Journal of Otolaryngology and Rhinology Research
Received 04 Sep 2023 | Revised 09 Sep 2023 | Accepted 15 Sep 2023 | Published Online 20 Sep 2023

DOI: https://doi.org/10.52845/JORR/2023/4.3.7

JORR 04 (03), 162–171 (2023)

ISSN (O) 2693-9282

REVIEW-ARTICLE

Common Drug Interactions in ENT: A Review of Antibiotics in Sinusitis

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Abstract

Introduction: Present day medical treatment often involves a polytherapeutic approach whereby patients receive several medications from multiple physicians, thereby risking adverse drug interactions. Checking for possible drug interactions in a busy clinical setting poses a challenge due to the time pressures of modern medical practice. Otolaryngologists and rhinology sub-specialists receive very little education in drug interactions, and easy to use reference materials are not readily available in most ENT offices. In this manuscript, we review potential drug interactions for one of the most commonly prescribed classes of medication that ENT specialists prescribe, antibiotics. We provide a practical reference for general otolaryngologists and rhinologists to utilize in their busy modern day clinical practices.

Methods/Results: Drug interactions for commonly prescribed antibiotics in ENT/rhinology practice were identified using PubMed and Cochrane Library database to search for articles published from inception until December 31, 2022. Full-text articles were reviewed to identify drug combinations that present risk and to identify specific management recommendations to reduce potential harm.

Discussion: Numerous drug-drug interactions exist between antibiotics and other commonly prescribed medications. These interactions can potentially lead to the development of toxic levels of a drug and harm. We provide an easily accessible summary of these interactions and management considerations that would allow ENTs/rhinologists to screen for these potential sources of harm in their busy clinical practices.

Key words: Drug interactions, sinusitis, antibiotics, ENT, otolaryngology, pharmacy

1 | INTRODUCTION

In present-day healthcare, patients often receive medications from multiple physicians or mid-level providers. This polypharmaceutical approach carries an inherent risk of an adverse interaction between medications. Checking for potential drug interactions in a busy clinical setting poses a challenge due to the time pressures physicians face in modern medical practice.

Otorhinolaryngology (ENT) and its subspecialties are surgical disciplines; teaching focuses primarily on anatomy, operative training, and surgical decision-making. After formal training, general ENTs who care for sinonasal patients and rhinology sub-specialists, who exclusively care for these patients,

are frequently called upon to make medical decisions and prescribe pharmacologic agents. Antibiotics are among the most common classes of medications ENTs prescribe. Checking for drug interactions when prescribing is essential. Unfortunately, rhinologists receive very little education in drug interactions, and easy-to-use reference materials are not readily available in most rhinology offices.

This manuscript reviews potential drug interactions for one of the most common classes of medications ENTs prescribe in sinusitis, antibiotics. Our objective is to provide a practical reference for general ENTs and rhinologists in busy modern-day practice.

2 | METHODS/RESULTS

We identified frequently prescribed medications in ENT/rhinology and potential drug interactions using PubMed and Cochrane Library databases to search for articles published from inception until December 31, 2022. Search terms included: "ENT," "otolaryngology," "prescribing patterns," "drug interactions," "polytherapy," "sinusitis," and "rhinitis." Screening of citations initially consisted of a review of titles and abstracts. Full-text articles were retrieved and reviewed for further eligibility and inclusion in the evaluation, as well as a secondary search of articles cited in reference lists of eligible articles from the primary search. We further focused on identifying commonly used drug combinations that presented a potential risk of adverse effects or reduced effectiveness due to modifications of pharmacokinetic (PK) or pharmacodynamic (PD) properties.

3 | DISCUSSION

Drug interactions are an essential consideration when providing medical care. Being cognizant of all medications a patient takes is critical, as is the risk of prescribing a new drug and recognizing its potential interactions with already prescribed medications.([1],[2]) There are several different types of drug-drug interactions to consider. Antagonistic interactions may reduce the effectiveness of a drug and render it ineffective in treatment or directly block the effect of the drug. Synergistic interactions may potentiate effects; however, their effect could be therapeutically favorable or undesirable, leading to toxicity. Drug effects on hepatic metabolism or renal clearance could also increase or decrease drug levels. Such alterations in drug metabolism could potentiate a therapeutic effect or cause an adverse effect.

In addition to drug-drug interactions, consideration should include interpatient physiologic variability, Age and gender differences in drug metabolism have been identified. Female geriatric patients have lower drug elimination rates, drug interactions that reduce drug clearance may cause problems.[3] Aging is associated with multiple physiologic and pathologic changes.1 The volume of distribution for lipophilic drugs can increase in elderly patients due to higher levels of adipose tissue; however, it can decrease for hydrophilic drugs due to a reduction of body water in such patients. Declining liver function with aging or other disease states can potentially reduce the "first pass" effect of drug metabolism and may lead to increased drug bioavailability. A general reduction in renal clearance in older patients or those with pre-existing kidney disease can also lead to higher or prolonged drug levels.([1],[4]) Older patients are also more likely to participate in polypharmacy with multiple concurrent medications.[1] ENTs and rhinologists should be particularly vigilant in prescribing to this patient population.

Assessing the risks and benefits of interactions may pose a challenge because some mild interactions may be acceptable if the benefit of the medication is highly favorable or if its use is short-term.

Antibiotics are frequently prescribed in ENT and particularly in the sub-specialty of rhinology. Therefore, a working knowledge of potential drug interactions with antibiotics is helpful for practitioners. Herein, we review the typical drug interactions that can occur when antibiotics are prescribed and offer practical management steps for practicing ENTs and rhinologists.

Supplementary information The online version of this article (https://doi.org/10.52845/JORR/2023/4.3.7) contains supplementary material, which is available to authorized users.

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4 | MACROLIDES

Commonly prescribed macrolide antibiotics include erythromycin, clarithromycin (Biaxin®), and azithromycin (Zithromax®). They effectively treat infections caused by several gram-positive cocci, atypical pathogens, and intracellular pathogens.[5] Macrolides can accumulate within white blood cells and achieve high concentrations at the site of infection. Reduction in pro-inflammatory cytokines such as interleukin-1b (IL-1b), IL-6, tumor necrosis factor-a (TNF-a), and IL-8 are immune-modulating effects seen with macrolides.[6],[7] Macrolides have been prescribed and studied widely in chronic sinusitis. Evidence suggests they are beneficial for patients suffering from phenotypes characterized by Th-1 inflammation with neutrophilic disease rather than Th-2 dominant eosinophilic disease.[8],[9],[10],[11] Macrolides have been used after sinus surgery on a long-term basis, specifically in those patients with chronic sinusitis.[12],[13] Several significant drug interactions can occur with macrolide use. One mechanism for interaction involves liver metabolism. The cytochrome P450 pathway via the enzyme CYP3A4 is responsible for the metabolism of erythromycin and clarithromycin.[5] Other medications metabolized by this enzyme, such as warfarin, benzodiazepines, and cyclosporine, will be metabolized or cleared more slowly when used concomitantly with macrolides, potentially resulting in higher drug levels and adverse effects. Macrolides can reduce the elimination of methylprednisolone, and a dose adjustment is recommended.[14] Additionally, "statin" medications potentially interact with macrolides and may lead to acute renal failure with rhabdomyolysis.[15],[16] It is important to note that azithromycin is a weak substrate of this enzyme and therefore has the least risk for interactions.[5]

5 | DOXYCYCLINE

Doxycycline is a derivative of the tetracycline class of antibiotics. Once or twice daily dosing makes it favored over tetracycline. Its antibiotic spectrum broadly covers gram-positive bacteria and some gram-negatives. In addition, it has immunomodulating effects that include reducing matrix metalloproteinase -9 (MMP-9), which has been identified as a contributing factor in chronic inflammation and matrix remodeling.[17] Doxycycline decreases eosinophilic cationic protein (ECP) and suppresses pro-inflammat ory cytokines.[18] It is well-absorbed through the gastrointestinal (GI) tract and penetrates sinus mucosa well.[19],[20]

Doxycycline has relatively few drug interactions, the classic is binding to divalent or trivalent cations when taken orally. This binding may lead to a reduction in doxycycline's effectiveness. Substances that contain calcium, magnesium, aluminum, or iron are relevant; therefore, it is necessary to counsel patients to avoid dairy products and antacids. Phenytoin, carbamazepine, and barbiturates may increase the metabolism of doxycycline, which leads to less drug availability and a reduction in effectiveness. Accordingly, a higher dose of doxycycline may be needed. Co-administration with warfarin can potentiate the anticoagulant effect, leading to an increased risk of bleeding and needing closer INR monitoring.[5]

5.1 | Trimethoprim-Sulfamethoxazole (Bactrim®)

Trimethoprim-Sulfamethoxazole is a broad-spectrum combination antibiotic commonly used in ENT/rhinology practice. It is useful for its activity against respiratory pathogens such as Streptococcus pneumonia, Haemophilus influenzae, and Moraxella catarrhalis. Trimethoprim-Sulfamethoxazole can also treat recalcitrant expressions of chronic sinusitis due to Staphylococcus aureus and methicillin-resistant Staphylococcus aureus. The mechanism of action is achieved by sequentially blocking enzymes in the biochemical pathway responsible for tetrahydrofolic acid production, which is necessary for bacterial DNA synthesis. Sulfamethoxazole, a sulfonamide, inhibits dihydrofolic acid production from its precursors. Trimethoprim competitively inhibits dihydrofolate reductase, thereby reducing the conversion of dihydrofolic acid to folic acid.

The combination is well absorbed orally through the GI tract and is distributed widely through tissue in the body, including the respiratory tract and cerebrospinal fluid. The liver partially metabolizes it, and the majority is excreted unchanged in the urine.

Trimethoprim-Sulfamethoxazole has multiple potential adverse effects, including nausea, vomiting, anorexia, and diarrhea in 4-8% of patients, and cutaneous reactions occur in 3-4% of patients most commonly manifested by rash, urticaria, or diffuse erythema.[21] Rare significant reactions such as Stevens-Johnson and toxic epidermal necrolysis have occurred.[22] Hyperkalemia and hypoglycemia can manifest in older patients and patients taking higher doses. Sulfonamides are also associated with hematologic adverse effects such as anemia, granulocytopenia, and thrombocytopenia on rare occasions.

Adverse drug effects of trimethoprim-sulfamethoxazole occur more frequently in HIV patients, so increased awareness and caution in this patient population is necessary.[22] Additionally, there are reports of small-for-gestational-age offspring in women exposed to the medication in the second and third trimesters. Caution should be exercised in considering this medication for use in pregnant women.[23]

Trimethoprim-Sulfamethoxazole can interact with several different medications through a variety of mechanisms. For example, trimethoprim- sulfamethoxazole decreases potassium excretion in the distal renal tubule. Therefore, a synergistic effect of hyperkalemia can occur when a patient takes this antibiotic with other medications that reduce potassium excretion. Such medications include potassium-sparing diuretics such as spironolactone (Aldactone®) and angiotensin-converting enzyme inhibitors,and angiotensin receptor blockers.[24],[25],[26] The risk of hyperkalemia is greater in patients with impaired renal function, diabetes, older age, or AIDS.[22],[23] Therefore, in diminishing renal function with a creatinine clearance of less than 30ml/min, the half-life of trimethoprim-sulfamethoxazole will be increased. In this patient population, one should reduce the dose of trimethoprim-sulfamethoxazole and monitor serum potassium levels.

Another interaction mechanism involves liver metabolism, specifically the cytochrome P450 enzyme system. The sulfamethoxazole component inhibits the 2C8 isoform of cytochrome P450, and trimethoprim inhibits the 2C9 isoform.[23] Inhibition of two isoforms means more potential drug interactions are possible. Two drugs that merit particular emphasis are oral hypoglycemic agents and warfarin.

Oral hypoglycemic agents primarily include sulfonylureas and meglitinides. Metabolism of these occurs via the cytochrome P450 system. Trimethoprim-Sulfamethoxazole inhibits their metabolism, thereby increasing the plasma levels of sulfonylureas and meglitinides. This leads to an increased release of pancreatic insulin andhypoglycemia.[27],[28] Hypoglycemia risk increases in patients with renal failure. Table 1 includes a list of common hypoglycemic agents and their brand names.

The liver, via the cytochrome P450 enzyme system, also metabolizes warfarin. Trimethoprim-Sulfamethoxazole inhibits its metabolism, leading to elevated blood levels of warfarin and an increased risk of bleeding.[29],[30] Close monitoring of INR is necessary with the concomitant use of warfarin and trimethoprim-sulfamethoxazole.

Trimethoprim-Sulfamethoxazole can interact through mechanisms involving drug transporters. Trimethoprim can inhibit the renal organic cation transporter, and sulfamethoxazole can inhibit the organic anion transporter transport systems that normally facilitate the renal elimination of several drugs.[31],[32] For example, this mechanism is responsible for the clearance of methotrexate. In response to the inhibition of these transporters, increased levels of methotrexate can lead to toxicities, including cytopenia, mucositis, hepatotoxicity, and GI symptoms if trimethoprim-sulfamethoxazole is co-administered. Therefore, co-administration should be avoided if possible.[33]

5.2 | Practical prescribing practices for trimethoprim-sulfamethoxazole include:

• Obtaining serum electrolyte evaluation to monitor potassium level a few days after starting trimethoprim -sulfamethoxazole in patients taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or spironolactone.
• Obtaining an INR (international normalized ratio) within three to four days of initiating trimethoprim-sulfamethoxazole in patients on warfarin.
• Monitoring blood glucose levels for hypoglycemia within a few days of starting trimethoprim-sulfamethoxazole in patients taking oral hypoglycemic agents (e.g., sulfonylureas and meglitinides).
• If possible, avoid prescribing trimethoprim-sulfamethoxazole in patients taking methotrexate and patients with glucose-6-phosphate dehydrogenase deficiency or patients in the first trimester of pregnancy.

5.3 | Fluoroquinolones

Although fluoroquinolones are not the first-line therapy in either acute or chronic sinusitis, they are essential in treating sinusitis. Fluoroquinolones are extremely useful in cases where endoscopically guided cultures reveal gram-negative organisms such as Pseudomonas aeruginosa or where first-line therapy is not tolerated or fails. Fluoroquinolones can also be essential in patients with a beta-lactam allergy. The most commonly prescribed fluoroquinolones in ENT/rhinology include ciprofloxacin, levofloxacin, and moxifloxacin, which present the advantage of oral administration.

Fluoroquinolones exert their bactericidal activity by binding to DNA gyrase and topoisomerase IV. This mechanism prevents the formation and relaxation of supercoiled DNA and fosters double-strand DNA breakage. The bactericidal effect is a concentration-dependent mechanism with peak efficiency seen at levels 10 to 12-fold higher than the MIC for the pathogen.[34] Concentration dependency is critical in dosing and avoiding interactions to achieve the desired effect.

Interactions primarily involve drugs that inhibit fluoroquinolone absorption, such as foods and supplements with multivalent cations, including magnesium, aluminum, iron, and calcium—the concurrent administration of magnesium-aluminum-containing antacids with ciprofloxacin results in almost complete loss of serum bioavailability.[34],[35] Chelation between the cation and fluoroquinolones is responsible for this interaction.[36]

Interactions involving metabolic inhibition of drugs administered concurrently with fluoroquinolones are associated with the cytochrome enzymes of the hepatic microsomal system. Fluoroquinolones inhibit specific cytochrome P450 isozymes responsible for theophylline and caffeine's first-stage oxidative reactions. Fluoroquinolones are estimated to reduce the metabolism of theophylline and caffeine by approximately 25% and can lead to toxicity and side effects such as nausea, vomiting, and CNS excitement.[36] The interactions raise the possibility of fluoroquinolones affecting other drugs dependent on this metabolic pathway. Reported anecdotal cases theorize potential interactions between fluoroquinolones and warfarin causing increased prothrombin time; however, studies have failed to demonstrate clinically significant results.[36] The degree of interaction between quinolones and methylxanthines can vary considerably among individuals. Patients receiving long-term warfarin therapy should be monitored for changes in prothrombin time when starting a fluoroquinolone.[36]

Fluoroquinolones have favorable side effect profiles and are associated with few significant drug interactions beyond multivalent cations. Adverse effects include GI disturbance, risk of tendinitis and rupture, myasthenia gravis exacerbation, and prolonged QT interval.[37] Achilles tendon rupture is of particular concern among patients with renal dysfunction or in combination with drugs that inhibit the renal secretion of quinolones. Fluoroquinolones are also not approved for use in children in the United States.

Using fluoroquinolones for milder rhinosinusitis cases may promote resistance of a broad spectrum of organisms to this class.[34] Responsible prescribing practices for rhinosinusitis involve avoiding fluoroquinolones as a first-line antibiotic in most situations.

5.4 | Clindamycin (Cleocin®)

In rhinology, clindamycin has utility in both acute and chronic sinusitis but is often considered a second-line agent. In acute sinusitis, clindamycin can be used as monotherapy if endoscopically guided cultures demonstrate infection by S pneumoniae. However, when treating empirically, clindamycin does not possess activity against two of the most common pathogens seen in acute rhinosinusitis in adults, H. influenzae, an anaerobic gram-negative bacillus, and M. catarrhalis, a gram-negative diplococcus, necessitating combination with other agents. In chronic sinusitis, typical use is in patients with penicillin allergy or intolerance. It has good activity against common pathogens in chronic sinusitis, such as S. aureus and anaerobes.

As part of the lincosamides family of antibiotics, clindamycin acts by reversibly binding the 50S ribosomal subunit of bacteria, suppressing protein synthesis. Its antimicrobial activity is concentration-dependent, where the dosing strategy should focus on maximizing the intensity of clindamycin exposure.

When taken orally, clindamycin requires being hydrolyzed by the gastrointestinal tract to be absorbed into the circulatory system, resulting in an antibiotic peak within 60 minutes.[38] When taken with food, the absorption of clindamycin is delayed but not decreased.[38],[39] Taking oral clindamycin with water is advised to minimize the risk of pill-induced esophageal ulceration. In the blood, it is bound to protein and metabolized by the hepatic CYP3A4 and 3A5 enzymes. It has significant distribution in the body's tissues but cannot cross the blood-brain barrier.[39] Clindamycin has a half-life of approximately 3 hours in adults before being excreted in the urine primarily and feces.[38] Side effects include gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and pseudomembranous colitis. Uncommon reactions include severe allergic reactions, agranulocytosis, azotemia, and thrombophlebitis.[38] A history of Crohn's disease, ulcerative colitis, or a history of pseudomembranous colitis are contraindications to its use. Patients with severe liver disease should have their liver function tests monitored while taking clindamycin.

Clindamycin presents few clinically significant drug interactions in the setting of an ENT/rhinology practice. However, in patients undergoing sinonasal surgery with general anesthesia, clindamycin should be used cautiously when non-depolarizing agents such as rocuronium are administered because of the potential effect on neuromuscular blockade.

5.5 | Amoxicillin

Amoxicillin is a broad-spectrum antibiotic considered first-line treatment for rhinosinusitis with or without clavulanate.[40] It covers against Streptococcus, H. influenzae, and anaerobes and the combination of amoxicillin-clavulanate provides coverage of S. aureus.

Amoxicillin has relatively few drug interactions; common interactions include warfarin and allopurinol. Amoxicillin may potentiate the effects of warfarin and increase the risk of bleeding. Patients taking warfarin and amoxicillin should have their INR closely monitored. Concomitant administration of amoxicillin with allopurinol increases the risk of severe skin rashes due to both medications having the potential to cause rashes.

5.6 | Cephalosporins

Five generations of cephalosporins are currently marketed, primarily differentiated by structure and spectrum of activity. Cephalosporins are generally perceived to have few drug interactions due to renal elimination; however, a few interactions are of note. Probenecid, used for gout treatment, increases concentrations of most cephalosporins by inhibiting their renal clearance; ceftazidime and ceftriaxone are exceptions.[41] As noted with tetracycline and fluoroquinolones, zinc and divalent cations may decrease the absorption of cephalexin. A pharmacokinetic study by Ding et al. showed a decreased Cmax, AUC, and T>MIC. Notably, reducing a time-dependent PK parameter such as T>MIC, a surrogate marker for efficacy, may result in therapeutic failure.[42]

5.7 | Metronidazole (Flagyl®)

Metronidazole is beneficial in treating anaerobic bacterial and protozoal infections, such as Clostridium difficile and Trichomonas vaginalis.[43] Metronidazole is a synthetic derivative of the compound azomycin, produced by various species of Actinobacteria. A prodrug, metronidazole is inactive until reduced to inhibit microbial DNA synthesis. Primary side effects include peripheral neuropathy, metallic taste, and GI side effects (e.g., diarrhea, nausea, and vomiting).

Metronidazole is not believed to be an inhibitor or inducer of most CYP enzymes and, overall, has few drug-drug interactions. However, there are reports of QTc prolongation, primarily when administered with other medications that prolong the QT interval, such as select antiarrhythmics, antidepressants, and antipsychotics. Another potential drug interaction requiring patient counseling is the consumption of alcoholic beverages (e.g., beer, wine, spirits) or concomitant administration of medications with alcohol content-the potential disulfiram reaction results in severe nausea and vomiting.

5.8 | Medico-Legal Aspects

In modern medical practice, we encounter an aging population with multiple co-morbidities necessitating concurrent treatment with multiple medications; accordingly, drug interactions are occurring more frequently.[44] These drug interactions can be potentially harmful to patients, therefore, it is important to inform patients of potential drug interactions before prescribing a drug.

As ENTs and rhinologists, we make considerable efforts to inform patients about the potential risk of surgery; however, we may not spend a comparable amount of time providing information about the risk of medical treatment, such as antibiotics, although they are considered far less risky, from a legal perspective, the principle of informed consent before treatment extends equally to medical therapy.[1] In that light, it is important to provide information about the risk-to-benefit ratio of medical as well as surgical therapy. Alerting patients to possible symptoms can allow for modification of therapy and reduction in adverse effects. Laboratory monitoring can also be helpful. These actions can improve patient care and help reduce malpractice claims related to drug-drug interactions.

6 | CONCLUSIONS

Modern healthcare practice has shifted towards a multi-disciplinary approach focused on teams of professionals managing their patient care specialty. This includes the primary care physician in the community, the admitting team in the hospital, and consultants in infectious disease, cardiology, pulmonary medicine, and many other medical specialties. This interprofessional collaboration leads to a poly-pharmaceutical approach whereby patients receive several medications from multiple providers-increasing the risk of drug interactions.

Pharmacists can be invaluable in checking for drug interactions; however, modern pharmacy practice has become as fast-paced and task saturated as medicine. The modern-day pharmacist verifies hundreds of prescriptions per day. A setting for a thoughtful review of patients' many medications for drug interactions is no longer available. Technology can address this challenge; however, computer software programs are "clunky" and take time to enter medications to check one against another. ENTs and rhinologists can significantly assist their patients by becoming familiar with the most common potential drug interactions for the most prescribed medications. In this review, we have presented potential drug interactions for one of the most prescribed classes of medication, antibiotics, and we have provided tables as easy-to-use reference materials for ENTs and rhinologists to use to screen for potential drug interactions in their busy practices (See Table 1 and 2).

Table 1: *Potential drug-drug interactions of common antibiotics used in clinical practice*

Antibiotic	Common interactions	Drug-Drug Interaction	Common Adverse Effects	Management
Amoxicillin	Warfarin	Disruption of intestinal flora	Reduces clearance	Reduce warfarin dose, check INR
	Allopurinol	Additive effect	Drug-related skin rash	Monitor
Azithromycin	Ketoconazole	N/A	Increased risk of torsade de pointes	Avoid use if possible; ECG at baseline if use medically necessary
Cephalosporins	Zinc, divalent cations	Binding to multivalent cations	Reduces effectiveness	Avoid divalent cations especially Zinc
	Probenecid	Inhibits renal clearance	Raises cephalosporin blood levels	Use alternate antibiotic
Clarithromycin	Most statins	CYP3A4 inhibition	Acute renal failure, rhabdomyolysis	Avoid vs reduce dose; use azithromycin
	Warfarin	CYP3A4 inhibition	Reduces clearance, increased bleeding risk	Reduce warfarin dose, check INR
	Benzodiazepines	CYP3A4 inhibition	Reduces clearance of some benzodiazepines (e.g., alprazolam)	Reduce benzodiazepine dose; consider lorazepam, or temazepam
	Prednisone	Reduces elimination	Reduced clearance	Reduce prednisone dose
Clindamycin	Non-depolarizing agents (rocuronium)	Increase neuromuscular blockade	Prolonged intraoperative paralysis and reversal	Use alternate antibiotic or anesthesia agents
Doxycycline	Antacids, dairy products. supplements (eg. Iron)	Binding to multivalent cations	Reduces effectiveness	Avoid antacids, dairy

	Phenytoin, carbamazepine barbiturates	CYP inducers	Reduce effectiveness of doxycycline	Adjust doxycycline dose higher
	Warfarin	Disruption of intestinal flora, or impairing prothrombin utilization	Potentiate anticoagulant	Monitor INR closely
Fluoroquinolones	Antacids, dairy products, supplements (eg. iron)	Multivalent cations	Reduces effectiveness	Avoid antacids, dairy.
	Methylxanthine (theophylline)	CYP inhibition	Increase theophylline toxicity	Lower theophylline dose, check level
	Warfarin	Disruption of intestinal flora	Potentiate anticoagulant	Reduce warfarin dose, check INR
Metronidazole	Antiarrythmics Antidepressents Antipsychotics	QTc prolongation	Arrythmia	Avoid if possible
Trimethoprim/Sulfamethoxazole	Spironolactone ACE Inhibitors Angiotensin receptor blockers	Decrease excretion of potassium in the distal renal tubule	Hyperkalemia	If Cr. Cl. <30ml/min reduce dose of TMP/SMX and check K+ Caution using in pregnancy and HIV patients
	Oral hypoglycemic agents	CYP inhibitor	Hypoglycemia	Reduce hypoglycemic dose, monitor glucose
	Warfarin	CYP inhibitor	Potentiate anticoagulant	Reduce warfarin dose, check INR
	Methotrexate	Renal organic transporters	Cytopenia, mucositis, hepatotoxicity, GI symptoms	Avoid TMP/SMX use; select alternate antibiotic

CYP=cytochrome P450; h=hour; PPI= proton pump inhibitors; TMP/SMX=Trimethoprim/Sulfamethoxaz-azole

Table 2: *Common medications and brand names*

Drug Class	Generic (Brand Name)
Angiotensin Converting Enzyme Inhibitors (ACEi)	• benazepril (Lotensin®) • quinapril (Accupril®) • captopril (Capoten®) • ramipril (Altace®) • enalapril (Vasotec®) • lisinopril (Prinivil®, Zestril®)
Angiotensin II Receptor Blockers (ARB)	• candesartan (Atacand®) • olmesartan (Benicar®) • irbesartan (Avapro®) • valsartan (Diovan®) • losartan (Cozaar®)
Anticoagulants	• warfarin (Coumadin®, Jantoven®)
Anticonvulsants	• phenytoin (Dilantin®) • carbamazepine (Tegretol®)
Benzodiazepines	• alprazolam (Xanax®) • clonazepam (Klonopin®) • diazepam (Valium®) • lorazepam (Ativan®)
Corticosteroids	• methylprednisolone (Medrol®) • prednisone (Deltasone®)
Immunomodulators	• cyclosporine (Neoral®, Sandimmune®) • methotrexate (Trexall®) • tacrolimus (Prograf®)
Meglitinides	• nateglinide (Starlix®) • repaglinide (Prandin®)
Potassium-Sparing Diuretic	• spironolactone (Aldactone®)
Statins	• atorvastatin (Lipitor®) • lovastatin (Mevacor®) • pravastatin (Pravachol®) • rosuvastatin (Crestor®) • simvastatin (Zocor®)
Sulfonylureas	• glimepiride (Amaryl®) • glipizide (Glucotrol®) • glyburide (Micronase®, DiaBeta®, Glynase PresTab
Uricosuric Agents	• allopurinol (Zyloprim®) • probenecid (Benemid®)

REFERENCES

1. Di Mizio G, Marcianò G, Palleria C, et al. Drug-Drug Interactions in Vestibular Diseases, Clinical Problems, and Medico-Legal Implications. Int J Environ Res Public Health. Dec 8 2021;18(24) doi:10.3390/ijerph182412936
2. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. May 2015;17 5(5):827-34. doi:10.1001/jamainternmed. 2015. 0324
3. Schwartz JB. The influence of sex on pharmacokinetics. Clin Pharmacokinet. 2003;42 (2):107-21. doi:10.2165/00003088-200342020-0 0001
4. Mortazavi SS, Shati M, Keshtkar A, Malakouti SK, Bazargan M, Assari S. Defining polypharmacy in the elderly: a systematic review protocol. BMJ Open. Mar 24 2016;6(3): e010989. doi:10.1136/bmjopen-2015-010989
5. Lees KA, Orlandi RR, Oakley G, Alt JA. The Role of Macrolides and Doxycycline in Chronic Rhinosinusitis. Immunol Allergy Clin North Am. May 2020;40(2):303-315. doi:10.1016/j.iac.201 9.12.005
6. Suzuki H, Shimomura A, Ikeda K, Oshima T, Takasaka T. Effects of long-term low-dose macrolide administration on neutrophil recruitment and IL-8 in the nasal discharge of chronic sinusitis patients. Tohoku J Exp Med. Jun 1997;182(2):115-24. doi:10.1620/tjem.182. 115
7. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. Feb 2006;116(2):189-93. doi:10.1097/01.mlg.0000191560.53555.08
8. Haruna S, Shimada C, Ozawa M, Fukami S, Moriyama H. A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis. Rhinology. Mar 2009;47 (1):66-71.
9. Suzuâi H, Iâeda h, Honma R, et al. Prognostic factors of chronic rhinosinusitis under long-term loï-dose macrolide therapy. lRL J

Otorhinolaryngol Relat Spec. May-Jun 2000;62(3):121-7. doi:10.1159/000027731

10. Zhang N, Van Zele T, Perez-Novo C, et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. J Allergy Clin Immunol. Nov 2008;122(5):961-8. doi:10.1016/j.jaci.2008.07.008
11. Cao PP, Li HB, Wang BF, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. J Allergy Clin Immunol. Sep 2009;124(3):478-84, 484.e1-2. doi:10.1016/j.jaci.2009.05.017
12 Haxel BR, Clemens M, Karaiskaki N, Dippold U, Kettern L, Mann WJ. Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. Laryngoscope. May 2015;125(5):1048-55. doi:10.1002/lary.25052
13. Amali A, Saedi B, Rahavi-Ezabadi S, Ghazavi H, Hassanpoor N. Long-term postoperative azithromycin in patients with chronic rhinosinusitis: A randomized clinical trial. Am J Rhinol Allergy. Nov-Dec 2015;29(6):421-4. doi:10.2500/ajra.2015.29.4244
14. LaForce CF, Szefler SJ, Miller MF, Ebling W, Brenner M. Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. J Allergy Clin Immunol. Jul 1983;72(1):34-9. doi:10.1016/0091-6749(83)90049-0
15. Patel AM, Shariff S, Bailey DG, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med. Jun 18 2013;158(12):869-76. doi:10.7326/0003-4819-158-12-201306180-00004
16. Lund M, Svanström H, Pasternak B, Hviid A, Melbye M. Concomitant use of statins and macrolide antibiotics and risk of serious renal events: A nationwide cohort study. Int J Cardiol. Oct 15 2018;269:310-316.doi:10.1016/j.ijcard.2018.06.110
17. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. Allergy. Jan 2004;59(1):54-60. doi:10.1046/j.1398-9995.2003.00364.x
18. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol. May 2010;125(5):1069-1076.e4. doi:10.1016/j.jaci.2010.02.020
19. Joshi N, Miller DQ. Doxycycline revisited. Arch Intern Med. Jul 14 1997;157(13):1421-8.
20. Sundberg L, Edén T, Ernstson S. Penetration of doxycycline in respiratory mucosa. Acta Otolaryngol. Nov-Dec 1983;96(5-6):501-8. doi:10.3109/00016488309132737
21. Lawson DH, Jick H. Adverse reactions to co-trimoxazole in hospitalized medical patients. Am J Med Sci. Jan-Feb 1978;275(1):53-7. doi:10.1097/00000441-197801000-00005
22. Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. Arch Intern Med. Feb 24 2003;163(4):402-10. doi:10.1001/archinte.163.4.402
23. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. Cmaj. Nov 8 2011;183(16):1851-8.doi:10.1503/cmaj.111152
24. Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med. Jun 28 2010;170(12):1045-9. doi:10.1001/archinternmed.2010.142
25. Marinella M. Severe Hyperkalemia Associated with Trimethoprim-Sulfamethoxazole and Spironolactone. Infectious Diseases in Clinical Practice. 1997;6(4):256-258.
26. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther. Jun 2012;30(3):e156-66. doi:10.1111/j.1755-5922.2010.00258.x
27. Roustit M, Blondel E, Villier C, Fonrose X, Mallaret MP. Symptomatic hypoglycemia associated with trimethoprim/sulfamethoxazole and repaglinide in a diabetic patient. Ann Pharmacother. Apr 2010;44(4):764-7.doi:10.1345/aph.1M597

28. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. Dicp. Mar 1990;24(3):250-1.doi:10.1177/106002809002400307
29. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. Clin Pharmacol Ther. Nov 2008;84(5):581-8. doi:10.1038/clpt.2008.150
30. Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. Arch Intern Med. Apr 12 2010;170(7):617-21. doi:10.1001/archinternmed.2010.37
31. Kosoglou T, Rocci ML, Jr., Vlasses PH. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. Clin Pharmacol Ther. Oct 1988;44(4):467-77. doi:10.1038/clpt.1988.181
32. Fujita T, Urban TJ, Leabman MK, Fujita K, Giacomini KM. Transport of drugs in the kidney by the human organic cation transporter, OCT2 and its genetic variants. J Pharm Sci. Jan 2006;95(1):25-36. doi:10.1002/jps.20536
33. Katchamart W, Bourré-Tessier J, Donka T, et al. Canadian recommendations for use of methotrexate in patients with rheumatoid arthritis. J Rheumatol. Jul 2010;37(7):1422-30. doi:10.3899/jrheum.090978
34. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. Jan 2004;130(1 Suppl):1-45. doi:10.1016/j.otohns.2003.12.003
35. Höffken G, Borner K, Glatzel PD, Koeppe P, Lode H. Reduced enteral absorption of ciprofloxacin in the presence of antacids. Eur J Clin Microbiol. Jun 1985;4(3):345. doi:10.1007/bf02013667
36. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med. Nov 30 1989;87(5a):76s-81s. doi:10.1016/0002-9343(89)90028-4
37. Rudmik L, Soler ZM. Medical Therapies for Adult Chronic Sinusitis: A Systematic Review. Jama. Sep 1 2015;314(9):926-39. doi:10.1001/jama.2015.7544
38. Murphy P, Bistas K, Le J. Clindamycin. StatPearls Publishing. 2023.
39. Dhawan VK, Thadepalli H. Clindamycin: a review of fifteen years of experience. Rev Infect Dis. Nov-Dec 1982;4(6):1133-53. doi:10.1093/clinids/4.6.1133
40. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. Apr 2015;152(2 Suppl):S1-s39. doi:10.1177/0194599815572097
41. Brown GR. Cephalosporin-probenecid drug interactions. Clin Pharmacokinet. Apr 1993;24(4):289-300.doi:10.2165/00003088-199324040-00003
42. Ding Y, Jia YY, Li F, et al. The effect of staggered administration of zinc sulfate on the pharmacokinetics of oral cephalexin. Br J Clin Pharmacol. Mar 2012;73(3):422-7. doi:10.1111/j.1365-2125.2011.04098.x
43. Dingsdag SA, Hunter N. Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms. J Antimicrob Chemother. Feb 1 2018;73(2):265-279.doi:10.1093/jac/dkx351
44. Rashid K, Khan Y, Ansar F, Waheed A, Aizaz M. Potential Drug-Drug Interactions in Hospitalized Medical Patients: Data From Low Resource Settings. Cureus. Aug 2021;13(8):e17336. doi:10.7759/cureus.17336

How to cite this article: William E. Bolger et al. Common Drug Interactions in ENT: A Review of Antibiotics in Sinusitis Journal of Otolaryngology and Rhinology Research. 2023;162−171. https://doi.org/10.52845/JORR/2023/4.3.7