DRUG INTERACTIONS

→ Drugs that **inhibit liver microsomal enzyme function** can impair the metabolism of cyclosporine, leading to increased cyclosporine blood concentrations and toxicity. Alternatively, enzyme-inducing drugs increase the metabolism of cyclosporine and may result in lowered cyclosporine blood levels and increased risk of transplant rejection.

→ The table outlines major drug interactions only, and is not all-inclusive. The majority of interactions are the result of effects on the cytochrome P450 3A4 enzyme.

Drug	Possible Mechanism / Onset and severity	Adverse Effects	Management
Drugs that DECREASE CSA			
Anticonvulsants: ➢ Phenytoin ➢ Carbamazepine ➢ phenobarbital, primidone	Enzyme induction ↑CSAmetabolism • delayed / major • delayed/ moderate • delayed / major	↓effectiveness of CSA which may lead to rejection	↑ CSA dose by 30% and monitor levels following addition, dose change or discontinuation
Antimicrobial: ➢ rifampin	Induction of hepatic enzymes • delayed / major	↓effectiveness of CSA which may lead to rejection	Monitor CSA levels following addition, dose change or discontinuation.

[1]- BC Transplant. (2021, May 13). MEDICATION GUIDELINES FOR SOLID ORGAN TRANSPLANTS. BC Transplant. (http://www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/Clinical%20Guidelines%20for%20Transplant%20Medications.pdf)

Drug	Possible Mechanism / Onset and severity	Adverse Effects	Management
B) Drugs that INCREASE CSA			
Antimicrobial: ➢ erythromycin, clarithromycin (Biaxin®) ➢ azole antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	↓CSA metabolism, ⟨↑rate of absorption, ↓volume of distribution • delayed / major ↓CSA/TAC/sirolimus metabolism • delayed/ moderate	↑CSA levels, ↑ ⟨risk of toxicity	Monitor CSA levels following addition, dose change or discontinuation. Monitor serum creatinine
Antidepressants: ➢ fluoxetine, fluvoxamine greater than sertraline, venlafaxine, mirtazapine, paroxetine	↓CSA metabolism • delayed/ moderate	↑CSA levels, ↑ ⟨risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor CSA levels closely
Cardiovascular: ➢ diltiazem, verapamil ➢ amiodarone	May inhibit hepatic metabolism of CSA •delayed / Major	↑CSA levels, ↑ ⟨risk of toxicity	Monitor CSA levels following addition, dose change or discontinuation

[1]- BC Transplant. (2021, May 13). MEDICATION GUIDELINES FOR SOLID ORGAN TRANSPLANTS. BC Transplant. (http://www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/Clinical%20Guidelines%20for%20Transplant%20Medications.pdf)

Drug	Proposed Mechanism and Possible effects	Management
Pharmacodynamic Interactions of Cyclosporine (CSA)		
➢ Aminoglycosides, Amphotericin B, NSAIDS, C0X-2 inhibitors(CSA and tacrolimus ONLY)	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
➢ HMG-CoA Reductase Inhibitors :Example: lovastatin, simvastatin, atorvastatin	CSA may ↓metabolism of these agents →accumulation of statin and toxicityMyalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
➢ Digoxin	↓volume of distribution of digoxin by 50-70%, ↑〈digoxin half-life by 30-40%, and increased digoxin levelsdigoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
➢ nifedipinephenytoin	Additive incidence of gingival hyperplasia with CSA Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible.Good dental/oral hygiene with regular dentist visits

[1]- BC Transplant. (2021, May 13). MEDICATION GUIDELINES FOR SOLID ORGAN TRANSPLANTS. BC Transplant. (http://www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/Clinical%20Guidelines%20for%20Transplant%20Medications.pdf)