Table 1 – Antibiotic Class Interactions with Warfarin

Drug Class	Effect on INR/Bleed Risk	Severity/Risk Rating*	Management
Cephalosporins Cefaclor Cefadroxil Cefazolin Cefepime Cefixime Cefprozil Ceftriaxone Cefuroxime Cephalexin	increases	moderate/C	Monitor for increased INR and for signs of bleeding when initiating a cephalosporin, and for decreases when discontinuing
Macrolides Azithromycin Clarithromycin Erythromycin	increases	moderate/C	Monitor for increased INR and for signs of bleeding when initiating a macrolide, and for decreases when discontinuing
Metronidazole	increases	major/D	Consider alternative agent. Monitor INR. Consider empiric warfarin dose reduction by 25-40%
Penicillins Amoxicillin Amox/Clavulanate Ampicillin* Cloxacillin Penicillin V*/G* *unlikely in oral formulations	Most in this class increase INR/bleed risk, with exceptions (see table 2)	moderate/C -more common in those with a broad spectrum of activity, high dose IV, and/or when combined with a beta-lactamase inhibitors (e.g. clavulanate)	Monitor for increased INR and for signs of bleeding when initiating a penicillin, and for decreases when discontinuing, including several days after cessation
Quinolones (fluroquinolones) Ciprofloxacin Levofloxacin Moxifloxacin Norfloxacin	increases	moderate/C	Monitor for increased INR and for signs of bleeding when initiating a quinolone, especially during the first few days of therapy, and for decreases when discontinuing
Sulfonamides Sulfamethoxazole Sulfisoxazole	increases	moderate/D	Monitor for increased INR and for signs of bleeding when initiating a sulfonamide, and for decreases when discontinuing. Consider empiric warfarin dose reduction by 10-25%
Tetracyclines Doxycycline Minocycline Tetracycline	may increase	moderate/C	Monitor INR

The table listing is intended as a guide to health care providers in diverse practice settings and should not be viewed as a complete representation of all interactions with warfarin.

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Table 2 – Common Antibiotics and Antifungals That Can Change INR/Bleed Risk

Drug	Effect on INR/Bleed Risk	Severity/ Risk Rating*	Mechanism	Management
Amoxicillin/ Clavulanate	increases	Moderate/C	unknown; may be due to decreased intestinal flora production of vitamin K.	Monitor INR.
Azithromycin	increases	moderate/C	possible decrease in warfarin metabolism	Monitor INR. Consider warfarin dose reduction in presence of other factors affecting INR**
Ciprofloxacin	increases	moderate/C	unknown; more common in elderly patients on many medications	Monitor INR. Some patients experience no change in INR. Consider empiric warfarin dose reduction by 10-15%
Clarithromycin	increases	moderate/C	Inhibition of warfarin metabolism (via CYP3A4)	Monitor INR. Consider empiric warfarin dose reduction by 15-25%
Cloxacillin	May increase or decrease	moderate/C	increase: unknown; evidence is limited for this interaction-based on a case report decrease: unknown; evidence is limited for this interaction-based on three case reports	Increase: Monitor INR. Consider warfarin dose reduction in presence of other factors affecting INR** Decrease: Monitor INR
Doxycycline	increases	moderate/C	unknown; possible inhibition of warfarin metabolism and/or protein binding displacement	Monitor INR. Consider warfarin dose reduction in presence of other factors affecting INR**
Erythromycin (including ophthalmic formulations)	increases	moderate/C	decrease in warfarin metabolism (via CYP3A4)	Monitor INR. Consider empiric warfarin dose reduction by 10-15%
Fluconazole	increases	moderate/D	inhibition of warfarin metabolism (via CYP3A4 and CYP2C9); interaction is more pronounced in patients with renal dysfunction	Consider alternative agent. Monitor INR. Consider empiric warfarin dose reduction by 25-30%, with eventual reductions up to 80%
Isoniazid	increases	moderate/C	inhibition of warfarin metabolism (via CYP2C9)	Monitor INR. Consider empiric warfarin dose reduction by 10-15%, with the potential for further reductions based on weekly INR monitoring
Itraconazole	increases	moderate/C	inhibition of warfarin metabolism (via CYP3A4 and CYP2C9)	Monitor INR. Consider empiric warfarin dose reduction by 25-30%
Ketoconazole	increases	moderate/C	inhibition of warfarin metabolism (via CYP3A4 and CYP2C9)	Monitor INR. Consider empiric warfarin dose reduction by 25-30%
Levofloxacin	increases	moderate/C	possible decrease in warfarin metabolism (via CYP1A2); clinical significance increased in the elderly	Monitor INR. Consider empiric warfarin dose reduction 0-15%
Metronidazole	increases	major/D	decrease in warfarin metabolism (via CYP2C9)	Consider alternative agent. Monitor INR. Consider empiric warfarin dose reduction by 25-40%
Miconazole (including oral, topical and vaginal formulations)	increases	moderate/D	inhibition of warfarin metabolism (via CYP3A4 and CYP2C9)	Consider clotrimazole as an alternative (no interaction). Monitor INR. Consider empiric warfarin dose reduction by 25-30%
Moxifloxacin	increases	major/C	possible inhibition of warfarin metabolism (via CYP1A2); clinical significance increased in the elderly	Monitor INR. Consider empiric warfarin dose reduction 0-25%

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Table 2 – Common Antibiotics and Antifungals That Can Change INR/Bleed Risk

Drug	Effect on INR/Bleed Risk	Severity/ Risk Rating*	Mechanism	Management
Rifampin/ Rifamycin derivatives	decreases	moderate-severe/C	induction of warfarin hepatic metabolism	Monitor INR. Consider empiric warfarin dose increase by 25-50%, with the potential for further increases based on weekly INR monitoring
Sulfamethoxazole (+/- Trimethoprim)	increases	severe/D	unknown; possible inhibition of warfarin metabolism and/or protein binding displacement	Consider alternative agent. Monitor INR. Consider empiric warfarin dose reduction by 25-40%
Terbinafine	May increase or decrease	moderate/C	unknown; evidence is limited for this interaction-based on a case report	Monitor INR
Tetracycline	increases	moderate/C	reduced plasma prothrombin activity	Monitor INR
Voriconazole	increases	major/C	inhibition of S-warfarin*** metabolism (via CYP2C9)	Monitor INR. Consider empiric warfarin dose reduction by 25-30%

The table listing is intended as a guide to health care providers in diverse practice settings and should not be viewed as a complete representation of all interactions with warfarin.

*Risk Rating taken from Lexi-comp.

C rating denotes monitoring therapy is necessary. "The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients."

D rating denotes a modification to the regimen is necessary. "A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents."

**Symptoms associated with infection, specifically fever, vomiting/diarrhea, and poor nutritional state can independently increase INR and the effects of warfarin

***S-warfarin is 2-5 times more active than the R-enantiomer

Related Information: A challenging aspect of warfarin management has always been keeping patients' INR within the therapeutic window. Once on a stable dose of warfarin, numerous factors can affect INR such as: intake of vitamin K, acute and chronic medical conditions, and drug interactions.

Warfarin is particularly susceptible to many mechanisms of drug interactions due to its pharmacokinetic features: it is well absorbed, 99% protein-bound, and metabolized via CYP450 enzymes. S-warfarin, which is metabolized by CYP2C9, is 2-5 times more active than the R-enantiomer, which is metabolized by CYP3A4. Drugs that induce or inhibit these enzymes can interact with warfarin, with more severe interactions seen with CYP2C9 interactions. These types of interactions take about 5 steady states to reach their full effect, with induction taking longer than inhibition. Another type of interaction is warfarin displacement from plasma proteins by other highly protein bound drugs.

There are also some interactions that affect the pharmacodynamics of warfarin. Warfarin acts to block the reduction of vitamin K. Reduced vitamin K is needed for the carboxylation of the vitamin k dependent clotting factors (II, VII, IX and X). Therefore, drugs that alter the amount of vitamin K in the body can effect INR. Broad-spectrum antibiotics are thought to act by altering intestinal flora, therefore hindering the body's ability to synthesize vitamin K. Finally, drugs that can effect bleeding and thrombosis through other mechanisms (e.g. platelet function), can interact with warfarin without changing the INR.

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