

COMMON DRUG-DRUG INTERACTIONS IN KIDNEY TRANSPLANT RECIPIENTS – A PRACTICAL GUIDE FOR THE FAMILY PHYSICIAN

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ABSTRACT

Kidney transplantation offers improved mortality and morbidity compared to dialysis in patients with end-stage kidney disease (ESKD) and is the preferred renal replacement therapy of choice. With their improved health status, kidney transplant recipients (KTRs) may seek care in the community as the first line of medical attention. With the increasing prevalence of ESKD in Singapore, family physicians will play an expanded role in the care of the KTR. To avoid allograft rejection, KTRs are on lifelong immunosuppressive therapy, which has potential for adverse drug-drug interactions and drug toxicity. It would be prudent to be aware of potential interactions between immunosuppressive agents and commonly prescribed medications in the primary care setting.

Keywords: Kidney transplant, drug-drug interactions, family physician, primary healthcare, immunosuppressants

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INTRODUCTION

Singapore has 2,225 ESKD patients per million population, placing it fourth globally in the prevalence of ESKD per population.¹ The incidence of ESKD is anticipated to continue to rise given an ageing population and the increasing prevalence of comorbidities, in particular diabetes mellitus.² Diabetic nephropathy accounted for 68.2 percent of patients on chronic dialysis.³

KTRs have significantly reduced mortality compared to their dialysis-dependent counterparts. Data from Singapore's Renal Registry showed 10-year patient survival rate of 31.9 percent for patients on dialysis; in stark contrast, KTRs had a 10-year patient survival rate of 85.3 percent.³ The superior survival rate of the KTR is in keeping with international data.¹ KTRs are emancipated from dialysis with substantially improved quality of life and decreased healthcare costs, both to the patient and to the healthcare system.⁴ As of 2019, there were 1,613 KTRs in Singapore, accounting for 17 percent of patients with ESKD receiving renal replacement therapy. KTR may receive a kidney allograft from a living or deceased donor. Given the scarcity of living donors, it is not uncommon to perform living donor kidney transplants across an ABO barrier (i.e., ABO-incompatible transplants). With advancements in desensitisation techniques and maintenance immunosuppression, KTRs with ABO-incompatible transplants have displayed comparable allograft and patient survival with their ABO-compatible counterparts.^{5,6}

IMMUNOSUPPRESSANTS IN KIDNEY TRANSPLANT

Though risk of rejection is highest in the first year post-transplant (estimated at about 10 percent), KTRs will require lifelong maintenance immunosuppressive medications to prevent immune-mediated rejection of the allograft.⁷ Broadly, maintenance immunosuppression commonly consists of a combination of three classes of immunosuppressants: an antimetabolite (also known as an anti-proliferative agent), a Calcineurin Inhibitor (CNI), and a corticosteroid (refer to **Table 1**). Antimetabolites include Mycophenolate Mofetil, Azathioprine, and mammalian target of rapamycin inhibitors. The exact dose and combinations of these medications vary based on the patients' immunological risk, metabolic profile, infective and/or neoplastic complications from immunosuppression.

Table 1. Commonly used immunosuppressants – the mechanisms of action and adverse effects

Class of Medication	Mechanism of Action	Common Adverse Effects
Antimetabolite/Anti-proliferative		
Mycophenolate Mofetil <i>Cellcept</i> ®, <i>Myfortic</i> ®	Inhibits inosine monophosphate dehydrogenase leading to intracellular guanosine depletion, semi-selectively prevents proliferation of lymphocytes	Gastrointestinal disturbances (in particular diarrhoea), Myelosuppression
Azathioprine <i>Imuran</i> ®	Inhibits DNA synthesis, prevents proliferation of lymphocytes	Hepatic dysfunction, Viral warts, Myelosuppression
Mammalian target of rapamycin inhibitor (mTORi) Everolimus, <i>Certican</i> ® Sirolimus, <i>Rapamune</i> ®	Inhibits the mammalian target of rapamycin and hence interleukin-2–driven T-cell proliferation	Mouth ulcers Rashes Peripheral edema Delayed wound healing Proteinuria Dyslipidaemia Myelosuppression Pneumonitis
Calcineurin inhibitor (CNI)		
Tacrolimus <i>Advagraf</i> ®, <i>Prograf</i> ®	Inhibits calcineurin phosphatase and T-cell activation	Tremulousness Alopecia Hyperglycemia Nephrotoxicity Hypertension
Ciclosporin <i>Neoral</i> ®		Hirsutism Hypertension Gingival hypertrophy Gout (more in Ciclosporin) Nephrotoxicity
Steroid		
Prednisolone	Activates glucocorticoid receptor with inhibition of cytokine transcription, inhibiting leucocyte function	Weight gain Hyperglycaemia Elevated blood pressure Osteoporosis Mood disturbances

These classes of immunosuppressants work synergistically to attenuate the immune response to the allograft. Because of the overlapping complexities in pharmacokinetics of combination therapy, KTRs are at risk of drug-drug interactions.

We shall illustrate some of these interactions with the following cases.

Case 1

A 30-year-old lady with ESKD from chronic glomerulonephritis received a kidney transplant from her husband five years ago. Her latest serum creatinine is 80 $\mu\text{mol/L}$.

Her medications include Prednisolone 5 mg OM, Mycophenolate Mofetil 500 mg BD, Tacrolimus 3 mg BD, and Co-trimoxazole 480 mg ON.

She is penicillin allergic.

She presents with cough and low-grade fever for four days with no chills nor rigours. She has left lower zone crepitation on auscultation of the lungs.

Blood pressure is 125/80 mmHg, oxygen saturation of 99 percent on room air.

CXR confirms mild left-sided pulmonary infiltrates.

A diagnosis of left-sided community acquired pneumonia is made.

Which antibiotic would you choose?

- A. PO Augmentin
- B. PO Levofloxacin
- C. PO Clarithromycin

mTORis and CNIs have a narrow therapeutic window; serum drug levels are monitored to ensure they are kept effective without unacceptable toxicity. Both classes have complex metabolism with multiple enzymatic pathways involved in their clearance. These enzymes include the P-glycoprotein efflux pump (p-gp) as well as the CYP450 family of enzymes, in particular the enzymes CYP3A4 and CYP3A5. The latter enzymes are essential to the metabolism of many drugs. If co-administered with drugs/supplements which act as competitive inhibitors of CYP450, the resulting combination can lead to an increase in mTORi/CNI serum levels, which may result in toxicity. Conversely, administration of drugs/supplements that induce or potentiate CYP450 enzyme activity will reduce plasma drug concentrations and risk rejection.

Common examples of CYP450 enzyme inducers and inhibitors are as listed in **Table 2**.

Table 2. CYP450-3A4 Inducers and Inhibitors

CYP450-3A4 Inducers (i.e., decrease serum CNI/mTORi drug levels)	CYP450-3A4 Inhibitor (i.e., increase serum CNI/mTORi drug levels)
Rifampicin Phenytoin Carbamazepine Phenobarbital St John's wort	Diltiazem / Verapamil Azoles Clarithromycin, Erythromycin Protease inhibitors (HAART) Grapefruit

She receives Clarithromycin 500 mg BD for 5 days.

She recovers from the pneumonia but presents the following week with complaints of tremors, headache, and elevated blood pressures with the following blood results:

K 5.4 mmol/L, Bicarbonate 18 mmol/L, Creatinine 130 $\mu\text{mol/L}$.

Her Tacrolimus trough return elevated at 18 ng/ml.

In the case above, the addition of Clarithromycin (a competitive inhibitor of CYP3A4) significantly decreased the metabolism of Tacrolimus, leading to high serum Tacrolimus levels. High Tacrolimus levels may manifest in malignant hypertension, gastrointestinal disturbances (diarrhoea), and neurotoxicity (nausea, tremulousness, seizures). Biochemically, the patient may present with transaminitis, acute kidney injury, or an acquired type IV renal tubular acidosis with hyperchloremic metabolic acidosis and hyperkalaemia.⁸

Whilst mild infections in KTRs may be managed in a primary healthcare setting, cases with unexplained fever, protracted diarrhoea, or fevers associated with renal dysfunction or with mental status changes should be promptly referred to the transplant centre.⁹

Thus, the safer antibiotic option would be Levofloxacin.

Case 2

A 55-year-old lady with ESKD from lupus nephritis had received a kidney transplant from her sister eight years ago. Her latest serum creatinine is 80 $\mu\text{mol/L}$.

Her medications include Prednisolone 5 mg OM, Mycophenolate Mofetil 500 mg BD, Ciclosporin 150 mg BD, and Co-trimoxazole 240 mg OM.

Despite attempts at lifestyle modification, her fasting LDL remains elevated at 4.2 mmol/L.

Which of the following statins are safe for her?

- A. Simvastatin 40 mg ON
- B. Rosuvastatin 5 mg ON
- C. Atorvastatin 10 mg ON

The mTORis and CNIs share common enzymatic pathways with statins, most importantly the CYP3A4 enzyme. The combination of CNI/mTORis and statin results in competition for these enzymes, which results in decreased metabolism of statin. Statins are also substrates of OATP1B1, which is inhibited by Ciclosporin. Due to these interactions between statins and Ciclosporin, combination therapy may result in a rise in statin drug levels by 6-8 times for Simvastatin and 5-20 times for Lovastatin.¹⁰

She was commenced on Simvastatin 40 mg ON.

She returned two weeks later with complaints of diffuse muscular aches and myopathy.

Creatinine Kinase	3,000 U/L
Creatinine	80 $\mu\text{mol/L}$
Aspartate transaminase	180 U/L
Alanine transaminase	35 U/L

Exposure to high statin concentrations has resulted in cases with myopathy and rhabdomyolysis. The patients at greatest risks are the elderly, female patients, and patients with impaired renal or hepatic function.¹¹ Statins that can be preferentially co-administered with CNI/mTORi include Fluvastatin, Pravastatin, Atorvastatin, and Rosuvastatin with the maximum daily dose limited to 40, 20, 10, and 5 mg respectively.¹⁰ Use of other statins should be initiated with caution; the lowest starting dose should be used and with close monitoring for signs or symptoms of toxicity.

In the case above, the safer statin options would be Rosuvastatin or Atorvastatin.

Case 3

A 40-year-old gentleman with ESKD from chronic glomerulonephritis had received a kidney transplant from his wife six years ago. His latest creatinine is 110 $\mu\text{mol/L}$.

His medications include Prednisolone 5 mg OM, Mycophenolate Mofetil 500 mg BD, and Tacrolimus 3 mg BD.

He had a recent addition of Diltiazem 90 mg BD as well as Losartan 25 mg OM.

He now presents with complaints of persistent postural giddiness with a blood pressure of 100/60 mmHg. There are no signs of sepsis.

His Diltiazem was stopped with improvement in blood pressure.

However, his recheck Tacrolimus trough level dropped despite reported consistent dosing of his medications.

What is the likely cause of these findings?

- A. Noncompliance to medication
- B. The cessation of Diltiazem
- C. Inappropriate timing of the drug trough level

The costs of immunosuppressants can be a financial burden for patients. To alleviate this, the co-administration of an inhibitor of the hepatic P-450 enzymes may be used to increase the blood levels of mTORi and CNIs (i.e., a booster), thereby keeping drug levels therapeutic whilst allowing a lower dose of oral medications.¹² Commonly used inhibitors include antifungal azoles or nondihydropyridine calcium-channel blockers, e.g., Diltiazem. Diltiazem is commonly used as it can concurrently treat hypertension, which is common in KTRs. In addition, if doses of the booster are omitted, the resultant fall in CNI/mTOR inhibitor levels is much less pronounced in patients boosted with Diltiazem compared to those using an azole.

The cessation of a booster such as Diltiazem explains the drop in drug levels in the aforementioned case. A fall to sub-therapeutic levels would risk inadequate immunosuppression and rejection of the allograft. Unless in cases of significant clinical urgency, cessation of Diltiazem should be done in consultation with the treating nephrologist due to the risk of rejection from sub-therapeutic drug levels.

Case 4

A 55-year-old lady with ESKD from hypertensive nephrosclerosis had received a kidney transplant from her sister 10 years ago. Her latest serum creatinine is 80 $\mu\text{mol/L}$.

Her immunosuppressants are Prednisolone 5 mg OM, Azathioprine 50 mg OM, and Ciclosporin 150 mg BD.

She reports having recurrent gout flares every two months. She has no evidence of tophi and declares no history of previous ureteric colic.

*Her laboratory work shows uric acid 460 $\mu\text{mol/L}$ and HLA-B*5801 is wild type.*

What would be the next course of action to achieve long-term gout control?

- A. Start Allopurinol
- B. Start Febuxostat
- C. Start Probenecid
- D. Change her immunosuppressant

Whilst hyperuricemia is common in KTRs, clinical gout is experienced in only 7.6 percent of the population within three years post-transplant.¹³

Pain relief in acute gout flares for KTRs may be managed with analgesia with the strict exclusion of nonsteroidal anti-inflammatory drugs including COX-2 inhibitors. A short course of prednisolone or renal dose-adjusted colchicine may also be used for treatment.

Urate-lowering therapies such as Allopurinol and Febuxostat should be avoided in patients who are concurrently taking Azathioprine. Azathioprine is rapidly and almost completely converted to its active metabolite 6-mercaptopurine (6-MP) in the liver under physiological state. 6-MP is then catabolised by xanthine oxidase (XO) or thiopurine methyltransferase to inactive metabolites. Xanthine oxidase inhibitors such as Allopurinol and Febuxostat substantially inhibit the catabolism of 6-MP. The resultant accumulation 6-MP causes significant myelosuppression manifesting in potentially life-threatening pancytopenia.^{14, 15}

Probenecid, a uricosuric agent, would be the option for urate-lowering therapy in the case above. If Probenecid fails to control her gout or if the creatinine clearance is too low to allow its use, consideration may be given to a change in immunosuppressive agents. For example, conversion from Azathioprine to Mycophenolate Mofetil (to allow the introduction of XO inhibitor) or a conversion from Ciclosporin to Tacrolimus (the former having a hazard ratio of gout development of 1.25 times that of Tacrolimus).¹³

CONCLUSION

Kidney transplantation offers the lowest mortality rates, lowest healthcare burden, and highest quality of life for patients with ESKD on renal replacement therapy. With the rising incidence of ESKD in Singapore and longevity of KTRs, we anticipate the number of KTRs to increase with time. Partnership between the family physician and the nephrologist should be enhanced to care for this group of patients who remain vulnerable to the detrimental effects of drug-drug interactions.

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