



## ERYTHROMYCIN USE AS BROAD SPECTRUM ANTI BIOTIC

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### **ABSTRACT**

Erythromycin is an antibiotic useful for the treatment of a number of bacterial infections. This includes respiratory tract infections, skin infections, chlamydia infections, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the newborn. Erythromycin may be used to improve delayed stomach emptying. It can be given intravenously and by mouth. An eye ointment is routinely recommended after delivery to prevent eye infections in the newborn. Erythromycin displays bacteriostatic activity or inhibits growth of bacteria, especially at higher concentration but the mechanism is not fully understood. By binding to the 50s subunit of the bacterial rRNA complex, protein synthesis and subsequent structure and function processes critical for life or replication are inhibited. Erythromycin is very rapidly absorbed, and diffuses into most tissues and phagocytes. Usual dosage range: -Oral: -Base: 250-500 mg every 6-12 hours. Erythromycin estolate has been associated with reversible hepatotoxicity in pregnant women in the form of elevated serum glutamic-oxalo acetic transaminase and is not recommended during pregnancy. Some evidence suggests similar hepatotoxicity in other populations. Erythromycin may affect neuromuscular transmission by acting presynaptically, so may produce or worsen symptoms of myasthenia gravis in patients with pre-existing postsynaptic defects. Exacerbations of myasthenia gravis have also been reported with the use of telithromycin and azithromycin.

**KEYWORDS:** chlamydia infections, syphilis, myasthenia gravis.

### **INTRODUCTION & HISTORY**

Erythromycin is an antibiotic useful for the treatment of a number of bacterial infections.<sup>[1]</sup> This includes respiratory tract infections, skin infections, chlamydia infections, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the newborn.<sup>[2]</sup> Erythromycin may be used to improve delayed stomach emptying.<sup>[3]</sup> It can be given intravenously and by mouth.<sup>[2]</sup> An eye ointment is routinely recommended after delivery to prevent eye infections in the newborn.<sup>[4]</sup>

Common side effects include abdominal cramps, vomiting, and diarrhea. More serious side effects may include *Clostridium difficile* colitis, liver problems, prolonged QT, and allergic reactions. It is generally safe in those who are allergic to penicillin.<sup>[2]</sup> Erythromycin also appears to be safe to use during pregnancy.<sup>[1]</sup> While generally regarded as safe during breastfeeding its use by the mother during the first two weeks of life may increase the risk of pyloric stenosis in the baby.<sup>[5][6]</sup> This risk also applies if taken directly by the baby during this age.<sup>[7]</sup> It is in

the macrolide family and works by decreasing the making of protein by bacteria.<sup>[2]</sup>

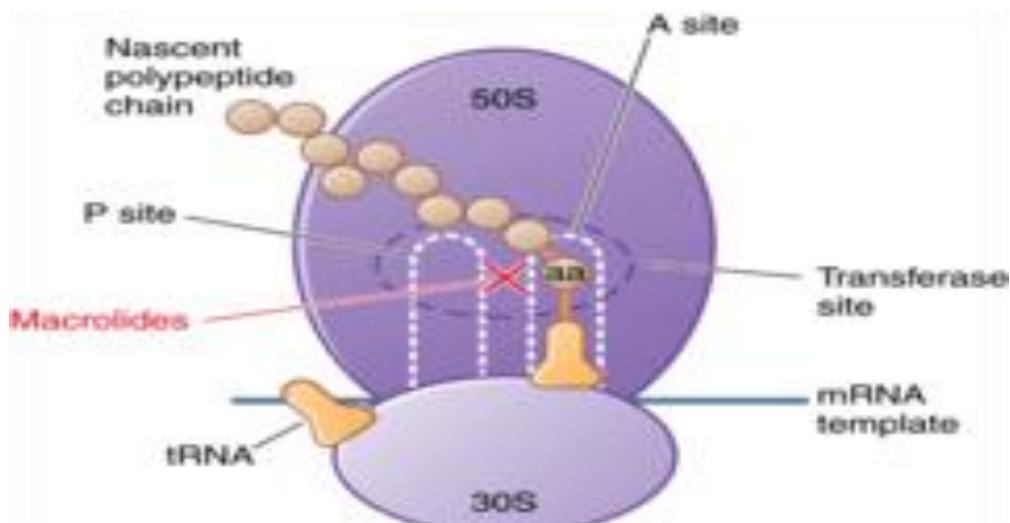
Erythromycin was first isolated in 1952 from the bacteria *Saccharopolyspora erythraea*.<sup>[2][8]</sup> It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.<sup>[9]</sup> It is available as a generic medication and is not very expensive.<sup>[5]</sup> The wholesale price in the developing world is between 0.03 and 0.06 USD per tablet.<sup>[10]</sup>

**Erythromycin:** Class: Antibiotic. Indications: Treatment of susceptible bacterial infections including *S. pyogenes*, some *S. pneumoniae*, some *S. aureus*, *M. pneumoniae*, *Legionella pneumophila*, diphtheria, pertussis, Chlamydia, erythrasma, *N. gonorrhoeae*, *E. histolytica*, syphilis and nongonococcal urethritis, and *Campylobacter* gastroenteritis; used in conjunction with neomycin for decontaminating the bowel.

## MECHANISM OF ACTION

Erythromycin displays bacteriostatic activity or inhibits growth of bacteria, especially at higher concentrations,<sup>[25]</sup> but the mechanism is not fully understood. By binding to the 50s subunit of the bacterial rRNA complex, protein synthesis and subsequent structure and function processes critical for life or replication are inhibited.<sup>[25]</sup> Erythromycin

interferes with aminoacyl translocation, preventing the transfer of the tRNA bound at the A site of the rRNA complex to the P site of the rRNA complex. Without this translocation, the A site remains occupied, thus the addition of an incoming tRNA and its attached amino acid to the nascent polypeptide chain is inhibited. This interferes with the production of functionally useful proteins, which is the basis of this antimicrobial action.



## Pharmacokinetics

Erythromycin is easily inactivated by gastric acid; therefore, all orally administered formulations are given as either enteric-coated or more-stable salts or esters, such as erythromycin ethylsuccinate. Erythromycin is very rapidly absorbed, and diffuses into most tissues and phagocytes. Due to the high concentration in phagocytes, erythromycin is actively transported to the site of infection, where, during active phagocytosis, large concentrations of erythromycin are released.

## Metabolism

Most of erythromycin is metabolised by demethylation in the liver by the hepatic enzyme CYP3A4. Its main elimination route is in the bile with little renal excretion, 2%-15% unchanged drug. Erythromycin's elimination half-life ranges between 1.5 and 2.0 hours and is between 5 and 6 hours in patients with end-stage renal disease. Erythromycin levels peak in the serum 4 hours after dosing; ethylsuccinate peaks 0.5-2.5 hours after dosing, but can be delayed if digested with food.<sup>[26]</sup>

Erythromycin crosses the placenta and enters breast milk. The American Association of Pediatrics determined erythromycin is safe to take while breastfeeding.<sup>[27]</sup> Absorption in pregnant patients has been shown to be variable, frequently resulting in levels lower than in nonpregnant patients.<sup>[26]</sup>

## Frequency, dosage & route of administration

Available dosage form in the hospital: 0.3% EYE OINTMENT, 0.5% EYE OINTMENT, 200MG/5 ML

SUSP, 400MG TAB, 500MG TAB, 250MG TAB(ethyl succinate), 2% LOTION, 2% OINTMENT.

Trade Names: Dosage: - maximum: 4 g daily - Ethylsuccinate: 400-800 mg every 6-12 hours; maximum: 4 g daily -I.V.: Lactobionate: 15-20 mg/kg/day divided every 6 hours or 500 mg to 1 g every 6 hours, or given as a continuous infusion over 24 hours; maximum: 4 g daily -Indication-specific dosing: - Bartonella spp infections (bacillary angiomatosis [BA], peliosis hepatitis [PH]) (unlabeled use): Oral: 500 mg (base) 4 times daily for 3 months (BA) or 4 months (PH) (Koehler, 1992; Rolain, 2004; Stevens, 2005; Tappero, 1993) -Chancroid (unlabeled use): Oral: 500 mg (base) 3 times daily for 7 days; Note: Not a preferred agent; isolates with intermediate resistance have been documented (CDC, 2010) -Gastroparesis (unlabeled use): -I.V.: 3 mg/kg administered over 45 minutes every 8 hours (Camilleri, 2013) -Oral: Patients refractory/intolerant to other prokinetic agents (eg, metoclopramide, domperidone): 250-500 mg (base) 3 times daily before meals. Limit duration of therapy, tachyphylaxis may occur after 4 weeks (Camilleri, 2013). -Granuloma inguinale (donovanosis) (unlabeled use): Oral: 500 mg (base) 4 times daily for 21 days (CDC, 2010) -Legionnaires' disease: Oral: 1.6-4 g (ethylsuccinate) daily or 1-4 g (base) daily in divided doses for 21 days. Note: No longer preferred therapy and only used in nonhospitalized patients. - Lymphogranuloma venereum: Oral: 500 mg (base) 4 times daily for 21 days; Note: Preferred therapy for pregnant or lactating women (CDC, 2010) - Nongonococcal urethritis (including coinfection with C.

trachomatis): Oral: 500 mg (base) 4 times daily for 7 days or 800 mg (ethylsuccinate) 4 times daily for 7 days. Note: May use 250 mg (base) or 400 mg (ethylsuccinate) 4 times daily for 14 days if gastrointestinal intolerance. - Pertussis: Oral: 500 mg (base) every 6 hours for 14 days -Preop bowel preparation: Oral: 1 g erythromycin base at 1, 2, and 11 PM on the day before surgery combined with mechanical cleansing of the large intestine and oral neomycin.

### **Adverse Effects**

Gastrointestinal disturbances, such as diarrhea, nausea, abdominal pain, and vomiting, are very common because erythromycin is a motilin agonist.<sup>[14]</sup> Because of this, erythromycin tends not to be prescribed as a first-line drug. It may be useful in treating gastro paresis due to this promotility effect. Intravenous erythromycin may also be used in endoscopy as an adjunct to clear gastric contents.

More serious side effects include arrhythmia with prolonged QT intervals including *torsades de pointes*, and reversible deafness. Allergic reactions range from urticaria to anaphylaxis. Cholestasis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are some other rare side effects that may occur.

Studies have shown evidence both for and against the association of pyloric stenosis and exposure to erythromycin prenatally and postnatally.<sup>[15][16]</sup> Exposure to erythromycin (especially long courses at antimicrobial doses, and also through breastfeeding) has been linked to an increased probability of pyloric stenosis in young infants.<sup>[17][18]</sup> Erythromycin used for feeding intolerance in young infants has not been associated with hypertrophic pyloric stenosis.<sup>[17]</sup>

Erythromycin estolate has been associated with reversible hepatotoxicity in pregnant women in the form of elevated serum glutamic-oxaloacetic transaminase and is not recommended during pregnancy. Some evidence suggests similar hepatotoxicity in other populations.<sup>[19]</sup>

It can also affect the central nervous system, causing psychotic reactions, nightmares and night sweats.<sup>[20]</sup> It may also alter the effectiveness of combined oral contraceptive pills because of its effect on the gut flora. Erythromycin is an inhibitor of the cytochrome P450 system, which means it can have a rapid effect on levels of other drugs metabolised by this system, e.g., warfarin.

### **Drug Interactions**

Erythromycin is metabolized by enzymes of the cytochrome P450 system, in particular, by isozymes of the CYP3A superfamily, CYP3A.<sup>[21]</sup> The activity of the CYP3A enzymes can be induced or inhibited by certain drugs (e.g. dexamethasone) which can cause it to affect the metabolism of many different drugs, e.g. erythromycin. If other CYP3A substrates — drugs that are broken down by CYP3A — such as simvastatin

(Zocor), lovastatin (Mevacor), or atorvastatin (Lipitor) — are taken concomitantly with erythromycin, levels of the substrates increase, often causing adverse effects. A noted drug interaction involves erythromycin and simvastatin, resulting in increased simvastatin levels and the potential for rhabdomyolysis. Another group of CYP3A4 substrates are drugs used for migraine such as ergotamine and dihydroergotamine; their adverse effects may be more pronounced if erythromycin is associated.<sup>[20]</sup> Earlier case reports on sudden death prompted a study on a large cohort that confirmed a link between erythromycin, ventricular tachycardia, and sudden cardiac death in patients also taking drugs that prolong the metabolism of erythromycin (like verapamil or diltiazem) by interfering with CYP3A4.<sup>[22]</sup> Hence, erythromycin should not be administered to people using these drugs, or drugs that also prolong the QT interval. Other examples include terfenadine (Seldane, Seldane-D), astemizole (Hismanal), cisapride (Propulsid, withdrawn in many countries for prolonging the QT time) and pimozide (Orap). Theophylline, which is used mostly in asthma, is also contraindicated.

Erythromycin may affect neuromuscular transmission by acting presynaptically, so may produce or worsen symptoms of myasthenia gravis in patients with pre-existing postsynaptic defects. Exacerbations of myasthenia gravis have also been reported with the use of telithromycin and azithromycin.<sup>[23]</sup>

Erythromycin and doxycycline can have a synergistic effect when combined and kill bacteria (*E. coli*) with a higher potency than the sum of the two drugs together. This synergistic relationship is only temporary. After approximately 72 hours, the relationship shifts to become antagonistic, whereby a 50/50 combination of the two drugs kills less bacteria than if the two drugs were administered separately.<sup>[28]</sup>

**Renal Impairment:** Slightly dialyzable (5% to 20%); supplemental dose is not necessary in hemo- or peritoneal dialysis or in continuous arteriovenous or venovenous hemofiltration. Common side effect: QTc prolongation, torsade de pointes, pruritus, rash, Abdominal pain, anorexia, diarrhea, infantile hypertrophic pyloric stenosis, nausea, vomiting, Cholestatic jaundice (most common with estolate), hepatitis Pregnancy Risk Factor: B.

### **CONCLUSION**

Erythromycin appears to be equally effective when given orally (as ethylsuccinate or estolate) or intravenously (as lactobionate). Significantly, no serious adverse effects have been reported in studies in which erythromycin has been used for its prokinetic effects, although fatal reactions have followed the intravenous administration of erythromycin to neonates in antibiotic doses.

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