

METHOTREXATE – INTERACTIONS

This is for high dose methotrexate defined as greater than or equal to 500 mg/m²

Interactions involving displacement from binding proteins are clinically insignificant as long as renal function is intact. Consider avoiding drugs which are greater than 90% protein bound in patients with pre-existing renal impairment. Unless otherwise noted, recommendations are based on the elimination pattern of the potentially interacting drug, not on clinical experience.

Recommendations are based on literature where available and/or the characteristics (e.g. extent of protein binding, renal clearance including tubular secretion) of the potentially interacting drug. Decisions made for individual patients should take into consideration the clinical situation of the patient (e.g. induction vs consolidation therapy, renal and hepatic function), the methotrexate dose to be administered (low vs high) and the availability of alternative therapies.

DRUG	PROTEIN BINDING (%)	ELIMINATION	EFFECT ON METHOTREXATE DOSE INTENSITY	RECOMMENDATION
Acyclovir	9-33	75-80% renal clearance: 30-40% TS	Likely ↑	AVOID
Allopurinol	less than 1% oxypurinol not bound to plasma proteins	5-7% renal clearance; ~70% renal clearance as oxypurinol (active metabolite); oxypurinol: significant GF and TS	Likely ↑	Use with caution
Amphotericin	90-95 (mainly to lipoproteins)	mainly hepatic; 3% renal clearance	Likely no direct effect	Consider another antifungal agent due to possible decreased renal function associated with amphotericin therapy
Amoxicillin	17	43-80% renal clearance; GF; significant TS	↑	AVOID ¹
Ampicillin	15-25	60-90% renal clearance; GF; significant TS	↑	AVOID
CefaCLOR	Less than 20	50-80% renal clearance; significant TS	Likely ↑	AVOID
CeFAZolin	70-92	80-100% renal clearance; GF; 50-80% TS	Likely ↑	AVOID

DRUG	PROTEIN BINDING (%)	ELIMINATION	EFFECT ON METHOTREXATE DOSE INTENSITY	RECOMMENDATION
cefepime	20	85% excreted in the urine as unchanged drug (via organic cation transporter OCTN2 that is NOT involved in the transport of methotrexate)	Likely none	OK
CefoTAXime	3-50	hepatic and renal clearance; 40-60% renal clearance; 24% renal clearance for active metabolite; significant TS	Likely ↑	AVOID
Cefprozil	35-45	60-70% renal clearance, significant TS	Likely ↑	AVOID
CeftAZIDime	5-24	80-90% renal clearance; GF; TS insignificant	Likely none to minimal	OK ^{2,3}
CefTRIAxone	58-96 (concentration dependent)	33-65%, 40-70% renal clearance (age dependant); GF; TS insignificant	Likely none	OK
CefUROXime	33-50	GF; 50% TS	Likely ↑	AVOID
Cetirizine	93	60-70% renal clearance via GF and some via tubular secretion	Likely minimal	Use with caution. Theoretical risk. Do NOT hold if patient suffering hypersensitivity reaction.
CephALEXin	6-15	70-100% renal clearance; GF; significant TS	Likely ↑	AVOID
Ciprofloxacin	16-43	15-50% renal clearance: 50% TS	↑	AVOID ⁴
Clarithromycin	7-50 (concentration dependant); mainly to α_1 -acid glycoprotein	20-30% renal clearance; TS unknown	Likely none	Use with caution
Clindamycin	60-94(concentration dependant)	insignificant renal clearance	Likely none	OK
Cloxacillin	90-96	GF; significant TS	Likely ↑	AVOID

DRUG	PROTEIN BINDING (%)	ELIMINATION	EFFECT ON METHOTREXATE DOSE INTENSITY	RECOMMENDATION
Cotrimoxazole	tmp-44;sulfa-70	GF; significant TS	↑	AVOID ²
Dapsone	50-90	5-20% unchanged 70-85% metabolites 5-20% TS	Likely none to minimal	Use with caution
Dexlansoprazole		hepatic metabolism; inhibits renal hydrogen ion pump	↑	AVOID ⁸
Enalapril	50-60	Hepatically hydrolysis to active metabolite; parent & metabolite renally cleared; metabolite cleared via TS	Likely minimal	Use with caution
Erythromycin	base- 73-81 estolate- 96	insignificant renal clearance	Likely none	OK
Esomeprazole		Hepatic metabolism; inhibits renal hydrogen ion pump	↑	AVOID ⁶
Fluconazole	11	60-80% renal clearance; insignificant TS	Likely none	OK
Gentamicin	less than 10	GF; insignificant TS	Likely no direct effect	Consider another agent due to possible decreased renal function associated with aminoglycoside therapy
Lansoprazole	97	hepatic metabolism; inhibits renal hydrogen ion pump	↑	AVOID ⁶
Levofloxacin	24-38	87% renal clearance (both glomerular filtration and tubular secretion)	↑	AVOID ⁶
6-mercaptopurine	20	7-39% renally cleared	Likely none to minimal	OK

DRUG	PROTEIN BINDING (%)	ELIMINATION	EFFECT ON METHOTREXATE DOSE INTENSITY	RECOMMENDATION
Meropenem	2	70% renal clearance; significant TS	Likely ↑	AVOID ⁵
Metronidazole	less than 20	hepatic and renal clearance; TS insignificant	Likely none	OK
Midazolam	97	not renally cleared	Likely none	OK
Morphine	low	85% renally cleared; no TS	Likely none	OK
NIFEdipine	92-98	80% cleared hepatically	Likely none	OK
Nitrofurantoin	60	GF with TS	Likely ↑	Use with caution
Omeprazole	95	hepatic metabolism; 72-80% renal elimination; inhibits renal hydrogen ion pump	↑	AVOID ⁶
Oseltamivir	3(carboxylate); 42 (phosphate)	99% renal: 50% TS	Likely ↑	AVOID
Pantoprazole		hepatic metabolism; inhibits renal hydrogen ion pump	↑	AVOID ^{6,8}
Penicillin G	45-68	60% renal clearance of penicillin G and active metabolites (10% GF; 90% TS)	Likely ↑	AVOID
Penicillin V	75-89	30-65% renal clearance of penicillin V and active metabolites (GF; significant TS)	Likely ↑	AVOID
Pentamidine	69	less than 5% renal clearance	Likely none	OK
Piperacillin	16-22	80% renal clearance; significant TS	↑	AVOID ⁷
Ranitidine	Low	Extensive hepatic metabolism; 15-70% renal elimination (dose dependent); some TS via cationic transport system	Likely none to minimal	OK
Rifampin	89	3-30% renal clearance	Likely none	OK
Rabeprazole		hepatic metabolism; inhibits renal hydrogen ion pump	↑	AVOID ⁸
Tobramycin	<10	70-95% renal	Likely no direct effect	Consider another agent due to



DRUG	PROTEIN BINDING (%)	ELIMINATION	EFFECT ON METHOTREXATE DOSE INTENSITY	RECOMMENDATION
				possible decreased renal function associated with aminoglycoside therapy
Trimethoprim	45	50-80% GF and TS	Likely ↑	AVOID
Vancomycin	10-50	70% renal clearance: insignificant TS	Likely none	OK

NOTE: All NSAIDS, proton pump inhibitors and penicillin drugs should be avoided.

GF = glomerular filtration; TS = tubular secretion

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