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MACROLIDE ANTIBIOTICS: A REVIEW

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Abstract:
Macrolides are a class of broad-spectrum antibiotics of large molecular size. The class includes erythromycin, clarithromycin, and azithromycin, among others. Macrolides are used to treat both local and systemic infections, including infections of the skin, respiratory tract, gastrointestinal tract, and genital tract. They also exhibit anti-inflammatory and immunomodulatory properties

Erythromycin, the first macrolide antibiotic discovered, has been used since the early 1950s for the treatment of upper respiratory tract and skin and soft tissue infections caused by susceptible organisms, especially in patients who are allergic to penicillin. Several drawbacks, however, have limited the use of erythromycin, including frequent gastrointestinal intolerance and a short serum half-life. Advanced macrolide antimicrobials synthesized by altering the erythromycin base have resulted in compounds with broader activity, more favorable pharmacokinetics and pharmacodynamics, and better tolerability. Two of these agents, clarithromycin and azithromycin have been used extensively for the treatment of respiratory tractinfections, sexually transmitted diseases, and infections caused by Helicobacter pylori and Mycobacterium avium complex.
Key words- *Resistance, Chemistry*

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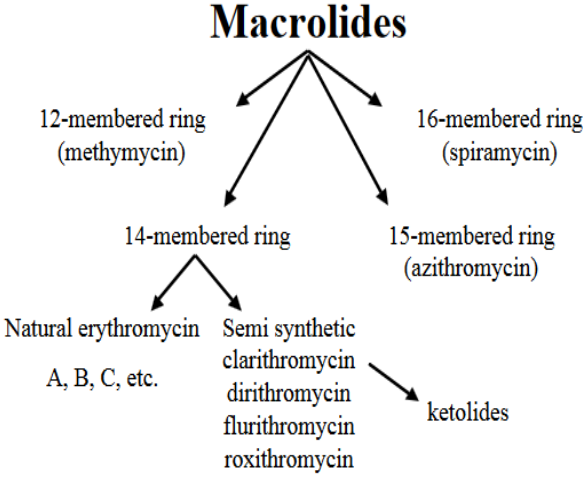
INTRODUCTION:

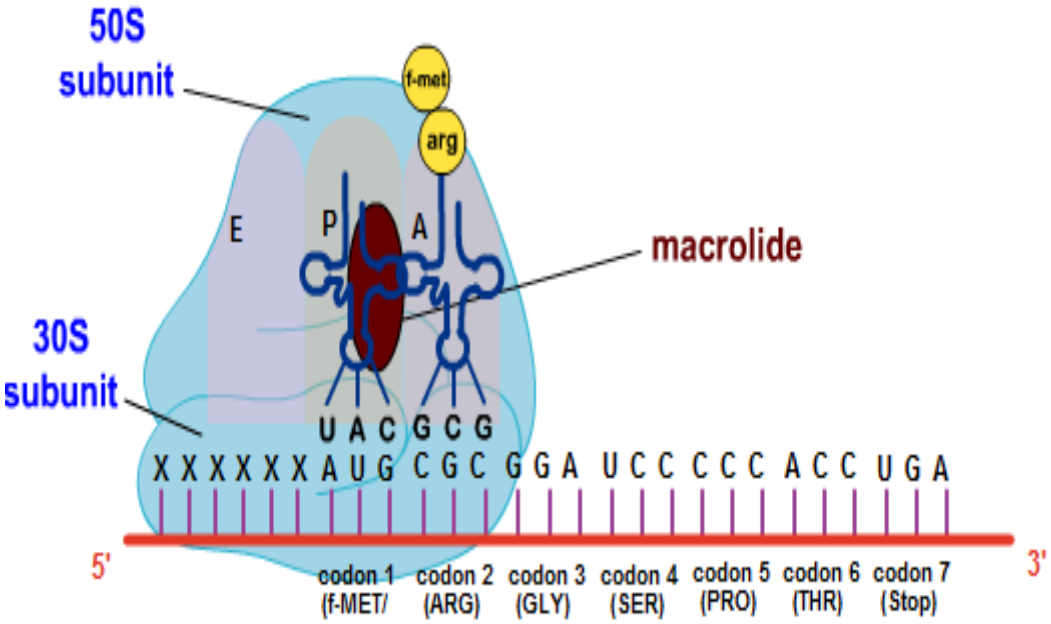
Macrolide antibiotics have a durable history of successful development, effectiveness, and safety since their discovery in 1952. Macrolides range from the prototypical erythromycin with a 14-membered lactone ring to members containing 15-(azithromycin) and 16-membered lactone rings to novel semisynthetic macrolide products such as azithromycin, an engineered ketolide derived from the founding erythromycin structure. The macrolides are bacteriostatic antibiotics with a broad spectrum of activity against many gram-positive bacteria. Currently available macrolides are well tolerated, orally available and widely used to treat mild-to-moderate infections. [1,2]

Erythromycin was initially isolated in 1952 from Streptomyces erythreus; the other macrolide antibiotics are semisynthetic derivatives. The five macrolide antibiotics have a similar range of activities, being bacteriostatic against many strains of streptococci, staphylococci, clostridia, corynebacteria, listeria, haemophilus sp., moxicella, and Neisseria meningitidis. Clarithromycin and azithromycin are more active than erythromycin against several gram-negative bacteria as well as Mycoplasma pneumonia, Helicobacter pylori, Toxoplasma gondii, cryptosporidia and several atypical mycobacteria. Fidaxomicin is not absorbed orally and is used in ten-day oral courses to treat Clostridium difficile associated diarrhea. Macrolide antibiotics act by inhibiting protein synthesis of bacteria by binding to the 50S ribosomal element. Resistance occurs by several mechanisms. [3,4]



MECHANISM OF ACTION

The macrolides are bacteriostatic antimicrobials. They reversibly bind to domain V of 23S ribosomal RNA (rRNA) of the 50s subunit of the bacterial ribosome inhibiting RNA-dependent protein synthesis



RESISTANCE

Macrolide resistance in streptococci arises from either an alteration of the drug binding site on the ribosome by methylation (MLSB resistance) or by active drug efflux. The efflux mechanism is mediated by the macrolide efflux (mef) genes and is specific for 14- and 15-membered macrolides.3 Macrolide resistance is usually low level (minimum inhibitory concentrations [MICs] 1–32 mg/L), and in vitro susceptibility to ketolides, lincosamides, and streptogramins is maintained.9 Methylation of an adenine residue in domain V of the 23S rRNA, mediated by the erythromycin ribosome methylase (erm) genes, prevents binding of the macrolides and ketolides to domain V and results in high level macrolide resistance (MIC _64 mg/L). Ketolides presumably maintain their antimicrobial activity by virtue of their ability to bind to an alternative site—domain II of the 23S rRNA. Methylase may be either induced or constitutively expressed, and resistance to erythromycin implies cross-resistance to clarithromycin and azithromycin. Clarithromycin

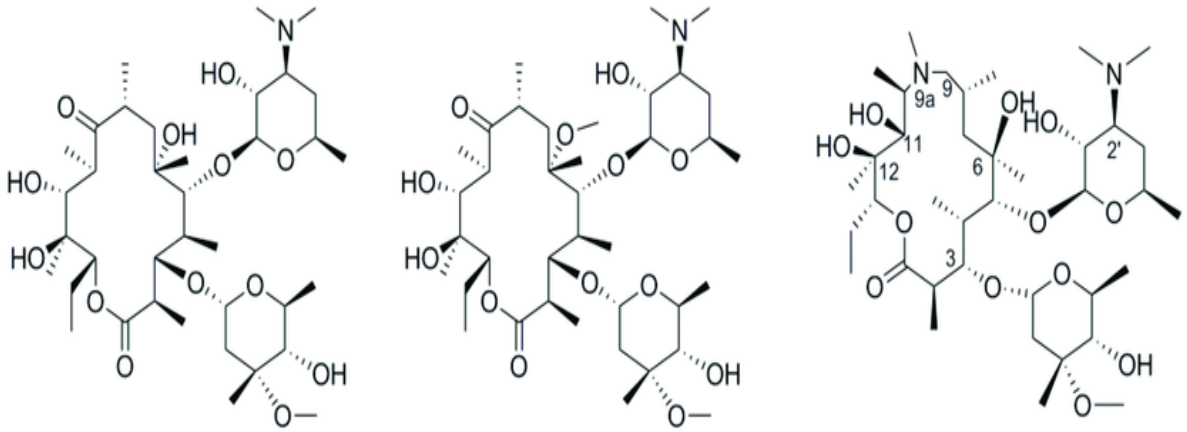
and azithromycin can induce methylase production but telithromycin does not. Decreased susceptibility to telithromycin in streptococci has been associated with a variety of mutations in the erm(B) gene and its promoter region, ribosomal proteins L4 and L22, and in the 23S rRNA. [5,6,7]

CHEMISTRY

Erythromycin's structure consists of a macrocyclic 14-membered lactone ring attached to twosugarmoieties (a neutral sugar, cladinose, andanaminosugar, desosamine). In the acidic environment of the stomach, it is rapidly degraded to the 8,9-anhydro-6,9-hemiketal and then to the 6,9,9,12-spiroketal form. The hemiketal intermediate may be responsible for the gastrointestinal adverse effects associated with erythromycin.

Clarithromycin (6-O-methylerythromycin) is synthesized by substituting a methoxy group for the C-6 hydroxyl group of erythromycin. This substitution creates a more acid-stable antimicrobial and prevents the degradation of the erythromycin base to the hemiketal intermediate, which results in improved oral bioavailability and reduced gastrointestinal intolerance.2 Clarithromycin is available as immediate-release tablets (250 or 500 mg), extended release tablets (500 mg), and granules for oral suspension (125 or 250 mg/5 mL).

Azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is formed by inserting a methyl-substituted nitrogen in place of the carbonyl group at the 9a position of the aglycone ring. The resulting dibasic 15-membered ring macrolide derivative is more appropriately referred to as an azalide. This change produces a compound that is more acid stable and has a longer serum half-life (t1/2), increased tissue penetration, and greater activity against gram negative organisms compared with erythromycin.2 Azithromycin is available as 250-, 500- or 600-mg immediate release tablets, 2-g microsphere extended-release powder, oral suspension.[6,7,8]



PHARMACOKINETICS

The pharmacokinetic properties of macrolide antibiotics differ based on their chemical structure. In low pH environments, such as in the stomach, erythromycin is degraded. The 8,9-anhydro-6,9-hemiketal intermediate is inactive as an antibiotic but may cause the gastrointestinal adverse effects that have been associated with erythromycin. This intermediate is then further metabolized into the inactive anhydroerythromycin, erythromycin-6,9;9,12-spiroketal . Clarithromycin is more acid-stable than erythromycin and is not degraded as extensively in the stomach. Azithromycin is even more stable at low pH, resulting in a longer serum half-life and increased concentrations in tissues compared to erythromycin. As a result of their better stability at low pH, azithromycin has an oral bioavailability of 37% and clarithromycin has an oral bioavailability of 55%, compared to an oral bioavailability of 25% for erythromycin . Peak serum concentrations of azithromycin and clarithromycin are lower than for erythromycin of the same dose.[9,10]

Macrolide absorption in the intestine is thought to be limited by P-glycoprotein (ABCB1) efflux transporters, which are encoded by the ABCB1 gene. ABCB1 is also believed to mediate excretion of macrolides into the bile. Because ABCB1 is involved in the transport of many other drugs, erythromycin and clarithromycin participate in drug-drug interactions [6]. One example is that erythromycin and clarithromycin have been found to increase the uptake and concentrations of pravastatin and simvastatin by inhibiting their efflux through ABCB1 [6]. As discussed later,

macrolide inhibition of CYP3A4 may also decrease statin metabolism and increase concentrations.[11]

Macrolides are lipophilic and are widely distributed in blood and tissues [5, 10]. Once in the bloodstream, macrolides preferentially bind alpha-1-acid glycoprotein (AGP) (encoded by the gene ORM1), the binding protein found in the highest concentration after albumin [10]. Erythromycin is 70–80% bound to AGP in the plasma [10]. However, azithromycin is 93% unbound in the plasma, but only 16% unbound in liver tissue [12].

Macrolides concentrate in phagocytes, which then transport the drug to the site of infection [7]. Concentrations in phagocytes of clarithromycin and azithromycin are 400 times and 800 times that of what is found in the serum, respectively [5]. Macrolide concentrations in tissues are 50 times that of what is found in the plasma, and macrolides partition especially into the spleen, liver, lungs, and kidneys [13]. Macrolides are found in the peritoneal fluids and breast milk, but do not partition greatly into the cerebrospinal fluid, where they are found at only 2–13% that of plasma concentrations.

Erythromycin and clarithromycin are substrates of SLCO1B1 and SLCO1B3 for uptake into the hepatocytes [6]. Erythromycin undergoes extensive metabolism by CYP3A4 in the liver, with 80% inactivated through demethylation before ~60% is excreted in the bile and ~40% in the urine [5]. The major metabolite is N-desmethylerythromycin. Clarithromycin is also thought to be metabolized by CYP3A4 in the liver into the inactive metabolite N-desmethylclarithromycin and the active metabolite 14-(R)-hydroxyclarithromycin [5]. Clarithromycin and erythromycin are thought to inhibit CYP3A4 by forming inactive complexes with CYP3A4 through their nitrosoalkane metabolites [14, 15]. Due to its inhibition of CYP3A4 and ABCB1, erythromycin has been shown to result in a sixfold increase in the AUC of simvastatin, which is metabolized by CYP3A4. Additionally, rhabdomyolosis is associated with the concomitant use of erythromycin and lovastatin, presumably due to increased concentrations of lovastatin due to reduced metabolism and reduced efflux [14].

In contrast to erythromycin and clarithromycin, azithromycin does not seem to interact with SLCO1B1 or SLCO1B3 [6]. Azithromycin has been shown to be a weak substrate for CYP3A4, to be minimally metabolized by the enzyme, and to neither induce nor inhibit CYP3A4 activity [16]. Only about 6% of azithromycin is recovered in the urine, with most being excreted unchanged in the bile, through both MRP2 (encoded by the gene ABCC2) and ABCB1 [5, 12]. MRP2 is thought to play a smaller role in excretion of azithromycin into the bile than does ABCB1

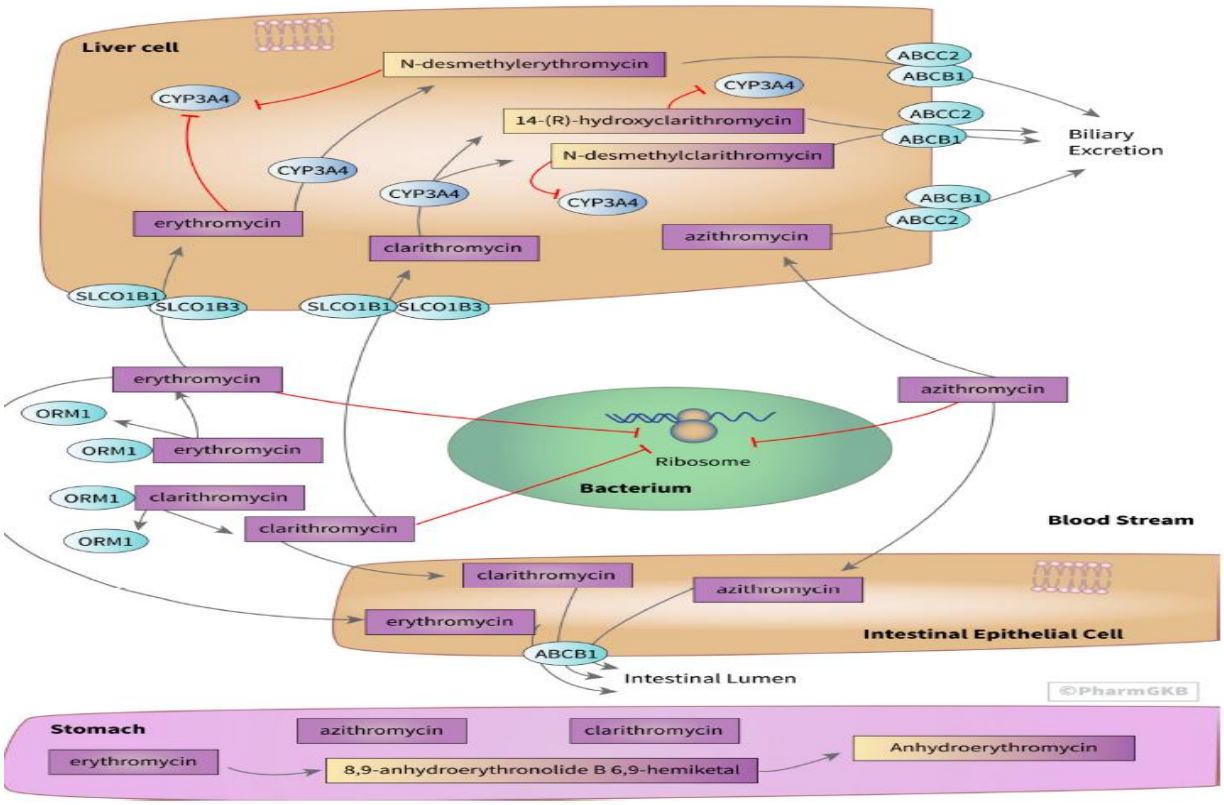


Fig 1 Transport, metabolism and mechanism of action of the macrolide antibiotics erythromycin, clarithromycin, and azithromycin

PHARMACODYNAMICS

Macrolides stop bacterial growth by inhibiting protein synthesis [17]. Through reversibly binding to the 50S subunit of the 70S bacterial ribosomes, macrolides block further translation of proteins [17]. As a result, macrolides are effective against actively dividing organisms. Depending on the organism and the drug concentration, macrolides may be bacteriostatic, stopping bacterial growth, or bactericidal, killing the bacteria [18]. Efficacy of the drug is optimized according to the percentage of time of a dosing interval that is spent with concentrations above the minimum inhibitory concentration [13]. This mechanism of action creates a low barrier for bacteria developing resistance to the drugs if ribosomal structure or the affinity of the macrolide change, or if efflux of the drug increases through modification of the bacterial macrolide efflux (mef) genes [2, 7]. A summary of the mechanisms through which macrolides can cause resistance can be found in Zuckerman, et al. 2011 [2]. In 2001, rates of resistance to erythromycin were 16.3% in Canada and 31.5% in the United States [5].

Though rare, macrolide treatment can cause liver injury, resulting in the inability to secrete bile and in inflammation [14]. The risk factors for whether this reaction will occur are not known, but the mechanism may be through an immunological reaction such as concomitant infection of the liver, through the production of hepatotoxic metabolites, or through the induction of cell signaling pathways leading to hepatocyte death [19]. Hepatotoxicity is seen much more rarely in patients taking azithromycin than in patients taking erythromycin [14]. Clarithromycin has better activity against gram positive bacteria compared to azithromycin, and azithromycin has better activity against gram negative bacteria compared to clarithromycin. Because of the low permeability of the cell walls of gram-negative bacteria, the greater stability and tissue concentrations of azithromycin is thought to improve its ability to penetrate gram negative bacteria and to stop bacterial gene translation and growth [2]. Both of these newer macrolides are better against both gram negative and gram-positive bacteria than erythromycin is, and cause fewer side effects [2].

CLINICAL USE

Clarithromycin, azithromycin, and telithromycin are effective against the most frequently isolated bacterial causes of pharyngitis, otitis media, and sinusitis. A 5- day course of the extended-release formulation of clarithromycin, azithromycin, or telithromycin is equally as effective as a 10-day course of penicillin for the treatment of streptococcal pharyngitis.For the treatment of acute sinusitis, clarithromycin had equivalent efficacy compared with cefuroxime axetil, levofloxacin, or ciprofloxacin.

Various trials have demonstrated the efficacy of clarithromycin, azithromycin, and telithromycin for treatment of lower respiratory tract infections, including acute bronchitis, acute exacerbation of chronic bronchitis (AECB), and community-acquired pneumonia. Most studies involved patients who were not hospitalized. Studies have shown equal efficacy of clarithromycin compared with ceftibuten, cefaclor, cefuroxime axetil, and cefixime for the treatment of lower respiratory tract infections.

Azithromycin and clarithromycin have been shown to be effective in the treatment of community-acquired pneumonia in patients who require hospitalization. Monotherapy with intravenous azithromycin was equally effective as a respiratory fluoroquinolone or a b-lactam plus macrolide regimen for patients hospitalized with community-acquired pneumonia.

Antibiotic therapy for H pylori–associated peptic ulcer disease decreases ulcer recurrence and promotes healing. Triple-therapy regimens that consist of clarithromycin, amoxicillin, or metronidazole and an antisecretory agent for 7 to 14 days are preferable for the treatment of H pylori infections. [18,19]

ADVERSE EFFECTS

Gastrointestinal intolerance is the primary adverse side effect of the newer macrolides but they occur at a significantly reduced rate when compared with erythromycin. The most common adverse effects reported with azithromycin were diarrhea (3.6%), nausea (2.6%), abdominal pain (2.5%), and headache or dizziness (1.3%). Laboratory abnormalities were infrequent and minor, including transient increases in transaminases in 1.5% of patients. Only 0.7% of patients discontinued azithromycin therapy compared with 2.6% of patients who receive comparative medications. [20,22]

Gastrointestinal adverse effects (primarily diarrhea) occurred in 17% of patients treated with the 2-g extended-release microsphere formulation of azithromycin. Adverse events related to the intravenous infusion of azithromycin were pain at the injection site (6.5%) and local inflammation (3.1%).The most common adverse reactions reported with clarithromycin were similar (eg, nausea, 3.8%; diarrhea, 3.0%; abdominal pain, 1.9%; and headache, 1.7%).

There was no difference in the spectrum and frequency of adverse reactions between the extended-release or immediate-release formulations of clarithromycin. Gastrointestinal adverse events with the extended-release formulation tended to be

less severe and resulted in fewer discontinuations of the medication. Laboratory abnormalities were also rare and included abnormal liver function test results and decreased white blood cell counts. Overall, less than 3% of patients receiving clarithromycin withdrew from studies because of adverse effects. Clarithromycin has been associated with teratogenic effects in animal studies and should not be used in pregnant patients.[22]

DRUG INTERACTIONS

Several reviews have discussed drug interactions between either clarithromycin or azithromycin and other agents.Clarithromycin, like erythromycin, is oxidized by the cytochrome P450 system, primarily the CYP3A4 subclass of hepatic enzymes. This converts clarithromycin to a nitrosalkalane metabolite that forms an inactive metabolite/enzyme complex by binding to the iron of the CYP3A4 enzyme. This interaction inhibits the CYP3A4 enzymes and results in decreased clearance of other agents given concurrently that are metabolized by the same enzyme system. Clarithromycin is a less potent inhibitor of the CYP 3A4 enzymes than erythromycin and azithromycin interferes poorly with this system. Appropriate dose reductions and clinical and therapeutic drug level monitoring are necessary when drugs metabolized by the CYP3A enzymes are given concurrently with clarithromycin. The concurrent use of cisapride, pimozide, terfenadine, and aztemizole with clarithromycin is contraindicated because of the possible cardiotoxic effects of these agents and the occurrence of torsades de pointes. The concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated because of the risk of acute ergot toxicity. Other medications such as benzodiazepines (eg, triazolam, midazolam, alprazolam), HMG-CoA reductase inhibitors (eg, lovastatin, simvastatin, atorvastatin), class 1A antiarrhythmic agents (eg, quinidine, disopyramide), theophylline, carbamazepine, warfarin, sildenafil, colchicine, and cyclosporine should be used cautiously when given with clarithromycin.19 These drug-drug interactions are less likely to occur with azithromycin, because it is not a potent inhibitor of the CYP3A enzymes. There are case reports of toxicity related to coadministration of azithromycin and lovastatin, warfarin, cyclosporine, disopyramide and theophylline, however, Clarithromycin and azithromycin have been associated with digoxin toxicity presumably due to inhibition of intestinal and renal P-glycoproteins. [22,23]

CONCLUSION:

The advanced macrolides (azithromycin and clarithromycin) are structural analogs of erythromycin that have similar mechanisms of action. These antimicrobials have several distinct advantages over erythromycin, including improved oral bioavailability, longer half-life (allowing once- or twice-daily administration), higher tissue concentrations, enhanced antimicrobial activity, and reduced gastrointestinal adverse effects. Clarithromycin and azithromycin have been used extensively for the treatment of upper and lower respiratory tract infections. Erythromycin, interacts with more proteins than azithromycin, whose structure results in different transport and metabolism of the drug. As a result, azithromycin exhibits a lower number of interactions with proteins and has increased activity against gram negative bacteria as a result of higher tissue concentrations. Clarithromycin, also a newer macrolide with better performance than erythromycin, may have improved activity against some strains of bacteria compared to azithromycin.

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