Management of Medications in Organ Transplantation

The First Affiliated Hospital, Sun Yat-sen University

Pan Chen

Pan Chen Ph.D.
Deputy Director, the Department of Pharmacy at the First Affiliated Hospital of Sun Yat-sen University

- Dr. Pan Chen currently serves as the Deputy Chief Pharmacist and Master's Supervisor, as well as the Deputy Director of the Department of Pharmacy at the First Affiliated Hospital of Sun Yat-sen University.

- Dr. Chen serves on the Clinical Pharmacology/Quantitative Pharmacology Committee of the Chinese Pharmacological Society; chairs both the Immunosuppressive Pharmacy Committee of Guangdong Pharmaceutical Association

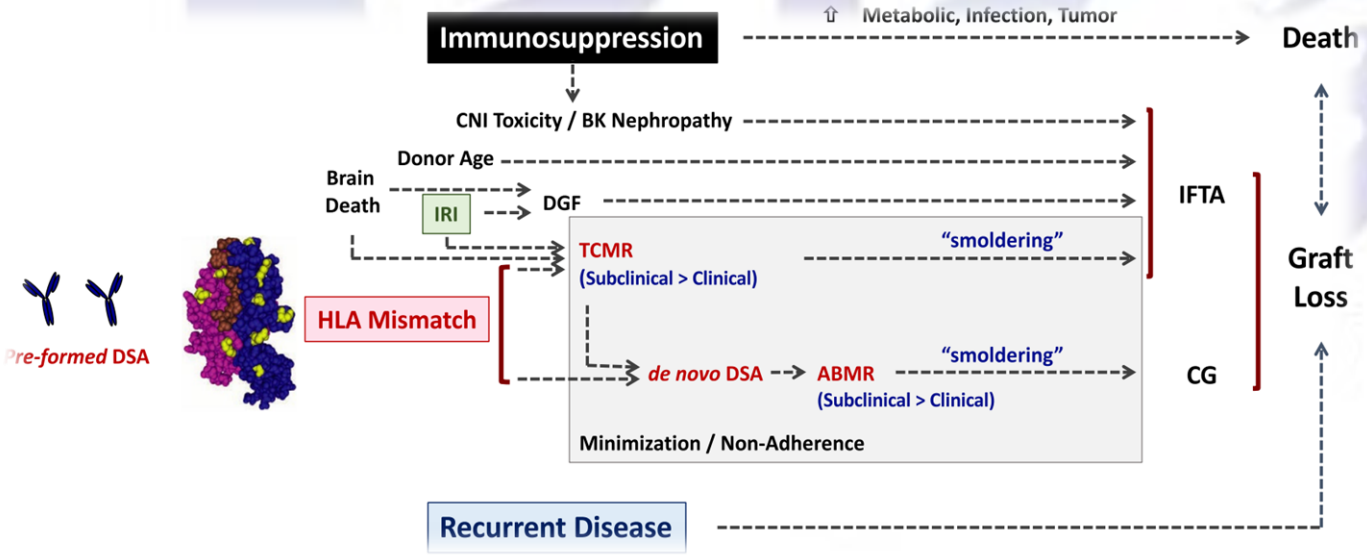
- Dr. Chen is actively involved in clinical pharmacy within the organ transplant center and holds qualifications as a clinical pharmacist educator in organ transplantation, accredited by the Chinese Medical Association. His primary research interests lie in multi-omics-based personalized administration of immunosuppressant.

- His research has been supported by the National Natural Science Foundation of China. He has published over 30 articles in journals such as the *BJP*, *BJCP*, *DMD* and *Rheumatology*. In recognition of his contributions to clinical pharmacy, he was awarded Outstanding Clinical Pharmacist by the Chinese Medical Association in 2018, and recognized as Outstanding Talent in Hospital Pharmacy by the Chinese Pharmaceutical Society in 2021.

Contents

Introduction

- Organ transplantation is an effective medical method to save patients with end-stage organ failure, saving tens of thousands of patients' lives every year.
- With the development of transplant surgery and the increase of donors, the 5-year survival rate of patients has been greatly improved, and the proportion of patients with long-term survival has also increased year by year.
- The complexity and persistence of drug administration for organ transplant recipients bring both opportunities and challenges for pharmacists in the field of organ transplantation.



Am J Transplant. 2020;20:12–22

Responsibilities of the sot pharmacist

Pretransplant

- Identify contraindications to transplantation
- **Plan induction and maintenance of IMS regimens**
- **Identify patients who are colonized with resistant organisms**
- **Recommend appropriate perioperative antimicrobials based on colonization with resistant organisms**
- Participate in transplant candidate selection by communicating medication related concerns
- Design vaccination schedules
- Assess medication adherence and health literacy level
- Identify and educate low health literacy patients
- Provide education on posttransplant information and expectations to all patients
- Identify patients at risk of poor adherence to help overcome barriers
- **Identify financial or other barriers to obtaining prospective posttransplant medications**
- **Identify any major drug interactions with IMS to potentially eliminate before transplantation**

American Journal of Transplantation 23 (2023) 1375–1387

Responsibilities of the sot pharmacist

Peritransplant

- **Attend daily rounds with a prospective evaluation of individual pharmacotherapy**
- **Coordinate development and implementation of drug therapy protocols, assist in ensuring protocol adherence, and measure outcomes with these protocols**
- **Provide medication reconciliation, medication therapy management, and discharge counseling**
- **Provide pretransplant and posttransplant medication education**
- **Optimize pharmacotherapy to maximize patient and center-specific outcomes**
- **Provide comprehensive medication management including but not limited to therapeutic drug monitoring**
- **Provide pharmacotherapeutic support evidenced by daily documentation of activities in the patient's medical record**
- Facilitate transplant discharge medication access by identifying and mitigating barriers to acquisition and uses- Coordinate and support effective transitions of care (between phases of transplant care, during pediatric to adult transition of care, and with transfer to other providers or institutions)

American Journal of Transplantation 23 (2023) 1375–1387

Responsibilities of the sot pharmacist

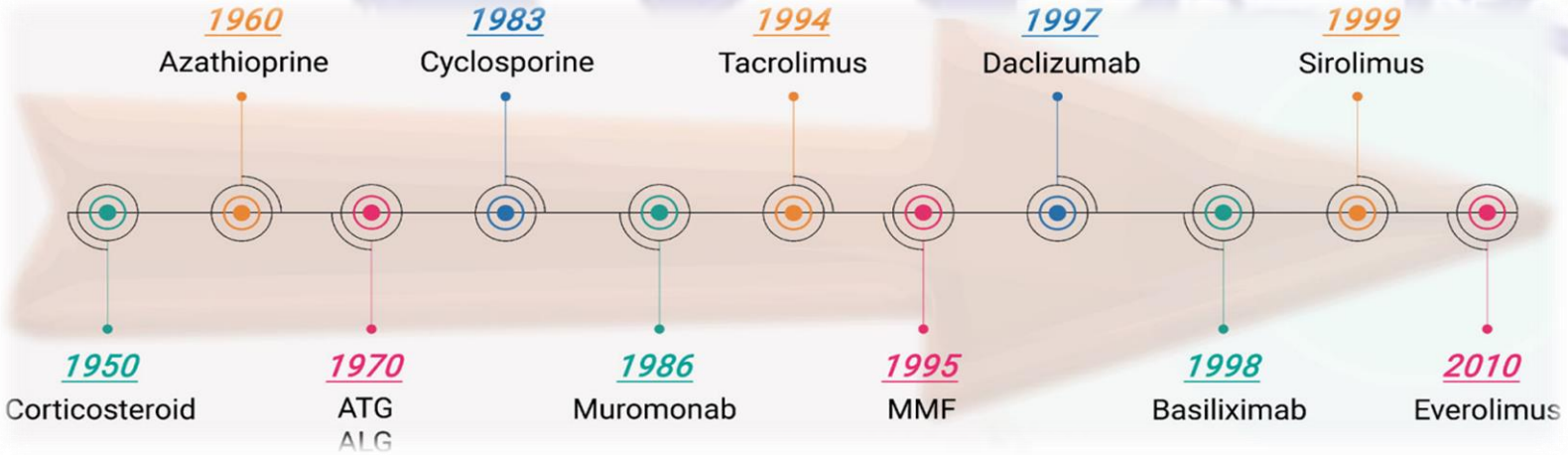
Posttransplant/outpatient

- **Manage IMS regimen**
- **Manage chronic disease states**
- Follow-up vaccination schedules
- Ensure continued proper access to medications and medical supplies
- Practice stewardship endeavors to optimize outcomes
- Coordinate and support effective transitions of care (between phases of transplant care, during pediatric to adult transition of care, and with transfer to other providers or institutions)
- **Assess and encourage medication adherence by identifying and removing barriers where possible- Provide ongoing education**

American Journal of Transplantation 23 (2023) 1375–1387

Immunosuppressants for SOT recipients

- Calcineurin Inhibitors: Cyclosporine/Tacrolimus
- Mycophenolic Acids: Mycophenolate Mofetil/Mycophenolate Sodium
- Azathioprine
- Sirolimus
- Glucocorticoids: Prednisone/methylprednisolone
- Basiliximab/Anti-thymocyte Globulin



Immunopharmacology and Immunotoxicology, 43:6, 651-665

Immunosuppressive maintenance therapy in renal transplantation

Classification	Drug name	Initial dosing regimen	Basis for dosing adjustment
CNI	CsA	3-6 mg/kg/d in 2 divided doses	The dose can be adjusted according to drug concentration. Targeted ranges of trough concentration are 150-300 ng/mL in the first month post-transplantation, 150-250 ng/mL in 1-3rd month post-transplantation, 120-250 ng/mL in 4-12th month post-transplantation, and 80-120 ng/mL in more than 1 year post-transplantation.
	Tac	0.05-0.15 mg/kg/d in 2 divided doses (once daily for extended release capsules)	The dose can be adjusted according to drug concentration. Targeted ranges of trough concentration are 8-12 ng/mL in the first month post-transplantation, 6-10 ng/mL in 1-3rd month post-transplantation, 4-10 ng/mL in 4-12 month post-transplantation, and 4-8 ng/mL in more than 1 year post-transplantation. For denovo anti-donor specific antibody positive renal transplant recipients with stable renal function, maintenance of trough concentrations greater than 6 ng/mL is recommended. The initial dose can be adjusted according to the cytochrome P450 (CYP) 3A5 genotype of patients: standard dose for slow metabolizer (CYP3A5*3/*3); 1.5-2 times of the standard dose for rapid metabolizer (CYP3A5*1/*1 or CYP3A5*1/*3) but the daily dose should not higher than 0.3 mg/kg.

Immunosuppressive maintenance therapy in renal transplantation

Classification	Drug name	Initial dosing regimen	Basis for dosing adjustment
Antimetabolic drugs	MMF	0.75-1.0 g twice daily	The dose can be adjusted according to MPA concentration. The effective therapeutic AUC (determined by the HPLC method) range of MPA is 30-60 (mg·h)/L. The values measured by the enzyme-multiplied immunoassay technique (EMIT) are higher than that measured by the HPLC method, so the targeted range of AUC increases accordingly.
	EC-MPS	360-720 mg twice daily	The dose can be adjusted according to MPA concentration. The effective therapeutic AUC (determined by the HPLC method) range of MPA is 30-60 (mg·h)/L. The values measured by the EMIT are higher than that measured by the HPLC method, so the targeted range of AUC increases accordingly.

Immunosuppressive maintenance therapy in renal transplantation

Classification	Drug name	Initial dosing regimen	Basis for dosing adjustment
Antimetabolic drugs	Azathioprine	1-2 mg/kg once daily	The dose can be adjusted according to the patient tolerance.
	Mizoribine	2-3 mg/kg/d, taking a dose all at once in the morning or in 2 divided doses; gradually reducing to 1-3 mg/kg/d for maintenance treatment.	The dose can be adjusted according to drug concentration. Targeted range of trough concentration: 1-3 mg/L.
	Leflunomide	When BK virus infection or BK virus nephropathy is confirmed, leflunomide can be used for maintenance therapy, with a loading dose of 50 mg once daily for the first 3 to 5 days, followed by 20 mg once daily.	The dose can be adjusted according to the patient tolerance.
mTOR inhibitor	SRL	Loading dose of 6 mg once daily for the first day, followed by 2 mg once daily.	The dose can be adjusted according to drug concentration. Targeted range of trough concentration: 4-8 μg/L.
Glucocorticoid	Prednisone	Starting at 10-60 mg/d, gradually decreasing to 10-15 mg/d by day 30 post-transplantation, 10 mg/d in 2-3rd month post-transplantation, and adjusting to 5.0-7.5 mg/d or a lower dose for maintenance therapy after half a year.	The dose can be adjusted according to the patient tolerance.

Blood concentration monitoring of immunosuppressants

CsA

- The peak concentration (C_2) or trough concentration (C_0) of CsA in blood can be monitored after transplantation.
- **Targeted ranges of C_0 and C_2 are 150-300 ng/mL and 1000-1500 ng/mL within the first month post-transplantation, 150-250 ng/mL and 800-1200 ng/mL in the 1-3rd month post-transplantation, 120-250 ng/mL and 600-1000 ng/mL in the 4-12th month post-transplantation, and 80-120 ng/mL and >400 ng/mL in more than 1 year post-transplantation, respectively.**
- For initial treatment at the early postoperative stage, CsA concentrations can be monitored every other day until the targeted range is reached.
- CsA concentrations should be measured when patients exhibit decreased renal function that indicates possible rejection or CsA related nephrotoxicity, or when CsA concentrations may be altered.

Tac

- The blood trough concentration of Tac can be monitored after transplantation and the monitoring frequency is the same as CsA.
- **Targeted ranges of trough concentrations are 8-12 ng/mL within the first month post-transplantation, 6-10 ng/mL in the 1-3rd month post-transplantation, 4-10 ng/mL in the 4-12th month post-transplantation, and 4-8 ng/mL in more than 1 year post-transplantation.**

Blood concentration monitoring of immunosuppressants

MPA

- The area under the concentration-time curve (AUC) of MPA can be monitored after transplantation.
- **The AUC of MMF can be calculated by the 4-point method of blood concentration at 0.5 h (C0.5), 1.5 h (C1.5), 4 h (C4), and 9 h (C9), or by the 10-point method at 0 h (C0), 0.5 h (C0.5), 1 h (C1), 1.5 h (C1.5), 2 h (C2), 3 h (C3), 4 h (C4), 6 h (C6), 9 h (C9), and 12 h (C12); the AUC of EC-MPS can be calculated by the blood concentration at 0 h (C0), 1 h (C1), 2.5 h (C2.5), 4 h (C4), 5 h (C5), 6 h (C6), 7 h (C7), 8 h (C8), 9 h (C9), 10 h (C10), and 12 h (C12).**
- The effective therapeutic range of AUC determined by HPLC method is 30-60 (mg·h)/L.
- It is recommended to monitor the AUC of MPA in the early stage after transplantation and if adverse drug reactions occur.

Sirolimus

- The target trough concentration in blood of SRL is 4-8 μg/L post-transplantation.
- The trough concentration can be monitored after 3 to 4 days of the loading dose.
- when the dose is adjusted, concentration monitoring should be performed after the new maintenance dose is continuously used for 7-14 days.

Immunosuppressive combination regimen

CNI-based triple immunosuppressive regimen

"Tac + MPA + glucocorticoids" was recommended as the standard immunosuppressive regimen.

- Tac is usually initiated right after surgery and its C0 should be measured on day 3 of therapy. The dose should be adjusted in time if necessary to attain the C0 target within 1 week post-transplantation.
- **Testing the patient's CYP3A5 genotype before transplantation will help to determine the initial dose of Tac.** Mutations at the CYP3A5*3 (rs776746) locus will slow down the metabolism of Tac in vivo, so a standard dose is sufficient for slow metabolizers; rapid metabolizers should take 1.5 to 2.0 times of the standard dose, but the daily dose should not higher than 0.3 mg/kg.
- The dose of MPA drugs should take into account the patient's gender, body weight, test indicators (e.g., blood leukocyte count) and tolerance to the drug.
- The routine use of glucocorticoids follows the principle of decreasing doses, with prednisone, for example, starting at 30 mg/d and decreasing gradually to 5.0-7.5 mg/d or lower for maintenance therapy.

Immunosuppressive combination regimen

CNI-based triple immunosuppressive regimen

- For low-risk individuals who took the CNI-based immunosuppressive regimen for a long time and have not experienced rejection, the maintenance treatment can be switch to a CNI-free immunosuppressive regimen if they develop a chronic increase in serum creatinine that is confirmed to be related to the CNI nephrotoxicity. The use of CNI-free immunosuppressive regimens is currently controversial, and is not recommended, particularly for initial use after renal transplantation, which requires close attention to safety and tolerability issues.
- To avoid nephrotoxicity induced by CNI in the elderly patients, patients with delayed recovery of transplanted kidney function or general donor kidney quality are usually sensitive to CNI nephrotoxicity, an immunosuppressive regimen of low CNI combined with adequate/enhanced MPA can be used.

Drug interactions of immunosuppressants

Interactions of antifungal drugs and immunosuppressants

Antifungal drugs	Affected immunosuppressants		
	CsA	Tac	SRL
Fluconazole	Increases CsA concentration	Up to 5-fold increase of Tac (oral) concentration and nosignificant change of Tac (intravenous)	Increases SRL concentration
Itraconazole	Increases CsA concentration, which recommends reduction of CsA dose in half	Increases Tac concentration	Increases SRL concentration
Voriconazole	70% increase in AUC with CsA, which recommends reduction of CsA dose in half	2-fold increase in C_{max} and 3-fold increase in AUC with Tac, which recommends two-third reduction in Tac dose	6.6-fold increase in C_{max} and 11-fold increase in AUC with SRL, which avoid combination
Posaconazole	Increases CsA concentration, which recommends 25% reduction in CsA dose	121% increase in C_{max} and 358% increase in AUC with Tac, which recommends two-third reduction in Tac dose	6.7-fold increase in Cmax and 8.9-fold increase in AUC, which recommends nine-tenth reduction in SRL dose

Drug interactions of immunosuppressants

Drug interactions of CsA

Type of Drug Interaction	Interaction Strength	Co- administered drugs
Increase CsA concentration	Class D	Clarithromycin, chloramphenicol, **voriconazole, itraconazole, posaconazole, ketoconazole**
	Class C	Pentaerythritol, azithromycin, erythromycin, **diltiazem**,nicardipine, verapamil, metoclopramide, amiodarone, propafenone, fluconazole
Reduce CsA concentration	Class D	**Rifampicin, phenobarbital, carbamazepine, phenytoin sodium**
	Class C	Rifabutin, methylprednisolone, prednisone, prednisolone, oxytetracycline
	Class X	Atorvastatin, simvastatin, lovastatin, doxorubicin, Tac
Concentration affected by CsA	Class D	Rosuvastatin, fluvastatin, pravastatin, SRL, reserpine, glibenclamide, colchicine, etoposide
	Class C	Dabigatran etexilate, digoxin
Efficacy affected by CsA	Class D	Caspofungin, some NSAIDs
	Class C	Aminoglycosides, amphotericin B, angiotensin II receptor antagonists

Drug interactions of immunosuppressants

Drug interactions of Tac

Type of Drug Interaction	Interaction Strength*	Co- administered drugs
Increase Tac concentration	Class D	**Voriconazole, itraconazole, posaconazole, ketoconazole, fluconazole**, clarithromycin, chloramphenicol, **ritonavir**
	Class C	**Wuzhi preparation**, clotrimazole, erythromycin, azithromycin, diltiazem, verapamil, estrogen derivatives, proton pump inhibitors, levofloxacin, metoclopramide, tigecycline
Reduce Tac concentration	Class D	**Rifampicin, phenobarbital, carbamazepine, phenytoin sodium**
	Class C	Rifabutin, rifapentine, nafcillin sodium
Concentration affected by Tac	Class X	CsA
	Class C	Colchicine, estrogen derivatives
Efficacy affected by Tac	Class C	Aminoglycosides, some NSAIDs, amiodarone

Drug interactions of immunosuppressants

Drug interactions of MPA

- When MPA is combined with drugs that interfere with the enterohepatic circulation, the latter decreases the efficacy of MPA.
- MPA, when combined with acyclovir (Class C) or ganciclovir (Class C), both competitively excreted through the renal tubules, leading to increasing blood concentration of antivirals and increasing risk of adverse drug reactions.
- Magnesium hydroxide (Class D), aluminum hydroxide (Class D) may reduce the absorption of MPA when combined with MPA due to antacid effect or chelation. So the combination of EC-MPS is not recommended, while if combined with MMF. it is recommended to take aluminum hydroxide at least 2 h after the administration of MMF.
- MPA does not affect the pharmacokinetics of CsA, but **CsA (Class D) affects the hepatic and intestinal circulation and can decrease blood concentration of MPA.**
- Proton pump inhibitors (Class C) may reduce blood concentrations of MMF when used in combination with MMF due to interference with absorption of MPA and/or hydrolysis due to elevated gastric pH, whereas EC-MPS are not affected by this, making EC-MPS more advantageous when using proton pump inhibitors.
- Rifampicin (Class D) may reduce blood concentration of MPA by induction of CYP3A4 when combined with MPA.

Chronic disease management in renal transplant patients

Management Content：Focus of early follow-up

Early follow-up is performed within 3 months after renal transplantation. The patients are followed up 1-2 times a week within the first month post-transplantation and once every 1-2 weeks in the 2-3rd months post-transplantation.

◆ **What physicians concerned about**

- **The assessment is based on the patient's condition and requires an assessment of immunosuppressant therapy, including the achievement of plasma concentration and determination of rejection reactions.** Annual screening should include dermatological and cardiovascular examinations, and the recipients should also be subjected to routine examination programs, special types of examinations and tumor screening.
- **Routine tests** include routine blood and urine test, blood biochemistry (liver function, kidney function, blood glucose, blood lipids), urine microalbumin, 24h Urine protein measurement, immunosuppressant plasm concentration and ultrasound of allograft kidneys. Special tests include lymphocyte subset tests, immunoglobulin series tests, virus tests (e.g., BK virus, cytomegalovirus, EB virus, JC virus, hepatitis B virus, hepatitis C virus), panel reactive antibody, donor-specific antibodies.
- **Tumor screening** includes imaging tests such as chest X-ray film or lung CT, ultrasound of the abdomen, urinary system and thyroid. Female patients may undergo breast and gynecologic ultrasound and be examined for tumor markers.

Chronic disease management in renal transplant patients

Management Content：Focus of early follow-up

◆ **What pharmacists concerned about**

- The medication history of the patients is collected for drug reorganization, and the indication of drug use, whether the drug administration plan is reasonable and the administration method is correct are reviewed;
- Monitor blood concentration of drugs, evaluate the therapeutic effects and safety of drugs, and make recommendations for modification of dosing regimens when necessary;
- Identify, resolve, and prevent drug-related problems;
- Report and manage (suspected) adverse drug events;
- Manage potential or actual drug-drug or drug-food interactions;
- Compliance education.

Chronic disease management in renal transplant patients

Management Content：Focus of interim follow-up

Interim follow-up is performed once every 2-4 weeks in the 4-6th months post-transplantation.

- **What physicians concerned about**

The focus of this phase of follow-up is **the timely detection and management of acute rejection reactions and various infections (especially pulmonary infections)**. According to the patient's individual situation, follow-up examinations such as routine examinations, special types of examinations and tumor screening are selectively prescribed.

- **What pharmacists concerned about**

It is necessary to strengthen the monitoring of the blood concentration of immunosuppressants, timely adjust the dosage of drugs, develop personalized drug regimens, and guard against rejection reactions and drug toxicity; at the same time, the monitoring of adverse reactions to immunosuppressants should be strengthened, focusing on events such as hypertension, hyperglycemia, hyperuricemia and dyslipidemia.

- **Content of medication education for patients**

At this stage, the blood concentrations of immunosuppressants are still in the intensive adjustment period, the immune function of the body is still at a low level, and the risk of pulmonary infection is greater; therefore, the recipients should be informed to strengthen the prevention and self-monitoring of pulmonary infection.

Chronic disease management in renal transplant patients

Management Content： Focus of long-term follow-up

The patients are followed up once a month in the 7-12th month post-transplantation; once a month or twice a quarter in the 13-24th month; every 1-2 months from 3rd to 5th year, and at least once every quarter after 5 years post-transplantation. For recipients with unstable graft function, follow-up frequency should be increased as appropriate.

◆ What physicians/pharmacists concerned about

- the immunosuppressant dose is at the maintenance level, and the ability of the recipient to resist infection is gradually recovering, allowing him to resume normal life and work.
- The key points of follow-up at this stage are as following: **focusing on the monitoring and prevention of cardiovascular diseases, infections, and malignant tumors, actively dealing with abnormalities of hypertension and metabolic indicators**, and selectively prescribing follow-up examinations such as routine examinations, special types of examinations and tumor screening examinations according to the individual conditions of patients.

Management of adverse reactions

Common adverse reactions of drugs

Glucocorticoids

- Glucocorticoids can induce or aggravate infection; predispose patients to post-transplant diabetes and osteoporosis, metabolic bone disease; hinder tissue repair, delay granulation tissue formation, hinder healing of surgical wounds, trauma and other ulcers; long-term use may cause centripetal central obesity, full-moon face, buffalo back hump, hirsutism, acne, peptic ulcers, muscle atrophy and weakness, hypertension, hyperlipidemia, growth inhibition in children and hyperalgesia.

Management of adverse reactions

Common adverse reactions of drugs

CsA

- N**ephrotoxicity** manifested as increased serum creatinine levels, decreased glomerular filtration rates.
- **Hepatotoxicity** manifested as elevated liver enzymes and bilirubin. The hepatotoxicity usually happens in the first month of administration with high-dose CsA and decreases after CsA dose reduction.
- **Neurotoxicity** manifested as impaired consciousness, convulsions, visual disturbances, loss of motor function, dyskinesia, and psychiatric disorders.
- Hyperkalemia, gastrointestinal reactions (e.g., anorexia, nausea and vomiting), hirsutism, gingival hyperplasia with bleeding and pain.
- Allergic reactions, pancreatitis, leukopenia, Raynaud's syndrome, diabetes mellitus and hematuria are less common adverse reactions.
- An increased risk of lymphoma and other malignant tumors.

Tac

- Opportunistic infections (e.g., polyomavirus infection and cytomegalovirus), **neurological reactions** (e.g., headache, insomnia, weakness, tremor, and abnormal sensation), and gastrointestinal reactions (e.g., nausea, vomiting and diarrhea).
- Other common adverse events include hypertension and leukocytosis.
- The toxicities of kidney and liver, nephrotoxic reactions, hyperkalemia and hypomagnesemia may occur.
- **Islet cytotoxicity of Tac can lead to secondary hyperglycemia.**
- An increased risk of lymphoma and other malignancies in patients receiving Tac.

Management of adverse reactions

Common adverse reactions of drugs

MMF and mycophenolate sodium

- Adverse events include opportunistic infections such as cytomegalovirus and herpes virus infections;
- the incidence of **myelosuppression** such as leukopenia in peripheral blood is around 2%, which should be closely monitored during the administration, especially at the beginning.
- Common **gastrointestinal reactions** (e.g., nausea, vomiting and **diarrhea**) are mostly dose-dependent.
- When combined with other immunosuppresants, MMF and mycophenolate sodium may increase the risk of lymphoma and other malignant tumors (especially skin cancer).

Mizoribine

- **Hyperuricemia** is a common adverse reaction. Compared to azathioprine or anti-proliferative MMF, myelosuppressive effects on mizoribine such as thrombocytopenia and erythrocytopenia are less severe. Loss of appetite, nausea, abdominal pain, and diarrhea may occur occasionally.

Management of adverse reactions

Common adverse reactions of drugs

Sirolimus

- The most frequent adverse reaction is **hyperlipidemia**, the mechanism of which is still unclear.
- The risk of angioedema is increased when sirolimus is combined with angiotensin converting enzyme inhibitors.
- Sirolimus is closely associated with the development of **proteinuria**, especially in recipients with diabetes mellitus after conversion.
- It is possible to induce sirolimus-related interstitial pneumonia.
- Moreover, sirolimus can lead to myelosuppression, poor incisional healing, peripheral edema, lymphedema, pleural effusion, and pericardial effusion.
- Sirolimus is shown to increase the incidence of infection and may possibly induce lymphoma and skin malignancies.

Management of postoperative complications

Patients with diabetes mellitus

- For patients who develop or are at high risk of post-transplant diabetes mellitus, an early glucocorticoid withdrawal strategy with **close monitoring of Tac blood concentrations** is recommended.
- After the first month post-transplantation, the withdrawal of corticosteroids may be considered for stable recipients without rejection, while Tac dosage is reduced and lower blood levels (4-7 μg/L) are maintained, to improve or reverse glucose metabolism disorders.

Patients with hypertension

- **Corticosteroids are an important factor of affecting post-transplant hypertension**, but the effect tends to decrease with the application of a new immunosuppressive regimen.
- **Tac has a less impact on post-transplant hypertension than CsA**, the conversion to a Tac-based immunosuppressive regimen may be considered if hypertension is determined to be associated with CsA use.
- Sirolimus has a lesser effect on hypertension.
- Common immunosuppression modification regimens include: early post-transplant lower-dose CNI, CNI replacement and reduction or withdraw of corticosteroids.

Management of postoperative complications

Patients with hyperlipidemia

- CsA, sirolimus and corticosteroids can elevate blood lipid levels.
- Since Tac has a low effect on blood lipid, **it is recommended for patients with hyperlipidemia to take a Tac-based immunosuppressive regimen, as well as consider to reduce or withdrawal corticosteroids**. If the hyperlipidemia after transplantation is confirmed to be associated with the use of immunosuppresants and the transplanted kidneys are functionally stable, it can be considered to take a replacement of CsA with Tac or take a regimen of reduced dose of CNI combined with mycophenolic acid.
- **Sirolimus should be administrated with caution in severe dyslipidemia**.
- Dyslipidemia can occur as early as the first 3 months after transplantation, with the highest incidence of dyslipidemia occurring at the 6th to 9th months post-transplantation. Therefore, patients' blood lipid levels should begin to be monitored during the pre- and peri-operative period, and be reviewed monthly within 6 months after transplantation. According to lipid levels and treatment effect, blood lipid as well as urine protein, should be monitored every 1-3 months from 7th to 12th months post-transplantation, and should follow up at least once a year.

Management of postoperative complications

Patients with tuberculosis (TB)

- Since rifamycin has multiple drug interactions with immunosuppresants, it is suggested to treat active TB preferably before transplantation.
- For patients with non-severe TB, an anti-TB regimen without the combination of rifamycin may be considered as well as the use of rifapentine instead of rifampicin to reduce interactions with CNI and sirolimus.
- **Blood levels of CNI and sirolimus should be monitored during treatment**. In kidney transplant patients who require concomitant rifampicin antituberculosis therapy, acute rejection can be induced by a sudden drop in Tac concentrations due to rifampicin.
- For some patients, it is specially difficulty to achieve the desired Tac concentration even after increasing dose. Thus, the drug interaction between rifampicin and Tac has become an important cause of transplant kidney failure in TB patients. **The additional administration of Wuzhi tablets can both increase the Tac blood concentration up to the therapeutic window to reduce the risk of acute rejection, and keep the anti-tuberculosis treatment with rifampicin.**
- Post-transplant TB reminds lower immune function of patients. Under the premise of stable transplanted kidney without adverse reactions to anti-tuberculosis drugs, effective anti-tuberculosis therapy should be administered with sufficient quantity and duration as much as possible. **It is not advised to reduce dose of anti-tuberculosis drugs only due to drug interactions or deliberately increase the concentration of CNIs.**
- **The function of the transplanted kidney, T-lymphocyte subpopulation and urinary routine can be monitored dynamically to promptly adjust treatment regimens when changes are detected.**

Medication instructions for pregnant and lactating patients

Relatively safe drugs with low risk of fetal malformation

- **Recommendations for hormone use:**

Prednisone and methylprednisone are relatively safe to use in all periods of pregnancy. Methylprednisone has a similar placental transfer rate to that of prednisolone, but doses less than 15 mg/d (prednisone or its equivalent) are preferred. The use of glucocorticoids containing fluoride in their structures should be avoided in early pregnancy, such as dexamethasone and betamethasone. Both prednisone and methylprednisone can be used during breastfeeding. However, breastfeeding should be avoided within 4 h of prednisone administration if the dose is more than 20 mg/d.

Medication instructions for pregnant and lactating patients

Relatively safe drugs with low risk of fetal malformation

- **Recommendations for CsA use:**

CsA and Tac can increase the risk of neonatal complications such as low body mass infants and intrauterine growth retardation, but there is no increased risk of the incidence of congenital malformations in the fetus. **It is relatively safe to use the lowest effective dose of CsA throughout pregnancy**. Mothers taking CsA should not be prevented from breastfeeding, which can be allowed when the benefits outweigh harms to the infant.

- **Recommendations for Tac use:**

It is relatively safe to use the lowest effective dose of Tac throughout pregnancy. Tac is excreted in breast milk, but the amount in breast milk is only 1% of the maternal dose, and the proportion reaching the newborn is even lower. Mothers taking Tac should not be prevented from breastfeeding, which can be allowed when the benefits outweigh harms to the infant.

Medication instructions for pregnant and lactating patients

Drugs with a high risk of fetal malformation

- **MMF and mycophenolate sodium:**

MMF and mycophenolate sodium increase the risk of early miscarriage and congenital malformations during pregnancy. Abnormal limb and face are the most common congenital malformations. **Both medicines are contraindicated during pregnancy.** They should be discontinued at least 3 to 6 months prior to planned pregnancy or egg retrieval, which may be replaced with azathioprine at doses not exceeding 2 mg/kg. There are no available data on the excretion of MMF and mycophenolate sodium in breast milk, therefore, it is not recommended to use these drugs during breastfeeding.

Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Case presentation

- A 7-month-old male infant was diagnosed with hereditary nephrotic syndrome (*NPHS1* gene complex heterozygous mutation, chronic kidney disease stage 1).
- Considering the long-term benefit, the infant received allograft kidney transplantation after relevant preoperative examination and exclusion of surgical contraindications.
- His body mass index was 13.93 kg/m^2, with a height of 59 cm and a weight of 4.85 kg.

Design of initiation immunosuppression protocol

- The immunosuppressive induction regimen consisted of basiliximab (10 mg I.V. on day 1 and day 4), methylprednisolone (50 mg I.V. for 3 days)
- The maintenance regimen consisted of cyclosporine (75 mg/day diluted with 20 mL of 5% normal saline, continuously intravenous pumping, 1 ml/h), mycophenolate mofetil (125 mg three times daily, nasal feeding) and prednisone (2.5 mg once daily initially, nasal feeding).

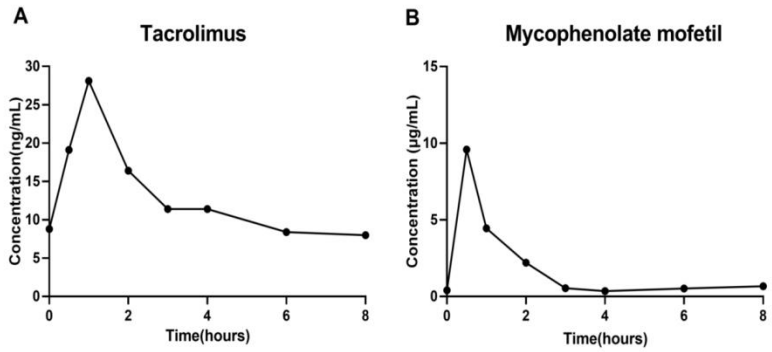
Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Adjustment of immunosuppressive regimen based on TDM

Post-transplantation days	Cyclosporine IV pumping			Tacrolimus Q8H		CREA(μmol/L)	eGFR(mL/min/1.73m²)	Cys C(mg/L)	ALT(U/L)	AST(U/L)
	daily dose(mg)	V(ml/h)	C_0(ng/ml)	daily dose(mg)	C_0(ng/ml)					
Day 1	75.00	1	**>500**			12	179.57	0.77	13	37
Day 2	25.00	2	**>500**			10	215.45	0.62	12	32
Day 3	5.00	2	**47.7**			9	239.34	0.81	10	27
Day 4	10.00	4	**120.6**			8	269.26	0.74	8	26
Day 6	20.00	2	**313.3**			10	215.45	0.81	9	33
Day 8	20	2	**311.2**			10	215.45	0.90	20	43
Day 13	18.00	2	**290.8**			9	239.34	0.92	22	46
Day 15				1.5		12	179.57	1.19	29	49
Day 18				1.5	13.4	14	153.83	1.44	**73**	**126**
Day 20				1.5	16.4	15	143.59	1.66	**75**	**114**
Day 22				0.75		14	153.83	1.45	**108**	**161**
Day 23				0.75	10.2	14	153.83	1.09	**95**	**81**
Day 25				0.75	7.9	13	165.70	1.04	**59**	**57**
Day 28				0.75	7.6	12	179.57	1.17	**65**	**67**
Day 30				0.75	8.1	15	143.59	1.07	**70**	**72**
Day 35				0.75		16	134.62	1.13	**50**	**55**
3 months after discharge*				0.525	8.8	21	102.57	1.08	**45**	**47**

PK parameters	Tacrolimus	Mycophenolate mofetil
Dose	0.525 mg	0.083 g
T_{max}	1 h	0.5 h
C_{max}	28.1 ng/ml	9.59 μg/ml
$T_{1/2}$	8.5 h	2.81 h
$AUC_{0\text{-}8h}$	**102.53 ng.h/ml**	**13.23 μg.h/ml**
V_d	20.93 L	25.46 L
CL	1706.9 ml/h	6273.62 ml/h
MRT	10.83 h	3.57 h



Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Question to be discussed

Why choose cyclosporine injection for continuous pumping and then change to tacrolimus orally?

- I.V. pumping avoids the influence of potential gastrointestinal disturbance on the absorption of CNI, and contribute to more rapid and stable anti-rejection effect.
- Tacrolimus is more suitable for long-term CNI anti-rejection therapy and has been shown to be more effective in preventing immune rejection and reducing kidney damage.

Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Question to be discussed

Why was the administration frequency of tacrolimus and mycophenolate designed to be Q8H?

- **Status:** Pediatric receptors require higher doses of tacrolimus and mycophenolic acid (mg/kg) than adults to achieve similar therapeutic C0 because drug elimination is faster in the pediatric population.
- **Countermeasures:** Increase the frequency of a single dose without change VS increase the frequency of a single dose without change
- **Note:** Given long-term medication adherence, dosing three times a day may not be friendly. For adults and school-age children, the frequency of Q8H administration is not an appropriate choice unless necessary, such as the occurrence of serious drug-related adverse reactions.

Maintain adequate anti-rejection while minimizing adverse reactions

Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Question to be discussed

Treatment window for Tacrolimus and mycophenolate in children?

- The IATDMCT consensus report recommends: for adult receptors at low immune risk, when combined with IL-2 receptor blocker induction therapy, tacrolimus has a C0 target range of 4-12 ng/mL (preferably >7ng/mL) and a minimum AUC0-12h threshold may be 150 ng ħ/mL; The target concentration of mycophenolic acid AUC0-12h is recommended to be 30-60 μg·h/mL.
- There is no strong evidence to support the recommendation of target C0 or AUC levels for both drugs in the pediatric population, especially when administered three times a day.
- According to the AUC0-8h of 102.53 ng ħ/mL and 13.23 μg·h/mL, the AUC0-24h of tacrolimus and Myfetil of this patient were 307.58 ng ħ/mL and 39.69 ng ħ/mL, respectively.
- The dose of tacrolimus and mycophenolate was maintained considering that the child had stable renal function but mild pediatric diarrhea.

Pharmacist-led case

Case: Immunosuppression scheme design for a 7-month-old infant receiving kidney transplantation

Question to be discussed

Identification of liver injury associated with CNI

- The infant's liver enzyme levels increased significantly immediately after the conversion from cyclosporine to tacrolimus.
- **Liver damage may not only be due to tacrolimus, cyclosporine that has not been eliminated may be a double risk factor for liver damage.**

Liver injury identificaiton: Cyclosporine vs. tacrolimus? A study of CNI-related liver injury based on real-world data needed.

Study of adverse drug reactions extended from case

Incidence, clinical phenotype, and susceptibility factors of tacrolimus-related liver injury in patients after kidney transplantation: a nested case-control study

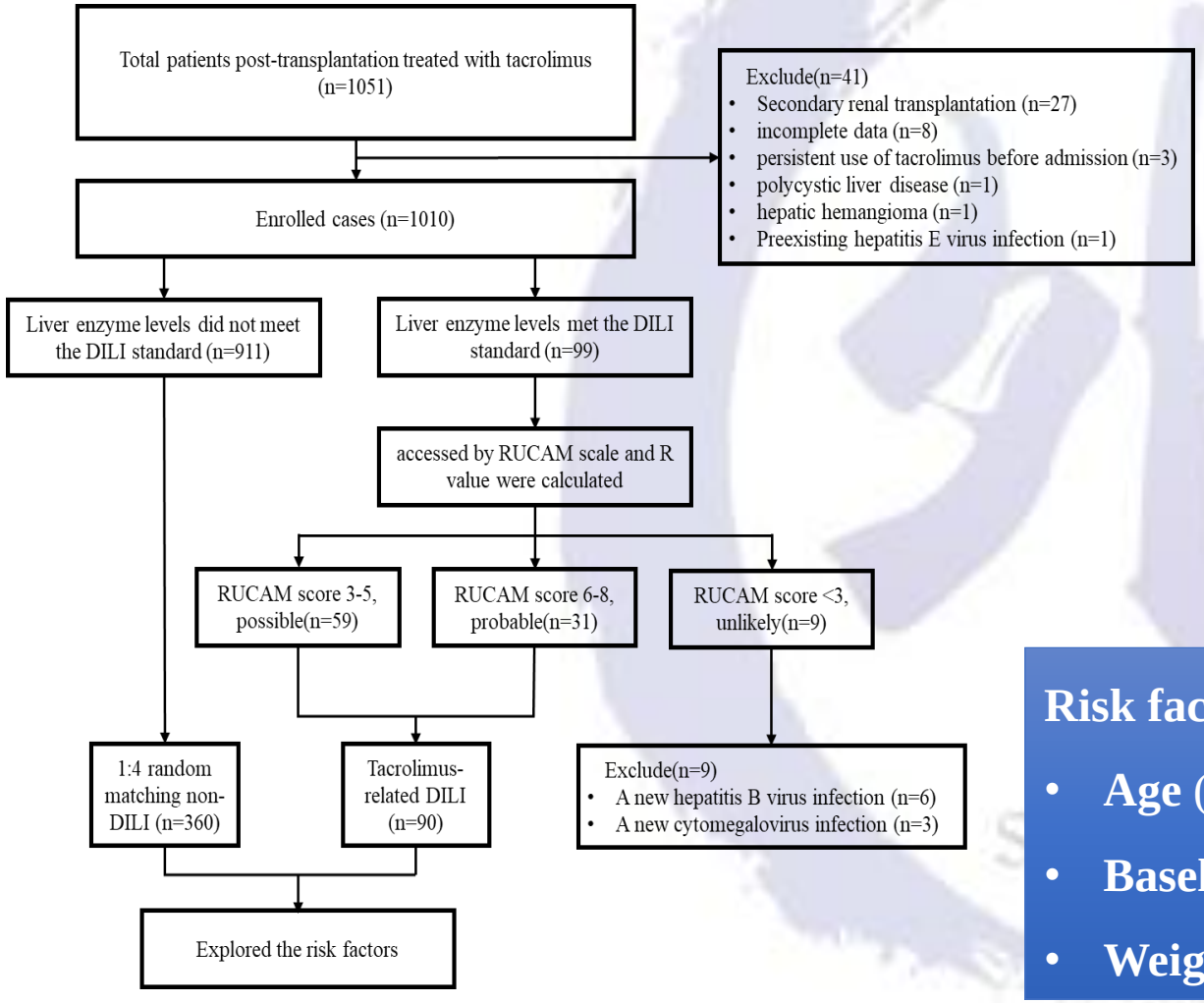
Real-world data of adverse drug reactions are more representative

At present, CNI-related liver injury is based on RCT of drug label and post-marketing case reports, and no real-world studies have been seen.

- The fact sheet describes the incidence as "common," with clinical manifestations of cholestasis and jaundice, hepatocyte injury and hepatitis, and cholangitis.Cases reported in the literature are increasing gradually.
- In the clinical practice of diagnosis and treatment, attention began to be paid to CNI related liver injury.

CNI related liver injury reports
1. J Physiol Biochem. 2016 Jun;72(2):133-44
2. Ren Fail. 2013;35(10):1434-5
3. Int J Clin Pharmacol Ther. 2015 May;53(5):363-71.
4. J Nippon Med Sch. 2008 Jun;75(3):187-91
5. Bone Marrow Transplantation, (1997) 20, 1095–1098
6. Transpl Int. 2012 Oct;25(10):e111-2
7. Ren Fail. 2013;35(5):735-7
8. Transplant Proc. 2000 Nov;32(7):1694-5
9. Transplantation. 1981 Dec;32(6):488-9
10. Ann Thorac Surg. 2010 May;89(5):1664-5.

Inclusion and exclusion process



- The incidence was 8.9% (95% CI = 7.2-10.7%).
- Cholestatic liver injury was the main manifestation (75.6%).
- Mild liver injury was predominant (98.9%).
- The median onset time of abnormal liver enzymes was 15 days.
- The median time to onset of liver injury was 42 days.
- Reduction was the main treatment method (87.8%).
- The outcome of liver injury was improved or recovered in 76.7% of patients.
- The median recovery time of liver injury was 65 days, and that of cholestasis was longer.

Risk factors:

- **Age** (OR = 0.971, 95% CI = 0.949–0.994, P = 0.006)
- **Baseline ALP level** (OR = 1.015, 95% CI = 1.006–1.025, P = 0.002)
- **Weight** (OR = 0.960, 95% CI = 0.940–0.982, P < 0.001)

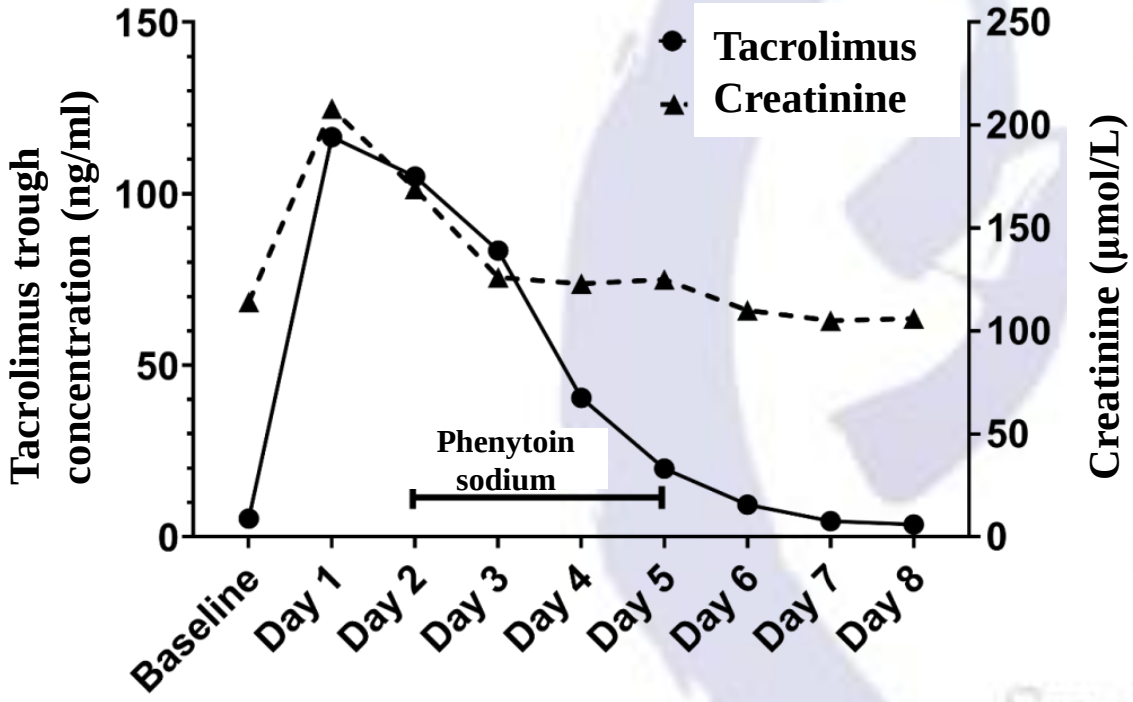
Pharmacist-led case

Treatment of Paxlovid induced tacrolimus overdose poisoning

- Male, 65 years old, 5 years after kidney transplantation
- Previous history: Tacrolimus 2.5 mg Q12H, mycophenol sodium 0.36 g Q12H, methylprednisolone 2 mg QD. The serum concentration of tacrolimus was maintained between 4.00 and 8.00 ng/mL, and the serum creatinine was 110umol/L
- The patient took Paxlovid (300 mg/100 mg Q12H) for COVID-19 for 1 day, and the dose of tacrolimus remained the same. After 1 day, the Tacrolimus trough concentration was 116.50 ng/mL, and serum creatinine was 169 μmol/L, and diarrhea occurred at the same time (full stool, no pus and blood stool, no abdominal pain, abdominal distension, and no nausea and vomiting).
- **Pharmacist suggestion: Stop Paxlovid and tacrolimus, and take phenytoin sodium orally (200 mg Q8H on day 1-2; Day 3 200 mg QD, 100 mg QN; Day 4 200 mg QD)**

Pharmacist-led case

Treatment of Paxlovid induced tacrolimus overdose poisoning



- Tacrolimus trough concentration decreased to 9.40 ng/mL, serum creatinine decreased to 110 μmol/L; After treatment, the patient had no diarrhea, abdominal pain, or abdominal distension.
- Two days after discontinuation of phenytoin sodium, tacrolimus and mycophenolate sodium were resumed. The trough concentration of tacrolimus was 5.60 ng/mL and the serum creatinine was 106 μmol/L.

Pharmacist-led case

Treatment of Paxlovid induced tacrolimus overdose poisoning

Pharmaceutical considerations in the rescue process of tacrolimus poisoning

- **It is difficult to remove excessive tacrolimus from the body by hemodialysis**: tacrolimus is highly bound to red blood cells and hemoglobin, and has poor water solubility and relatively large molecular weight.
- **Enzyme induction was used to counter enzyme inhibition**: This interaction ritonavir is a potent inhibitor of CYP3A enzyme and P-glycoprotein, resulting in a significant increase in their concentrations when combined with tacrolimus." However, compared with CYP enzyme inhibition, CYP enzyme induction takes longer to become effective.
- **Phenytoin sodium is more suitable for the rescue of toxicity caused by tacrolimus overdose**: common CYP3A enzyme inducers, rifampicin, phenytoin sodium, carbamazepine and St. John's wort, etc. Phenytoin sodium is a dose-dependent and potent CYP3A enzyme inducer, which is metabolized by the liver and has few short-term adverse reactions.
- **Phenytoin itself should be monitored for adverse effects**: Tacrolimus can also increase the concentration of phenytoin sodium in the body, and adverse reactions of phenytoin sodium may occur. Adverse central nervous system reactions such as drowsiness and ataxia should be monitored.

A pharmacokinetic study extending from the case

PK characteristics of nematavir/ritonavir in patients in renal transplantation

Pharmacokinetic parameters of nematavir

subject	HL_Lambda_z (h)	Tmax (h)	Cmax (ng/ml)	AUCINF_obs (h*ng/ml)
PR1	4.048473	4	7424.768	75502.65
PR2	3.650233	2	9658.756	85643.68
PR3	5.478869	2	11628.15	133057
PR4	19.30964	4	11391.88	348183.6
PR5	3.05566	4	7135.605	62518.56
PR6	5.185172	4	9069.312	97749.02
PR7	5.512281	4	8014.374	91146.99
PR8	41.2869	4	13349.57	777870.8
mean	10.9409	3.5	9709.051	208959
sd	13.34265	0.92582	2232.631	247707.9

Pharmacokinetic parameters of ritonavir

subject	HL_Lambda_z (h)	Tmax (h)	Cmax (ng/ml)	AUCINF_obs (h*ng/ml)
PR1	3.966672	4	1332.491	10932.3
PR2	3.382987	2	3520.134	20130.39
PR3	4.532894	4	5034.449	36235.85
PR4	3.392075	2	2873.712	23515.37
PR5		8	429.7295	
PR6	5.872688	4	941.3826	10242.02
PR7	3.27126	4	1331.725	9943.096
PR8	35.23341	0	942.5856	42891.88
mean	8.521713	3.5	2050.776	21984.41
sd	11.81439	2.329929	1597.236	13235.26

The pharmacokinetic profiles of nematavir/ritonavir in renal transplant recipients vary widely

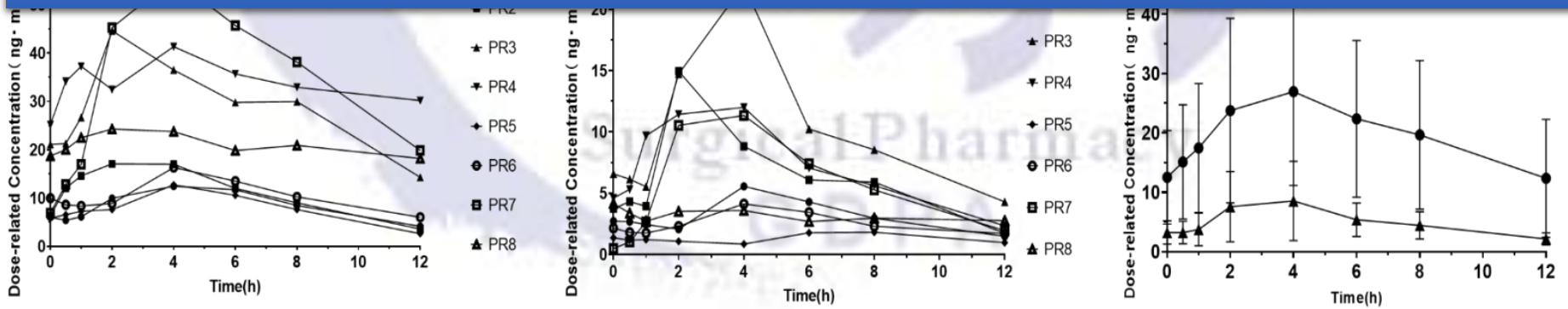


Figure 1. Plasma concentrations of Nirmatrelvir(A) and Ritonavir(B) versus time.

A pharmacokinetic study extending from the case

Nematavir/ritonavir interaction with tacrolimus in patients after renal transplantation

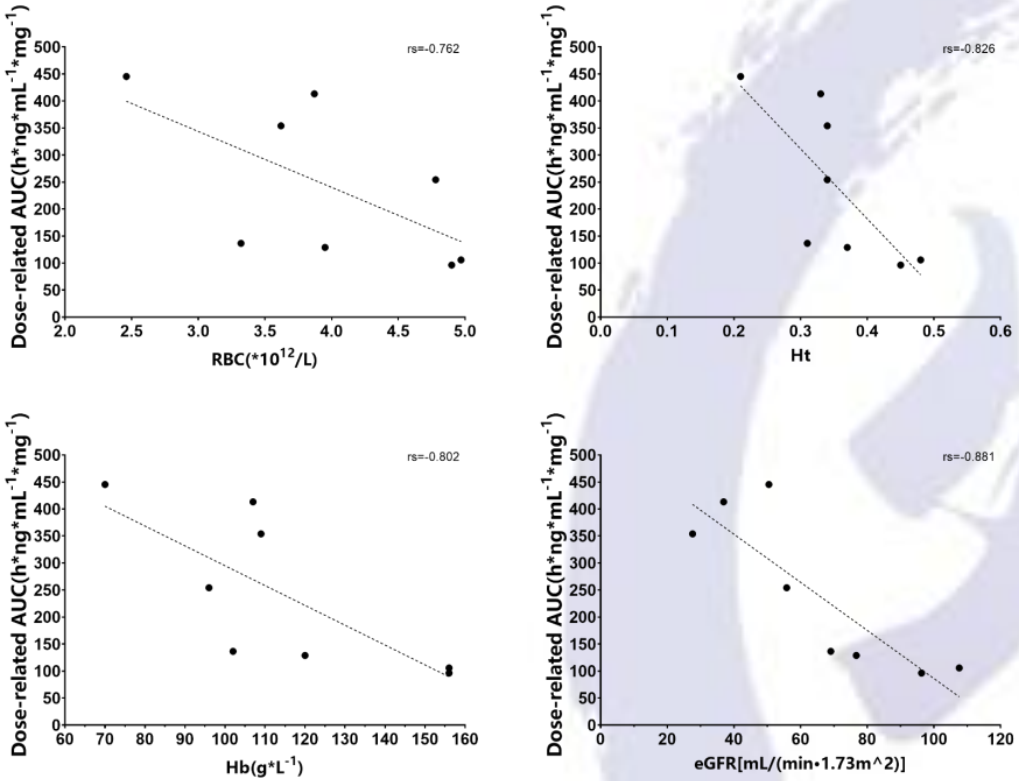


Figure 2. The relationship between the RBC(A), Ht(B), Hb(C) and eGFR(D) with the value of Nirmatrelvir AUC0-12 h/Dose.

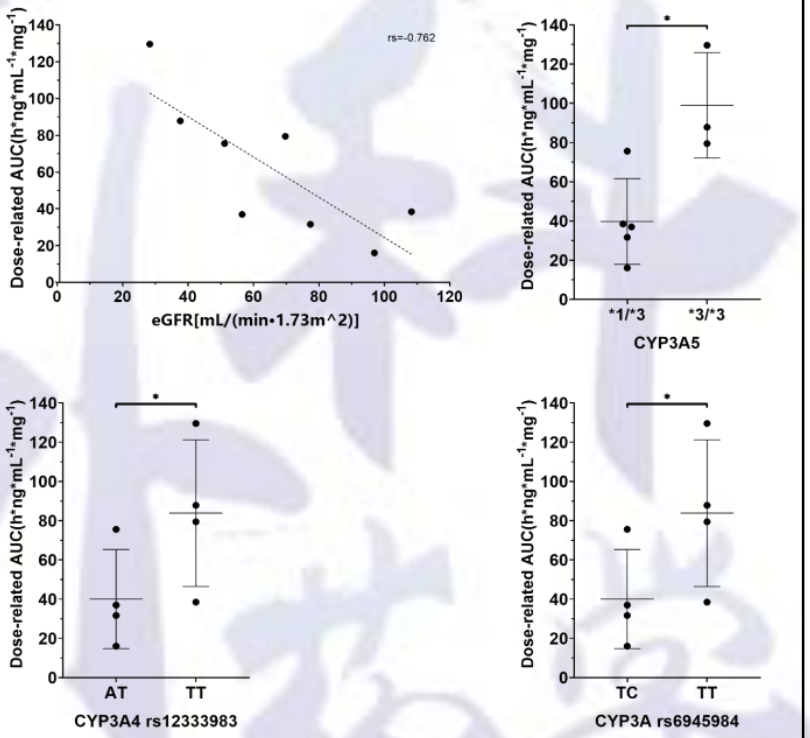


Figure 3. The relationship between the eGFR(A) with the value of Ritonavir AUC0-12 h/Dose and the difference between genotype, including total CYP3A5 (B), CYP3A4 rs12333983 (C) and CYP3A rs6945984(D).

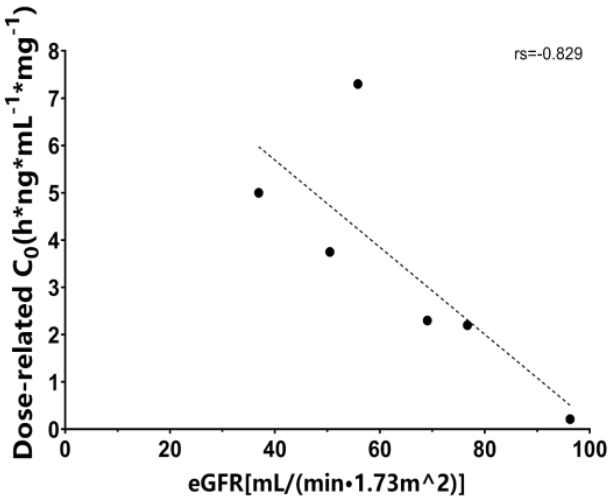


Figure 4. The relationship between the eGFR with th value of Tacrolimus C0/Dose

- **Factors including creatinine clearance (Ccr) and CYP3A5 genotype are associated with in vivo exposure to nematavir/ritonavir.**
- **Throughout the course of neimatvir/ritonavir treatment (both before and after treatment), it is recommended to adjust the dose of calcineurin inhibitor (CNI) based on renal function to avoid exposure to CNI toxicity.**

Summary

- The complexity and persistence of drug use in organ transplant recipients brings opportunities and challenges to pharmacists in organ transplant medicine.
- The responsibility of transplant pharmacists covers medication management before transplantation, during perioperative period, after transplantation and follow-up period.
- Pharmacists should participate in drug clinical research, which will not only help transplant patients gain long-term benefits, but also enhance the value of pharmacists.
- Ongoing economic evaluations of transplant clinical pharmacy services are needed to fully confirm the impact of transplant pharmacists and advocate for increased transplant pharmacist staffing.

Thank you !