Guide to the management of kidney transplant recipients

Background
For many patients with end stage kidney disease, kidney transplantation offers many benefits over treatment with dialysis. Although transplantation is not suitable for all patients, many do benefit from improved survival and health. Unfortunately, there are significant risks related to the immunosuppressive treatment. These risks include an increased susceptibility to infections (both “usual” infections and “atypical” infections) and an increased risk of developing malignancies. Monitoring immunosuppressive treatment is an important part of the management of kidney transplant recipients.

Immunosuppressive treatment
Most transplant patients will require maintenance immunosuppression with at least two agents from different classes. Potential interactions with these drugs are an important consideration when prescribing, as significant harm can arise from this. Immunosuppressants must never be stopped, unless directed by a renal physician. Common drug interactions will be covered separately. The drugs used are listed below.

1. Calcineurin inhibitors (CNIs - Ciclosporin and Tacrolimus). This class of drugs acts by reducing the production of interleukin-2, which is an important mediator in the process of acute rejection.
   Ciclosporin is monitored by trough levels (ie taken before the dose has been taken). Individual patients will have their own target levels, but as a general rule (for patients who are >12 months post transplant), we aim for levels between 50 - 100 ng / ml. There are 2 formulations available – Neoral and Sandimmune. These cannot be used interchangeably. Side effects include gum hypertrophy, hirsuitism, renal impairment and hypertension.
   Tacrolimus is also monitored by trough levels, and again, each patient will have their own target levels. As a guide (for patients who are >12 months post transplant), we aim for levels between 5 – 8 ng / ml. A number of formulations are available – Prograf, Advagraf and Adoport. These cannot be used interchangeably. Side effects include hypertension, tremor, susceptibility to diabetes and renal impairment.

2. Anti-proliferative agents (Azathioprine and Mycophenolate). These agents act by reducing the proliferation of lymphocytes, thereby reducing susceptibility to rejection.
   Azathioprine acts by inhibiting the DNA synthesis of lymphocytes. Levels are not monitored. Side effects include leucopaenia, bone marrow suppression, skin rashes and hair loss.
Mycophenolate also acts by inhibiting the DNA synthesis of lymphocytes. 2 different formulations are available – mycophenolate mofetil (appears as “mycophenolate” on correspondence) and mycophenolate sodium (appears as “mycophenolic acid” on correspondence). These cannot be used interchangeably. Although therapeutic drug monitoring is available, levels are not commonly used to determine dosage. Common side effects include diarrhoea and electrolyte disturbances (hypomagnesaemia, hypokalaemia and hypocalcaemia).

3. Sirolimus is not a calcineurin inhibitor. It acts by inhibiting the response to IL-2 (rather than the production as with the calcineurin inhibitors). Sirolimus is also monitored by trough levels, and again, each patient will have their own target levels. As a guide (for patients who are >12 months post transplant), we aim for levels between 5 – 8 ng / ml. Side effects include skin problems (such as acne), proteinuria, anaemia, delayed wound healing, lung problems (interstitial pneumonitis) and predisposition to diabetes.

4. Prednisone (prednisolone) is a steroid. Generally, due to side effects, if patients require long term steroid therapy we would aim to minimise the dose to 5mg daily. This dose may need to be increased temporarily at times of physiological stress (such as surgery or acute sepsis). Side effects include osteoporosis, predisposition to diabetes, truncal weight gain, skin thinning, easy bruising, glaucoma and cataracts.

### Important drug interactions / drugs to avoid

<table>
<thead>
<tr>
<th>Drug or substance to avoid</th>
<th>Interaction</th>
<th>Reason</th>
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<tbody>
<tr>
<td>NSAIDs (including topical)</td>
<td>NA</td>
<td>Risk of Acute Kidney Injury (AKI)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>NA</td>
<td>Risk of AKI</td>
</tr>
<tr>
<td>Macrolide antibiotics (eg erythromycin, clarithromycin)</td>
<td>CNIs (ciclosporin and tacrolimus) and sirolimus</td>
<td>Drug toxicity and AKI</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Azathioprine</td>
<td>Drug toxicity and severe blood dyscrasias</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>CNIs and sirolimus</td>
<td>Drug toxicity and AKI</td>
</tr>
<tr>
<td>“Azole” anti fungal agents (eg fluconazole)</td>
<td>CNIs and sirolimus</td>
<td>Drug toxicity and AKI</td>
</tr>
<tr>
<td>St John’s Wort</td>
<td>CNIs and sirolimus</td>
<td>Sub-therapeutic levels and risk of acute rejection</td>
</tr>
<tr>
<td>Grapefruit and pomegranate</td>
<td>CNIs and sirolimus</td>
<td>Drug toxicity and AKI</td>
</tr>
<tr>
<td>Anti-epileptics (carbemazepine and phenytoin)</td>
<td>CNIs and sirolimus</td>
<td>Sub-therapeutic levels and risk of acute rejection</td>
</tr>
<tr>
<td>Certain statins</td>
<td>Ciclosporin</td>
<td>Myositis, drug toxicity and AKI</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>CNIs and sirolimus</td>
<td>Sub-therapeutic levels and risk of acute rejection</td>
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</tbody>
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If in doubt, please contact the renal transplant nurses for further advice.
Vaccinations and travel

Transplant recipients will be immunosuppressed, so some vaccines will be unsuitable (eg live vaccines). Wherever possible, potential recipients should be vaccinated before transplantation, especially for vaccines that would be contraindicated in the post transplant period (eg varicella). For the transplant recipient who wishes to travel, he / she should be encouraged to visit a travel clinic beforehand. Prophylactic anti-tuberculous therapy is not recommended for travel to high risk areas. Patients are also advised to ensure that they have enough supply of medications for the duration of travel, have adequate travel insurance and take a travel letter with them (supplied by the renal unit).

<table>
<thead>
<tr>
<th>Safe vaccines</th>
<th>Contraindicated vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>MMR (measles, mumps and rubella), or given as individual vaccines</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Polio (live oral)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yellow fever</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Varicella</td>
</tr>
<tr>
<td>Haemophilus influenza B (HIB)</td>
<td>BCG</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Typhoid (live oral)</td>
</tr>
<tr>
<td>Polio (killed)</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td></td>
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<tr>
<td>Pertussis</td>
<td></td>
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<tr>
<td>Influenza</td>
<td></td>
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<tr>
<td>Typhoid (killed)</td>
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Infections in the transplant recipient

Infections in kidney transplant recipients are a common occurrence. Treatment with antibiotics should take account of potential interactions with immunosuppressants. Transplant recipients are also susceptible to “atypical” infections such as cytomegalovirus (CMV).

1. **Respiratory tract infections.** Should be treated in the same manner as in patients who are not immunocompromised. Antibiotics that interact with immunosuppressants (such as clarithromycin and erythromycin) should be avoided. If in doubt, please consult with the transplant nurses. Due to the possibility of atypical infection, or other causes for symptoms, there should be a low threshold for arranging imaging, such as a chest X-ray.

2. **Urinary tract infections.** Should be treated if symptomatic. Often, if patients are asymptomatic, patients are not treated, but advice should be sought from the transplant team. Antibiotics that interact with immunosuppressants (such as clarithromycin and erythromycin) should be avoided. Additionally, antibiotics such as trimethoprim should also be avoided if possible (elevates serum creatinine) and nitrofurantoin should be avoided if eGFR<60 ml/min.
3. **Varicella.** Shingles should be treated with aciclovir (dose adjusted for renal function) for seven days. Please inform the renal team before starting treatment as there is a risk of interaction with ciclosporin. Additionally, the anti-proliferative agent may need to be held temporarily, but this decision should only be made by the renal team.

Chicken pox is a medical emergency. This can still occur in transplant recipients who have previously demonstrated immunity or who have been previously vaccinated. The patient will need admission to hospital and isolation. Treatment is with intravenous aciclovir (dose adjusted for renal function) and possibly intravenous immunoglobulin (discuss with microbiologist). Additionally, the anti-proliferative agent may need to be held temporarily, but this decision should only be made by the renal team.

4. **Cytomegalovirus (CMV).** Symptoms of CMV disease include fever, leucopenia, or organ involvement (including hepatitis, pneumonitis, pancreatitis, gastritis, colitis, meningoencephalitis, myocarditis and chorioretinitis). Often, symptoms can be non specific (eg weight loss) and may not, at first, be attributed to CMV. Diagnosis is by CMV PCR. Serology is not used for diagnostic purposes. Treatment is with valganciclovir, and should only be initiated by the renal team. Immunosuppression may also need modification, but again, this should only be done by the renal team.

**Cancer screening**

Cancer is a major cause of both morbidity and mortality in renal transplant recipients. Transplant recipients are at an increased risk for the development of skin and solid organ malignancies and lymphoma (post transplant lymphoproliferative disease or PTLD). No additional screening outside national guidelines is currently advised for transplant recipients, but careful attention should be paid to any symptoms suggestive of malignancy and there should be a low threshold for further investigation. Transplant recipients should be actively encouraged to attend screening test appointments (cervical, breast and colon).

**Hypertension**

Most antihypertensives can be used safely in renal transplant recipients. Diltiazem should be avoided in patients taking tacrolimus, ciclosporin or sirolimus (risk of interaction). If diuretics, ACE inhibitors or angiotensin receptor blockers are to be used then this should only be after consulting the renal department, as renal function will need careful monitoring.

**Contraception and pregnancy**

Reproductive function is usually impaired in patients receiving dialysis but this is usually restored after transplantation. It is, therefore, important that patients receive adequate counselling about effective contraception in the post-transplant period to avoid unplanned pregnancies. All contraceptive agents are safe to use in transplant recipients, although progesterone could interact with tacrolimus and ciclosporin. The renal team should be informed so that levels can be monitored and doses adjusted if necessary. Calcineurin inhibitors and mycophenolate also reduce efficacy of the oral contraceptive pill.
For transplant recipients who are planning to conceive, immunosuppression may need modification beforehand. This should only be done by the renal unit. Both mycophenolate and sirolimus are contraindicated in pregnancy. Pregnancy in transplant recipients should be co-managed by a centre that is familiar with the management of such patients. This is usually undertaken by the Silver Star Unit in Oxford and a referral should be made at the earliest opportunity.

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