Safety of the medication during breastfeeding is unclear. It has been reported that because only low levels are found in breast milk and the medication has also been used in young children, it is unlikely that breastfed infants would suffer adverse effects⁴³. Nevertheless, it is recommended that the drug be used with caution during breastfeeding⁷.

Resistance:

Resistance to macrolides including azithromycin usually results from one of four mechanisms:

- Ribosomal protection by inducible or constitutive production of methylase enzymes, mediated by expression of *ermA*, *ermB*, and *ermC*, which modify the ribosomal target

and reduce drug binding (staphylococci, streptococci, *B. fragilis*, *Clostridium perfringens*, *Corynebacterium diphtheriae*, and *Listeria* and *Legionella* species)

- Drug efflux by an active pump mechanism (encoded by *mrsA*, *mefA*, or *mefE* in staphylococci, group A streptococci, or *S. pneumoniae*, respectively)
- Macrolide hydrolysis by esterases produced by Enterobacteriaceae
- Chromosomal mutations that alter a 50S ribosomal protein (found in *B. subtilis*, *Campylobacter* species, mycobacteria, *Str. pneumoniae*, *H. pylori*, *M. pneumoniae*, *Escherichia coli*, *Str. pyogenes*, and *Staph. aureus*)

The most common type of resistance is a plasmid-mediated ability to methylate ribosomal RNA, resulting in decreased binding of the antimicrobial drug. This can lead to cross-resistance between erythromycin, other macrolides, lincosamides, and streptogramin B, as they share a common binding site on the ribosome and this pattern of resistance is known as the MLSB phenotype. Incidence of resistance to azithromycin and other macrolides is higher among penicillin-resistant strains than among penicillin-sensitive strains⁴⁴.

Contraindications and warnings:

- It is contraindicated in patients with prior history of hypersensitive reactions to any of the macrolides and in persons with a history of cholestatic jaundice/liver dysfunction associated with prior use of azithromycin.
- It must not be prescribed in patients with cystic fibrosis, generalized bacterial infection or severely ill patients.
- *Clostridium Difficile*-associated diarrhea can occur with its use.
- Can cause QT Prolongation – hence must not be given in patients with known QT interval prolongation, patients with proarrhythmic conditions like uncorrected or hypomagnesaemia or hypokalaemia, decreased heart rate, and with antiarrhythmics like quinidine, procainamide, dofetilide, amiodarone, sotalol⁴⁴.

CONCLUSION

Azithromycin's pharmacokinetics and tolerability make it particularly useful in the treatment of sexually transmitted infections, intracellular enteric pathogens and for prophylaxis of mycobacterial disease. Following oral administration, serum concentrations of azithromycin are lower than those of erythromycin, but this reflects the rapid and extensive movement of the drug from the circulation into intracellular compartments resulting in tissue concentrations exceeding those commonly seen with erythromycin. Gastrointestinal tolerance is better than that of

erythromycin. Azithromycin is subsequently slowly released, reflecting its long terminal phase elimination half-life relative to that of erythromycin. These factors allow for a single dose or single daily dose regimen in most infections, with the potential for increased compliance among outpatients where a more frequent antimicrobial regimen might traditionally be indicated. It is also useful for treating a range of respiratory diseases. Unfettered use of azithromycin, particularly for its immunomodulatory properties, is of concern in light of macrolide resistance. Novel non-antibiotic macrolides may be used for this role in future.

REFERENCES:

1. Hamilton-Miller, JM. "Chemistry and Biology of the Polyene Macrolide Antibiotics". *Bacteriological Reviews*. American Society for Microbiology. 1973. 37 (2): 166–196.
2. <http://pharmaxchange.info/press/2011/06/mechanism-of-action-of-macrolides/>
3. Bright, G. M., et al.: *J. Antibiot.* (Tokyo) 41:1029, 1988.
4. Peters, D. H., Friedel, H. A., and McTavish, D.: *Drugs* 44:750, 1992.
5. Drew RH, Gallis HA. Azithromycin-Spectrum of activity, pharmacokinetics, and clinical applications. *Pharmacotherapy*, 1992. 12: 161-173.
6. Ballow CH, Amsden GW. Azithromycin: the first azalide antibiotic. *Ann Pharmacother*, 1992. 26: 1253-1261.
7. "Azithromycin". The American Society of Health-System Pharmacists. Retrieved Aug 1, 2015.
8. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther* 2014; 143:225-45.
9. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. "Clinical guideline: management of gastroparesis". *The American Journal of Gastroenterology*, Jan 2013. 108(1): 18–37; quiz 38.
10. Salvador Alvarez-Elcoro, Mark J.ENZLER. The Macrolides: Erythromycin, Clarithromycin, and Azithromycin. June 1999. 74(6); 613–634
11. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther*. 2014 Aug; 143(2):225-45.

12. Peters DH, Friedel HA, McTavish D. Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs*. 1992 Nov; 44(5):750-99.
13. Greenwood, David (2008). *Antimicrobial drugs: chronicle of a twentieth century medical triumph* (1. publ. ed.). Oxford: Oxford University Press. p. 239.
14. "WHO Model List of Essential Medicines". World Health Organization. October 2013. Retrieved 22 April 2014.
15. Hamilton, Richart. *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning
16. *Drugs.com International trade names for Azithromycin* Page accessed Jan 14, 2015
17. "Azithromycin". *International Drug Price Indicator Guide*. Retrieved 4 September 2015.
18. <http://www.drugs.com/pro/zithromax.html>
19. Beringer P, Huynh KM, Kriengkauykiat J, Bi L, Hoem N, Louie S. Absolute bioavailability and intracellular pharmacokinetics of azithromycin in patients with cystic fibrosis. *Antimicrob Agents Chemother* 2005; 49:5013-7.
20. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. *J Antimicrob Chemother* 1990; 25 Suppl A: 73-82.
21. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther* 2014; 143:225-45.
22. Laurence L. Brunton, Keith L. Parker, Donald K. Blumenthal, Iain L.O. Buxton. *Goodman and Gilman's Manual of Pharmacology and Therapeutics*. P.784.
23. *Wilson and Griswold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* 12th edition. Lippincott Williams & Wilkins. Edited by John M. Beale, Jr. John H. 311.
24. Sampaio E, Rocha M, Figueiredo LC, Faveri M, Duarte PM, et al. Clinical and microbiological effects of azithromycin in the treatment of generalized chronic periodontitis: a randomized placebo-controlled clinical trial. *J Clin Periodontol*, 2011. 38: 838-46.
25. Schmidt EF, Bretz WA. Benefits of additional courses of systemic azithromycin in periodontal disease case report. *N Y State Dent J*. 2007. 73: 40-45.
26. Hicks, LA; Taylor TH, Jr; Hunkler, RJ. "More on U.S. outpatient antibiotic prescribing, 2010". *The New England Journal of Medicine*. Sep 19, 2013. 369 (12): 1175–1176.

27. Williams JD. Spectrum of activity of azithromycin. *Eur J Clin Microbiol Infect Dis*. 1991 Oct; 10(10):813-20.
28. Essentials of Medical Pharmacology, Seventh Edition, KD Tripathi. Jaypee Brothers Medical Publishers (P) Ltd. P. 755-756.
29. Zuckerman JM, Qamar F, Bono BR. Macrolides, ketolides, and glycyclines: azithromycin, clarithromycin, telithromycin, tigecycline. *Infect Dis Clin North Am* 2009; 23:997-1026, ix-x.
30. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Criner GJ. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365:689-98.
31. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother* 2014; 58:511-7.
32. Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. *J Otolaryngol* 2007; 36:257-63.
33. Mori F, Pecorari L, Pantano S, Rossi M, Pucci N, De Martino M, Novembre E. "Azithromycin anaphylaxis in children.". *Int J Immunopathol Pharmacol*, 2014. 27 (1): 121–6.
34. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366:1881-90.
35. Isbister, GK. Risk assessment of drug-induced QT prolongation. *Aust Prescr* 2015; 38:20-4.
36. McCall KL, Anderson HG, Jones AD. Determination of the lack of a drug interaction between azithromycin and warfarin. *Pharmacotherapy* 2004; 24:188-94.
37. Beckey NP, Parra D, Colon A. Retrospective evaluation of a potential interaction between azithromycin and warfarin in patients stabilized on warfarin. *Pharmacotherapy* 2000; 20:1055-9.
38. Mergenhagen KA, Olbrych PM, Mattappallil A, Krajewski MP, Ott MC. Effect of azithromycin on anticoagulation-related outcomes in geriatric patients receiving warfarin. *Clin Ther* 2013; 35:425-30.
39. Baxter KE, Preston CL. Stockley's drug interactions: a source book of interactions, their mechanisms, clinical importance and management. 10th ed. London: Pharmaceutical Press; 2013.

40. Ten Eick AP, Sallee D, Preminger T, Weiss A, Reed MD. Possible drug interaction between digoxin and azithromycin in a young child. Clin Drug Investig 2000; 20:61-4.
41. Strandell J, Bate A, Hägg S, Edwards IR. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009; 68:427-34.
42. US azithromycin label" (PDF). FDA. February 2016.
43. <https://en.wikipedia.org/wiki/Azithromycin>.
44. <http://www.antibiotics-info.org/azithromycin.html>



AJPHR is
Peer-reviewed
monthly
Rapid publication
Submit your next manuscript at
editor@ajphr.com / editor.ajphr@gmail.com