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**Review Article**

# Pharmacovigilance of Antimicrobial Drug: Azithromycin

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## ABSTRACT

Pharmacovigilance of antimicrobial drugs is critical for ensuring their safety and efficacy in clinical use. Azithromycin, a widely used macrolide antibiotic, is commonly prescribed for a variety of bacterial illnesses, such as respiratory and sexually transmitted diseases. Despite its general safety profile, concerns regarding adverse drug reactions (ADRs), resistance, and interactions with other drugs necessitate continuous monitoring. This review explores the pharmacovigilance data associated with Azithromycin, highlighting common and rare ADRs, such as gastrointestinal disturbances, cardiovascular effects, and potential risks in vulnerable populations. Moreover, the role of pharmacovigilance systems in detecting and managing these effects is emphasized, alongside the importance of post-marketing surveillance to assess long-term safety. Effective pharmacovigilance can guide healthcare professionals in optimizing treatment protocols and minimizing the risks of Azithromycin use, ensuring better patient outcomes and public health.

## INTRODUCTION

The area of medication development known as pharmacovigilance addresses issues linked to identifying, tracking, and averting harmful pharmacological effects [1]. Since many licensed medications have the potential to cause adverse responses, patient safety is the primary goal in PV. Researchers must be wary of any severe side effects, even while the advantages of medications and vaccinations to patients outweigh the risks when considering the risk/benefit ratio [2]. Regarding this investigation, an adverse drug reaction (ADR) report is a report that a patient or health professional sends when a patient receiving one or more antibiotics experiences an undesirable impact. Innovative techniques to monitoring antimicrobials are still being proposed by the scientific community, while some have suggested using pharmacovigilance data as a potential source of antimicrobial stewardship knowledge initiatives [3]. Being the totality of all species that are too tiny to be visible with the human eye, the microbial world is rich, varied, and pervasive. In addition to bacteria and viruses, there are countless varieties

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of multicellular creatures present. [4,5] The basis of the global ecology is also the microbial world. A group of substances known as To combat infectious diseases, antimicrobial medications have been developed to prevent, reduce, or eliminate the proliferation of microbial predators. Most of these antimicrobials have their origins in natural products, where they were first employed by different species to protect themselves from microbial attack [6,7]. Antimicrobials used to treat and prevent infectious diseases have caused microorganisms to evolve resistance to the antibiotic, which has led to an evolutionary response [8]. A wide variety of medications known as antimicrobials are used to treat and prevent diseases in people, animals, and plants [9]. The goal of these drugs is to either eliminate or inhibit the growth of the microorganisms that cause disease. But over time, antimicrobial resistance (AMR) arises when the same microbes acquire the ability to resist the antimicrobial effects of once-effective drugs [10].

AMR poses a serious threat to both public health and global development. It raises mortality, increases medical expenses, and lengthens hospital stays [11]. Antimicrobial resistance jeopardizes both the basis of modern medicine and the feasibility of a successful, global public health response to the ongoing danger of infectious diseases. In the absence of coordinated and prompt global action, the world is rapidly approaching a post-antibiotic age where common illnesses could once again be fatal [12]. One of the most regularly recommended medications is an antibiotic [13]. The two most often prescribed classes were penicillin (23%) and macrolides (22%). The most often recommended antibiotics were amoxicillin and azithromycin [14,15].

One of the most often prescribed antimicrobial drugs in the United States is azithromycin, a broad-spectrum macrolide antibiotic. This erythromycin derivative covers a number of gram-positive organisms and exhibits markedly enhanced effectiveness against gram-negative bacteria, such as Enterobacteriaceae [16,17]. One of the macrolide antibiotics that is most frequently recommended is azithromycin. Mostly in the respiratory system, It is employed to treat a number of ailments. Azithromycin is used in treatment strategies that are both short-term and long-term. Patients receiving long-term, low-dose macrolide therapy, for example, have demonstrated great success in treating chronic airway conditions such bronchial asthma, chronic bronchitis, and widespread panbronchiolitis [18–21].

The antibiotic azithromycin is listed in Schedule H1 of the 1945 Drugs and Cosmetics Regulations. Schedule H1 medications must only be sold at retail with a prescription from a licensed healthcare professional.

Numerous ailments are treated with azithromycin, such as:

infection with H. pylori

Diarrhea in travelers

Legionnaires' illness

The whooping cough, or pertussis

Lyme illness

Babesiosis

Azithromycin may exacerbate myasthenia gravis (MG) symptoms. It may also interact with other disorders like liver, renal, or low blood potassium or magnesium.

**Classification Of Antimicrobial:**

| | |
|---|---|
| **Beta-lactams** | A beta-lactam 'ring' is one of the beta-lactams that attaches itself to the bacterial enzymes' active site. The subclasses of this antibiotic include carbapenems, monobactams, cephalosporins, and penicillins [22]. |

| | |
|---|---|
| **Macrolides** | Macrolides are a type of chemical that Saccharopolyspora erythraea produces. These antibiotics have 14–16 atoms in their molecule, making them lactone-ring antibiotics. Azithromycin, oleandomycin, clarithromycin, and erythromycin are the four types of macrolides. A nitrogen atom is part of a cycle of azalides, including azithromycin [23]. |
| **Tetracyclines** | Many Streptomyces species produce tetracyclines. Tetracyclines are made up of four hydrocarbon rings in their chemical structure. For these antibiotics to inhibit bacterial protein synthesis, the amino group in position C4 and the keto-enolic tautomers in locations C1 and C3 of the A ring are required. The antibacterial qualities depend on the C4 amino group. Tetracene's nucleus is partially hydrated in these antibiotics. There are three generations of tetracyclines: first, second, and third [24]. |
| **Aminoglycosides** | Cyclohexane, guanidino-derivatives, and glycoside derivatives with one or more OH groups that contain OH and NH2 are the structures of these antibiotics. Some were from Micromonospora or the Streptomyces genus. These antibiotics include gentamicin, neomycin, streptomycin, and kanamycin [25]. |
| **Glycopeptides** | Glycopeptides are glycosylated cyclic or polycyclic non-ribosomal peptides produced by groups of filamentous actinomycetes. These treatments target gram-positive bacteria by binding to the acyl-D-Ala-D-Ala terminus of the forming peptidoglycan and then cross-linking peptides inside and between peptidoglycan on the outer surface of the cytoplasmic membrane [26]. |
| **Polyenes** | The number of conjugated carbon-to-carbon double bonds, the size of the conjugated ring, and the presence or absence of an aromatic component or hexosamine sugar vary amongst polyenes [27]. |

**Azithromycin**

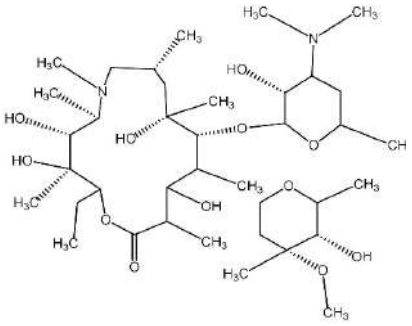
**Mechanism Of Action:**

The 23S region of the 50S bacterial ribosomal subunit is where azithromycin binds, as other macrolide medicines do. By preventing the growing protein and aminoacyl-tRNA from navigating the ribosome,it stops bacteria from synthesizing proteins. Since azithromycin is less likely to separate from the gram-negative ribosome than erythromycin, it is more effective against gram-negative infections [33]. As a bacteriostatic medication, azithromycin primarily stops bacteria from growing instead of destroying them like other macrolides and protein-synthesis inhibitors do. Nonetheless, it has been shown that azithromycin, especially at larger doses, has a bactericidal effect on certain bacteria, such as streptococci and H. influenzae [34–35]. In non-bacterial organisms (i.e., apicomplexan parasites such as Babesia sp., Plasmodium sp., and Toxoplasma sp.), azithromycin inhibits the 50S ribosome in the parasite apicoplast, an organelle derived from endosymbiosis with bacterial-like protein-synthesis machinery that performs essential metabolic tasks [36–37]. In addition to its antibacterial qualities, azithromycin is a potent immunomodulator that has been shown to dramatically reduce airway neutrophilia, IL-8 gene expression, and C-reactive protein levels in lung transplant recipients [38]. Because of its antiviral qualities in vitro, azithromycin has sparked interest in treating SARS-CoV-2 experimentally. By inducing the formation of RIG-I-like helicases, azithromycin enhanced the rhinovirus-induced expression of interferons in COPD patient cultured cells but not in healthy patient cultured cells in vitro [39].

**Chemistry :**

The 9A carbonyl group in the aglycone ring of erythromycin A is replaced with a methyl-substituted nitrogen to produce the semisynthetic compound azithromycin (Figure 1). Because of the additional nitrogen atom that was inserted, azithromycin is better known as an azalide rather than a macrolide. In a number of crucial chemical properties, the resultant dibasic, 15-membered

ring molecule differs from erythromycin. First, as will be noted, the significant variations in the drug's pharmacokinetics can be explained by the second nitrogen atom's altered acid-base characteristics. Furthermore, enteric coating of the medication to prevent gastric acid is not necessary because azithromycin, in contrast to erythromycin, is resistant to acid-catalysed destruction.



**Azithromycin**

**Pharmacology:**

Protein synthesis is inhibited by azithromycin's reversible binding on the bacterial ribosome [40–41].

In both healthy individuals and those with cystic fibrosis, the medication's absolute oral bioavailability ranges from 35 to 42% [42–43].

Although azithromycin is usually taken orally, there is an intravenous version available for those who cannot take oral drugs.

Treatment duration varies according to indication and intensity. Some sexually transmitted illnesses typically only require one dose.

Treatment for respiratory tract infections often lasts a few days, while treatment for mycobacterial infections typically lasts several months. For specific recommendations, refer to the guidelines [44].

**Pharmacokinetic:**

Absorption:

When used orally, azithromycin does not need to be shielded from stomach acids because it is an acid-stable antibiotic. It is readily absorbed, however when the stomach is empty, absorption is enhanced. The time to peak concentration (Tmax) for oral dosage formulations in adults is between 2.1 and 3.2 hours [45]. The bioavailability of azithromycin is around 37%. A single oral 500 mg dose produces a peak plasma concentration of around 0.35–0.45 mg in about two hours [46].

Distribution:

After oral administration, azithromycin has a wide distribution in tissues, with an apparent steady-state volume of distribution of 31.1 L/kg. Due to its high concentration in phagocytes, azithromycin is aggressively transported to the infection site [47]. Active phagocytosis results in the release of large amounts. Azithromycin's concentration in tissues can be more than 50 times that of plasma due to ion trapping and its high lipid solubility [Reference required]. Because of its half-life, azithromycin can be administered in large doses and yet sustain bacteriostatic levels in the diseased tissue for several days [48]. To effectively combat Chlamydia trachomatis, the medication is concentrated in macrophages and polymorphonucleocytes [49].

Metabolism :

Azithromycin is usually the parent molecule found in serum and tissue. It is a final excretory event, with approximately 35% of its metabolism occurring in the liver, where biotransformation by demethylation occurs concurrently with excretion [50].

Elimination :

Over the course of a week, azithromycin is mostly removed unaltered in the feces, billiary excretion, and transintestinal secretion. Urine contains around 6% of the received dose as unaltered medication [51].

**Pharmacodynamic :**

Macrolides treat bacterial infections and stop bacterial growth by blocking the synthesis and translation of proteins. 4. Because of its additional immunomodulatory qualities, azithromycin has been used to treat long-term respiratory inflammatory conditions.H [52]. Among influenzae's defense mechanisms against macrolides are ribosomal methylase, innate or acquired efflux pumps, and modifications to ribosomal proteins or RNA [53].

**Administration :**

There are two dosing forms for azithromycin: oral and parentral. Azithromycin is typically administered once day for three to five days at a dose of 250 mg or 500 mg; in cases of severe infection, a greater dose may be prescribed [54].

Oral Formulation: These consist of 250 mg and 500 mg pills as well as packets (one gram of powder is dissolved in sixty milliliters of water). Food may or may not be consumed with administering dosage [55].

Intravenous (IV): is offered in a 500 mg reconstitution solution without preservative. It is not recommended to administer azithromycin by intravenous bolus or intramuscular injection [56].

Opthalmic Solution : 1% is used to treat bacterial pinkeye and comes in a 2.5 ml container [57].

Azithromycin exhibits superior intracellular accumulation and tissue penetration. Excretion is mostly biliary, while metabolism is hepatic [58]. Its extended half-life and broad tissue and intracellular distribution enable once-daily dosing and a shorter treatment duration than other antimicrobials (for instance, a chromydia infection can be treated with a single dose of 1 g of azithromycin instead of 100 mg of doxycycline twice daily for 7 days). Regardless of creatinine clearance, patients with renal disease or failure may be prescribed azithromycin. Most of the time, there is no need to change the dosage [59].

**Pediatric Patient:**

| **Infection** | Acute otitis media | Acute bacterial sinusitis | Community-acquired pneumonia | Pharyngitis/ tonsillitis |
|---|---|---|---|---|
| **Recommended Dose/Duration of Therapy** | 30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5. | 10 mg/kg once daily for 3 days. | 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5. | 12 mg/kg once daily for 5 days. |

- **Adult Patient:**

| **Infection** | Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated | Acute bacterial exacerbations of chronic bronchitis (mild to moderate) | Acute bacterial sinusitis | Genital ulcer disease (chancroid) Non-gonococcal urethritis and cervicitis | Gonococcal urethritis and cervicitis |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| **Recommended Dose/Duration of Therapy** | 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5. | 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 or 500 mg once daily for 3 days. | 500 mg once daily for 3 days. | One single 1 gram dose. | One single 2 gram dose. |

**Antiviral Effect:**

On a wide range of viruses, including Zika, Ebola, influenza H1N1, and respiratory syncytial virus, azithromycin has demonstrated antiviral efficacy in vitro [60]. RIG-I enjoy The RNA helicase family known as receptors serves as a cytoplasmic sensor of molecular patterns linked to pathogens. In response to viral infection, they mediate the synthesis of cytokines and interferons [61]. It has been shown that AZ stimulates the expression of type I and III interferons and, in a concentration-dependent way, activates RIG-I like receptors in cultured bronchial epithelial cells from patients with COPD [62]. According to an in-vitro investigation, AZ alone has an effect on SARS-CoV-2, although other studies only observed this effect when paired with hydroxychloroquine [63].

**Immunomodulatory Effect :**

Apart from their antibacterial characteristics, macrolides have been shown to have immunomodulatory or anti-inflammatory actions in vitro and in animals [64]. Human effects were first documented in the management of diffuse panbronchiolitis, where macrolides are linked to better lung function and prognosis, primarily based on evidence from retrospective studies and non-controlled trials [64]. Enhanced respiratory function and fewer respiratory exacerbations are linked to six months of treatment for cystic fibrosis [65]. In patients treated for bronchiolitis obliterans syndrome following lung transplantation, azithromycin resulted in a slight improvement in lung function (mean 8.8%) at seven months,[66] However, following a hematopoietic stem cell transplant, it did not differ from a placebo in terms of bronchiolitis obliterans syndrome [67]. In order to reduce cytokine storm in sepsis and epidemic respiratory virus infections, azithromycin and other macrolides have also been suggested for usage [64]. 1 It has been used to treat a number of inflammatory disorders, both respiratory and non-respiratory. Due to worries about rising antibiotic resistance and the paucity of direct clinical evidence for many illnesses, this usage has been contentious [64,68]. Antimicrobial resistance may not be exacerbated by novel non-antibiotic macrolides that have immunomodulatory effects [68].

**Bronchiectasis :**

Azithromycin decreased the frequency of exacerbations in non-cystic fibrosis bronchiectasis, according to three randomized, double-blind, placebo-controlled trials. According to the EMBRACE trial, persons with bronchiectasis on CT scans and at least one lung exacerbation treated with antibiotics during the previous year experienced fewer exacerbations when taking azithromycin three times a week for six months as opposed to a placebo [69]. Adults with radiologically diagnosed bronchiectasis and at least three respiratory infections treated with antibiotics in the previous year (daily azithromycin medication over 12 months) experienced fewer exacerbations (median 0 vs. 2), according to the BAT trial [70]. Lastly, the Bronchiectasis Intervention Study examined indigenous children in Australia and New Zealand who had experienced at least one pulmonary exacerbation throughout the previous 12 months and had either

chronic suppurative lung disease or non-cystic fibrosis bronchiectasis. The incidence of pulmonary exacerbations was half that of those who received a placebo after taking azithromycin once a week for up to 24 months. Nonetheless, the authors observed that children receiving azithromycin had a higher prevalence of macrolide-resistant bacteria (46% vs. 11%) [71].

**Asthma and chronic obstructive pulmonary disease :**

The best regimens and subgroups have not yet been determined, and trials in children and adults with asthma and chronic obstructive pulmonary disease (COPD) have been modest and have had inconsistent results. Macrolides may help patients with neutrophilic asthma, but more research is required [72].

**Clinical Efficacy :**

In a wide range of viral respiratory infections, macrolides have demonstrated their therapeutic effectiveness [73]. According to Lee et al., the addition of azithromycin to oseltamivir dramatically decreased the synthesis of proinflammatory cytokines in hospitalized patients with influenza A pneumonia, with a tendency toward a quicker recovery of symptoms [74]. Kakeya et al. evaluated patients with mild influenza A pneumonia who received management with azithromycin and oseltamivir within 48 hours of the onset of symptoms. Without affecting cytokine and chemokine expression levels, azithromycin greatly improved the remission of fever and sore throat [75]. Crucially, both clarithromycin and azithromycin were included in this secondary analysis of an observational study. The potential advantages of azithromycin in this situation might have been understated because clarithromycin has demonstrated less immunomodulatory activity [76,77]. Recently Ishaqui et al. demonstrated that the addition of azithromycin (initiated 6-8h after diagnosis) significantly improved meaningful clinical outcomes as length of stay or the need for respiratory support during hospitalization[78]. Guidelines encourage its use in conjunction with beta-lactams for the treatment of CAP, including in patients admitted to the intensive care unit (ICU), particularly in critically ill patients [79, 80]. Even when macrolide-resistant strains were present, the administration of macrolides was linked to a significant decrease in mortality in intensive care unit patients, indicating that the immunomodulatory qualities may be responsible for this discrepancy [81,82]. This approach in outpatients has been examined in other studies. The time to clinical recovery for azithromycin alone and azithromycin plus hydroxychloroquine was evaluated by Guerin et al. in comparison to outpatient standard of care [83]. According to a recent evaluation, high-risk outpatients with symptoms should be treated with hydroxychloroquine and azithromycin [84]. This study suggests that early outpatient sickness differs greatly from later disease, and that combination therapy may provide significant clinical benefits in this context [84].

**Indications :**

One of the most often given antimicrobial medications in the US is azithromycin, a broad-spectrum macrolide. It is a derivative of erythromycin that offers protection against numerous gram-positive organisms and has significantly increased effectiveness against gram-negative bacteria, including Enterobacteriaceae [16,17].

- Azithromycin works against many "atypical" bacteria, including chlamydiae (like Chlamydia trachomatis and Chlamydophila psittaci), legionella (like Legionella pneumophila), mycoplasma (like Mycoplasma pneumoniae), and mycobacteria (like Mycobacterium avium), because it inhibits the synthesis of bacterial proteins rather than

peptidoglycan cell walls like beta-lactam agents do [85].

- The FDA has approved azithromycin for the treatment of community-acquired pneumonia (CAP) due to its ability to combat Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis [86].
- Acute otitis media and acute exacerbation of chronic obstructive pulmonary disease (COPD) are among the other upper respiratory infection processes for which azithromycin has been authorized for usage [87].
- Azithromycin is also approved to treat pharyngitis caused by Streptococcus pyogenes as an alternative to beta-lactam agents; infections of the skin or skin structure caused by Streptococcus pyogenes, Streptococcus agalactiae, or Staphylococcus aureus; treatment and prevention of M. avium complex (MAC) infections in patients with advanced acquired immunodeficiency syndrome (AIDS); and sexually transmitted infections such as chlamydia, gonococcal disease, chancroid (caused by Hemophilus ducreyi), and Mycoplasma genitalium [88–92].
- In addition to its effectiveness against some protozoal organisms, azithromycin is occasionally used off-label in conjunction with antiprotozoal medications, such as atovaquone, to treat parasitic disorders such Babesia sp. (e.g., B. microti), Plasmodium sp. (e.g., malaria), and Toxoplasma gondii [93–95].
- It is unknown how azithromycin will be used to treat viral infections, such as those caused by the respiratory syncytial virus and the new coronavirus SARS-CoV-2 [96–100].
- Finally, azithromycin is also used off-label to prevent bronchiolitis obliterans (BO) in patients who have had lung transplants over an extended period of time [101].

**Contraindications :**

- Patients who have experienced severe hypersensitivity (such as anaphylaxis or SJS) to azithromycin or another macrolide antibiotic in the past should not take azithromycin. Clinicians should also exercise caution while using azithromycin and other drugs that lengthen the QTc interval at the same time (such as antipsychotics).
- Patients on pimozide, a first-generation antipsychotic, should not take azithromycin. The same cytochrome that metabolizes pimozide, CYP3A4, is inhibited by macrolide antibiotics. Using azithromycin and pimozide together can result in unsafe plasma concentrations of pimozide, which can cause QTc prolongation and potentially fatal arrhythmias. Avoiding this interaction is still advised even though azithromycin inhibits CYP3A4 less effectively than other macrolides [102,103].
- Azithromycin also inhibits the cell membrane glycoprotein transporter p-glycoprotein/ABCB1. Azithromycin may be somewhat contraindicated for medications that are P-glycoprotein substrates, especially those that are also CYP3A4 substrates. Small-molecule calcitonin gene-related peptide (CGRP) antagonists and colchicine are two examples [104,105].
- In lung transplant patients, azithromycin efficiently maintains FEV and reduces bronchiolitis obliterans (BO) without affecting overall survival; however, a study comparing azithromycin and a placebo for the prevention of BO in hematopoietic stem cell transplant (HSCT) recipients showed that azithromycin reduced BO-free and overall survival. Therefore, it is not recommended that HSCT recipients receive long-term azithromycin prophylaxis.[106].

**Adverse Effects :**

- Although azithromycin is usually well tolerated, headache, dizziness, and gastrointestinal distress are very typical side effects that affect 1–5% of patients. Additionally, 1.5% of patients have been observed to have transient elevations in transaminases [112]. Azithromycin has also been linked to hearing loss or impairment, even in individuals with COPD who had normal hearing at baseline. In several cases, this loss or impairment seemed to be irreversible [113,114]. There have also been published case reports of hearing loss following brief use [115].
- Similar to other macrolides, azithromycin has been linked to polymorphic ventricular tachycardia and torsades de pointes, as well as QTc prolongation [116]. Azithromycin use was linked to both a minor but substantial absolute increase in cardiovascular death and an increased risk of cardiovascular death in comparison to amoxicillin, according to a large retrospective cohort research. Among patients with the highest baseline cardiovascular risk, these effects were most noticeable [116]. However, in a group of young and middle-aged adults, another large cohort research did not find an elevated risk of cardiovascular death [117].
- Hepatotoxicity, which primarily consists of hepatic damage within one to three weeks of pharmaceutical administration, is also infrequently linked to azithromycin. Elevated transaminase values and cholestatic jaundice are clinical signs of hepatotoxicity [118].
- Similar to other macrolides, azithromycin frequently causes gastrointestinal side effects such nausea and diarrhea. All macrolides stimulate stomach motility by activating intestinal motilin receptors in a dose-dependent manner. (Due to this mechanism, erythromycin is frequently used by clinicians to treat gastroparesis.) [119].
- Anaphylaxis and Stevens-Johnson syndrome (SJS), two potentially fatal hypersensitivity responses to azithromycin, are incredibly uncommon [120,121].
- The two most frequent side effects are stomach pain (3%), and diarrhea (5%).Less than 1% of patients discontinue their medication because of adverse effects. There have been reports of allergy, skin rashes, and nervousness [121]. Azithromycin use has been linked to Clostridium difficile infections [122]. Unlike certain other antibiotics, such rifampin, azithromycin has no effect on the effectiveness of birth control. There have been reports of hearing loss [123].
- People have occasionally experienced delirium or cholestatic hepatitis. An infant's acute heart block from an accidental intravenous dosage left them with persistent encephalopathy [124,125].
- Azithromycin "may cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm," according to a 2013 warning from the US Food and Drug Administration (FDA). According to a 2012 research, the medicine may raise mortality rates, particularly in people with heart issues, as compared to people taking alternative antibiotics like amoxicillin or no antibiotic at all, the FDA said. People with preexisting problems, such as those with aberrant QT intervals, low blood potassium or magnesium levels, a slower than usual heart rate, or those who take specific medications to treat irregular heart rhythms, are particularly vulnerable, according to the warning [126,127,128].

**Monitoring :**

Adverse effects that necessitate medication modification or azithromycin termination are

uncommon, and the majority of azithromycin treatment periods are brief [107]. In the event that hepatotoxicity symptoms appear (such as jaundice or increased transaminases), azithromycin should be stopped immediately. Many patients who receive long-term azithromycin prophylaxis—such as lung transplant recipients for BO prophylaxis or AIDS patients for MAC prophylaxis—experience gastrointestinal side effects, particularly when taking higher doses (such as 600 mg or 1200 mg). Lowering the dosage or switching to twice-daily dosing may be an option for these patients [108,109].

**Toxicity :**

QTc prolongation is linked to azithromycin, just like it is to other macrolides. Azithromycin can cause serious or even fatal arrhythmias such torsades de pointes, especially in patients who have a history of QTc interval disruption, cardiac arrhythmia, or concurrent use of other drugs linked to QTc prolongation. Azithromycin appeared to have a less pronounced proarrhythmic impact in animal trials, although being linked to comparable QTc prolongation to other macrolides [110]. Azithromycin seldom causes substantial hepatotoxicity, but macrolides are known to cause mixed hepatocellular/cholestatic drug-induced liver injury. Liver damage is nearly often reversible with little lasting damage if azithromycin is stopped quickly. Azithromycin-induced hepatotoxicity frequently manifests as immunoallergic symptoms such fever, rash, and eosinophilia. Anaphylaxis, SJS, and drug reaction with eosinophilia and systemic symptoms (DRESS) are examples of severe immunoallergic reactions that are uncommon [111]. Most patients finish the recommended term of azithromycin, and gastrointestinal toxicity is frequent although usually minor. The activation of pro-motility receptors in the gastrointestinal system by azithromycin is primarily responsible for this toxicity.

**Clinically significant interactions of azithromycin :**

- If azithromycin is taken with other medications that lengthen the QT interval, it should be used extremely carefully [129].
- A number of published papers indicate that azithromycin may increase the effectiveness of warfarin; however, because of patient characteristics and research design, clinical outcomes resulting from excessive anticoagulation caused by warfarin are debatable. Interactions have not been found in some retrospective series [130,131]. or discovered an interaction without any negative consequences [132]. Patients on warfarin who need azithromycin should have their INR closely monitored because of the current lack of clarity regarding interactions.
- Pharmacokinetic modeling points to a decreased everolimus clearance [133].
- Digoxin toxicity may be increased by macrolides, such as azithromycin. It has to do with P-glycoprotein. After beginning azithromycin, a 31-month-old baby showed signs of digoxin toxicity, according to a case study [134].
- Colchicine levels may rise as a result of azithromycin use, which could be harmful [135,133].
- Azithromycin and statin usage together may raise the risk of rhabdomyolysis [136].
- Antacids (magnesium, aluminum) taken together may lower the peak concentration of azithromycin.

**Pharmacovigilance of Azithromycin :**

According to an azithromycin pharmacovigilance research:

Adverse events were reported by 4.4% of patients.

Adverse events in 88 patients were probably caused by azithromycin.

Most adverse events were digestive tract issues

97% of patients followed their treatment plan.

One macrolide antibiotic that is frequently used to treat bacterial infections is azithromycin. It can be administered intravenously or orally. The following adverse effects are possible with azithromycin:

Acute liver damage is an uncommon side effect of azithromycin.

Heart or blood vessel problems: The use of azithromycin may raise the risk of severe heart or blood vessel issues. You should get in touch with your physician right once if you encounter:

- Blurred vision
- Chest pain
- Dizziness
- Lightheadedness
- Fainting
- Fast or irregular heartbeat
- Difficulty breathing
- Unusual weakness or fatigue
- Confision

Additionally, azithromycin is listed as an antibiotic with a higher risk of developing antimicrobial resistance on the World Health Organization's (WHO) Watch list.

Azithromycin pharmacovigilance is tracking the medication's safety profile, identifying and evaluating side effects, and putting precautions in place to reduce risks. This is the detailed procedure:

**Pre-Marketing Phase**

1. Preclinical trials: Analyze the pharmacokinetics, pharmacodynamics, and toxicity of azithromycin.
2. Clinical trials: To evaluate safety, effectiveness, and tolerability, conduct Phase I–III trials.

**Post-Marketing Phase**

1. Spontaneous reporting: Gather reports of adverse events from patients, medical professionals, and literature.
2. Pharmacovigilance centers: Provide specialized facilities for documenting and assessing unfavorable occurrences.
3. Signal detection: Use data analysis to find any safety issues.
4. Risk assessment: Analyze detected signals to ascertain their severity and cause.
5. Risk minimization: Put policies in place to reduce hazards that have been recognized (e.g., updated labeling, teaching materials).
6. Periodic safety update reports (PSURs): Report to regulatory bodies on a regular basis.
7. Post-marketing surveillance: Perform registries, cohort studies, or observational studies.

**Regulatory Involvement**

1. Regulatory submissions: Send safety information to the appropriate authorities (e.g., FDA, EMA).
2. Labeling updates: Update the label to include the most recent safety information.
3. Safety communications: As needed, issue recalls, warnings, or alerts.

**Pharmacovigilance Activities**

1. Adverse event monitoring: Monitor and evaluate unfavorable occurrences.
2. Signal management: Assess possible safety issues and take appropriate action.
3. Risk management planning: Create plans to reduce the hazards that have been identified.
4. Quality assurance: Make that the data is accurate, comprehensive, and consistent.

**Tools and Databases**

1. WHO-UMC Database: worldwide database for reports of adverse reactions.
2. FDA Adverse Event Reporting System (FAERS): adverse event report database in the United States.
3. EudraVigilance: adverse reaction reports in the EU database.

**Challenges and Opportunities**

1. Data quality issues: reporting that is either inaccurate or lacking.
2. Underreporting: not recording every negative event.

3. Big data analytics: Leveraging advanced analytics for signal detection.
4. Artificial intelligence/machine learning applications: Increasing the effectiveness of pharmacovigilance.

**Future prospects of Azithromycin :**

Azithromycin's future prospects include:

Potential treatments for other infections:

Azithromycin's potential for treating typhoid, malaria, trachoma, and coronary artery disease is still being investigated.

Treatment for respiratory tract infections:

Numerous respiratory tract infections can be successfully treated with the powerful antibiotic azithromycin. In the upcoming years, it is anticipated that the prevalence of respiratory tract infections would increase globally.

Repurposing as a COVID-19 treatment:

Since azithromycin has been used to treat other coronavirus illnesses, its safety, cost, and accessibility make it a desirable option for COVID-19 treatment. However, a positive evaluation cannot be supported just by scientific findings.

Macrolide resistance:

Azithromycin's unrestricted use raises concerns due to macrolide resistance. In the future, novel non-antibiotic macrolides might be employed for this purpose.

## CONCLUSION

Pharmacovigilance of azithromycin, a widely used macrolide antibiotic, is essential to ensure its safe and effective use in treating bacterial infections. This process involves monitoring, assessing, and minimizing the risks associated with azithromycin, particularly given its broad use and potential adverse effects. while azithromycin remains a valuable antibiotic with a broad spectrum of action, ongoing pharmacovigilance is essential to balance its benefits and risks. This includes monitoring for adverse reactions, managing drug resistance, and ensuring appropriate use to safeguard public health.

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