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Different Azithromycin Protocols in Preterm Premature Rupture of Membranes

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Abstract:

Preterm premature rupture of membranes (PPROM) is a major obstetric complication associated with increased risks of maternal infection, neonatal morbidity, and preterm birth. Antibiotic therapy is commonly used to prolong pregnancy latency and reduce infectious complications. Azithromycin has emerged as a potential alternative to erythromycin in latency antibiotic regimens due to its favorable pharmacokinetic profile, broad antimicrobial spectrum, and better tolerability. Several recent studies and clinical guidelines have explored different azithromycin protocols for the management of PPROM, with varying dosing strategies and durations of treatment.

Keywords: PPROM, Azithromycin, Preterm premature rupture of membranes, Latency antibiotics, Chorioamnionitis, Obstetric infections.

Introduction:

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and high tissue penetration. It was approved by the FDA in 1991. This antibiotic is mainly used to treat respiratory, enteric, and genitourinary infections. It can also be used for some sexually transmitted and enteric infections instead of other macrolides. Azithromycin is structurally related to erythromycin with enhanced activity against gram-negative bacteria (including Enterobacteriaceae) and provides coverage of many gram-positive organisms. The conditions treated by azithromycin are major contributors to infectious disease morbidity and mortality in the United States. It is the most frequently prescribed antimicrobial drug in the United States, with over 7 million prescriptions **(1).**

History

In 1980, a team of researchers at the pharmaceutical company Pliva in Zagreb, former Yugoslavia discovered azithromycin. The company patented it in 1981. In 1986, Pliva and Pfizer signed a licensing agreement, giving Pfizer exclusive rights to sell azithromycin in Western Europe and the United States, while Pliva sold it in Central and Eastern Europe. Pfizer launched azithromycin under the brand name Zithromax in 1991. Patent protection for azithromycin ended in 2005 **(2).**

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Chemical structure

Azithromycin (9-deoxy-9α-aza-9α-methyl-9α-homoerythromycin) has the chemical formula $C_{38}H_{72}N_2O_{12}$ and a molecular weight of 749 $g \cdot mol^{-1}$. It belongs to the azalide subclass of macrolides, which are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. It contains a 15-membered ring and has a methyl-substituted nitrogen instead of a carbonyl group at the 9a position on the aglycone ring. This structural difference allows azithromycin to prevent its metabolism, setting it apart from other macrolides **(3).**

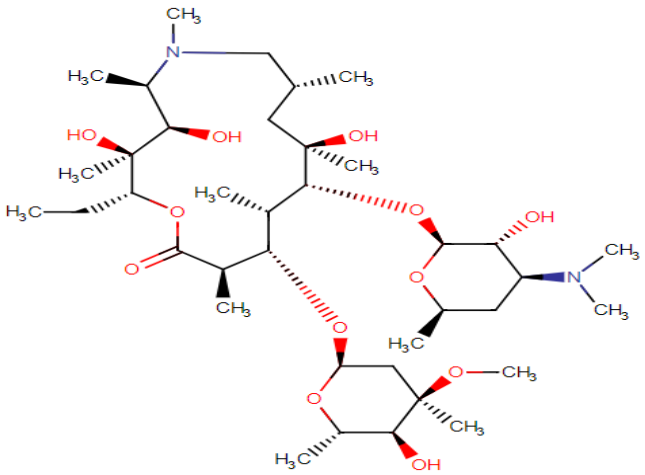

Figure 1: Chemical structure of azithromycin **(3).**

Pharmacodynamics

Azithromycin, like other macrolide antimicrobials, works by stopping bacterial growth through the inhibition of protein synthesis and translation. This helps in treating bacterial infections. Azithromycin is highly stable at a low pH, which gives it a longer serum half-life and increases its concentrations in tissues compared to erythromycin. Azithromycin primarily acts as a bacteriostatic agent, meaning it inhibits bacterial growth rather than directly killing organisms. However, especially at higher doses, azithromycin has been shown to have a bactericidal effect against certain bacteria, such as streptococci and H. influenzae **(4).**

Mechanism of Action

Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit, inhibiting bacterial protein synthesis. It does this by interrupting the transpeptidation and translocation steps of protein synthesis, as well as by preventing the assembly of the 50S ribosomal subunit. This results in the control of various bacterial infections. The strong affinity of macrolides, including azithromycin, for bacterial ribosomes, is consistent with their broad-spectrum antibacterial activities **(5).**

In non-bacterial organisms (i.e., apicomplexan parasites such as Babesia spp., Plasmodium spp., and Toxoplasma spp.), azithromycin inhibits the 50S ribosome present in the parasite apicoplast. The apicoplast is an endosymbiosis-derived organelle with bacteria-like protein-synthesis machinery, performing critical metabolic functions **(6).**

In addition to its antimicrobial activity, azithromycin is also a potent immunomodulator. It has been used in chronic respiratory inflammatory diseases for this purpose, and has been shown to markedly reduce airway neutrophilia, IL-8 gene expression, and C-reactive protein levels in lung transplant recipients **(7).**

Azithromycin has shown antiviral properties in laboratory studies, generating interest in its potential for treating SARS-CoV-2. In cultured cells of COPD patients, azithromycin increased the expression of RIG-I-like helicases, thus enhancing the production of interferons in response to rhinovirus. However, this effect was not observed in cultured cells from healthy patients **(8).**

Bacterial susceptibility

Azithromycin exhibits relatively broad but shallow antibacterial activity against most isolates of the following microorganisms, both in vitro and in clinical infections. It inhibits some Gram-positive bacteria, some Gram-negative bacteria, and many atypical bacteria **(9).**

Gram-positive microorganisms:

- Staphylococcus aureus (Methicillin-sensitive only)
- Streptococcus pyogenes (Group A streptococci; GAS)
- Streptococcus agalactiae (group B streptococci; GBS)
- Beta-hemolytic streptococci (Groups C, F, G)
- Streptococcus pneumoniae.

Gram-negative microorganisms:

- Haemophilus ducreyi
- Haemophilus influenzae
- Moraxella catarrhalis
- Bordetella pertussis
- Neisseria meningitidis
- Neisseria gonorrhoeae.

Anaerobic microorganisms:

- Clostridium perfringens
- Prevotella bivia
- Peptostreptococcus species.

Atypical microorganisms:

- Chlamydia species
- Legionella spp.

- Mycoplasma spp.
- Ureaplasma urealyticum **(9).**

Bacterial Resistance

Resistance to macrolides is associated with: 1) the inability of the organism to take up the antibiotic, 2) the presence of efflux pumps, 3) a decreased affinity of the 50S ribosomal subunit for the antibiotic due to methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms, and 4) the presence of plasmid-associated erythromycin esterases in gram-negative organisms such as the Enterobacteriaceae **(10).**

Azithromycin demonstrates cross resistance with erythromycin. The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA target, most often by formation of methyltransferases. Ribosomal modifications can determine cross resistance to other macrolides, lincosamides, and streptogramin B (MLS_B phenotype) **(10).**

Pharmacokinetics

Absorption

The absolute bioavailability of azithromycin is 37% following oral administration (250-mg capsules). Macrolide absorption in the intestines is believed to be mediated by P-glycoprotein (ABCB1) efflux transporters, which are known to be encoded by the ABCB1 gene **(3).**

Azithromycin is stable in stomach acid, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but absorption is greater on an empty stomach **(11).**

Distribution

The protein binding of azithromycin in the serum varies in humans, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL. After oral administration, azithromycin is widely distributed in tissues with an apparent steady-state volume of distribution of 31.1 L/kg. Significantly greater concentrations of azithromycin have been measured in the tissues rather than in plasma or serum. The lung, tonsils, cervix, and prostate have shown a particularly high rate of azithromycin uptake. Extensive tissue distribution was confirmed by examination of additional tissues and fluids, including bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder **(1).**

Azithromycin is highly concentrated within macrophages and polymorphonuclear cells, allowing for effective activity against Chlamydia trachomatis. Additionally, in vitro incubation techniques have shown that azithromycin is concentrated in phagocytes and fibroblasts. Studies conducted in vivo have demonstrated that the concentration of azithromycin in phagocytes may aid in its distribution to inflamed tissues. The tissue-to-blood concentration ratio of azithromycin can be more than 50 times higher with a half-life ($t_{1/2}$) of 2–4 days in most tissues, due to ion trapping and its high lipid solubility **(12).**

Metabolism

In vitro and in vivo studies to assess the metabolism of azithromycin have not been performed, although minimal, this drug is eliminated by hepatic demethylation **(13).**

Metabolites are devoid of significant antimicrobial activity. Azithromycin does not interact with CYP450 isozymes present in liver and is not associated with the pharmacokinetic drug interactions seen with erythromycin and other macrolides **(14).**

Elimination

The concentration of azithromycin in the blood decreases in a two-phase pattern after taking a single 500 mg oral or IV dose resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, primarily as unchanged drug, is a major route of elimination. Over a 1-week period, approximately 6% of the administered dose appears as unchanged drug in urine **(15).**

Indications

Azithromycin is used to treat various infections, including:

Community-acquired pneumonia, low to moderate severity in adults and pediatric patients (6 months of age and older) due to C. pneumoniae, H. influenzae, M. pneumoniae, or S. pneumoniae in patients appropriate for oral therapy. The CDC recommends 500 mg PO as a single dose on Day 1, followed by 250 mg PO once daily on| Days 2-5 **(16).**

Pharyngitis/tonsillitis in adults and pediatric patients (2 years of age and older) caused by S. pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy. The CDC recommends 500 mg PO as a single dose on Day 1, followed by 250 mg PO once daily on| Days 2-5 **(17).**

Uncomplicated skin and skin structure infections in adults due to S. aureus, S. pyogenes, or S. agalactiae. Abscesses usually require surgical drainage. The CDC recommends 500 mg PO as a single dose on Day 1, followed by 250 mg PO once daily on| Days 2-5 **(18).**

Acute bacterial sinusitis in adults due to H. influenzae, M. catarrhalis, or S. pneumoniae. The CDC recommends 500 mg PO once daily for 3 days (**19).**

Acute bacterial exacerbations of chronic bronchitis in adults due to H. influenzae, M. catarrhalis, or S. pneumoniae. The benefits of long-term prophylaxis must be carefully evaluated for each patient in comparison to the risk of cardiovascular and other adverse effects. The CDC recommends taking 500 mg PO once daily for 3 days or 500 mg PO as a single dose on Day 1, followed by 250 mg PO once daily on| Days 2-5 **(20).**

Acute otitis media in pediatric patients (6 months of age and older) caused by H. influenzae, M. catarrhalis or S. pneumoniae. The CDC recommends 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 **(21).**

Genital ulcer disease (chancroid) in men due to H. ducreyi. Efficacy of chancroid treatment in women has not been established due to the small number of women included in clinical trials. The CDC recommends one single 1 gram dose **(22).**

Non-gonococcal or Gonococcal Urethritis and Cervicitis due to C. trachomatis or N. gonorrhoeae. The CDC recommends a single 1-gram dose for Non-gonococcal Urethritis and a single 2-gram dose for Gonococcal Urethritis **(23).**

Acute pelvic inflammatory disease caused by C. trachomatis, N. gonorrhoeae, or Mycoplasma genitalium in patients needing initial IV therapy. If anaerobic microorganisms are suspected to be contributing to the infection, antimicrobial agent with anaerobic activity should be used in combination with azithromycin. The CDC recommends 500 mg IV once daily for 1-2 days, followed by 250 mg PO once daily to complete a 7-day course of therapy **(24).**

Prophylaxis of disseminated Mycobacterium avium complex (MAC) disease in advanced HIV infection. The CDC recommends a dosage of 1200 mg PO once weekly alone or in combination with rifabutin. For treating disseminated MAC infections, The CDC recommends a dosage of 600 mg PO once daily along with ethambutol **(25).**

Azithromycin is not licensed [off-label] for treatment of trachoma, mild or moderate typhoid due to multiple-antibacterial resistant organisms, Lyme disease, or prophylaxis of group A streptococcal infection **(26).**

Limitation of Use

Azithromycin should be used only to treat confirmed or highly suspected bacterial infections to prevent drug-resistant bacteria and preserve medication effectiveness. It should not be used in patients with pneumonia who are not suitable for oral therapy due to moderate to severe illness or risk factors such as any of the following: **(27)**

- Patients with cystic fibrosis
- Patients with nosocomial infections
- Patients with known or suspected bacteremia
- Patients requiring hospitalization
- Elderly or debilitated patients
- Patients with serious underlying medical conditions that can lower the immune system, such as immunodeficiency or functional asplenia.

Azithromycin should not be used for viral infections such as the common cold. Its safety and effectiveness for treating genital ulcers in women, ear infections, sinus infections, and

community-acquired pneumonia in children under 6 months of age, as well as for throat or tonsil infections in children under 2 years of age, are not known **(10).**

Available Forms

Azithromycin is available as a generic medication. Azithromycin is administered in film-coated tablet (250mg and 500mg), capsule, oral suspension (100mg/5mL and 200mg/5mL), intravenous injection (500mg/vial), granules for suspension in sachet (1 gram dissolved in ¼ cup or 60 ml of water), and ophthalmic solution (1% is available in a 2.5 ml bottle) **(28).**

Adverse effects

Azithromycin is generally considered a safe antimicrobial agent, and only a few patients discontinue azithromycin due to adverse effects. It is also considered safer and has fewer cardiac adverse effects than other macrolides (i.e., erythromycin and clarithromycin) **(29).**

The most common adverse reactions of azithromycin are related to gastrointestinal distress, such as diarrhea (5 to 14%), nausea (3 to 18%), abdominal pain (3 to 7%), or vomiting (2 to 7%). These reactions occur due to the activation of intestinal motilin receptors, which stimulate gastric motility. (Erythromycin is often prescribed for treating gastroparesis based on this mechanism) **(30).**

Clostridium difficile infection has been reported with the use of azithromycin but to a lesser degree than other common antimicrobial classes (e.g., clindamycin, fluoroquinolones, and cephalosporins) **(31).**

Like other macrolides, azithromycin can prolong the QTc interval and is linked to torsades de pointes and polymorphic ventricular tachycardia. A large study found that azithromycin is associated with a small increase in cardiovascular death, especially compared to amoxicillin, with the highest risk observed in patients with pre-existing cardiovascular issues **(32).**

However, another large cohort study did not find an increased risk of death from cardiovascular causes in a population of young and middle-aged adults **(33).**

Reversible hearing loss, sometimes with tinnitus, has been reported after long-term therapy with azithromycin. In rare cases, azithromycin can also cause constipation, hepatitis, hepatic failure, syncope, insomnia, agitation, anxiety, asthenia, paraesthesia, nervousness, hyperactivity, thrombocytopenia, hemolytic anemia, interstitial nephritis, acute renal failure, photosensitivity, and discoloration of the teeth and tongue **(26).**

Life-threatening hypersensitivity reactions to azithromycin, such as anaphylaxis and Stevens-Johnson syndrome (SJS), are extremely unusual **(34).**

Contraindications

Azithromycin is contraindicated in patients who have known hypersensitivity (e.g., anaphylaxis or SJS) to azithromycin, erythromycin, any macrolide or ketolide drug. It is also avoided in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior azithromycin use. Additionally, caution should be exercised when using azithromycin together with other medications that prolong the QTc interval, such as antipsychotics **(35).**

Warning and precautions Most courses of treatment with azithromycin are short, and adverse effects requiring therapy adjustment or discontinuation of azithromycin are rare **(29).**

Azithromycin should be immediately discontinued if serious allergic and skin reactions occur. It should also be discontinued if signs of liver damage develop, such as jaundice or elevated transaminases **(36).**

For patients receiving long-term azithromycin prophylaxis (e.g., AIDS patients for MAC prophylaxis or lung transplant recipients for BO prophylaxis), many patients experience gastrointestinal adverse effects, especially at higher doses (e.g., 600 mg or 1200 mg). In these patients, reducing the dose or twice-daily dosing may be a consideration **(37).**

The use of azithromycin has been associated with prolongation of the QTc interval and cases of torsades de pointes, which can be fatal. This risk should be taken into consideration when treating patients with certain cardiovascular disorders, including known QTc prolongation or a history of torsades de pointes, as well as those with proarrhythmic conditions and those taking other drugs that prolong the QTc interval **(38).**

Some observational studies have indicated a potential two-fold increased short-term risk of acute cardiovascular death in adults exposed to azithromycin compared to other antibacterial drugs, such as amoxicillin. It is important to weigh this potential risk against the treatment benefits when prescribing azithromycin **(32).**

Clostridioides difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. if CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued **(31).**

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy. Patients should be evaluated if muscle weakness occurs **(39).**

Drug interactions

Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of

azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted **(10).**

Warfarin

Concomitant use of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly **(10).**

Use in specific populations

Pregnancy

Azithromycin is classified as a pregnancy category B drug. Studies on rats and mice have been conducted using doses up to moderately maternally toxic levels (e.g., 200 mg/kg/day). These doses, when adjusted for body surface area, are approximately 4 and 2 times the human daily dose of 500 mg. In these animal studies, no harmful effects on the fetus due to azithromycin were observed. However, there are currently no conclusive and well-controlled studies conducted on pregnant women. Since animal studies do not always predict human response, azithromycin should only be used during pregnancy if clearly needed **(40).**

Lactation

Azithromycin is present in human milk. Non-serious adverse reactions have been reported in breastfed infants after maternal administration of azithromycin. There is no available data on how azithromycin affects milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for azithromycin and any potential adverse effects on the breastfed infant from azithromycin or from the underlying maternal condition **(41).**

Hepatic Impairment

Azithromycin is primarily metabolized by the liver. Therefore, caution is advised when prescribing azithromycin to patients with impaired liver function, especially in cases of severe impairment **(10).**

Renal Impairment

There is limited data available for patients with a renal glomerular filtration rate (GFR) of less than 10 mL/min, so caution should also be exercised when prescribing azithromycin to these patients **(10).**

Guidelines recommendations for the use of azithromycin in PPROM

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued a bulletin on managing preterm premature rupture of membranes (PPROM). The management approach depends on gestational age and complicating factors. For PPROM before 34 weeks, ACOG recommends expectant management, including hospitalization and monitoring for risks such as infection and labor progression. A single course of antenatal corticosteroids is advised based on gestational age to reduce neonatal risks. For women with PPROM before 32 weeks at risk for imminent delivery, magnesium sulfate is suggested for fetal neuroprotection **(42).**

To minimize maternal and neonatal infections and reduce complications associated with gestational age, the American College of Obstetricians and Gynecologists (ACOG) recommends a 7-day regimen of antibiotics for women experiencing preterm premature rupture of membranes (PPROM) who are less than 34 weeks pregnant. The suggested treatment includes a 2-day course of intravenous (IV) ampicillin (2 g every 6 hours) combined with IV erythromycin (250 mg every 6 hours). This is followed by a 5-day course of oral amoxicillin (250 mg every 8 hours) and oral erythromycin (333 mg every 8 hours). If erythromycin is not tolerated or unavailable, azithromycin can be used as an alternative, such as a single oral dose of 1 g. In some facilities, clinicians have chosen to administer azithromycin instead of erythromycin in these situations **(42).**

The ACOG guideline highlights three retrospective studies that compared erythromycin and azithromycin for PPROM, showing no significant differences in latency duration between the two. A cost analysis found that substituting azithromycin for erythromycin significantly reduces expenses **(43).**

Additionally, ACOG recommends that women with PPROM and a viable fetus who qualify for intrapartum group B streptococcus (GBS) prophylaxis should receive this treatment during labor, regardless of previous antibiotic use **(42).**

There is controversy surrounding the use of latency antibiotics for late preterm cases (34 weeks gestation or later) **(44).**

A commentary on an ACOG bulletin criticized the organization for lacking references to support its opposition to these antibiotics for managing late preterm premature rupture of membranes (PPROM) **(45).**

The commentary advocated for their use in patients with PPROM between 34 and 36 weeks of gestation. In response, ACOG acknowledged that while evidence supports the use of these antibiotics before 34 weeks, the benefits for patients between 34 and 36 weeks remain unproven **(44).**

Some international organizations support prophylactic antibiotic use for PPROM **(46).**

The 2022 guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC) recommend giving antibiotics to women diagnosed with preterm premature rupture of

membranes (PPROM) from the time the baby could survive outside the womb up to 34 weeks of pregnancy **(46).** Two antibiotic regimens are suggested: 1) A macrolide (such as erythromycin, azithromycin, or clarithromycin) either alone or with Group B Streptococcus (GBS) coverage for two days if GBS status is unknown or positive. 2) A combination of ampicillin/amoxicillin and a macrolide, regardless of GBS status. For azithromycin, the recommended dosages are either a single oral dose of 1 g or an initial dose of 500 mg to 1 g orally followed by 250 mg every 24 hours for four days. To support the use of azithromycin, the SOGC guideline references the same retrospective studies as ACOG, in addition to a 2021 meta-analysis **(47).**

The Royal College of Obstetricians and Gynecologists (RCOG) and the National College of Gynecologists and Obstetricians of France (CNGOF) recommend erythromycin but not azithromycin for preterm premature rupture of membranes (PPROM) **(48).**

The 2019 RCOG guidelines suggest administering erythromycin for up to 10 days after a PPROM diagnosis, or until the woman is in established labor (whichever is sooner), without specifying gestational age. For women who can't tolerate erythromycin or have contraindications, oral penicillin is considered for 10 days or until established labor (whichever is sooner) **(48).**

The 2019 CNGOF guideline recommends that antibiotic prophylaxis should be initiated upon admission for PPROM. Options include amoxicillin, a third-generation cephalosporin, and erythromycin, which can be used individually or in combination (as per professional consensus) for a duration of 7 days **(49).**

Literature on azithromycin for PPROM

The 2021 meta-analysis by Seaman et al., referenced in the SOGC guideline, aimed to assess the impact of erythromycin and azithromycin on the length of latency and the incidence of clinical chorioamnionitis in patients with preterm premature rupture of membranes (PPROM) **(47).**

The meta-analysis included five cohort studies with a total of 1,289 women **(47).** Of these, 781 received azithromycin, while 508 received erythromycin. Four of the studies, all conducted in the United States, involved patients who were given both azithromycin or erythromycin along with ampicillin, followed by amoxicillin **(50)**. The fifth study, carried out in Iran, included patients who received only macrolide antibiotics **(51).**

Patients were given intravenous erythromycin at a dosage of 250 mg every 6 hours for 2 days, followed by oral erythromycin (either 333 mg or 500 mg every 8 hours, depending on the institution) for an additional 5 days. If there was a shortage of erythromycin in the hospital, azithromycin was used instead, with the specific regimen varying by institution. Options for azithromycin included: a single 1 g oral dose, 500 mg orally on the first day followed by 250 mg daily for 4 days, or 500 mg intravenously for 2 days followed by 500 mg orally for 5 days. Around 50% of women in the studies were given 1 g orally once. Antenatal corticosteroids for fetal lung

maturity were administered in four studies; one study did not report administration of antenatal corticosteroids **(47).**

All the studies included in the analysis were assessed as having a low risk of bias. Out of the 5 studies, the average estimated gestational age at the time of PPROM diagnosis was found to be similar between women who received erythromycin (29.6±2.6 weeks) and those who received azithromycin (29.7±2.0 weeks), resulting in a mean difference of 0.20 weeks (95% confidence interval [CI], 0.43 to 0.83; P [heterogeneity statistic], 84%) **(47).**

The delivery methods were similar for patients receiving either treatment. The average latency period was almost the same for women treated with erythromycin (6.6 days) and azithromycin (6.7 days), showing a negligible difference of 0.07 days (95% CI, 0.45 to 0.60; P < 0.01). The median prevalence rates of clinical chorioamnionitis were 25% (95% CI, 12 to 32) for erythromycin and 14% (95% CI, 9 to 24) for azithromycin. Overall, the incidence of clinical chorioamnionitis was lower in patients treated with azithromycin compared to those treated with erythromycin, with a pooled odds ratio of 0.53 (95% CI, 0.39 to 0.71; P < 0.01) **(47).**

The meta-analysis had a major limitation in that it only included cohort studies and did not have any randomized trials directly comparing the two macrolides. Additionally, three out of the five studies were conducted at individual institutions. The choice of macrolide was based on drug availability, and the dosing was left to the physician's judgment, which might have affected the outcomes **(52).**

The meta-analysis excluded a retrospective study involving patients with membrane rupture between 34 0/7 and 36 6/7 weeks of gestation, with a median of 34 weeks **(47).**

This study assessed outcomes for women treated with a combination of azithromycin and amoxicillin (a single oral dose of azithromycin 1 g, followed by amoxicillin 2 g IV every 6 hours for 2 days, and then 250 mg orally three times a day for 5 days) compared to a historical control group that received erythromycin alone (250 mg orally four times daily for 10 days). The results showed that women given azithromycin and amoxicillin experienced a longer median period from membrane rupture to delivery (5.5 days) compared to those on erythromycin (2 days), with a statistically significant difference ($p<0.001$). There were no notable differences in the mode of delivery or the need for maternal high dependency unit admission **(53).**

After the 2021 meta-analysis, two new studies have been conducted on the use of azithromycin for preterm premature rupture of membranes (PPROM). **(54).**

One recent retrospective cohort study from Taiwan aimed to identify the best broad-spectrum antibiotic for treating PPROM. This study involved 133 Taiwanese women diagnosed with PPROM before 34 weeks and delivering after 24 weeks. Participants underwent microbiological analysis through cervical cultures and received empiric treatment with cefazolin (1 g IV every 8 hours) until delivery or until no bacterial growth was detected in the cultures. For

those allergic to cefazolin, clindamycin (900 mg IV every 8 hours) was given instead. The average age of the patients was 34.9 years, and the average time from PPROM to delivery was 3.37 days. Out of the 133 women studied, 121 had positive culture results, leading to a total of 248 culture results due to the possibility of multiple pathogens being identified in the cervical cultures **(55).**

The most frequently identified pathogens were Lactobacillus (27.8%), Streptococcus (12.9%), and Staphylococcus (12.09%). Resistance testing revealed a high rate of resistance to ampicillin among gram-negative pathogens, suggesting the necessity for at least a second-generation cephalosporin. In gram-positive pathogens, erythromycin also showed significant resistance, indicating that ampicillin or a second-generation cephalosporin may be required. Although the hospital did not conduct a sensitivity test for azithromycin, the authors referenced numerous studies that support its effectiveness in treating Ureaplasma infections. Considering the culture and resistance results alongside existing research, the authors recommended a treatment regimen combining azithromycin (1 g orally on admission to address Ureaplasma and support pregnancy) with an intravenous third-generation cephalosporin for the first two days, followed by amoxicillin (500 mg orally every 8 hours) for an additional five days as the best approach for managing preterm premature rupture of membranes (PPROM). **(55).**

The conclusion was drawn based on an extrapolation because azithromycin was not used in the research. Furthermore, the bacterial composition and resistance rates observed in this single-center study from Taiwan may not accurately represent those in other areas or populations, such as in the United States. Other limitations of the study include its retrospective design and the lack of testing for Ureaplasma, a prevalent bacteria associated with PPROM **(52).**

Lastly, a retrospective multicenter cohort study conducted in 2023 included 287 women with preterm premature rupture of membranes (PPROM) who received azithromycin as part of their antibiotic treatment to prolong latency. The study aimed to evaluate the effect of prolonged azithromycin use on the duration of latency in PPROM patients. The women, ranging from 23 0/7 to 33 6/7 weeks of gestation, were divided into two groups. One group received limited azithromycin (less than 2 days) with options of 1000 mg orally once, 500 mg intravenously once, or 500 mg orally for up to 2 days. The other group received extended azithromycin (7 days) with an initial 2-day intravenous dose of 500 mg followed by 5 days of 500 mg orally. All participants also received standard treatment with intravenous ampicillin for 2 days, followed by oral amoxicillin for 5 days. Additionally, those who tested positive for Group B Streptococcus (GBS) during labor were given intravenous penicillin, regardless of their latency antibiotic regimen **(54).**

The average maternal age was about 30 years, with an average body mass index of around 30 kg/m², and the majority of the patients were Black. There were 165 patients in the limited azithromycin group and 122 in the extended azithromycin group. The primary endpoint, which was the length of gestational latency, was significantly longer for women who received extended azithromycin compared to those on limited azithromycin. The adjusted median gestational latency

for the limited azithromycin group was over 3 days longer (2.6 days [interquartile range, 2.2 to 3.1]) compared to 5.8 days (interquartile range, 4.8 to 6.9) for the extended azithromycin group, with a p-value of less than 0.001 **(54).**

No differences in chorioamnionitis or adverse neonatal outcomes were observed between the two groups. However, the study had limitations due to its retrospective design and the use of concurrent medical treatments that could have influenced the results, such as additional magnesium for neuroprotection and extra antibiotics for urinary infections **(54).**

Literature conclusion of azithromycin for PPROM

Clinical practice guidelines and several studies support the use of azithromycin for managing ruptured membranes in preterm prelabor (PPROM). The American College of Obstetricians and Gynecologists (ACOG) and the Society of Obstetricians and Gynecologists of Canada (SOGC) both recommend azithromycin as an alternative to erythromycin for women with PPROM. These recommendations are primarily based on retrospective studies showing similar latency and neonatal outcomes for both antibiotics, along with better tolerance and lower costs for azithromycin **(46).**

A 2021 meta-analysis further reinforced these findings, comparing erythromycin and azithromycin in treating PPROM at less than 34 weeks' gestation. The analysis indicated similar latency and neonatal outcomes between the two macrolides and a lower incidence of clinical chorioamnionitis in patients treated with azithromycin **(47).**

Additional evidence comes from two recent retrospective cohort studies. One Taiwanese study suggested that a combination of azithromycin, a third-generation cephalosporin, and amoxicillin is the optimal regimen for managing PPROM **(55).**

A separate retrospective study concluded that extending the administration of azithromycin (for seven days) significantly increased latency without increasing adverse maternal or neonatal outcomes **(54).**

Despite generally favorable findings, these studies have several limitations, particularly the inherent drawbacks of retrospective reviews. Prospective, randomized clinical trials with larger study populations are necessary to further investigate the safety and efficacy of azithromycin compared to other agents for the treatment of PPROM **(52).**

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