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KDIGO 2024 1A recommendation[4] CKD Guideline

Abbreviations: CKD: Chronic kidney disease; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; RRR: Relative risk reduction; uACR: Urine albumin-creatinine ratio; KDIGO: Kidney Disease Improving Global Outcome

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The Cover Shot

Gift of Life

Organ transplant is not a birthright bestowed upon a lucky few, but the gift from organ donors. In a time when so many patients are struggling with organ failure, the current butterfly logo design from the Department of Health, symbolising organ donation, gives us a ray of hope.

Donating an organ is a priceless gift, freeing patients from the tyranny of diseases like kidney failure or liver cirrhosis. If you are looking for a little rest and relaxation, there's nowhere better than Tai Po Kau to witness the nature. A butterfly like this one reminds us of the precious gift from our altruistic organ donors (and their families).

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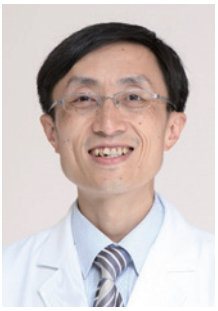

Dr Kai-ming CHOW

As highlighted by the contributing authors in this issue of Medical Diary, organ transplantation remains the most effective treatment of kidney and liver failure. We also learn from a patient, Bill Wong, how kidney and liver transplantation has transformed his life. Patients with organ failure, in other words, have to endure the illness with little chance of survival unless the organ transplant is available. The organ transplant is not a birthright bestowed upon a lucky few, but the gift from organ donors. The number of solid organ transplantations constrained by the limited donor pool worldwide. The psychological burden of waiting for solid organ transplantation is best captured by a local survey reporting a high prevalence of ideas of impending death (18.6%) and suicidal thoughts (6.8%)[1].

Are there ways to increase the lifesaving organs and reduce the long waiting times and waitlist mortality? Recently, reports of genetically modified pig kidneys that survived after pig-to-human xenotransplantation have made headlines[2]. Despite its potential, the full potential or benefits remain to be seen. In contrast to the experimental field of xenotransplantation, there are now more clinical data to support the safety of organ donation after circulatory death. This means the chance to expand the donor pool, which has previously been limited to patients after the declaration of brain death. Encouraging results of organ transplants from donors after circulatory death are not limited to kidney or liver transplantation. The Donors after Circulatory Death Heart Trial has reported noninferiority of transplantation from heart donors after circulatory death with respect to survival at six months[3]. Another area of interest is the role of deep learning applications in identifying brain-dead patients. An automated digital screening tool has recently been developed to aid in the early identification of patients who are at risk of developing brain death during critical care. Such a screening tool had a sensitivity of 100% in identifying patients who eventually developed brain death, with no false negative results[4]. The tool, in addition to the electronically automated referrals to organ procurement organisation or transplant coordinators[5], could have increased the odds of identifying organ donors.

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Dancing with the Snake

Prof Bernard MY CHEUNG

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Prof Bernard MY CHEUNG

As the Chinese New Year begins, the dreamy dragon makes way for the savvy snake. The snake has a special status in Medicine; the Rod of Asclepius, with a serpent winding round a rod, is the very symbol of Medicine. Contrary to popular belief, most snakes are not poisonous. Indeed, snakes are shy creatures hiding in caves and grass. Hence, there is a saying in Chinese, 打草驚蛇, meaning beat the grass and startle the snake. Snakes lie low and make no noise. They hibernate in winter when food is scarce. How they can wriggle their way out of trouble and adapt to the environment is a lesson to us all.

Many useful medicines came from snakes. Captopril was isolated from the venom of a type of Brazilian viper. The most profitable drug class at the moment, the GLP1-receptor agonists, were originally discovered in the saliva of a large lizard called the Gila monster. Snakes, including their blood and bile, have many medicinal uses in Traditional Chinese Medicine, not least in the snake soup served in winter.

In Chinese culture, the Snake is regarded as a symbol of good fortune, plentiful harvest, and reproduction. People born in the year of the snakes are said to have intelligence, passion and determination. The year 2025 is a challenging one for Hong Kong, especially for the business sector. I hope that the people and businesses in Hong Kong can emulate the snake in being level-headed, conserving its resources and anticipating opportunities, as well as shedding its skin and changing its shape according to the landscape.

In preparing for the transformation in healthcare in the brave new world of AI, the Federation, through its medical conferences, seminars and webinars, and most importantly, the Medical Diary, is a trusted guide. In this regard, we owe our gratitude to Dr Raymond Lo, the Chief Editor, and all the authors who contributed insightful and educational articles to bring us up to date in diverse medical fields.

On behalf of the Federation of Medical Societies of Hong Kong, may I wish you a very happy and successful new year. May the Year of the Snake bring you good health and good fortune!

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Landscape of Organ Transplant and Donation in Hong Kong

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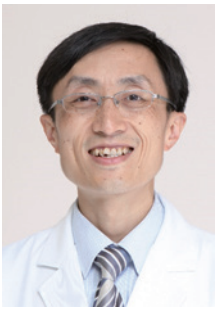

Dr Kai-ming CHOW

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Despite better quality of life and superior survival outcomes after kidney transplant for end stage kidney disease, there is a major gap in long transplantation waiting lists. The number of patients on the kidney transplant waiting list in the United States, for instance, was 289.7 per million population (pmp) in 2009[1], and this has remained high at 260.0 pmp in 2024. The shortage of donor organs in Hong Kong is even worse, as reflected by the number of patients awaiting kidney transplants over 334.8 pmp in 2024. As of September 2024, there were over 2,480 patients waiting for kidney donation in Hong Kong. A cross-sectional territory-wide questionnaire survey has previously demonstrated huge psychological impact of long waiting time for the waitlisted patients with organ failure: 18.6% of patients with longer waiting time perceived impending death and 6.8% had suicidal ideation[2].

To overcome the hurdle or bottleneck of limited organ donor pool, we should make efforts to work through each step of organ donation. A step-by-step analysis provides a framework to tackle donor organ shortage, as listed in Table 1.

The first step is signing up for organ donors. The current platform, the Centralised Organ Donation Register CODR, requires us to actively sign up at the website, followed by verification of personal information and wish. In some countries, this action is facilitated by some "nudging" strategies. The "nudging" registration is based on the behavioural economics theory from Thaler and Sunstein. For example, when a citizen renews the driver's license, he or she can check the box to become an organ donor[3]. In the United States, a smartphone user can go to the Health app and register on Donate Life America; the information will then be sent to a national computer system. This has been developed to cater for passive-positive donors, namely, those who support organ donation but have yet to register as potential donors. A previous survey found that almost two-thirds of people who are willing to donate their organs after death have not registered on the Centralised Organ Donation Register in Hong Kong[4]. Understanding and removing barriers to passive-positive donor behaviour would be an important step[5]. The role of performance feedback relative to peers could also be explored. A successful

Table 1: Framework of improving organ donor shortage (Composed by the authors)

Steps of organ donation and procurement	Strategies	Examples	Potential impact
Citizen registration for potential organ donor after death	Public education	1. Culture sensitive and age-appropriate education	√
	Target passive-positive behaviour[5]	1. Signing up on registry at the time of obtaining a driver's license[3] 2. Performance feedback on organ donor signing rate[7]	√√ √√
	Influence peers and inform next of kin[5]	1. Open announcement of wish to encourage followers	√
Identification of potential donor after death	Optimisation of donor referral	1. Regular donor audit to identify missed donation opportunities[8-10]	√
	Systematic identification of brain death	1. Standardised clinical triggers of deceased organ donor referral[11] 2. Automated digital screening for patients at high risk for brain death[13]	√√ √
	Maximise donor pool	1. Donation after circulatory death 2. Donor with HIV infection (to patients living with HIV)[14] and HCV infection (to uninfected patients)[15] 3. Monitoring organ nonuse rate and audit[17] 4. Implementation of machine perfusion technologies[19,21] 5. Xenotransplantation	√√ √√ √ √ √√ (if successful)
Organ procurement organisation coordinator	Manpower to coordinate donation	1. Full time hospital organ procurement organisation coordinator[22,23] 2. Communication training for coordinators[27] 3. Continuing professional development for healthcare professional[36]	√ √√ √
Donor family consent or approach	Facilitation of decision-making during donor family consent	1. Public education 2. Encouraging communication of donation wish to family member or next-of-kin 3. Removing disincentive or provision of incentive for family consent[33]	√ √ √√

Abbreviation: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

example is the electricity bill with visual feedback or eco-feedback on household electricity consumption, which can have a positive influence on the individual intrinsic motivation and self-image concerns. This tool has been shown to be effective in nudging the behaviour of energy saving, and confirmed in a meta-analysis on feedback research for household electricity conservation from 1976 to 2024[6]. To extrapolate the behavioural psychology on electricity consumption to organ donor registration, a similar nudge strategy has been tested in Ontario, where customer service representatives provide services to residents including public health insurance registration and promotion of organ donor registration. One default option is regular e-mail reminders to the customer service representatives on their mission. A more innovative option is individual feedback: the number or proportion of customers who have signed up to the organ donor registry in the previous six months (expressed both numerically and graphically)[7]. In a randomised controlled trial, the innovative feedback strategy resulted in a 25% increase in daily signups[7].

The single step of signing up as a donor is not the panacea to improving the donation rate. After committing a contract verbally or in writing, we should go one step further. Registered donors should be encouraged to speak up and inform others. Not surprisingly, human beings strive for consistency in our commitments, but more so when we are being watched. The most effective stamp to seal a contract is to share the contract on our social media platforms and let others - and not just the next-of-kin-know. This is one of the best ways to enlist one's followers to hold one accountable. At the same time, this is a tool for someone who has signed up as an organ donor to encourage their followers to do the same. In case you cast doubt on the effectiveness of this chain effect, think about the famous ice bucket challenge.

Regular audits have been suggested to monitor the donation and transplantation system performance. In brief, the audits serve to estimate the number of potential donors and quantify the actual donors. Could there be the failure to identify potential donors? What are the areas for improvement? A scoping review of 52 publications recently identified that missed donation opportunities are higher for donation after circulatory death[8]. According to a local hospital chart review and audit in 2014, the failure of healthcare professionals to identify potential donors accounted for 14% of potential organ donor loss[9]. The next question, obviously, is how much better we have been performing after these 10 years. Clinical audits should not cease after analysis and reporting of data; ongoing efforts should include the implementation of changes and re-audit and the so-called audit cycle. Variation in organ donation across regions or organisations is the primary reason for auditing and benchmarking. Important formula of gauging performance include donor identification rate, missed identification rate, donor referral rate, missed referral rate, approach rate, and consent rate[10].

Apart from the audit cycle to improve awareness of clinical teams or healthcare professionals, a more robust mechanism without relying on human behaviour can trigger donor referral. As such, automated electronic donor referral has been proposed, based on predefined parameters which can be captured by the hospital's electronic health record. Examples of parameters include mechanical ventilation state, intensive care unit stay because of a neurocritical injury and a Glasgow Coma Scale of ≤ 5. Analysis of such a system in three Texas hospitals, using a difference-in-difference analysis with Poisson regression, showed that automated referral was associated with a 45% increase in donor referral, and a 92% increase in organ donors[11]. With the improvement of digital technology, there is also the recent development of an automated digital screening tool to prospectively identify intensive care patients who are at risk of developing brain death. Artificial intelligence applications include machine learning models capturing clinical data and developing algorithms to achieve early prediction of events such as cardiac arrest or brain death[12]. Implementation of such automated screening algorithm in intensive care units of a tertiary care hospital had been associated with a 93% decrease in the risk of missing patients who were retrospectively classified as impending brain death and thus being potential donors. The screening tool was promising with high sensitivity approaching 100% in identifying patients who eventually developed brain death, with no false negatives and an overall accuracy of 88.9%[13].

As shown in Table 1, the donor pool should be addressed to meet the substantial organ need. To date, kidney transplantation from donors with human immunodeficiency virus (HIV) to recipients with HIV has been demonstrated to be noninferior to kidney transplantation from donors without HIV, including composite outcomes of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection[14]. To further maximise the use of good-quality hepatitis C virus HCV-infected organs, the opioid epidemic and availability of direct-acting anti-HCV drugs have enabled successful transplantation of kidneys from HCV-infected donors to patients without HCV[15]. On the other hand, the donor pool from these infected organs is limited by the relatively low prevalence of HIV and HCV in Hong Kong as compared to other countries. Other sources, such as organs following euthanasia, have been explored in countries like the Netherlands[16].

Before xenotransplantation can be successfully performed in human subjects, we rely heavily on human organs. Up to one-quarter of kidneys recovered for transplant are not transplanted[17], and some organs are rejected because of worry about inferior outcomes. For example, donor kidneys with acute kidney injury have been shown to have favourable long-term transplant outcomes despite short-term less-than-ideal events[18]. Judicious use of donors with acute kidney injury should be considered a feasible strategy in expanding the transplant donor pool. Another important measure to expand the donor pool is the utilisation of technology, such as pulsatile machine perfusion to improve organ storage and transplant outcomes, mitigating delayed graft function in kidney transplantation[19]. As proven in a randomised study, machine perfusion is superior to therapeutic hypothermia in reducing delayed graft function after kidney transplant from brain-dead organ donors[20]. An updated Cochrane meta-analysis also

confirmed that continuous non-oxygenated hypothermic machine perfusion is superior to static cold storage for deceased donor kidney transplantation, reducing delayed graft function, improving graft survival and proving cost-effective[21].

Organ procurement organisation coordinators, also known as hospital transplant coordinators, play a key role in the donation process or roadmap. Although cost-effectiveness analysis has not been studied, the implementation of a full-time in-house coordination team fully dedicated to organ procurement is reported to improve the donation rate. An observational study in Brazil showed that implementation of full-time organ procurement organisation coordinators was associated with an improvement of the referral rate by 132% and conversion rate by 390%[22]. The reasons for such results are not difficult to understand, because more time and interaction with families can build closer relationships and allow better grief reaction management[22,23]. In the setting of brain-dead donors, education and support of a grieving family are essential. A large study of over 100,000 ventilated donor referrals in the United States reported that organ procurement organisation coordinators which conduct more family approaches have substantially higher donation rates, even after adjusting for differences in patient characteristics[24]. Furthermore, a dedicated team with an aggressive donor management, as exemplified by the Spanish model, has been considered an important component to achieve early identification of potential donors, early and comprehensive resuscitation with fluids, vasopressors and hormone therapy before consent for organ donation[25].

Skill-based training is essential to enhance the communication skills of organ procurement organisation coordinators who face the challenging task of obtaining consent. Multiple regression analysis previously showed that the family consent rate would be higher in the context of decoupling (when the family understands and accepts brain death before discussion of organ donation is begun, with consent request from the procurement coordinator, and donation is requested in a quiet, private place[26]. The communication task encompasses providing time for family decision, preparing family for grief, providing emotional support with sensitivity and empathy, and asking for authorisation without coercion or pressure. Intervention by means of online plus in-person training, live practice and feedback using simulated family scenarios could be provided to organ procurement organisation coordinators. In a parallel group randomised controlled trial of organ procurement organisation coordinator intervention, a structured communication skill-based training has been shown to result in an increased authorisation rate, and even more so for coordinators with less tenure[27]. Continuing professional development training should not be limited to organ procurement organisation coordinators and has to target other healthcare professionals in order to improve the understanding of brain death, the organ donation process, and foster sensitive communication in supporting family members. Previous survey of doctors of the intensive care units revealed limited communication skills of physicians in influencing a family's decision to provide consent[28]. The willingness and competency of doctors and nurses to break bad news, care for the bereaved, and start the dialogue of organ donation referral are also key factors to impact the organ donation process[29].

Last but not least, the final step of consent appears to be the bottleneck in the organ donation process. Lack of consent to donation remains the primary cause of organ shortage in the various countries including the United States[30] and the United Kingdom[31]. The Refusal rate from families of potential organ donors was reported at 48%, 39% and 41% in Hong Kong[9], the United States[30], and United Kingdom[31] respectively.

Of equal, and perhaps even greater, importance will be an intervention at motivating family consent for organ donation. We acknowledge the challenges when almost all countries do not allow healthcare professionals to overrule family members' objections to donation after a patient's death, sometimes even after the patient had registered one's intention to donate[32]. Making a decision to permit organ donation after the circulatory or brain death of a beloved family member is perhaps one of the most difficult ones during the bereavement stages. Should we provide motivation in addition to encouragement? Insofar as the intrinsic motivation of organ donors is not jeopardised, there have been proposals to explore the extrinsic motivation for the honourable but difficult act in a sensitive and cautious manner[33]. One of the suggestions is the provision of the funeral service for deceased organ donors in a fully regulated and transparent manner as a token of appreciation for the donor's honourable act to contribute to the society. Clearly, the overarching principle for any proposed system should be for the good of the community and less so for the benefit of the donor family. This is based on cultural and religious beliefs, as well as an increasing awareness that willingness to donate organs is a commendable act. The family, in particular, is expected to struggle in grief reaction and to cope with a complex decision-making process in a difficult lifetime situation. Some family members might factor in the benefit of honouring the "dying wish" of a deceased relative, and their own attitudes toward organ donation. Some might view the organ donation as a traumatic decision with inherent incentives and disincentives which affect the decision rules at a critical moment. By applying the utility theory and decision theory to the donor family decision making, we should consider the distance of the relationship between donor and recipient. This is an important variable in the equation. In the context of organ donation to a close family member, the influence of risk or incentives is much lower. On the other hand, the significance of incentives and disincentives becomes increasingly relevant in non-directed organ donation. In theory, moral norm occupies a much lower position in deceased organ donation than in the scenario of living organ donation. People tend to have a moral obligation to donate to members of in-group or close relatives; the contribution of moral norm is much less evident in deceased organ donation[34]. In short, donor's family might not necessarily be motivated to give consent for the donation. When intrinsic motivation, such as purely altruistic or charity, might not suffice, the final decision is much more likely to be modified by extrinsic

motivation and the appreciation from the society. Arguably, the provision of funeral expenses at the time of donation would be more acceptable than incentives that include predeath benefits (and the likelihood of receiving benefits but without becoming a donor). For example, an Australian survey of 2005 respondents reported that over 80% of respondents viewed a positive impact of partial reimbursement of funeral expenses, as well as favouring nonmonetary incentives[35].

In conclusion, policymakers should have a comprehensive understanding of the role of each stakeholder and each step of the organ donation process. Public education, donation after circulatory death, maximising roles of organ procurement organisations or transplant coordinators, and removing disincentives for family consent of organ donations have the potential to address the barriers of organ donation.

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Long-term Complications after Kidney Transplantation

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INTRODUCTION

Kidney transplantation (KT) remains the best treatment option for patients suffering from end stage kidney disease (ESKD) because it improves the overall survival and quality of life when compared with patients on dialysis[1,2]. After kidney transplantation, patients require life-long immunosuppression in order to prevent acute and chronic rejection, and maintain allograft function. With the advances in immunosuppression, there is a significant improvement in acute rejection rate and short-term allograft survival. However, death with functioning graft (DWFG) remains a leading cause of long-term allograft failure in kidney transplant recipients (KTRs)[3]. In this review, we would like to discuss three important causes of DWFG, namely infection, cancers and cardiovascular diseases in KTRs.

INFECTION

Infection is an important cause of morbidity and mortality in KTRs. A number of factors including donor- and recipient-derived factors, net state of immune suppression and antimicrobial use as prophylaxis determine the risk of infection at a particular time. In general, KTRs go through three different time periods after transplantation: within first month, first month to first year and beyond first year post-transplant[4,5]. The timeline of post-transplant infections can be summarised in Table 1. We will focus on the management of some pathogens common in KTRs in this section.

Table 1. Timeline of some common infections after kidney transplant

Time after transplant	< 1 month	1 month -1 year	> 1 year
Source	Nosocomial infections Donor and recipient-derived infections	Opportunistic infections Activation of latent infections	Community acquired infections Rarely opportunistic infections
Pathogens / types of infection	Antibiotic resistant organisms (MRSA, VRE, CRE) Wound infection Pneumonia Urinary tract infection Catheter-related infection Surgical site infection *Clostridium difficile*	HBV/HCV Herpesviruses Polyomaviruses *Mycobacterium tuberculosis* *Pneumocystis jiroveci* *Cryptococcus neoformans* *Nocardia, Listeria,* Toxoplasmosis *Strongyloides* Leishmania PTLD	Pneumonia Urinary tract infection *Nocardia* Aspergillus Mucormycosis Late onset CMV JC polyomavirus / PML Influenza PTLD HBV/HCV

CMV, cytomegalovirus; CRE, carbapenem-resistant enterobacterales; HBV, hepatitis B virus; HCV, hepatitis C virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PML progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; VRE, vancomycin-resistant enterococci

Bacterial infections are common in the immediate postoperative period. Common sites involve the urinary tract, respiratory tract and wound. Urinary tract infections (UTIs) is the most common bacterial infections in KTRs and accounts for 30% of all hospitalisations for sepsis in these patients[6]. Risk factors for bacterial UTIs include older age, female sex, prolonged urinary catheter use and acute rejection episodes. With the emergence of a growing consensus, UTIs can be classified as asymptomatic bacteriuria (AB), simple cystitis (uncomplicated UTI), pyelonephritis (complicated UTI) and recurrent UTI[6,7]. AB is defined as the presence of > 105 bacterial colony-forming units per millilitre (CFU/mL) in the urine without systemic or urinary symptoms. AB can result from contamination of urine specimen, and should not be considered and treated as UTIs uniformly. Simple cystitis is defined as > 103 CFU/mL of uropathogen in urine culture, associated with lower urinary symptoms such as dysuria, frequency, or urgency, but no systemic symptoms or indwelling urinary device. Pyelonephritis is defined as > 104 CFU/mL of uropathogen in urine and at least one of the following: fever, allograft pain, chills, malaise, or bacteremia with the same organism in urine. Recurrent UTI is defined as ≥ 3 episodes of UTIs within one year. Escherichia coli is the most common pathogen of UTIs in KTRs. For simple cystitis, the most narrow-spectrum antibiotic (according to culture and sensitivity results) should be used to complete the course of treatment. However, data on the exact duration of therapy is limited and can vary between five and ten days. On the other hand, pyelonephritis requires longer treatment in terms of 14-21 days. Complications of pyelonephritis, including abscesses and emphysematous pyelonephritis, require drainage and even more prolonged course of antimicrobial treatment[6]. Management of recurrent UTIs involves assessment of underlying abnormalities which allows better prevention. A structural and functional

urinary tract workup should be considered. Ultrasound and computed tomography are useful for anatomical evaluation, while voiding cystourethrography can assess vesicoureteral reflux and urodynamic studies can evaluate outflow obstruction or bladder dysfunction[6].

Cytomegalovirus (CMV) infection is the most common opportunistic infection in KTRs. It can occur as primary infection, reinfection, or reactivation of latent infection and predisposing factors include donor seropositivity (especially if the recipient is seronegative), and use of potent immunosuppressive regimens, especially antilymphocyte antibodies. CMV infection is defined as evidence of CMV replication in blood, regardless of symptoms while CMV disease requires the presence of infection together with symptoms including fever, thrombocytopenia, leukopenia, or evidence of tissue invasion such as retinitis, pneumonitis, gastrointestinal tract ulcers, and hepatitis. CMV infection is important in KTRs because it can increase mortality and reduce allograft survival[8]. Universal prophylaxis and preemptive therapy are the two main prevention strategies that exist for CMV infection[5]. Diagnosis of CMV relies on nucleic acid testing including CMV-polymerase chain reaction (PCR) or pp65 antigenemia[9]. PCR is highly sensitive and a negative PCR virtually excludes CMV infection. The pp65 antigenemia level correlates with disease manifestations and can be used to monitor treatment outcome. However, not all patients with CMV disease exhibit viremia, and identification of CMV cytopathic changes or CMV antigens by immunohistochemistry remains the gold standard for diagnosis of tissue-invasive disease[8]. Intravenous ganciclovir and /or oral valganciclovir together with reduction of immunosuppression are the mainstay of treatment. In case of treatment failure, ganciclovir resistance should be considered and common resistance mutations include those in the genes that encode UL97 phosphotransferase and the viral DNA polymerase gene UL54[9]. Antiviral treatment for those with ganciclovir-resistant or refractory CMV include maribavir, foscarnet, and cidofovir. Oral valganciclovir is commonly used in high-risk recipients as prophylaxis[5, 10].

BK polyomavirus (BKV) and *JC polyomavirus* (JCV) belong to the family Polyomaviridae. Among the KTRs who develop polyomavirus-associated nephropathy (PVAN), 95% are due to BKV while 5% are due to JCV. Most patients with PVAN manifest as renal dysfunction, while some can develop ureteric obstruction from stenosis or stricture. PVAN can occur in 1-10% of KTRs and contributes to allograft loss in 15-50% of cases[4,11]. Detection of BKV DNA in plasma provides a sensitive method for identifying BKV infection and BKV-associated nephropathy can be confirmed by histology. To date, there is no effective antiviral therapy for PVAN. The cornerstone of treatment is the reduction of immunosuppressive agents[9].

Pneumocystis jiroveci (also known as *Pneumocystis carinii*) has been an important cause of severe pneumonia within the first six months after transplantation. *Pneumocystis jirovecii* pneumonia (PJP) should be considered in KTRs with clinical presentation of fever, dry cough, and severe dyspnea or hypoxemia that is disproportionate to the less severe chest radiography abnormalities. While not expected to occur in patients with effective trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, PJP can occur after prophylaxis discontinuation in 0.3-2.5% of cases[12]. Diagnosis relies on the detection of the organism in respiratory specimens. Bronchoalveolar lavage should be performed in suspected PJP cases, with a sensitivity of 80-95%. Transbronchial or open lung biopsy is the gold standard for diagnosis, offering additional diagnostic value through lung histology, though it is usually reserved for diagnostically challenging cases[12]. Other clues include serum lactate dehydrogenase > 300 IU/mL and elevated 1,3-beta-D-glucan[5]. TMP-SMX remains the first-line treatment and prophylaxis option for PJP. No second-line agents (such as the combination of atovaquone plus levofloxacin or pentamidine) have been shown to provide better protection than TMP-SMX. The duration of therapy is at least 14 days for PJP treatment; and 6 to 12 months for PJP prophylaxis. TMP may also cause elevated serum creatinine and adequate hydration is needed[5, 12].

Mycobacterium tuberculosis (TB) remains one of the major post-transplant infections, especially in certain parts of the world. Presentation can be atypical in KTRs and disseminated disease or extra-pulmonary sites involvement can occur in approximately one third of cases[13]. The diagnosis of active TB in KTRs requires a high index of suspicion. Detection of *M. tuberculosis* in culture from clinical specimens, *M. tuberculosis* DNA using PCR, demonstration of caseating granuloma in histology, and chest radiography are the choice of tests for diagnosis. Since rifampin affects the cytochrome p450 pathway, it can significantly reduce the blood concentration of calcineurin inhibitors, increasing the risk of rejection.

Fungal infections can occur in different forms in KTRs. Types of infections depend on the patients' exposure history as well as the net state of immunosuppression. Prior colonisation, broad spectrum antibiotics, presence of diabetes mellitus, viral coinfection, potent immunosuppression, neutropenia and critical illness are all risk factors[5]. *Candida* and *Cryptococcus* species are the most frequently isolated yeasts, while most frequent filamentous fungi (molds) isolated are *Aspergillus* species. Oral candidiasis is common and can be prevented with oral nystatin. With the use of potent immunosuppressive regimens, invasive fungal infections can also occur, which include invasive aspergillosis, invasive candidiasis, cryptococcus, etc. Antifungal agents include liposomal amphotericin B, echinocandin (such as micafungin, caspofungin and anidulafungin) and azoles (such as voriconazole). The choice of these agents depends on the site of infection, involved pathogen and the potential for drug interactions. If azoles (such as voriconazole) are used in KTR, caution should be made to adjust the dose of immunosuppression including calcineurin inhibitors (cyclosporine and tacrolimus) and mammalian target of rapamycin inhibitors.

CANCER

Cancer emerges as a major cause of death among patients suffering from ESKD, especially after KT. There has been a two- to three-fold increase in overall cancer

incidence in KTRs when compared with the age and gender matched general population but the magnitude of cancer risk varies by cancer site and geographical areas. Cancers with the highest relative risks in KTRs include post-transplant lymphoproliferative disease (PTLD), Kaposi's sarcoma, lip cancer and cancers of the anogenital tract. On the other hand, cancers which do not show an elevated risk in transplant populations are breast cancer and prostate cancer. Although post-transplant non-melanoma skin cancer (NMSCs) are common in the Caucasians, the incidence is low in the Chinese transplant population[14-19]. The reasons for the elevated risk are multifactorial. These include transplant-specific factors such as long-term immunosuppression and oncogenic viral infections, in addition to those baseline factors already known to increase cancer risk in the general population such as increasing age, smoking, and prolonged sun exposures. Certain cancers, such as renal cell carcinoma and urinary tract cancers, are related to the duration of ESKD[15, 20-21].

Immunosuppressive agents remain the most important modifiable factor in the development of cancers in transplant recipients. However, it is hard to assess the impact of individual drug on cancer development because of the use of multidrug regimens in these patients. At present, there is no conclusive evidence to suggest one particular type of immunosuppression is more carcinogenic than others. However, induction therapy with antilymphocyte globulin, particularly OKT3 (muromonab-CD3), has been found to be associated with a higher risk of lymphoma while interleukin 2-receptor antagonists was not associated with increased lymphoma incidence after KT[22]. For maintenance therapy, cyclosporine exerts direct effects on cancer development and progression through the TGF-β or IL-6 overexpression pathways[23]. Tacrolimus, another calcineurin inhibitor, also stimulates TGF-β expression and exerts its neoplastic effects. In addition, calcineurin/NFAT inhibition can counteract p53-dependent cancer cell senescence thereby increasing tumourigenic potential[24]. The oncogenic potential of azathioprine is also well recognised. It photosensitises the skin and causes mutagenic reactive oxygen species production, leading to a higher risk of NMSCs in organ transplant recipients[25]. In general, overall cancer risk seems to be mediated by the dosage and duration of immunosuppressive drugs rather than individual components of the drug regimen[26].

KTRs are vulnerable to develop primary viral infection or reactivation of latent infection because of the immunocompromised state. It is well recognised that oncogenic viruses are associated with post-transplant cancers and important examples include *Epstein–Barr virus* (PTLD and nasopharyngeal carcinoma), *human papillomavirus* (lip and anogenital cancers), *human herpes virus 8* (Kaposi's sarcoma), hepatitis B and C viruses (hepatocellular carcinoma)[27]. In addition, different studies also described the detection of BKV in urinary tract cancers in KTRs which postulates an aetiologic role for BKV in urothelial carcinogenesis[28].

Once cancers develop, the risk of mortality is high. Observational data in different populations have shown that the overall risk of cancer death in KTRs is approximately 1.8-2.3 times higher when compared with the age- and sex-matched general population. The risk is particularly greatest among those with PTLD, melanoma and urogenital cancers, with an overall risk of cancer-related death greater than 5-10 times that of those without transplants[14, 29].

The mainstay of treatment for post-transplant cancers, especially those related to immunosuppressed status such as PTLD and Kaposi's sarcoma, is the judicious reduction of overall immunosuppression load. However, there are no standard guidelines concerning how the medication should be adjusted. Patients should be well-informed about the adverse effects and the adjustment of immunosuppressive regimen should be balanced between the risk of acute rejection and cancer progression[19]. On the other hand, cancer screening can be used to improve the clinical outcome of KTRs. Guidelines adopted in the general population (screening for colorectal cancer, cervical cancer, breast cancer, prostate cancer and hepatocellular carcinoma) have been used as the reference[26].

CARDIOVASCULAR DISEASE

KTRs remain at higher risk for cardiovascular disease (CVD)-related mortality and morbidity when compared with the general population. Moreover, CVD is the leading cause of death in KTRs with a functioning allograft. The significant higher CVD risk in this population can be contributed by the factors including the metabolic effects of immunosuppressive regimens, hypertension, post-transplant diabetes mellitus (PTDM), dyslipidemia, obesity and allograft dysfunction[29].

1. Hypertension: In addition to preexisting hypertension, transplant-related factors such as immunosuppressive drugs and kidney allograft dysfunction are all involved in the development of hypertension after KT. In stable KTRs, blood pressure control targets should mirror non-transplant chronic kidney disease settings in order to reduce end organ damage[30]. The American College of Cardiology Foundation/American Heart Association 2017 Guidelines on Blood Pressure Management recommend a treatment target of < 130/80 mmHg for these patients[31].

2. PTDM: The development of PTDM and worsening of preexisting DM is a major CVD risk factor in KTRs. Calcineurin inhibitors, especially tacrolimus, affect pancreatic beta cell function and increase the risk of PTDM[32]. Use of corticosteroids as maintenance therapy is another important risk factor for PTDM. In a meta-analysis study, lower risk of PTDM was shown in patients using steroid-free immunosuppressive regimens when compared with steroid maintenance group. However, an increased risk of acute rejection was observed in steroid withdrawal group[33]. With the increased CVD risk in patients suffering from PTDM, regular monitoring of glycated haemoglobin levels is needed to provide early and goal directed management[29].

3. Dyslipidemia: Dyslipidemia is common after KT, which can be aggravated by PTDM, obesity, proteinuria and immunosuppression. Several classes of immunosuppressive agents including corticosteroids and mammalian target of rapamycin inhibitors are associated with abnormal lipid profiles[29]. KTRs are recommended to receive statin according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[34]. On the other hand, data on use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in KTRs are very scarce. The results of a recent small cohort study support the use of evolocumab in very high cardiovascular risk transplant patients who cannot achieve adequate lipid control with standard lipid-lowering agents[35]. A recent network meta-analysis also suggested the advantage of PCSK9 inhibitors for reducing adverse event and all-cause mortality of KRT[36]. Further long-term follow-up studies, however, are required to assess the benefits of PCSK9 inhibitors in this group of patients[35].

Atrial fibrillation (AF) represents the most common sustained arrhythmia in patients with chronic kidney disease and was associated with an increased risk of death and graft loss[37]. Patients with AF usually require anticoagulation for stroke prophylaxis and warfarin has been the drug of choice for a long time. Currently data on the use of new direct oral anticoagulants (DOACs) in KTRs are limited. Types of DOACs, their dosing adjustments in renal dysfunction and potential drug interaction are all important to maintain efficacy and safety profile of these drugs in transplant patients[29]. In retrospective, small observational studies, DOACs were shown to be effective and safe in KTRs. In addition, there was no significant interaction of apixaban or rivaroxaban with calcineurin inhibitors[38, 39].

Heart failure is a major cause of mortality and morbidity in patients with ESKD and KT is associated with improvement in ejection fraction over time in most patients. Restoration of renal function and reversal of the uremic milieu may contribute to the improvement or restoration of myocardial mechanics and function in patients with underlying cardiomyopathy. Although the negative impact of preexisting and de novo heart failure on kidney transplant outcome has been widely described, further studies are needed to define the best strategies for use of heart failure therapy in these patients[29].

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Dermatology Quiz

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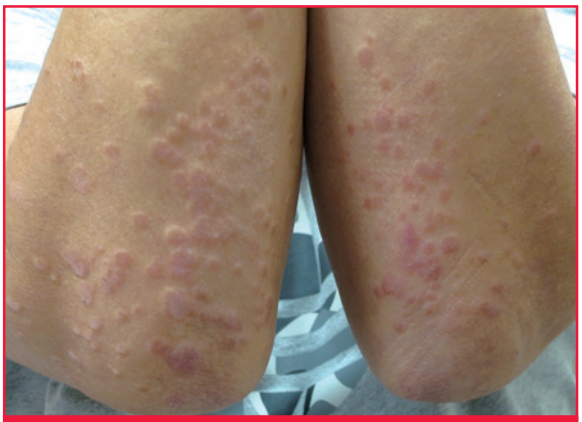

Fig. 1: Multiple skin coloured papules and plaque on the bilateral forearm

This 48-year-old man complained of a gradual onset of generalised multiple flesh-coloured papules over trunk and limbs. There was not many symptoms except mild itchiness. There was no precipitating factor. Physical examination revealed generalised flesh to erythematous coloured papules, which were several milometres large and some were coalesced to form annular plaque. Fig. 1 shows the lesions on the bilateral forearm of the patient.

Questions

1. What are the differential diagnoses of his skin lesion?
2. What investigation are you going to order?
3. How do you treat this patient?

(See P.27 for answers)

Liver Transplantation in Adults - Who to Refer?

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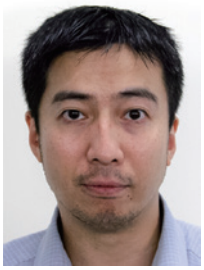

Dr James FUNG

Liver transplantation (LT) is an established curative treatment for patients with liver failure, hepatocellular carcinoma (HCC), and for selected metabolic and congenital disorders. Despite universal vaccination and widespread availability of effective antiviral therapies, chronic hepatitis B (CHB) remains the most common primary disease aetiology in patients undergoing LT in Hong Kong[1]. The major reason for this is that a significant number of chronic carriers remain undiagnosed in the absence of a territory-wide screening strategy. Therefore, a proportion of patients who present with complications of CHB infection will be unaware of their carrier status beforehand. Although chronic hepatitis C remains a significant primary liver disease for LT in the Western world, it has become rare in our region, due to the expansion of direct acting antivirals (DAAs) to cover all subjects infected with the hepatitis C virus (HCV). Currently, virtually all known HCV carriers have now been treated with DAA therapies with extremely high sustained virological response. In addition, metabolic dysfunction-associated steatotic liver disease (MASLD), one of the leading primary liver diseases for LT in the Western world, remains a minor disease indication for LT in Hong Kong, although it is likely there will be an increasing incidence in the future with the rising prevalence of MASLD in the general population[2]. Another common disease indication for LT in the West is alcoholic liver disease, which is now increasingly observed also in Hong Kong. The following review will summarise the current common indications for LT in adults, and when to refer these patients for transplant assessment.

LIVER FAILURE

Liver failure remains the most common indication for LT, and can be broadly divided into acute, acute on chronic, and chronic liver failure. There has been much debate and disagreement over the definitions of the various types of liver failure, and no single consensus definition exists. Irrespective of the specific definitions, it is of paramount importance to recognise the clinical presentation of acute liver failure (ALF) and acute on chronic liver failure (ACLF), so that early discussion with the LT team can take place, and LT assessment can be performed in a timely manner.

Acute liver failure

Acute liver failure (ALF) can be characterised as a rapid development of hepatic encephalopathy, coagulopathy, and jaundice as a result of severe hepatic injury in subjects without known pre-existing liver diseases[3]. The hepatic encephalopathy may be very subtle on initial presentation, and measurements of blood ammonia levels may be useful to support the diagnosis. The systemic inflammatory response that occurs with ALF may lead to the development of extrahepatic multiorgan failures associated with high mortality. Prior to the availability of LT, ALF carried a high mortality of over 80%[4]. One of the most important determinants of transplant-free survival is the underlying cause of liver injury, with paracetamol overdose, acute hepatitis A or E, and ischaemic hepatitis having a more favourable outcome[5]. In contrast, those with acute hepatitis B, drug-induced liver injury (other than paracetamol), and autoimmune hepatitis tends to be associated with poorer outcomes.

The King's College Criteria (KCC) is the most commonly used criteria to determine the prognosis and the need for LT[6,7]. However, it is important to remember that the KCC provides guidance only to a certain extent with limitations. For instance, an estimated 30% of subjects who die may not fulfil the KCC, and almost 20% who survive may fulfil the KCC. There are many other scoring systems available to prognosticate ALF, but all with similar limitations.

Therefore, it is essential to have clinical vigilance, and all ALF patients should be discussed with the LT team at the time of admission to determine whether the patient needs to be transferred to the LT unit for further management and transplant assessment. These include patients with jaundice and evidence of coagulopathy (INR > 1.5), with or without hepatic encephalopathy. It is vital that one does not wait for clinical deterioration, or delay referral until the patient fulfils the KCC, as this is almost always too late. LT assessment can be time -consuming, and for patients with ALF, the window for LT is often very narrow. With the subsequent development of multiorgan failure and cerebral oedema, these patients will rapidly become untransplantable. The low number of organ donors in Hong Kong also means that ALF patients often succumb while awaiting a LT. Hence earlier referral, timely assessment and listing, will increase the chance of these patients receiving LT.

Acute on chronic liver failure

Acute on chronic liver failure (ACLF) has become a hot topic in hepatology within the last decade, but to date there is no consensus definition[8-10]. Similar to ALF therefore, there are many definitions that exist for this disease entity, with significant differences. The

name itself would suggest two components: an acute precipitating injury, and an underlying pre-existing chronic liver disease. A general description of ACLF would include an acute liver injury with evidence of liver dysfunction (jaundice and coagulopathy), which may be complicated by extra-hepatic organ failures (kidney, brain, lung, or circulation), and associated with high short-term mortality, in a subject with previously diagnosed or undiagnosed with chronic liver disease, with or without cirrhosis. The underlying pathophysiology may be similar to those with ALF, with underlying systemic inflammation leading to multiorgan dysfunction[11].

In Hong Kong, by far the most common cause of ACLF is severe flare secondary to underlying CHB, given the high prevalence of hepatitis B infection in subjects aged over 35 years. The major reason for this is the fact that this age group did not receive universal HBV vaccination, which started in 1988. In subjects with CHB, spontaneous hepatitis flare is the most common acute liver insult, due to previous undiagnosed CHB infection, or less commonly, from non-compliance or stopping antiviral therapy with subsequent reactivation[12]. Infrequently, severe flares from HBV reactivation due to immunosuppression or chemotherapy can occur. This is in contrast to the West where alcoholic liver disease is the most common underlying liver disease in ACLF subjects, with acute infection being the most common liver insult[13].

Similar to ALF, all patients admitted with ACLF should be discussed with the LT team for consideration of LT in the absence of any absolute contraindications. For more severe cases and those with signs of deterioration, early transfer of eligible patients to the transplant unit is of paramount importance. In the absence of a universal definition of ACLF, the Asia Pacific Association for the Study of the Liver (APASL) definition is probably the most applicable for our patients with HBV-related ACLF, and those with bilirubin > 85 umol/L and INR > 1.5 with or without hepatic encephalopathy should be discussed with the LT team[10]. These patients can deteriorate rapidly, especially once they develop extrahepatic organ failures or encephalopathy.

Chronic liver failure

Chronic liver failure remains one of the major indications for LT. The most common type of chronic liver failure includes those with decompensated cirrhosis and complications of portal hypertension. In Hong Kong, common primary liver diseases in this group include CHB, alcoholic liver disease, and autoimmune liver diseases, including autoimmune hepatitis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis. Less common causes include chronic hepatitis C, MASLD, and Wilson's disease.

These patients often present with jaundice, ascites, hepatic encephalopathy, coagulopathy, or variceal bleeding. However, not all require LT, unless they have recurrent complications such as refractory ascites, or recurrent encephalopathy and/or variceal bleeding. These patients should be referred for consideration of LT, irrespective of the MELD score, in the absence of obvious contraindication.

In addition, some patients may present with synthetic dysfunction with mainly jaundice or coagulopathy in the absence of other symptoms. In general, those with a MELD score ≥ 15 or Child-Pugh B/C should be considered for transplant, and referred to the LT clinic. However, with a low MELD score, and with the low organ donation rates in Hong Kong, the chance of receiving a LT can be low.

For patients with PBC, the Mayo risk score, calculated as R = 0.871 loge (bilirubin in mg/dL) + (−2.53) loge (albumin in g/dL) + 0.039 age in years + 2.38 loge (prothrombin time in seconds) + 0.859 (edema score of 0, 0.5, or 1), is commonly used to determine the prognosis[14]. An abbreviated version of the Mayo score using specific cut-offs for the five parameters may be used, with the sum total of the corresponding scores in brackets representing the final score as follows: age (years) < 38 (0), 38-62 (1), ≥ 63 (2); bilirubin (mg/dL) < 1 (0), 1-1.7 (1), 1.7-6.4 (2); albumin (g/dL) > 4.1 (0), 2.8-4.1 (2), < 2.8 (2); prothrombin time normal (1), prolonged (2); oedema absent (0), present (1)[15]. A cut-off score of 6 may be considered as the minimal threshold for LT, and referred for transplant consideration.

HEPATOCELLULAR CARCINOMA

The development of HCC usually occurs on the background of cirrhosis, the latter being a pre-malignant and carcinogenic state. A frequent exception to this is subjects with CHB, where a proportion of carriers may develop HCC without established cirrhosis. Currently, patients with HCC need to be within the University of California San Francisco (UCSF) criteria (1 lesion ≤ 6.5cm, or ≤ 3 lesion each ≤ 4.5cm, with total ≤ 8cm, without evidence of extrahepatic disease and vascular invasion) to be eligible for LT in Hong Kong[16]. LT offers the unique opportunity to be curative for unresectable HCCs for both clearance of tumour and for the underlying cirrhosis. Therefore, patients with unresectable HCC within the UCSF criteria should be referred to the LT team for transplant consideration. For those beyond UCSF criteria in the absence of extrahepatic disease, and with a suitable living donor available, individual cases can be considered[17]. For those with HCC beyond criteria, downstaging can be considered to see whether the tumour can be treated and reduced in size to within transplantable criteria[18].

For patients on the waiting list, bridging therapy in the form of locoregional treatment (such as transarterial chemoembolisation, stereotactic body radiation therapy etc.) may be administered to prevent tumour progression and reduce the chance of drop-out when the tumour progresses beyond criteria[19]. Despite meticulous work-up prior to LT to exclude extrahepatic disease, approximately 15% of patients transplant for HCC will have either intra- or extrahepatic recurrence after LT[20].

CONGENITAL DISORDERS

LT may be curative for some congenital and metabolic disorders, of which some will present in adulthood. These may include subjects with biliary atresia, glycogen storage disease, familial amyloidotic polyneuropathy, primary oxalosis, and polycystic liver disease.

Polycystic liver

Patients with adult polycystic liver disease may be indicated for LT due to massive hepatomegaly severely affecting quality of life, or develop complications that can be treated by LT, including severe malnutrition, hepatic venous outflow obstruction, ascites, portal hypertension, variceal haemorrhage, or recurrent cyst infections[21]. These patients should be referred to the LT clinic for transplant consideration if they do not have any absolute contraindication, irrespective of their underlying MELD score, which may be normal. Patients with polycystic liver disease on the LT waiting list will be granted MELD-exception points while awaiting transplant.

CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Not all patients are eligible for LT despite having the indication, and therefore patients should be screened prior to referring to the LT unit. Some of the contraindications to LT are relative, and individual cases may be considered[22]. These are listed in table 1. If in doubt, always discuss with the transplant team for eligibility.

Table 1: Contraindications/relative contraindications to liver transplantation (Composed by the author)

Contraindications	Comments
Active alcohol abuse or alcohol intake in patients with alcoholic liver disease	A six-month abstinent period is required for alcoholic liver disease to be eligible for deceased donor LT in Hong Kong. Shorter abstinent periods may be considered for patients with living donor available.
Uncontrolled sepsis/systemic infections	
Extrahepatic malignancies	A Five-year malignancy-free period is required to be eligible for deceased donor LT in Hong Kong
Uncontrolled/limiting medical co-morbidities	Advanced cardiovascular, pulmonary, or neurologic disorders
Advanced age	Poorer outcome after age ≥ 70
Uncontrolled psychiatric conditions	
Poor social support and environment	
Severe malnutrition or frailty	

SUMMARY

Liver failure, including ALF, ACLF, and CLF, remains the most common transplant indication in adults. Another common indication is HCC, and LT should be considered for those with irresectable lesions if they fulfil the UCSF criteria. There are many other less common indications that are not discussed in detail here, and beyond the scope of this review. CHB remains the most common underlying primary liver disease aetiology for patients needing LT, highlighting the need for better territory-wide screening of at-risk individuals.

The window of opportunity for LT is often narrow, especially for those who present with ALF or ACLF. Therefore, it is imperative that early discussion with the LT team takes place in order for eligible patients to be transferred to the LT centre for assessment in a timely fashion. The LT assessment process is labour intensive, involving many specialty consultations, including cardiology, respiratory medicine, clinical psychology, anaesthesiology, and dental. To expedite the assessment, preliminary investigations such as echocardiography and cross-sectional imaging may be performed at the referring hospital.

The bottleneck for LT remains the availability of donor organs. The deceased organ donors per million people is less than five in Hong Kong, and is far less than that in Western countries. To mitigate this organ shortage, approximately half of all LT performed are living donor LT. Unfortunately, the numbers are still suboptimal, and many patients awaiting LT will eventually succumb to their illness due to the lack of donor grafts. To this end, there must be an ongoing effort to promote organ donation in Hong Kong, so that more lives can be saved.

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Drug Use in Kidney Transplant Recipients: What Primary Care Physicians Need to Know

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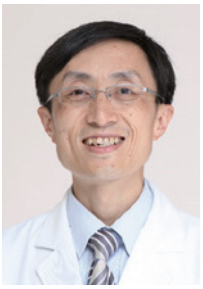

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 January 2025.

Kidney transplantation is currently the best and most effective treatment of kidney failure. Kidney transplant recipients have increased utilisation of healthcare resources, and are at risk of developing complications. This requires primary care physicians or emergency department doctors to be aware of key aspects related to the caution of medication use and interaction for patients after kidney transplant.

The purpose of this review is to provide general medical doctors an overview of commonly encountered scenarios involving medication use and caution during the care of patients who have received kidney transplants.

WHAT SHOULD I DO WHEN KIDNEY TRANSPLANT RECIPIENTS DEVELOP DIARRHOEA?

Patients with kidney transplants frequently experience ailments which might trigger primary care physician consultation. Among them, acute diarrhoea illness is one of the commonest, comprising more than half of the gastrointestinal complications of kidney transplant recipients[1,2]. At three years after kidney transplant, the incidence of diarrhoea was more than 20% according to a cohort of more than 40,000 kidney transplant recipients in the United States[3].

First-line management should include adequate fluid and electrolyte replacement. Clinicians can help preserve kidney function by encouraging oral intake, and prescription of oral rehydration solutions. Intravenous rehydration is not necessary if the patients are able to tolerate oral intake. The use of dilute apple juice has also been supported by randomised clinical trial in children with mild gastroenteritis[4].

Clinical management of diarrhoea should also include investigation of the causes (Table 1) and looking out for consequences of diarrhoea on immunosuppression drug levels. It is important to screen for infectious cause of diarrhoea[1,5]. Hand hygiene for caretakers of patients with gastroenteritis should be emphasised. Washing hands with soap and water (rather than alcohol-based hand disinfection) is encouraged because pathogens like Clostrioides difficile and norovirus cannot be killed by alcohol. First-line microbiological investigation include stool culture (and multiplex polymerase chain reaction if available) and Clostrioides difficile PCR. As a matter of fact, C. difficile accounts for most infectious diarrhoea within the first months after kidney transplantation[6]. If these tests come back negative, second-tier testing should include a search for viral pathogens, parasites and cytomegalovirus viraemia. It is important to recognise chronic norovirus infection as an emerging infectious cause of posttransplant diarrhoea[7,8]. Because of the immunocompromised state, patients with kidney transplants manifest with more chronic than acute, self-limiting symptom of norovirus infection. The chronic gastroenteritis of norovirus in immunocompromised patients may last for many months. The prolonged stool shedding and chronic sequelae of watery diarrhoea will sometimes lead to weight loss, malnutrition and wasting[7,9].

Endoscopic investigation remains the gold standard for histopathologic confirmation of cytomegalovirus CMV gastrointestinal disease[10]. In case of persistent diarrhoea, empiric antidiarrhoeal medications such as loperamide might be considered. Probiotics have been gaining popularity, but there is a lack of safety data and solid evidence[11]. In terms of the immunosuppression, the tacrolimus drug levels should be monitored. Within two weeks of gastroenteritis, enterocyte damage reduces the activity of the P-glycoprotein efflux pump (which transports absorbed tacrolimus out of enterocytes into the intestinal lumen), thus leading to an elevated level of tacrolimus[5,12]. In other words, tacrolimus dose might need to be temporarily reduced, until the increased bioavailability returns to normal, usually 1-2 weeks after the onset of enteritis (regeneration time of injured enterocytes)[12]. Because the management of diarrhoea in kidney transplant recipients can involve multi-pronged strategies, referral to the transplant nephrologists would sometimes be indicated. Reducing the dose of mycophenolate mofetil in the context of persistent diarrhoea can be an option, but the risk of rejection and decreased allograft survival should be balanced with the benefit of managing gastrointestinal symptoms[13]. Other reasonable options include drug switch to an enteric-coated mycophenolate or azathioprine[5].

WHAT SHOULD I DO WHEN KIDNEY TRANSPLANT RECIPIENTS DEVELOP GOUT?

Patients with kidney transplants frequently experience develop hyperuricaemia and, in some cases, gout. The major reason for their propensity to have gout, besides uric acid deposition before kidney transplant, is the medication use of calcineurin inhibitor especially cyclosporine.

One of the largest studies included nearly 30,000 United States Medicare kidney transplant recipients, and showed an increased risk of new-onset gout with cyclosporine compared with tacrolimus, with an adjusted hazard ratio of 1.25[14]. On the other hand, the prevalence of gout remains high in the era when tacrolimus has increasingly replaced cyclosporine[15]. Another retrospective study involving 35 kidney transplant recipients with conversion from cyclosporine to tacrolimus showed no significant lowering of uric acid levels after switch[16]. Other important risk factors predictive of new-onset gout after kidney transplantation include male sex, older age, higher recipient body mass index, and lower graft function[14].

Since acute gout is a painful and disabling but self-limiting condition, the main purpose of treatment is to reduce symptoms and shorten flare duration. Topical ice is useful but mostly serves as an adjuvant treatment. Three common first line management of gout flare include colchicine, nonsteroidal anti-inflammatory drugs NSAIDs, and glucocorticoids[17,18]. In patients with kidney transplants, colchicine is the least favoured because of the increased half-life in chronic kidney disease and enhanced drug toxicity with concomitant use of cyclosporine, which strongly inhibits the cytochrome P450 CYP3A4 component and the P-glycoprotein drug transporter[19]. If needed, short course of NSAIDs can be used cautiously but the drug is relatively contraindicated in chronic kidney disease. Because of the unpredictable renal response to NSAIDs, we recommend using oral glucocorticoids as the first-line therapy for managing gout flare in most kidney transplant recipients. The initial dose of prednisolone is 30 mg once daily, or less if the patient has a history of response to lower doses. The prednisolone dose can be tapered over one week to the dose previously used for maintenance immunosuppression. Diabetes alone (unless poorly controlled) is not a contraindication to the use of glucocorticoids, although patients with diabetes should be warned of the need to monitor glucose, and often anticipation of glucose-lowering medication adjustment[19]. Underscoring the importance of early and optimal flare treatment, the 2020 American College of Rheumatology ACR gout treatment guideline recommend an at-home "pill-in-a-pocket" strategy to allow patients to have timely access of effective treatment once they identify early signs of flare onset[17]. This is a reasonable approach for kidney transplant recipients as long as they have education on proper drug use and monitoring.

In terms of chronic management of gout, the importance of lifestyle modification cannot be overemphasised. Patients should be counselled to minimise intake of alcohol (especially beer), fructose (sugar-sweetened beverages), and a purine-rich diet (meats, shellfish). Before considering urate-lowering therapy, the clinician should review the patient's medication list and try to reduce or discontinue thiazide or loop diuretics[19]. Furthermore, there is potential benefit in maximising (repurposing) drugs that have an additional role in lowering serum urate levels. To this end, clinicians should be familiar with the drugs that affect serum urate levels. Sodium-glucose cotransporter-2 inhibitor SGLT2i, among them, is the most promising agent to protect patients from developing gout, as demonstrated by numerous secondary analyses of randomised controlled trials, pharmacoepidemiology studies and one meta-analysis[20,21]. In a large meta-analysis of 62 randomised controlled trials of different SGLT2i including empagliflozin, canagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin, the drugs resulted in a mean reduction in serum urate concentrations of 37 μmol/L in follow-up over 4 to 206 weeks[21].

Interestingly, the urate-lowering capacity might not be a class effect (as what has been shown by the drug class sodium-glucose cotransporter-2 inhibitor) but is limited to a single drug within the class. A well-known example is angiotensin II receptor blocker. There is heterogeneity of angiotensin II receptor blockers' effect on uric acid transporter across the renal tubule lumen. Previous studies have confirmed the unique reduction of urate level by losartan, but not other drugs within class, such as valsartan, telmisartan, olmesartan or candesartan. Likewise, a randomised controlled trial of 351 Chinese hypertensive patients compared the effect of losartan and irbesartan. Despite comparable effect on blood pressure, there was significantly more reduction of serum urate reduction after eight weeks of losartan than irbesartan[22] . On the basis of the unique uricosuric effect of losartan, the 2020 ACR gout treatment guideline conditionally recommended "choosing losartan preferentially as an antihypertensive agents for patients with gout, regardless of disease activity[17]".

The benefits of starting urate-lowering therapy should be discussed with the patients. On the other hand, most established indications for starting urate-lowering therapy include any of the following: presence of tophi, recurrent gout flares (defined as ≥ 2 per year), evidence of gout related joint damage (erosive change as shown on any modality of radiographic image)[17,18].

Allopurinol or febuxostat have been suggested as first-line urate-lowering therapy in kidney transplant patients. Either of these two xanthine oxidase inhibitors should be avoided to be prescribed to patients receiving azathioprine, because all xanthine oxidase inhibitors block the metabolism of azathioprine (and its active metabolite 6-mercaptopurine). This would lead to the accumulation of azathioprine and severe bone marrow toxicity. Although reduction of azathioprine dose and close monitoring of white blood cell count can theoretically reduce the risk, a safer option would be switch of azathioprine to other immunosuppression such as mycophenolate mofetil. If allopurinol is chosen, patients have to be educated on the risk of allopurinol hypersensitivity syndrome. This rare but potentially life-threatening condition, characterised by severe cutaneous eruptions, eosinophilia, and acute hepatic

and renal injury, can be associated with the HLA-B*5801 allele[23]. Because of high prevalence of this allele among Asian patients including Han Chinese, Korean, and Thai descent, routine testing for HLA-B*5801 before starting allopurinol is cost-effective in patients of Asian ancestry[24].

Irrespective of the urate-lowering therapy choice, the drug should be initiated at a low dose. Proper patient education is most important to ensure an understanding of indefinite treatment duration. The key is to allow shared decision-making, although the current literature favours treat-to-target strategy (such as a treatment target of serum urate level < 360 μmol/L) over a treat-to-avoid-symptoms strategy[18]. Most experts advise giving concomitant anti-inflammatory prophylaxis therapy (such as prednisolone, colchicine, NSAIDs for three months, or longer duration if frequent ongoing flares) when initiating urate-lowering therapy[17,18,25], in order to avoid the paradoxical occurrence of gout flares during the initial phase. Such paradoxical flare is probably secondary to the mobilisation of monosodium urate crystals from intra-articular deposits as serum urate levels decline. The faster and greater reduction, the more risk is expected[26]. In a recent randomised double-blind placebo-controlled trial, the placebo did not meet the prespecified noninferiority margin compared with colchicine 0.5 mg daily in the prevention of gout flares in the first six months of starting allopurinol using the 'start-low go-slow' dose escalation method[27]. However, there was no difference in the mean number of gout flares over the entire 12-month period[27]. Since colchicine is relatively contraindicated or poorly tolerated in kidney transplant patients, a tenable option would be low-dose glucocorticoids (such as prednisolone 7.5 to 10 mg daily) during the initiation phase. The recommended maximum starting dose of allopurinol is 100 mg daily, or 50 mg daily in individuals with moderate-to-severe kidney function impairment[25].

WHEN SHOULD I WITHHOLD DRUGS INCLUDING MAINTENANCE IMMUNOSUPPRESSION?

Many doctors will encounter kidney transplant recipients who require surgery or present with infection. A common question is the need or safety of withholding immunosuppression drugs[28].

When patients are being kept fasting for surgery, they should be allowed to continue immunosuppression with sips of water. This practice is to minimise subtherapeutic level of immunosuppression and thus the risk of acute rejection. When patients are unable to swallow capsules and require feeding or nasogastric tube, it would be important to check the compatibility of drugs for such purpose. Table 3 summarises the information to guide the administration via feeding tube, based on published literature, product packet insert and pharmacotherapy consideration. For example, contents of immediate-release capsules of tacrolimus can be mixed in water and flushed through a nasogastric tube. Or else, oral suspension can be administered in a 1:1 (mg:mg) ratio using previously established dosing. Practical details of such administration should be further confirmed with pharmacists[29]. For example, cyclosporine is available in two formulations. The usual formulation cyclosporine modified, Neoral, might be switched to Sandimmune microemulsion formulation when nasogastric tube administration is used. The bioavailability might vary between formulations. Drug level monitoring would be recommended after formulation switch[30]. Since tacrolimus is a highly lipophilic drug with variable absorption, high-fat meals can reduce tacrolimus bioavailability. In general, we recommend kidney transplant recipients to either take the oral drug consistently with or without food, or to take the oral drug on an empty stomach one hour before or two hours after meal. The interference of food with tacrolimus absorption has been shown for immediate-release[31] and extended-release tacrolimus[32,33] preparation. Intuitively, concurrent enteral nasogastric feeding with tacrolimus administration would reduce drug absorption. It would be prudent to interrupt enteral feeding before and after tacrolimus.

Intravenous formulation is only suggested when the patients are unable to take oral medications postoperatively. If there is concern with adrenal suppression (after high doses of glucocorticoids and chronic suppression), high doses of parenteral glucocorticoid can be used. This is of particular relevance to major surgery under general or regional anesthesia associated with long recovery time. Published literature about glucocorticoid dosing perioperatively is limited. Instead of advocating supraphysiological replacement, most of the recent recommendations support that a short course of perioperative intravenous glucocorticoid with rapid taper and monitoring is sufficient[34]. Common regimens include hydrocortisone 100 mg intravenously at induction and every 8 hours perioperatively (for cases with proven or suspected adrenal insufficiency), followed by a reduced dose (but not the frequency) until the patient can be switched to regular oral medication. The glucocorticoid dose is usually halved the day after surgery. The maintenance dose is then resumed the second postoperative day[34,35].

Mammalian (mechanistic) target of rapamycin mTOR inhibitors is a class of immunosuppression drugs that require special attention perioperatively (Table 2). The two drugs of mTOR inhibitors, sirolimus and everolimus, act by blocking DNA and protein synthesis and proliferation of T, natural killer, and B cells. Higher wound complication rates with mTOR inhibitor use after kidney transplantation surgery had been reported in two randomised controlled studies[36,37] and several matched cohort observation studies[38-40]. Wound complications range from wound dehiscence, wound infection, lymphoceles, non-lymphocele perinephric fluid collection, incisional hernia, to the need for re-laparotomy. The current recommendation is to discontinue mTOR inhibitor at least one week prior to surgery and switch to calcineurin inhibitors, and switch back to mTOR inhibitor after wound is healed.

When kidney transplant recipients present to primary care or emergency department doctors with signs and symptoms of infection, the most appropriate initial management is assessment of the infection aetiology and coverage with appropriate antimicrobials. Besides

gastroenteritis mentioned above, respiratory and urinary tract infections are the most common causes[41]. The mainstay of treatment is antibiotics, the choice of which depends on the local and patient-specific susceptibility data. For instance, some kidney transplant recipients have a history of recurrent urinary tract infection secondary to multidrug-resistant pathogens such as those producing extended-spectrum beta-lactamase. The best practice is to review patient's recent microbiological culture and sensitivity information.

Because there are many classes of drugs that interact with calcineurin inhibitors, caution must be exercised before introducing new drugs such as antimicrobials[30]. Checking with a drug interaction app or consulting a pharmacist is recommended. The commonest mechanism of drug interaction involves either induction or inhibition of the hepatic cytochrome P450 system. Some potent P450 inhibitors such as azole antifungals may warrant up to an 80% reduction in cyclosporine or tacrolimus dose. Table 4 summarises the common immunosuppression drug interaction with antimicrobials. In addition to close monitoring during the treatment initiation phase with reference to potential drug interaction, attention should also be paid to the time period of drug discontinuation. For example, full effect of rifampicin for P450 enzyme induction takes up to two weeks after start, and the effect can persist for two weeks after discontinuation of rifampicin[42].

Because most infection could be accelerated by immunosuppression, there is often a temptation to withhold immunosuppression medication in an immunocompromised host temporarily. The decision and threshold to withhold immunosuppression should be different between a patient with rheumatoid arthritis and a patient with kidney transplantation. One of the challenges is to balance the risk of organ rejection and the benefit of better clearance of the infection. Owing to this concern, primary care doctors should preferably discuss with nephrology team before such decision. Patients should also be educated not to self-initiate alteration of the immunosuppression medication.

Table 1 lists the basic principles in immunosuppression medication management during infection. As with most medical decisions, there is often a need to have case-by-case consideration, especially when there is a lack of high-level evidence to guide the management. The recent scenario of the novel severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 infection serves as a good example to illustrate the principles of managing kidney transplant recipients. A randomised study involving 92 kidney transplant recipients without seroconversion after two or three doses of mRNA vaccine for the syndrome of coronavirus disease COVID 2019 showed that discontinuing mycophenolate mofetil or mycophenolic acid (from one week before until one week after vaccination) did not result in a higher response rate to mRNA booster vaccinations[43]. Although the study was underpowered, there were no acute rejection episodes after withholding mycophenolate mofetil or mycophenolic acid for two weeks[43]. After infection with SARS-CoV-2, not all kidney transplant recipients need to be hospitalised[44]. Decision regarding withdrawal of immunosuppression, however, is not easy. The key factors to consider include the immunological risk (of organ rejection): recent or second kidney transplant, previous history of rejection, high human leukocyte antigen HLA mismatches, donor blood group incompatibility, and the presence of donor-specific antibodies. At the same time, there should be another consideration: what exact role does immunosuppressive medication play in the disease course. With increasing knowledge on the disease trajectory and management of COVID-19, the efficacy of dexamethasone and immunomodulatory agents such as Janus kinase inhibitor and interleukin-16 inhibitor are being recognised. There is, therefore the management conundrum for when and whether immunosuppression should be reduced. The role of withdrawing or reducing immunosuppression in COVID-19, in other words, might not be as strong as managing other infections such as BK polyomavirus in kidney transplant recipients.

Furthermore, the risk of withdrawing immunosuppression in managing viral infection could be further magnified if the virus (such as CMV) has indirect cellular effect potentiating risk of allograft rejection[8,45]. To further complicate the issue of managing immunosuppression for kidney transplant recipients with COVID-19 infection, one of the purposes for withholding immunosuppression such as tacrolimus is to allow nirmatrelvir/ritonavir, a medication approved for early treatment of COVID-19. As mentioned in Table 4, ritonavir is a potent cytochrome P450 inhibitor, which can cause tenfold or higher increased drug level of cyclosporine or tacrolimus when used concurrently[46,47]. These concerns could justify the decision to withhold calcineurin inhibitor the day before (or immediately after) starting nirmatrelvir/ritonavir. Timing of resuming drug (often at reduced dose for tacrolimus) depends on subsequent therapeutic drug monitoring to minimise drug toxicity and risk of rejection[46,48].

In short, the overarching principle of managing infection of transplant recipients is first to save life, and second to avoid graft loss. In the absence of complicated drug interaction consideration, the usual step is keeping immunosuppression unless there is moderate to severe infection. Although strong evidence is lacking, most immunosuppression reduction strategy starts with stopping or reducing antimetabolites, after discussion with nephrology or transplant team. Worsening kidney allograft function after reduction of immunosuppression should prompt early evaluation with kidney biopsy[49].

CONCLUSION

Kidney transplant recipients are vulnerable to metabolic and infective complications. Owing to the background use of immunosuppression and often drug interactions, there should be a low threshold of consulting specialists, including pharmacists, infectious disease specialists, nephrology or transplant teams. Last but not least, patient education is essential.

Table 1: Stepwise algorithm for managing acute diarrhoea in kidney transplant recipients (Composed by the author)

First Tier	**Step 1:** Assess the need of hospitalisation for rehydration and consider oral rehydration therapy to correct fluid losses and electrolyte imbalance **Step 2:** Medication review and stopping non-immunosuppression that may cause diarrhoea, such as colchicine or oral magnesium **Step 3:** Screen for infectious causes of diarrhoea, including *Clostrioides difficile* polymerase chain reaction PCR, stool culture
Second Tier	**Step 4:** Second tier microbiological testing, including stool PCR for viral pathogen, ova and parasite, as well as cytomegalovirus CMV PCR assay from blood **Step 5:** Anti-motility drugs **Step 6:** Adaptation and monitoring of immunosuppression drug, such as switching mycophenolate mofetil and reduction of tacrolimus dose if persistent diarrhoea **Step 7:** Referral for endoscopy investigation of refractory diarrhoea, with diagnostic value on CMV disease[10]

Table 2: Clinical framework for managing immunosuppression in acute setting (Composed by the author)

Infection	**Rule 1:** No need to modify immunosuppression for mild or stable infection **Rule 2:** Consider does reduction or withholding antimetabolite immunosuppression (such as mycophenolate mofetil) for moderate infection **Rule 3:** Discuss with nephrologists if immunosuppression should be withheld (except for glucocorticoids) in case of severe or life-threatening infection
Surgery	**Rule 4:** Assess risk of adrenal insufficiency and consider high dose intravenous hydrocortisone cover on the first two days of operation **Rule 5:** No need to change immunosuppression except mammalian target of rapamycin mTOR inhibitor (which can impair wound healing) **Rule 6:** Stop mTOR inhibitor one to two weeks prior to surgery and switch to calcineurin inhibitors, and switch back to mTOR inhibitor after wound is healed **Rule 7:** Allow oral medication (with sips of water) if possible during nil-by-mouth period, and use intravenous formulation only if necessary (with pharmacist or nephrologist consultation)

Table 3: Compatibility of immunosuppression drug with nasogastric tube (Composed by the author)

Tacrolimus	**Immediate-release capsules**	1. Can be mixed with water and given via feeding tube 2. Avoid the use of polyvinyl chloride (PVC) materials (cups, tubing) which may reduce tacrolimus bioavailability[29] 3. Preferably adjust dose according to target trough concentrations, in view of a high variability of tacrolimus blood concentrations when administered via nasogastric tube
	Extended-release capsules	1. Not supposed to be crushed or divided 2. Opening capsules and mixing with 50 mL of water has been tested in non-PVC tube and non-PVC tube in de novo liver transplant recipients[50]
Cyclosporine	**Cyclosporine capsules (Neoral)**	1. Not for administration through feeding tube in general
	Liquid microemulsion cyclosporine (Sandimmune)	1. Liquid microemulsion cyclosporine can be considered but intravenous administration is preferred[51]
Mycophenolic acid derivatives	**Mycophenolate mofetil (MMF)**	1. Preferably use suspension instead of tablet (which is slow to dissolve)[52] 2. Administer separately from enteral feedings to avoid reduction in time to achieve maximum drug concentration[29]
	Mycophenolate sodium (MPS)	1. Not supposed to be crushed or cut 2. May cause tube obstruction because the drug would not disperse well after crushing the enteric-coated tablet
Sirolimus	1. Not recommended as the drug (thick suspension) requires more than 50 mL of water for dilution to allow feeding tube passage[52] 2. Oral suspension, if used, should be stirred vigorously and administered once drawn up, followed by flushing of nasogastric tube	
Everolimus	1. Limited information 2. Recommend to use orodispersible tablet[29]	

Table 4: Common drug interaction between calcineurin inhibitors (cyclosporine or tacrolimus) and antimicrobials (Composed by the author)

Antimicrobials	**Mechanisms and recommendation(s)**
Common drugs that increase calcineurin inhibitor levels	
Erythromycin, clarithromycin	Potent inhibition of cytochrome P450 Consider alternative macrolides such as azithromycin which has less impact on drug metabolism[53]
Protease inhibitors (such as ritonavir in medication for coronavirus infection)	Very potent inhibitors of cytochrome P450 Consider alternatives or adjust the medication (temporary withholding calcineurin inhibitors for a few days and resumption at a low dose under monitoring)
Azole antifungals such as voriconazole and itraconazole	Potent inhibition of cytochrome P450 Consider alternatives such as terbinafine for treatment of dermatophyte onychomycosis[54]
Common drugs that reduce calcineurin inhibitor levels	
Rifampicin	Potent inducer of cytochrome P450 (and P-glycoprotein multidrug efflux transporters) Consider monitoring of calcineurin inhibitor level after empirical increase of drug dose Consider alternatives such as rifabutin, a weaker inducer of cytochrome P450 3A4 and P-glycoprotein but with similar efficacy for tuberculosis[55]

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Drug Use in Kidney Transplant Recipients: What Primary Care Physicians Need to Know" by Dr Kai-ming CHOW and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or answer link: https://docs.google.com/forms/d/e/1FAIpQLSf3HOOg_-PuvMXHBVX95y_36O4x5Ndy0EraOsvD0A-81aZMCw/viewform or by mail to the Federation Secretariat on or before 31 January 2025. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

Questions 1 - 10: Please answer T (true) or F (false)

1. **Kidney transplant recipients with norovirus infection have a more chronic or protracted disease course than the normal population.**
2. **Diarrhoea can cause low drug level of tacrolimus.**
3. **Clarithromycin can increase drug level of calcineurin inhibitors (such as cyclosporine and tacrolimus).**
4. **There is no drug-drug interaction between febuxostat and azathioprine.**
5. **Losartan can have urate lowering effect.**
6. **For transplant recipients on prednisolone, the drug should be stopped perioperatively.**
7. **There is no need to modify or withhold immunosuppression drug for mild and stable infections among kidney transplant recipients.**
8. **The COVID-19 medication nirmatrelvir/ritonavir can cause drug interaction with tacrolimus.**
9. **Temporarily discontinuation of mycophenolate mofetil or mycophenolic acid can result in higher immune response rate to mRNA vaccine of COVID-19.**
10. **The recommended starting dose of allopurinol in kidney transplant recipients is 50 to 100 mg daily.**

ANSWER SHEET FOR JANUARY 2025

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2025 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Drug Use in Kidney Transplant Recipients: What Primary Care Physicians Need to Know

Dr Kai-ming CHOW

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Answer Link

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to December 2024 Issue

Management of Resistant Hypertension

1. F 2. T 3. T 4. F 5. F 6. F 7. F 8. T 9. T 10. T

My Life after Transplant

Mr Bill WANG

Chairman, Patient Liaison and Advisory Group, the International Society of Nephrology ISN

Mr Bill WANG

Being a recipient of a combined kidney and liver transplant, I have been grateful. To share my personal journey since 2018, I have to retrace my footsteps before my diagnosis of polycystic kidney and liver disease diagnosed two decades earlier.

The transplant experience has transformed my life in ways I dared not to imagine, and I hope to shed some light on what life after transplant truly means.

PERSONAL JOURNEY BEFORE TRANSPLANTATION

I was born in 1968 in Shanghai China, studied law in China and the U.S. and worked as a capital markets lawyer in New York, London and Hong Kong. The diagnosis of polycystic kidney disease came at my professional prime - it felt like a sudden break causing disorientation and a sinking feeling in my stomach. The prospect of following my other family members' less fortunate footsteps (including early death) was daunting, filled with uncertainty, fear, disappointment and a sense of fatalism. I chose to ignore - out of sight, out of mind - until the end stage kidney disease with liver cyst complications. I started to face the reality by seeking medical help and looking into literatures on the disease while I was on dialysis. The negative feelings slowly turned into hope as I was put on the waiting list for a combined liver and kidney transplant.

The day of my surgery was full of mixed feelings - a lot of hope but also a lot of uncertainties and anxieties - whether I could have both organs transplanted or whether I would survive the mega operation at all. I was trying to be calm and rational through suppressing the emotional and sentimental side of nerve signals before I was put to sleep.

Today, I am grateful for the second chance at life, thanking the miracle brought to me by the donor and donor family and the craftmanship of my surgeons and transplant specialists.

RECOVERY AFTER TRANSPLANT

Physical Recovery: The physical recovery post-transplant is a journey of its own. Adhering to a strict medication regimen was crucial for my recovery. Regular follow-ups with my healthcare teams ensured that I stayed on track and addressed any complications swiftly.

Emotional and Psychological Aspects: However, recovery is not just physical; it is profoundly emotional. Initially, there was relief mixed with anxiety about my new life.

Finding Support: Having a support system was invaluable. My family and friends stood by me, and the connection I found with fellow patients helped me navigate the complex feelings I experienced. Sharing stories and encouraging one another became a vital part of my healing.

Coping with Survivor's Guilt: I also grappled with survivor's guilt. Knowing that my transplant came at the cost of another person's life was heavy. I turned this guilt into motivation to advocate for organ donation, helping raise awareness about its importance in saving lives. Maintaining my own well-being is another way of thanking the loving gift from the donor family.

Celebrating Small Victories: I learned to celebrate small victories - like regaining my strength or returning to hobbies I loved. Each milestone became a reminder of the progress I was making, and I encourage all patients to acknowledge their achievements, no matter how small.

Mindfulness and Self-Care: Practising mindfulness and establishing self-care routines became essential. Techniques like meditation and mindful walking helped me manage stress and maintain a positive outlook.

ADVOCACY FOR PATIENT-CENTRED CARE

As a lawyer by training, being an effective counsellor and advocate was an integral part of my professional life. As a patient, passionately advocating for person-centred care is my new mission that calls for recognition that each patient is with unique experiences, needs and preferences and their care model has to be both tailored and holistic.

Experiences with Healthcare Providers and Healthcare System: As a fortunate beneficiary of the public healthcare system in Hong Kong, I have experienced both exemplary patient care and issues of lack of resources or misallocation thereof. Open communication with healthcare professionals and policymakers is crucial, where patients' voices and concerns can be heard and valued.

The Role of Patients: I encourage my fellow patients to take an active role in their own care. We should advocate for ourselves, ask questions, and express our concerns and preferences. It is about partnership creating in care and patient capacity building and upscaling in health and medical literacy.

ENGAGING IN SPORTS AND COMMUNITY

Physical activity is vital post-transplant. I discovered the joy of picking up table tennis again years after my fourth grade, which not only helped me regain my strength but also became a way to connect with others.

I now organise sports activities for fellow patients, encouraging them to engage in suitable exercises. Staying active has been transformative, fostering a sense of community and shared purpose.

My participation in various transplant games - medals aside - gives me the true reward of bonding with fellow transplant athletes all over the world.

The 5th Hong Kong Transplant and Dialysis Games was successfully organised in October 2024. And I am sure I will meet many of you this August in Dresden, Germany for the next World Transplant Games. Let's embrace this special event with noble spirit and graceful sportsmanship.

Sports aside, I am also sitting on the governance bodies of various NGOs, charities and patient organisations: Patient Liaison Advisory Group of International Society of Nephrology, Hong Kong Kidney Foundation, Hong Kong Transplant Sports Association, Safety and Quality Committee of Prince of Wales Hospital, Chinese University of Hong Kong. And I have just been invited to teach a seminar on Patient-Provider Partnership with the medical students at the University of Hong Kong as part of their medical ethics and humanity curriculum. Life is as busy as ever since my transplant.

CONCLUSION

Life after an organ transplant is a multifaceted journey. Mine has encompassed physical recovery, emotional healing, and the power of repurpose, reactivation and return to the community.

One takeaway is that patients, caregivers, healthcare professionals and advocates alike must collaborate in creating a supportive environment for transplant donors and recipients and their families and communities. Together, we can enhance the lives of those navigating this path after rising from severe adversities and wishing to live their lives to the fullest.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	★In-person / Zoom HKMA-HKSH CME Programme 2024-2025 Topic: Advances in Egg Freezing technology 7	★The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed 8	★Zoom Managing Atopic Dermatitis Naturally from Within: Latest Insights on Gut Microbiome Modulation & the Gut-Skin Axis 9	10	11
12	13	★Zoom Preventing the Preventable: Updates in Long-term Antiplatelet Management for Coronary Artery Disease Patients 14	15	★In-person / Zoom HKMA-HKSTP CME Programme 2025 Topic: Screening and Prognostication in Chronic Liver Diseases 16	★In-person The HKMA-KWC CME Lecture for District Health Network CME Programme in Physical Attendance Mode Topic: Extending Survivorship Care and Rehabilitation to Patients with Metastatic Cancer 17	18
19	★Zoom The HKMA-KWC CME Lecture for District Health Network CME Programme in Zoom Attendance Mode Topic: Bread and Butter for Providing Breast Cancer Survivorship Care in the Local Community: Based on The CONNECT Program Model 20	21	22	23	24	25
26	27	28	29	30	31	

Date / Time	Function	Enquiry / Remarks
7 2:00 PM **TUE**	**In-person / Zoom** **HKMA-HKSH CME Programme 2024-2025** **Topic: Advances in Egg Freezing technology** Organiser: The Hong Kong Medical Association and the Hong Kong Sanatorium & Hospital Speaker: Dr TANG Oi-shan Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, HK	HKMA CME Dept. Tel: 2527 8452 1 CME Point
8 7:30 AM **WED**	**The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker: Dr Tony TONG Ka-chun Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital; or via Zoom meeting	Dr Jason CHOW Tel: 2595 6456 Fax: 2965 4061 1.5 CME Point
9 2:00 PM **THU**	**Zoom** **Managing Atopic Dermatitis Naturally from Within: Latest Insights on Gut Microbiome Modulation & the Gut-Skin Axis** Organiser: The Hong Kong Medical Association Speaker: Dr Nicholas FUNG Siu-kay	HKMA CME Dept. Tel: 2527 8452 1 CME Point
14 2:00 PM **TUE**	**Zoom** **Preventing the Preventable: Updates in Long-term Antiplatelet Management for Coronary Artery Disease Patients** Organiser: The Hong Kong Medical Association Speaker: Dr Shek-yin AU	HKMA CME Dept. Tel: 2527 8452 1 CME Point
16 2:00 PM **THU**	**In-person / Zoom** **HKMA-HKSTP CME Programme 2025** **Topic: Screening and Prognostication in Chronic Liver Diseases** Organiser: The Hong Kong Medical Association Hong Kong Science & Technology Parks Speaker: Dr Rex HUI Wan-hin Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, HK	HKMA CME Dept. Tel: 2527 8452 1 CME Point
17 2:00 PM **FRI**	**In-person** **The HKMA-KWC CME Lecture for District Health Network CME Programme in Physical Attendance Mode** **Topic: Extending Survivorship Care and Rehabilitation to Patients with Metastatic Cancer** Organiser: The HKMA District Health Network HA-KLN West Cluster Speaker: Dr Henry WONG Chun-yip Venue: Crystal Ballroom, 2/F, The Cityview, 23 Waterloo Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 1 CME Point
20 2:00 PM **MON**	**Zoom** **The HKMA-KWC CME Lecture for District Health Network CME Programme in Zoom Attendance Mode** **Topic: Bread and Butter for Providing Breast Cancer Survivorship Care in the Local Community: Based on The CONNECT Program Model** Organiser: The HKMA District Health Network HA-KLN West Cluster Speaker: 1) Dr Tracy SHUM Chui-yu Tracy; 2) Dr Jessica LAI Wing-yu	HKMA CME Dept. Tel: 2527 8452 3 CME Point

Answers to Dermatology Quiz

Answers:

1. Major differential diagnoses include lichen planus, sarcoidosis, chronic idiopathic urticaria, erythema elevatum diutinum and generalised granuloma annulare.

   Granuloma annulare (GA) is a benign inflammatory dermatosis. It occurs in all age groups but rarely in infancy. The aetiology is unknown. It is probably a delayed hypersensitivity reaction to some triggers, including skin trauma and infections. It presents as dermal papules and sometimes annular plaques. Generally, there are several variants included localised GA, generalised GA and rarely perforating GA.

2. Granuloma annulare can be diagnosed clinically if the presentation is typical and characteristic. However, sometimes the presentation is not obvious and a skin biopsy may be needed to confirm the diagnosis. A skin biopsy may reveal necrobiotic degeneration of dermal collagen and palisaded granulomatous dermatitis. Since granuloma annulare, especially the generalised form, is associated with diabetes mellitus, hyperlipidemia and rarely with HIV infection, the concerned blood test should be considered for the patients.

3. Treatment of granuloma annulare is difficult. For localised granuloma annulare, it is often asymptomatic and likely to be recovered spontaneously. For some difficult lesions, potent topical steroid can be used. Cryotherapy and carbon dioxide laser may be considered for the localised recalcitrant lesions. On the other hand, the treatment for generalised granuloma annulare is difficult and no common consensus. Systemic steroids, isotretinoin, methotrexate, anti-malarials and even phototherapy have been used in generalised granuloma annulares in some case reports.

Dr Chi-keung KWAN
MBBS(HK), MRCP(UK), FRCP(Lond, Glasg, Edin), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Medicine)
Specialist in Dermatology and Venereology

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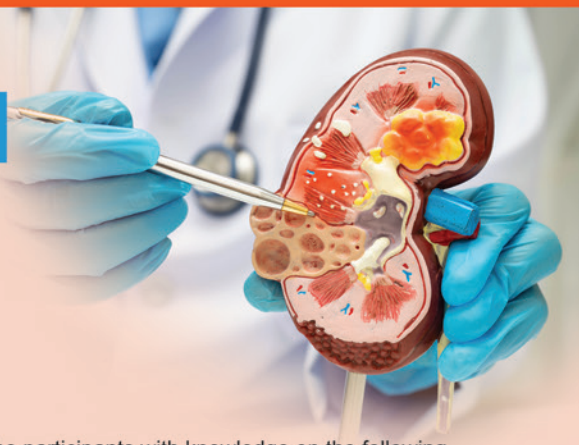
Certificate Course in

Common Urological Problems 2025

(Video Lectures)



Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Practising Urologists

Objectives:

The course aims to equip the participants with knowledge on the following common urological conditions:

1. Prostate Cancer - recent advances in diagnosis and treatment
2. Management of LUTS and surgical interventions for BPH
3. Approach in treating urinary tract infection and female voiding dysfunction
4. Updates on the management of common urological cancers
5. Approach to common penile and scrotal diseases
6. Urolithiasis - treatment in medical and surgical perspectives

Date	Topics	Speakers
27 Feb 2025	Recent Advances in the Diagnosis of Prostate Cancer	Dr. Lee Yue Kit Chris Specialist in Urology
	Surgical Management of Prostate Cancer	Dr. Ma Wai Kit Specialist in Urology
6 Mar 2025	Approach in Managing Patients with Lower Urinary Tract Symptoms	Dr. Lo Ting Kit Specialist in Urology
	Latest Surgical Interventions for Benign Prostatic Hyperplasia	Dr. Li Churk Fai Trevor Specialist in Urology
13 Mar 2025	Latest Guidelines on the Treatment of Urinary Tract Infection	Dr. Cheung Man Hung Phoebe Specialist in Urology
	Updates on the Management of Female Voiding Dysfunction	Dr. Cheung Ho Yuen Specialist in Urology
20 Mar 2025	Approach to Hematuria and its related Urological Cancers	Dr. Chiu Yi Specialist in Urology
	Approach to Renal Mass: From Investigations to Treatments	Dr. Law Tak Tsun Vincent Specialist in Urology
27 Mar 2025	Common Penile Diseases and Their Management	Dr. Fan Chi Wai Specialist in Urology
	Common Scrotal Diseases and Their Management	Dr. Wong Ka Wing Jason Specialist in Urology
3 Apr 2025	Management of Urolithiasis - From a Medical Perspective	Dr. Hung Hing Hoi Specialist in Urology
	Management of Urolithiasis - From a Surgical Perspective	Dr. Chau Hin Lysander Specialist in Urology

Dates : 27 February; 6, 13, 20, 27 March and 3 April 2025 (THUR)
Duration of Session : 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Language Media : Cantonese (Supplemented with English)
Quiz for Doctors : DOCTORS are required to complete a quiz after the completion of each lecture
Course Fee : HK$1,200
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : **20 February 2025**
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel: 2527 8898 Fax: 2865 0345 Email : toto.chan@fmshk.org

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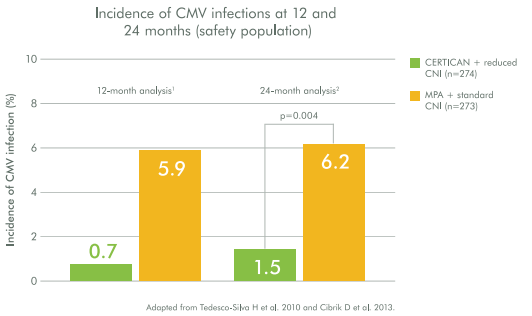
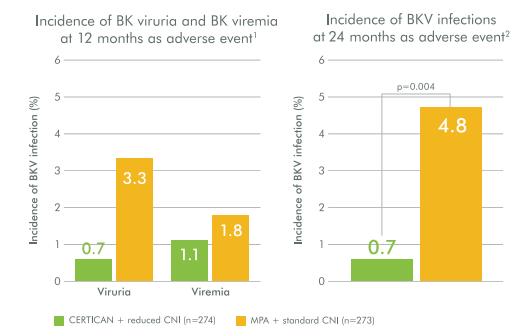


BKV SIGNIFICANT REDUCTION IN THE INCIDENCE OF VIRAL INFECTION



Very common side effects (>10%) including infections, headache, insomnia, anxiety, other metabolic, gastrointestinal and hematological side effects. Please refer to package insert for more details.[3]

BKV=BK polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; MPA=mycophenolic acid.

References: 1. Tedesco-Silva H Jr *et al. Am J Transplant* 2010; 10(6): 1401-1413. **2.** Cibrik D *et al. Transplantation* 2013; 95(7): 933-942. **3.** Certican full prescribing information

CERTICAN® Tablets

Important note: Before prescribing, consult full prescribing information. Presentation: Everolimus. Tablet containing 0.25, 0.5, 0.75, or 1.0 mg of everolimus. **Indications:** Kidney and heart transplantation. Certican is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, Certican should be used in combination with ciclosporin for microemulsion and corticosteroids. Liver transplantation. Certican is indicated for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids. Dosage: •Recommended general daily dose is 0.75 mg b.i.d. for kidney and heart transplant population. For the hepatic transplant population, recommended general daily dose is 1.0 mg b.i.d with the initial dose starting approximately 4 weeks after transplantation. •Whole blood trough levels of everolimus should be closely monitored in patients with impaired hepatic function. Dose should be reduced to approximately two-thirds in patients with mild hepatic impairment, to approximately one half in patients with moderate hepatic impairment and approximately one third of the normal dose for patients with severe hepatic impairment. •Very limited experience in children. **Contraindications:** Hypersensitivity to everolimus, sirolimus or to any of the excipients. **Warnings/Precautions:** •An increased risk of acute rejection and an improved renal function were observed in patients who discontinued the administration of ciclosporin from month 4.5 after renal transplantation compared with those who continued the administration of ciclosporin. •Caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the Certican/ciclosporin/steroid regimen. •Increased risk of developing lymphomas and other malignancies, particularly of the skin. •Oversuppression of the immune system with increased susceptibility to infections, especially infections with opportunistic pathogens (bacterial, fungal, viral, protozoal) which can include BK virus- associated nephropathy which can lead to kidney graft loss and the potentially fatal JC virus- associated progressive multiple leukoencephalopathy (PML). •Patients should be monitored for hyperlipidemia. •Angioedema has been observed with Certican, in the majority of cases reported, patients were receiving ACE inhibitors as co-medication. •Proteinuria is increased in transplant recipients and may increase in severity when Certican is substituted for a calcineurin inhibitor in a maintenance therapy renal transplant patient with pre-existing mild proteinuria. •Reduced doses of ciclosporin are required for use in combination with Certican in order to avoid renal dysfunction. In liver transplant study Certican with reduced exposure tacrolimus has not been found to worsen renal function in comparison to standard exposure tacrolimus. Regular monitoring of blood drug levels (everolimus and ciclosporin), proteinuria and renal function is recommended. •Coadministration of everolimus with known strong CYP3A4 inhibitors and inducers is not recommended unless the benefit outweighs the risk. •Increased risk of kidney arterial and venous thrombosis, resulting in graft loss, mostly within the first 30 days post-transplantation. •Certican, like other mTOR inhibitors, can impair healing increasing the occurrence of post-transplant complications. Lymphocele is the most frequently reported such event in renal transplant recipients and tends to be more frequent in patients with higher body mass index. The frequency of pericardial and pleural effusion is increased in cardiac transplant recipients and the frequency of incisional hernias in liver transplant recipients. •The concomitant administration of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy. •Cases of interstitial lung disease (ILD), some fatal, have been reported with Certican. Mostly, the condition resolves after discontinuation of Certican and/or addition of glucocorticoids. However, fatal cases have also occurred. •Certican may increase the risk of new-onset diabetes mellitus. Blood glucose concentrations should be monitored closely in patients treated with Certican. •There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. Potential risk for male infertility with prolonged Certican therapy. **•Women of child-bearing potential:** Highly effective contraception methods must be used while receiving Certican, and for up to 8 weeks after ending treatment. **•Pregnancy:** Should not be used during pregnancy unless clearly necessary. **•Breast-feeding:** Should not be used by breast-feeding women. **•Excipients:** Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Interactions:** •Caution should be exercized when co-administering everolimus with CYP3A4- and CYP2D6-substrates having a narrow therapeutic index.•Caution with concomitant use of rifampicin, rifabutin or ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin or ritonavir, as it may be necessary to modify the dose of Certican. •Caution with inducers of CYP3A4 (e.g St. John's Wort, anticonvulsants, (e.g carbamazepine), phenobarbital, phenytoin, anti-HIV drugs (e.g efavirenz, nevirapine), erythromycin, verapamil, inhibitors of PgP, and moderate inhibitors of CYP3A4 (e.g. antifungal substances: fluconazole, calcium channel blockers: nicardipin, diltiazem, protease inhibitors: nelfinavir, indinavir, amprenavir, octreotide and midazolam. •Avoid grapefruit juice, grapefruit. •Avoid use of live vaccines. **Adverse reactions: •Very common (>10%)** Infections (viral, bacterial, fungal), lower respiratory tract infection, upper respiratory tract infection, urinary tract infections, anemia/erythropenia, leucopenia, thrombocytopenia, hyperlipidemia (cholesterol and triglycerides), new onset diabetes mellitus, hypokalemia, insomnia, anxiety, headache, venous thromboembolic events, hypertension, cough, dyspnea, diarrhea, nausea, vomiting, abdominal pain, pericardial and pleural effusion, peripheral edema, healing impairment, pain and pyrexia. **•Common (1 to 10%)** Malignant and unspecified tumors, skin neoplasms, wound infection, sepsis, pancytopenia, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, tachycardia, epistaxis, lymphocele, renal graft thrombosis, stomatitis/mouth ulceration, oropharyngeal pain, myalgia angioedema, acne arthralgia, pancreatitis, proteinuria, erectile dysfunction, renal tubular necrosis, incisional hernia and hepatic enzyme abnormal. **•Uncommon (0.1 to 1%)** Lymphomas, male hypogonadism, interstitial lung disease, hepatitis (non-infectious) and jaundice. **•Unknown** Pulmonary alveolar proteinosis, erythroderma and leukocytoclastic vasculitis. **Packs and prices:** 0.25mg, 0.5mg, 0.75mg and 1 mg Tablet (60's). Legal classification: P1S1S3. The materials for Certican contained in this virtual exhibition are approved for use only in Hong Kong. Prescribing information may vary depending on local approval in each country/location. Before prescribing any product, always refer to local materials such as the prescribing information and/or the Summary of Product Characteristics (SPC).

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