PHA-6020Y

Patient centred medicine from bench to bedside

Pharmaceutical care: Solid Organ Transplant Workshop

Learning Outcomes

- Clinically assess the appropriateness of a prescription chart for a new renal transplant recipient
- Identify the indication MoA and monitoring parameters of the therapy used
- Identify potential prescribing issues and provide appropriate alternative solutions, for medicines used in transplant.
- List important counselling points for patients newly started on these medicines

The screencasts spoke generally about transplants and some of the common drugs used during the transplant process.

This workshop concentrates on the drugs seen for **a 'standard' renal transplant**.

Any potential exam question(s) will relate to either renal transplant therapeutics or general information about transplant (screencast 1) or drugs used in transplant (screencast 2).

You are the pharmacist on the transplant ward and seeing this patient for the first time. His inpatient chart has been provided.

Mr P S is a renal transplant recipient. He received his new kidney last night. He is 6 foot 2 inches tall and his creatinine result this morning is 180 micromol/L.

UEA Training Prescription Chart

Number of drug charts in use: 1

Date	Surname	Forename	Sex	D/O/B	Hosptial No.	Weight (kg)	Height (cm)	Surface Area (m^2)	SAM?
Day 1	**S**	**P**	M	01/01/1969	123456	72 Estimate / **Actual**			Yes / **No**

Ward/ward change:	**Transplant**	**Patient address:**	**3 Hills Rd, Flatplace**
Consultant(s)	**Dr N Torey**		

DRUG SENSITIVITIES/ALLERGIES MUST BE ENTERED. If no allergies/sensitivites you must write 'NKDA' and sign and date.

Medicine/Substance	Description of allergy/sensitivity	Signature	Date
NKDA		*Dr N Torey*	*Day 1*

PRE-MEDICATION AND ONCE ONLY DRUGS

Pharm	Date	Drug (approved name)	Dose	Directions/ route/ other	Time to be given	Signature	Administered by Initials	Administered by Date
	Day 1	*Basiliximab*	**20mg**	**IV**	**5pm**	*N Torey*	NH	Day 1

Thromboprophylaxis Risk Assessment

Drug thromboprophyaxis recommended	**X**				
Drug thromboprophlaxis NOT recommende					

Prescribing

- Write clearly in black, indelible ink.
- Use approved drug names.
- All prescriptions must be signed and dated.
- If a drug is to be intentionally omitted by a prescriber or pharmacist, indicate this with an 'X' in the drug administration box.
- If a drug is being stopped, or a dose altered, draw a line through the whole prescription, sign and date.
- Doctors to re-write charts as required. Start dates should be transferred to new chart. Include cross-reference to drugs on other charts.

Drug omissions

If a drug is omitted, one of the below codes must be entered into the drug administration box.

1. Nil by mouth
2. Not required
3. Patient refused
4. Drug unavailable
5. Vomiting/nausea
6. Patient off ward
7. No IV access
8. Other - reason must be recorded in notes
9. Contra-indicated

Self administration of medicines (SAM)

If a patient is suitable for SAM they can initial in the relevant drug administration box or a nurse can write 'SAM' in the box.

Prescribers

Signature	*Dr N Torey*
Bleep no.	**5893**
Print name	**Doctor N Torey**
Signature	***Dr Jones***
Bleep no.	**3210**
Print name	**KE Jones**
Signature	
Bleep no.	
Print name	
Signature	
Bleep no.	
Print name	
Signature	
Bleep no.	
Print name	

Pharmacy codes

Pharm: Signature confirms checked/date

TTO ✓ = from locker; **H** = at home; **R** = relabel; ✱ = new supply at discharge

REGULAR MEDICINES 1

CHECK PAGE 1 FOR ALLERGY STATUS

Tick box to indicate time of admission or add other times ↓ / Date →				Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
1. Drug (approved name) **Advagraf**	Start date: Day 2	End date	06:00										
			08:00	✓	X	GN							
Dose **14mg**	Route **Po**	Frequency **BD**	12:00										
			14:00										
Indication		Pharm check	18:00	✓	X								
			22:00										
Prescriber's signature **N Torey**		Supply	00:00										
2. Drug (approved name) **Mycophenolate**	Start date: Day 2	End date	06:00										
			08:00	✓	X	GN							
Dose **1500 mg**	Route **Po**	Frequency **OD**	12:00										
			14:00										
Indication		Pharm check	18:00										
			22:00										
Prescriber's signature **N Torey**		Supply	00:00										
3. Drug (approved name) **Prednisolone**	Start date: Day 2	End date	06:00										
			08:00	✓	X	GN							
Dose **20mg**	Route **Po**	Frequency **OD**	12:00										
			14:00										
Indication		Pharm check	18:00										
			22:00										
Prescriber's signature **N Torey**		Supply	00:00										
4. Drug (approved name) **Dalteparin**	Start date: Day 2	End date	06:00										
			08:00										
Dose **2500 units**	Route **SC**	Frequency **OD**	12:00										
			14:00										
Indication		Pharm check	18:00	✓	X								
			22:00										
Prescriber's signature **N Torey**		Supply	00:00										
5. Drug (approved name) **Co-trimoxazole**	Start date: Day 2	End date	06:00										
			08:00	✓	X	GN	x		x		x	x		x
Dose **960mg**	Route **Po**	Frequency **OD**	12:00										
			14:00										
Indication m, w, f		Pharm check	18:00										
			22:00										
Prescriber's signature **N Tory**		Supply	00:00										

CHECK PAGE 1 FOR ALLERGY STATUS

REGULAR MEDICINES 2

CHECK PAGE 1 FOR ALLERGY STATUS

Tick box to indicate time of admission or add other times ↓ / Date →		Day 1	Day2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
6. Drug (approved name): Lansoprazole; Start date: Day 2; End date; Dose: 15mg; Route: PO; Frequency: OD; Indication; Pharm check; Prescriber's signature: N. Torey; Supply	06:00										
	08:00	✓	x	GN							
	12:00										
	14:00										
	18:00										
	22:00										
	00:00										
7. Drug (approved name): Nystatin; Start date: Day 2; End date; Dose: 1mL; Route: PO; Frequency: QDS; Indication; Pharm check; Prescriber's signature: N Torey; Supply	06:00										
	08:00	✓	x	GN							
	12:00	✓	x								
	14:00										
	18:00	✓	x								
	22:00	✓	x								
	00:00										
8. Drug (approved name): Paracetamol; Start date: Day 2; End date; Dose: 1g; Route: PO; Frequency: QDS; Indication; Pharm check; Prescriber's signature: N Torey; Supply	06:00										
	08:00	✓	x	GN							
	12:00	✓	x								
	14:00										
	18:00	✓	x								
	22:00	✓	x								
	00:00										
9. Drug (approved name); Start date; End date; Dose; Route; Frequency; Indication; Pharm check; Prescriber's signature; Supply	06:00										
	08:00										
	12:00										
	14:00										
	18:00										
	22:00										
	00:00										
10. Drug (approved name); Start date; End date; Dose; Route; Frequency; Indication; Pharm check; Prescriber's signature; Supply	06:00										
	08:00										
	12:00										
	14:00										
	18:00										
	22:00										
	00:00										

CHECK PAGE 1 FOR ALLERGY STATUS

AS REQUIRED DRUGS

CHECK PAGE 1 FOR ALLERGY STATUS

1. Drug (approved name) **Fentanyl**		Start date **Day 1**	Date	Day 2	Day 2	Day 2	Day 2						
Dose **10mcg**	Route **IV**	Max Frequency **every 5 mins**	Time	04:00	4.30	4.45	05.00						
Indication		Pharm check	Dose	10mcg	10mcg	10mcg	10mcg						
			Route	IV	IV	IV	IV						
Prescriber's signature **N Torey**		Supply	Given by	GN	GN	GN	GN						
2. Drug (approved name) **Meptazinol**		Start date **Day 2**	Date										
Dose **200mg**	Route **PO**	Max Frequency **TDS**	Time										
Indication		Pharm check	Dose										
			Route										
Prescriber's signature **N Torey**		Supply	Given by										
3. Drug (approved name)		Start date	Date										
Dose	Route	Max Frequency	Time										
Indication		Pharm check	Dose										
			Route										
Prescriber's signature		Supply	Given by										
4. Drug (approved name)		Start date	Date										
Dose	Route	Max Frequency	Time										
Indication		Pharm check	Dose										
			Route										
Prescriber's signature		Supply	Given by										
5. Drug (approved name)		Start date	Date										
Dose	Route	Max Frequency	Time										
Indication		Pharm check	Dose										
			Route										
Prescriber's signature		Supply	Given by										

CHECK PAGE 1 FOR ALLERGY STATUS

1. Using your knowledge, the screencasts and BNF, complete the table below for the drugs prescribed for Mr PS:

Drug	Indication / Drug class / brief mechanism of action / key monitoring parameters (therapeutic and toxic)
Basiliximab	**Indication:** Induction immunosuppression. **Drug class:** Monoclonal antibody immunosuppressant **Mechanism of action:** Chimeric monoclonal antibody against IL-2 (interleukin-2 receptor antagonist). Inhibits T-cell proliferation. **Therapeutic monitoring parameters:** Lack of acute rejection **Toxic monitoring parameters:** infections, hypersensitivity, BP, FBC (anaemia) Given at induction **and** 4 days after.
Advagraf (tacrolimus)	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Calcineurin inhibitor **Mechanism of action:** Inhibits early T-cell activation by inhibiting calcineurin, an enzyme involved in the transcription of genes encoding IL-2 and other cytokines. **Therapeutic monitoring parameters:** Lack of rejection, trough tacrolimus levels 5-15 (20) ng/mL **Toxic monitoring parameters:** Cr, eGFR, Ur, urine output (nephrotoxicity*, hyperkalaemia), GI, FBC, blood glucose (DM), BP, headache, tremor, seizures, peripheral neuropathy (neurotoxicity*), interactions (cyp 3A4 & p-glycoprotein), trough tacrolimus levels 5-15 (20) ng/mL, lipids, BP, hirsutism, gum hyperplasia UV light, lymphoproliferative disease/neoplams, vaccination, avoiding live vaccines, brand (must be the same), formulation (they are not equivalent) *can be dose dependent **metabolised in the liver (CYP-3A4) and p-glycoprotein – care with interactions. Highly plasma protein bound. Usually long term.
Mycophenolate mofetil	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Antiproliferative drug **Mechanism of action:** Inhibits inosine monophosphate dehydrogenase which is the rate limiting enzyme in the production of guanine nucleotide synthesis. Action is said to be lymphocyte specific. **Therapeutic monitoring parameters:** Lack of rejection **Toxic monitoring parameters:** method of administration as teratogenic, neoplasms, infections, FBC (neutropenia may require dose reduction cessation, leucopenia, anaemia), GI (D&V), interactions (drugs interfering with MPA enterohepatic recirculation-colestyramine/antibiotics), (potentially, not done regularly - MPA monitoring), contraception, LFT, renal function, avoid live vaccines

	UV light Usually long term.
Prednisolone	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Corticosteroid **Mechanism of action:** Is anti-inflammatory and affects most of the cells involved in the initiation of an episode of rejection. At maintenance doses, corticosteroids block the release and inhibit the action of cytokines – interleukins and interfere with T-cell activation. (Review year 2 material) **Therapeutic monitoring parameters:** Lack of rejection **Toxic monitoring parameters:** BP (hypertension), U&E (hypernatraemia, hypokalaemia), bone mineral density, eye examination (glaucoma), weight (fluid retention), lipids, blood glucose/HbA1c, GI, tapering course (adrenal suppression), psychiatric adverse reactions, Cushing's syndrome - moon face/thinning of the skin, malignancy, infections, chicken pox, avoid live vaccines, interactions (cyp 3A) Steroids are tapered down quite quickly but is done on a patient-by-patient basis, depending on the level of organ match, graft function and overall patient condition. Starting at 20mg immediately post-transplant, this can be reduced to 15mg at discharge (about day 5), and the further reduction is dictated by the doctor review that occurs in the twice weekly clinic appointments).
Dalteparin	**Indication:** VTE prophylaxis **Drug class:** LMWH **Mechanism of action:** LMWH – binds antithrombin III, which preferentially potentiates the inhibition of factor Xa and IIa. Factor Xa usually catalyses the conversion of prothrombin to thrombin. Decreased thrombin leads decreased fibrin and clot formation. **Therapeutic monitoring parameters:** Lack of VTE/clotting post surgery **Toxic monitoring parameters:** weight, platelets (thrombocytopenia), U&E (K+ inc), signs of bleeding and bruising, Cr/eGFR LMWH used while in hospital and changed to **aspirin 75mg OD (lifelong) at discharge**.
Co-trimoxazole	**Indication:** Prophylaxis against *pneumocystis jirovecii pneomonitis*. Classified as a common fungal lung infection in the environment causing illness in immunosuppressed patients. **Drug class:** Antibiotic. Sulfamethoxazole and trimethoprim combination drug. **Mechanism of action:** The two parts have different points of inhibition in the formation/utilisation of folate required by PJP to make DNA. **Therapeutic monitoring parameters:** No pneumocystis jiroveci infection

	Toxic monitoring parameters: headache, hyperkalaemia, rash, N&D – common. Less common but important – LFTs (hepatic necrosis), skin (life threatening skin and cutaneous adverse effects i.e. Stevens-Johnsons syndrome), FBC (blood dyscrasias Usually used for 6 months.
Lansoprazole	**Indication:** GI protection against therapy associated with GI disturbance (i.e. steroids) and surgery **Drug class:** Proton pump inhibitor **Mechanism of action:** Activated PPI reacts with the sulphydryl group of the H+/K+ ATPase (proton pump) responsible for the transport of hydrogen ions out of the parietal cells. **Therapeutic monitoring parameters:** No ulcer formation due to surgery or corticosteroids **Toxic monitoring parameters:** GI infection, Mg, osteoporosis, LFT, FBC, GI, use (stop when able), interaction with tacrolimus (metabolised by 3A4 and 2C19) Stop once steroids completed.
Nystatin (oral fluconazole is considered in those patients on highly immunosuppressive treatment, i.e. alemtuzumab)	**Indication:** prophylaxis against *Candida spp.* Increased risk due to high dose steroids and immunosuppression. **Drug class:** Antifungal **Mechanism of action:** Oral polyene that binds ergosterol in the fungal cell membrane resulting in increased permeability, cell leakage and cell death. **Therapeutic monitoring parameters:** No oral/GI candida **Toxic monitoring parameters:** usually very well tolerated. Large doses can lead to N/V/D Usually used for 1 month
Paracetamol	**Indication:** Base line pain relief. **Drug class:** Analgesia **Mechanism of action:** Central COX inhibition **Therapeutic monitoring parameters:** Pain control **Toxic monitoring parameters:** weight, max dose, alcohol, malnutrition, (LFT, FBC) PRN at discharge.
Fentanyl	**Indication:** Post operative pain relief **Drug class:** Opioid analgesia **Mechanism of action:** Strong and potent opioid agonist **Therapeutic monitoring parameters:** Pain relief **Toxic monitoring parameters:** constipation, RR, drowsiness, flushing, N&V, skin reactions, palpitations Mainly hepatically metabolised making it a safer opioid pain relieve in patient with potentially poor renal function. Used first few days pot surgery.
Meptazinol	**Indication:** Post operative pain relief step down **Drug class:** Weak opioid analgesia **Mechanism of action:** Mixed opioid agonist/antagonist action.

	Therapeutic monitoring parameters: Pain relief **Toxic monitoring parameters:** As above PRN at discharge.

The type/combination of immunosuppression required depends upon the type of graft and organ and therefore the intensity of the immune response.

Allograft – same species but different individuals – degree of immune response and likelihood of rejection therefore depend on the degree of histocompatibility of the donor and recipient and the type of organ (eyes trigger little immune response/heart, kidney, liver are highly vascular and elicit a greater response). Matching tries to allocate patients to organs with the best match to minimise the immune response. But wherever there is even slight differences (i.e. non-identical individuals) the transplantation of an organ will provoke an immune response. For this reason patients receive immunosuppression. This will be needed for as long as the graft is functioning but will vary over time (both in dose and the number of drugs required) - immediately after transplant patients are at the highest risk of rejection so the highest doses and higher target levels (i.e. for tacrolimus) are required. Over time, doses/target levels may be able to be reduced.

Patients receive 'induction' immunosuppression at the time of transplant and are then started on a maintenance regime.

Maintenance therapy consists of a **COMBINATION** of the different classes of immunosuppression, i.e. a calcineurin inhibitor plus an anti-proliferative plus a corticosteroid.

As more immunosuppressive drugs were developed it was found that by using a combination the patient had a more positive outcome in terms of **reduced rejection** and **reduced side effects** due to not requiring as high a dose when used in combination as opposed to when used alone.

The drug chart shows the typical triple immunosuppression therapy for a patient post kidney transplant (note – different transplant centres may use slightly different regimes.

1. Identify any Pharmaceutical care issues with this prescription and document the action you would like to take.

Issues	**Action required**
Second dose of basiliximab not prescribed. To complete the course, the second dose should be given on day 4 (as per BNF).	Ask prescribers to prescribe basiliximab 20mg on day 4.
Monitoring parameters	
Therapeutic	**Toxic**

Issues	**Action required**
Advagraf is the modified release, **ONCE** a day tacrolimus preparation currently prescribed BD. This will lead to toxicity if it is not amended.	Dose stated in the BNF: 200-300 micrograms/Kg/day, therefore it should be 14mg to 21mg **ONCE** a day in the morning and closely monitor ask prescriber to amend.

	(0.15mg/kg PO Od is an example of dosing discussed in the screencast – this would equate to 10-11mg once daily for this patient)
Monitoring parameters	
Therapeutic	**Toxic**

Issues	**Action required**
Mycophenolate mofetil dose is incorrect it should be given twice a day. BNF dosing: 1g BD PO. Dosing discussed in the screencast: 750mg BD.	Ask prescriber to amend and prescribe a twice daily dose 750mg to 1g BD (based on local protocol).
Monitoring parameters	
Therapeutic	**Toxic**

Issues	**Action required**
Dalteparin dose too low based on the patients current renal function. Patient with a renal function over 20ml/min (and weight over 50kg) should receive 5000 units daily.	Ask prescriber to prescribe 5000 units once a day. Ensure starting Aspirin 75 mg OD occurs at discharge when the dalteparin is stopped.
Monitoring parameters	
Therapeutic	**Toxic**

Issues	**Action required**
No stop dates for supportive therapy on drug chart which may lead to inappropriate continuation of therapy.	Add stop dates - Co-trimoxazole generally 6 months, nystatin generally 4 weeks. Although this is the general rule, patients continue to be monitored in clinic and therapy adapted to patient needs.
Monitoring parameters	

Therapeutic	Toxic

Issues	Action required
Potentially missing valganciclovir depending on CMV status of patient and donor.	(See next question)
Monitoring parameters	
Therapeutic	**Toxic**
Lack of cytomegalovirus (PCR)	RF, Hb (anaemia), FBC (neutropenia, leukopenia, thrombocytopenia, pancytopenia), contraception, s/e D, N&V, dermatitis, cough, headache, loss of appetite, infection (V.common)

In addition to the above drugs, Mr PS is also started on prophylactic valganciclovir. In renal transplant patients this is used if either the patient or the donor is seropositive for Cytomegalovirus, CMV. This is done by measuring a patient's CMV IgG. CMV is a member of the herpes virus family which can be passed on via body fluids, tissue donation or it can be congenital. For immunocompetent individuals the primary infection is generally asymptomatic but can manifest as mononucleosis syndrome. An individual's immunity controls viral replication.

In those who are immunosuppressed it can cause severe illness. This can be especially detrimental for transplant recipients as CMV is associated with increased graft rejection. Renal clearance accounts for the majority of valganciclovir excretion.

1. 3. Using the patient's renal function, (using the Cockcroft and Gault equation) and the table below, please check what dose of valganciclovir the patient should receive and prescribe it on your drug chart.

CrCl (ml/min)	Maintenance/Prevention dose of valganciclovir
≥ 60	**900 mg (2 tablets) once daily**
40 – 59	**450 mg (1 tablet) once daily**
25 – 39	**450 mg (1 tablet) every 2 days**
10 – 24	**450 mg (1 tablet) twice weekly**

< 10	**not recommended**

Valcyte 450 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) – accessed 9/1/23

-Using Cockroft and Gault:

(140-55) x 1.23 x 72kg / 180 = 41.82 mL/min = 42mL/min

Therefore, 450mg ONCE a day would be the recommended dose.

The patient's renal function is likely to be quite variable after a transplant. Some patients require dialysis either periodically due to high potassium in the 24-48 hours post op or if their renal function does not improve (and therefore electrolytes imbalances occur). However, for the majority of patients their renal function can improve towards a normal range within 5 days and so calculations and adjustments are required during their hospital stay and then in their follow-up clinics post discharge.

Generally, this drug will be received for 3 months, high risk patients receive it for 6 months. CMV PCR is used to monitor CMV status of the patient.

If a patient develops the infection and receives treatment, once two negative results have been received they will continue with prophylaxis for a further 11 weeks.

Prescribe valganciclovir appropriately on your drug chart.

1. Mr PS is ready to be discharged tomorrow and you need to counsel him on his new medication. List the important counselling points for Advagraf, mycophenolate mofetil and prednisolone

Please review lecture slides and relevant monographs in the BNF

Advagraf –

Inform the patient of what the medicine is, its indication, how important it is, dose, frequency, potential important side effects (FOR EACH DRUG YOU ARE EXPECTED TO STATE THE IMPORTANT SIDE EFFECTS) and what needs to be done if they occur.*

Take ONCE a day on an empty (food reduces bioavailability) stomach (upon waking), wait approximately 1 hour afterwards before eating or having other medicines.

Swallow whole.

Stress that clinic check-ups are important so their therapy can be closely monitored.*
Monitoring is required for efficacy and toxicity monitoring as CNI are nephrotoxic, can cause HTN, hyperlipidaemia, tremor, neurotoxicity and diabetes.

On clinic days do NOT take until bloods have been taken (Bloods need to be a trough level, i.e. immediately prior to next dose). Remember to bring dose with to take after sample has been taken.

Make sure you take this regularly and are aware of the correct dose for you-doses are variable and change dependent upon the levels.*

Make sure you have adequate supply as you must not run out.*

Ensure you **always** have the same BRAND, check when collecting medication.

Ensure you take the correct strength, as it is available as 0.5mg, 1mg, 3mg and 5mg.

Avoid grapefruit juice-inhibits cyp450 and causes the increase in tacrolimus levels.

Avoid excessive exposure to sun light (UV light)-increased risk of cancers.*

Avoid use of live vaccines.*

Avoid high risk foods, those that could cause infection – unpasteurised cheese/milk, lightly cooked meat etc.*

Ensure any medical professional treating you is aware of this medicine as it has MANY interactions.*

Mycophenolate Mofetil

In addition to the * above.

Swallow whole do not crush or chew.

Food does not have an effect on this medication.

For men (our patient) - Importance of appropriate contraception during treatment and for 90 days after.

Importance of FBC monitoring.

Recognition and reporting of infection or unexplained bruising and bleeding.

Prednisolone

In addition to the * above.

Take in the morning.

Take with or after food.

Ensure you have adequate supply; these must not be stopped abruptly.

Ensure the patient has a steroid card and they are aware of the important information it contains.

Ensure you know what dose you should be taking as it is likely that this will change relatively frequently dependent upon your clinical condition.

* as for all transplant immunosuppression