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Inpatient Guideline for Management of Significant Warfarin Drug-Drug Interactions with Antimicrobial Agents

Purpose: The purpose of this guideline is to provide assistance with dose adjustment of warfarin when initiating antimicrobial therapy that may affect the INR

- Recommendations are intended for patients with expected antimicrobial interaction duration ≥3 days
- Please document antimicrobial drug-drug interactions in all pharmacy or medication management notes during the course of the interaction, including expected duration of interaction (if known)
- Antimicrobial agents not included in this document do not directly affect warfarin metabolism, but may alter normal GI flora and vitamin K production, which can impact INR values. Monitor INR and consider dose reduction in patients with INR increase >0.5 within 24 hours or >1 within 48 hours
- Warfarin dosing should include appropriate assessment of other factors that influence INR (clinical condition, dose of initiated antimicrobial, INR trends, other drug interactions, nutrition, compliance, etc.), and should ultimately be based on the clinical judgment of the provider

Table 1. Warfarin Dosing Recommendations for Significant Antimicrobial Interactions that INCREASE INR:

Significant Inhibitors of Warfarin Metabolism	INR at Start of Antimicrobial Interaction			Upon Discontinuation of Antimicrobial Interaction
	Therapeutic INR	Subtherapeutic INR*	Supratherapeutic INR GTR =Goal therapeutic range	Therapeutic INR¥
Metronidazole Sulfamethoxazole-trimethoprim Fluconazole Itraconazole Ketoconazole Voriconazole	Empiric warfarin dose reduction of 20-30%	• Give maintenance dose • Consider dose reduction in patient with INR increase >0.5 within 24hrs or >1 within 48 hrs	• GTR + (0.1-0.5): Decrease dose 25-40% • GTR + (0.6-1.9)β: Hold dose(s), then 25-50% dose reduction • INR >5 and/or bleeding: Hold warfarin and follow guideline for reversal of antithrombotic agents if bleeding	If patient was on a stable regimen prior to drug interaction, resume previous maintenance dose. Otherwise, empiric dose increase of 20%.
Ciprofloxacin Clarithromycin Erythromycin Isoniazid	Empiric warfarin dose reduction of 10-15%	• Give maintenance dose • Consider dose reduction in patient with INR increase >0.5 within 24hrs or >1 within 48 hrs within 48 hrs	• GTR + (0.1-0.5): Decrease dose 10-15% • GTR + (0.6-1.9)β: Hold dose(s), then 10-25% dose reduction • INR >5 and/or bleeding: Hold warfarin and follow guideline for reversal of antithrombotic agents if bleeding	If patient was on a stable regimen prior to drug interaction, resume previous maintenance dose. Otherwise, empiric dose increase of 10%.

* Avoid warfarin boosting at the start of warfarin-antimicrobial interaction

¥ For sub/supratherapeutic INR at discontinuation: monitor INR closely and adjust as appropriate

β Consider restarting warfarin therapy when current INR ≤ previous day's INR

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Table 2. Warfarin Dosing Recommendations for Antimicrobial Interactions with Potential to INCREASE INR:

Mild-Moderate Inhibitors of Warfarin Metabolism	INR at Start of Antimicrobial Interaction			Upon Discontinuation of Antimicrobial Interaction
	Therapeutic INR	Subtherapeutic INR	Supratherapeutic INR	Therapeutic INR¥
Azithromycin Doxycycline Levofloxacin Moxifloxacin Quinupristin-dalfopristin Telaprevir Boceprevir Simeprevir	No empiric dose reduction. Monitor INR. Consider dose reduction in patient with INR increase >0.5 within 24hrs or >1 within 48 hrs			If dose was reduced, resume dose from prior to interaction.

¥ For sub/supratherapeutic INR at discontinuation: monitor INR closely and adjust as appropriate

Table 3. Warfarin Dosing Recommendations for Antimicrobial Interactions that DECREASE INR:

Inducers of Warfarin Metabolism	INR at Start of Antimicrobial Interaction			Upon Discontinuation of Antimicrobial Interaction
	Therapeutic INR	Subtherapeutic INR	Supratherapeutic INR GTR =Goal therapeutic range	Therapeutic INR¥
Nafcillin/Oxacillin	Empiric dose increase of 25-50% starting 3-5 days post initiation of nafcillin	Increase dose by 30-50% of expected maintenance dose	• GTR + (0.1-0.5): Give expected maintenance dose • GTR + (0.6-1.9)β: Hold dose(s), then 10% dose reduction • INR >5 and/or bleeding: Hold warfarin and follow guideline for reversal of antithrombotic agents if bleeding	If patient was on a stable regimen prior to drug interaction, resume previous maintenance dose. Otherwise, monitor INR and adjust as needed.
Rifampin Rifabutin	Empiric dose increase of 20-30% starting 3-5 days post initiation of rifampin or rifabutin	Increase dose by 20-30% of expected maintenance dose		
Ritonavir or any protease inhibitor for HIV with ritonavir	Monitor INR closely, especially at initiation No empiric dose increase. Adjust warfarin dose as appropriate by INR			

¥ For sub/supratherapeutic INR at discontinuation: monitor INR closely and adjust as appropriate

β Consider restarting warfarin therapy when current INR ≤ previous day's INR

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Authors: Anticoagulation Subcommittee
Approved: Anticoagulation Subcommittee (09/08/14) P&T Committee (10/21/14)

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