Pearls for Managing the Transplant Recipient with Chronic Kidney Disease

Jennifer Harrison, BScHon, BScPhm, MSc
Pharmacy Clinical Site Leader, Toronto General Hospital
Assistant Professor, Status – University of Toronto,
Leslie Dan Faculty of Pharmacy
Clinical Appointee – University of Toronto,
Lawrence S Bloomberg Faculty of Nursing

Disclosures

- Financial relationships in the last 12 months
  - unrestricted educational grants from Novartis, Astellas, Pfizer
  - speaker honoraria, paid consultant and advisory board member for Astellas

Learning Objectives

1. Describe the prevalence, risk factors and consequences of CKD in nonrenal solid organ transplant recipients (NRSOTR)
2. Identify typical practice challenges in this population and management approaches
   - therapeutic drug monitoring
   - drug interactions with immunosuppression
   - common infectious complications

Background

- NRSOT activity is increasing
- Improved outcomes in NRSOTR has increased 'time at risk' → more observed cases of post-transplant CKD
- Demand for post-transplant nephrologist care now nearly equal to kidney transplant population

Ojo A. Semin Nephrol 2007;27:498

Canadian Solid Organ Transplant Activity and Graft Survival (2010)

Organ	Number of transplants	Est. 5-year graft survival
Kidney – deceased donor	647	81%
Kidney – living donor	413	90%
Liver – deceased donor	391	75%
Liver – living donor	64	78%
Lung	179	65%
Heart	154	80%

www.CIHI.ca

Acute Renal Failure After Solid Organ Transplantation

- Incidence
  - Heart: 20-30%
  - Liver: 46-61%
  - Lung: 5-60%
- RRT required in 10-15% of heart, 20-25% of liver, and 8-10% of lung transplant in first 30 d
- 50% reduction in 1-year survival in patients requiring peri-operative RRT

Ojo A. Semin Nephrol 2007;27:498

Prevalence of CKD after NRSOT

- Estimated that 80-100% of patients will have CKD at 36 months post-transplant

Table 1. Cumulative Risk of Stages IV to V CKD in Nonrenal Transplant Recipients

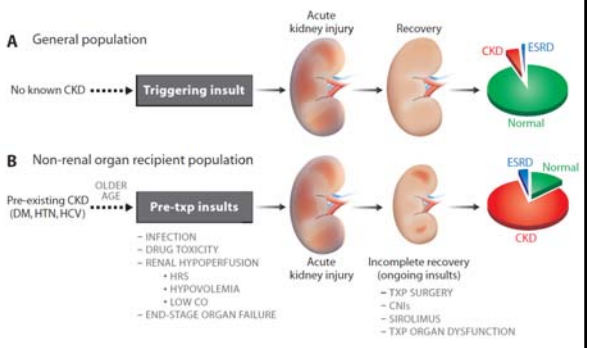
Time Since Transplantation, mo	Percentage of Recipients With Stages IV to V CKD				
	Heart	Heart-Lung	Intestine	Liver	Lung
12	1.9	1.7	9.6	8.0	2.9
36	6.8	4.2	14.2	13.9	10.0
60	10.9	6.9	21.3	18.1	15.8

Ojo et. al. NEJM 2003;346:931-940

Risk Factors for Post-Transplant CKD

Variable	Overall Relative Risk
Age (per 10-yr increment)	1.36
Pre-transplant GFR	
60 - 89 ml/min	1.38
30 - 59 ml/min	2.25
< 30 ml/min	3.41
Post-op ARF	2.13
Pre-transplant diabetes	1.42
Pre-transplant HTN	1.18
Pre-transplant Hepatitis C	1.15
Male	0.74

Ojo et. al. NEJM 2003;346:931-940



Bloom and Reese. JASN 2007;18:3031

Consequences of CKD in NRSOTR

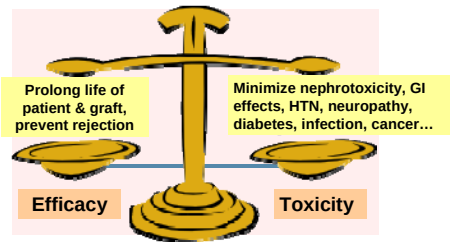
- May require changes in immunosuppression, anti-infective and other drug therapies
- ↑ rates of CVD, HTN, anemia, bone disease
- ↑ hospitalizations
- ↑ infectious complications
- ↑ risk graft dysfunction
- ↑ mortality (4-fold)
- ↑ use of health care resources

Ojo A. Semin Nephrol 2007;27:498

Strategies to Minimize Renal Injury in NRSOTR

- Avoid peri-op hypotension
- Minimize use of nephrotoxic drugs
- Optimize renal perfusion
- Appropriate and early treatment of HTN, diabetes, dyslipidemia as per guidelines
- Use of ACEI, ARB
- Optimize use of calcineurin inhibitors (CNI)
- Be vigilant in managing drug interactions

Goal of Immunosuppression in Transplantation



Optimize Balance

Immunosuppression Paradigm

Induction

- Short course of a potent parenteral agent given immediately post-transplant
- ↓ risk of early acute rejection

Maintenance

- Life-long immunosuppression
- Combination therapy to maximize efficacy and minimize toxicity (e.g. 'triple therapy')

Maintenance Therapy Options

1. Calcineurin inhibitor (CNI)
   - Cyclosporine or tacrolimus (Prograf® / Advagraf®)
2. Corticosteroids
3. Purine synthesis inhibitor
   - Mycophenolate mofetil (MMF (Cellcept®), mycophenolate sodium (Myfortic®), azathioprine
4. Proliferation signal inhibitor (mTOR inhibitor)
   - Sirolimus
   - Everolimus ("RAD", Certican®) – SAP drug

How do we choose the regimen?

- Factors to consider:
  - immunologic risk (*i.e.* risk of rejection)
  - risks of over-immunosuppression
    - cancer, infection
  - side effect profile / patient co-morbidities
    - risk of diabetes
    - cosmetic concerns
    - neuropsychiatric effects
  - other specific indications (*e.g.* AZA in IBD)
- Regimens vary by transplant centre

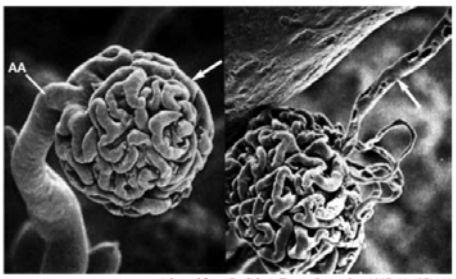
CNI Side Effect Profile

- Infection, malignancy → non-specific effect of all immunosuppression
- Tacrolimus
  - ↑ hyperglycemia, neurotoxicity, diarrhea
- Cyclosporine
  - ↑ hypertension, dyslipidemia, cosmetic concerns
- Nephrotoxicity (dose-related)
  - Acute – 25 – 40%
  - Chronic – most patients

The Problem of CNI Inhibition

- CNI = cornerstone of immunosuppression
- Reduction of CNI exposure → potential for organ dysfunction → indirect renal injury
- Pathophysiology of renal injury
  - dysregulation of vascular tone
  - tubulointerstitial nephropathy and fibrosis
  - central role of angiotensin II

EM Scanning of the Glomerulus Following CNI Exposure



Adapted from English *J. Transplantation* 1987;44:135-141

Optimizing CNI Exposure

- Delicate balance between risk to kidney vs. risk to transplanted organ
- Strategies:
  - reduce CNI and add or ↑ mycophenolate
  - reduce CNI and add sirolimus → caution!
  - conversion from CNI to sirolimus
  - withdraw CNI (? possible in liver recipients)
  - conversion from cyclosporine to tacrolimus (?)
- Importance of TDM

TDM in Transplantation

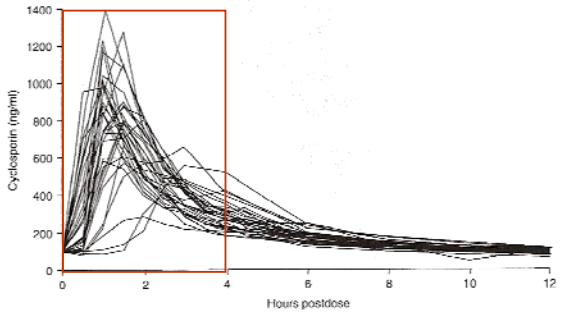
- TDM is a tool to enable balance between:
  - need for immunosuppression

  vs.
  - risks (infection, malignancy, toxicity)
- Stronger correlation between drug levels and nephrotoxicity vs. acute rejection

Factors Influencing PK of Immunosuppressants

- Age
- Race
- Type of organ
- Liver dysfunction
- Hepatitis C
- Small bowel length
- Gastrointestinal state
- Infection
- Inflammatory states
- Time post-transplant
- Hematocrit
- Albumin levels
- Diurnal variations
- Drug interactions
- Comorbidities (diabetes, CHF, etc.)
- Intestinal P-glycoprotein and CYP450 expression

Cyclosporine Pharmacokinetics



Levy G. Biodrugs 2001;15(5):279

Rationale for C_2 Monitoring

- C_2 is in region of highest PK variability
- Single sampling point defines CSA absorption
- Correlates with period of max CNI inhibition
- Less metabolite cross-reactivity interference
- Clinical benefit vs. C_0 in most SOTR
- Disadvantages
  - time-sensitive sampling errors (level 2 hrs post-dose ± 15 min)
  - assay factors- requires dilution of sample

Immunosuppressant Target Levels

- Modifying factors
  - type of transplant and time post-transplant
  - concomitant immunotherapy / use of induction
  - recipient immunologic risk, donor factors
  - infection, cancer history or other toxicity concerns
  - graft status and function
- Few RCTs to support specific targets and little data beyond 1 year

Suggested Target Cyclosporine Levels* (ng/mL)

Time post-transplant (months)	C_2 Liver	C_2 Heart	C_2 Lung	C_0 Lung
0 – 3	1000	1200	1200 – 1600	250 – 350
4 – 6	800	1000	1200 – 1400	250 – 300
7 – 9	600	800 – 1000	1000 – 1200	200 – 250
10 – 12	600	800	1000 – 1200	200 – 250
> 12	600	600 – 800	800 – 1000	150 – 200

*Note: Guideline only, targets should always be determined in the context of the individual patient. Reduce targets for combo of CNI + SRL.

Dose adjustment – may assume linear dose proportionality

Suggested Target Tacrolimus Trough Levels* (ng/mL)

Time post-transplant (months)	Liver	Heart	Lung
0 – 1	10 – 15	10 – 20	15 – 20
2 – 3	5 – 15	10 – 20	15 – 20
4 – 6	5 – 10	5 – 15	15 – 20
7 – 9	5 – 10	5 – 15	10 – 15
10 – 12	5 – 10	5 – 15	10 – 15
> 12	5 – 8	5 – 15	10 – 15

*Note: Guideline only, targets should always be determined in the context of the individual patient. Reduce targets by at least 50% for combo of CNI + SRL.

Dose adjustment – may assume linear dose proportionality

Sirolimus (SRL)

- Starting dose 2 – 5 mg daily (loading dose optional)
- Long $t_{½}$ (~62 h)
- Large inter- and intrapatient variability
- Trough levels correlate with AUC
- Levels: wait at least 7 days !!
- Linear dose proportionality assumed
- Therapeutic target (all organs): 5 – 15 ng/mL
  - lower end if combined with CNI (*e.g.* 5 – 8) and reduce CNI target

Mycophenolate (MPA)

- MPA monitoring controversial
  - wide inter-individual variability in MPA kinetics
  - no single time point accurately reflects exposure → practicality of doing MPA AUC?
  - some centres do trough levels in setting of toxicity but targets and dose adjustments unclear
- Further research is needed

TDM in Practice

- When to do a level and adjust?
  - initiating therapy or changing dose
  - suspect toxicity or non-adherence
  - managing drug interactions
  - managing complications due to over-immunosuppression
- For patients with stable graft function
  - would not ↑ dose/levels in most cases

Immunosuppressant Dosing in CKD

- CNI and sirolimus
  - extensive hepatic metabolism and biliary excretion, < 5% eliminated in urine
  - not removed by hemodialysis
- Mycophenolate
  - hepatic conversion to MPAG (inactive metabolite) with enterohepatic recirculation
  - MPAG eliminated in urine, some removal by dialysis
  - no recommended dose adjustments, but may need to ↓ dose if stage IV-V CKD and not on dialysis

Managing Drug Interactions with Immunosuppressants

Targets for Immunosuppressant Drug Interactions

- Intestinal delivery
  - Gastric pH, gastric emptying, food
- Active intestinal efflux pumps and metabolism
  - P-glycoprotein (P-gp), CYP450
- Hepatic first-pass effect
  - CYP450

Drug Interactions with Immunosuppressants

- CNI and SRL are substrates and inhibitors of CYP3A4 and P-gp
  - highly susceptible to drug interactions
  - oral bioavailability affected more than clearance
  - most data with cyclosporine
- Potential for serious clinical sequelae
  - graft rejection, toxicity

Agents Affecting CNI / SRL Exposure

↑ exposure

diltiazem, verapamil
erythromycin, clarithromycin
azoles
cimetidine
protease inhibitors
metoclopramide
amiodarone
grapefruit juice

↓ exposure

isoniazid
phenobarbital
phenytoin
rifampin
carbamazepine

Interactions with Azoles

- CYP3A4 and P-gp inhibition causes ↓ pre-systemic and hepatic metabolism of CNI, SRL
- Keto > itra ~ vori > fluconazole
- Magnitude of interaction depends on dose, time on therapy
- ↓ interaction with IV CNI
- Consider empiric dose adjustments when starting AND stopping azole

Management of Azole Interactions

	CSA Dose	Tac Dose	SRL Dose
Fluc > 200mg/d	↓ 21-50%	↓ 40%	↓ 50-70%
Itra	↓ 50-60%	↓ 50-60%	No data
Vori	↓ 50%; reduce dose by 50%	↓ 66%; reduce dose by 66%	↓ 90%; labelled contraindication*
Posa	↓ 0-30%; reduce dose by 25%	↓ 75-80%; reduce dose by 66%	Extent unclear; large dose ↓ req'd; labelled contraindication*

*may be used in combo if ↓ SRL by 75 - 90%

Dodds-Ashley E. Pharmacotherapy 2010; 30(8): 842

Statins and CNI

- Reports of myopathy/ rhabdomyolysis with cyclosporine, few with tacrolimus
- Inhibition of CYP3A4 metabolism, P-gp, other transport proteins → ↑ statin exposure
- Atorva-, prava- and simvastatin used commonly and generally considered safe at lower doses (esp. in combination with tacrolimus)

Mycophenolate Mofetil and PPIs

- GI complaints with mycophenolate frequent and often lead to dose reduction
- PPI use common after NRSOT
- MMF needs acidic pH for dissolution, hydrolysis to MPA
- ↑ gastric pH with PPI → ↓ MPA levels and AUC
- Effect on graft outcomes unclear
- No interaction with PPI and mycophenolate sodium
- Specific dose adjustment unclear, ↑ graft monitoring recommended

Gabardi and Olyaei. Ann Pharmacother 2012;46:1054

CNI and SRL

- CSA + SRL
  - ↑ SRL AUC 230% with co-administration
  - ↑ SRL AUC 80% if taken 4 hours apart
  - consistency important
- Tac + SRL ? not documented
- Combo of either CNI + SRL potentiates nephrotoxicity
  - ↓ targets for both with TDM

Other Significant Interactions

- Azathioprine and allopurinol
  - dose reduce azathioprine by 66 – 75%
- Cholestyramine
  - avoid if possible or space at least 4 hrs apart
- Sevelamer and mycophenolate
  - give sevelamer 2 hours after mycophenolate
- aminoglycosides, ampho B, vanco, NSAIDs
  - additive toxicity with CNI
  - avoid or use with caution

Common Sense Approach

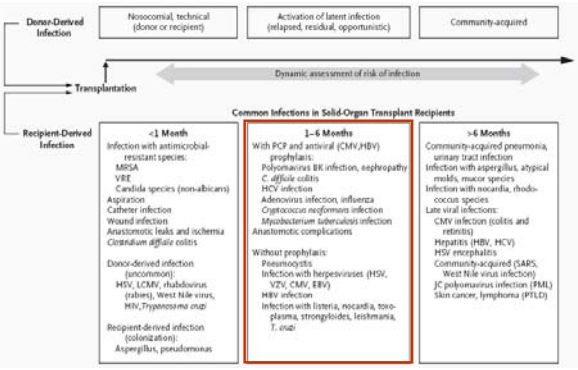
- Choose agent within class with least potential for interaction
- Avoid combos with potential for profound effects
- Empiric dose change to CNI/SRL if potential effects are large
- Dose adjust for renal/hepatic dysfunction
- Use TDM and monitor for adverse effects
- Monitor if start OR stop interacting drug

Infectious Issues in NRSOTR

Infection in Transplant Recipients

- Two key factors determine risk:
  - net state of immunosuppression
  - exposure to pathogens
- Consequences of infection:
  - direct effects (pneumonia, wound infection, abscesses, UTI, etc)
  - indirect effects (↑ risk opportunistic infection, allograft injury, role in oncogenesis)

Timeline of Infection Post-Transplant



Fishman J. NEJM 2007;357:2601

Challenges of Infection in a Transplant Patient

- More difficult to recognize infection
- May need intensified and/or extended duration regimen
- Drug interactions
  - ↑ CNI levels (macrolides, azoles)
  - ↓ CNI levels (rifampin, INH)
  - Additive nephrotoxicity (vanco, AG, ampho B)
- Minimize immunosuppression where possible

Infection Prophylaxis

- Most common concerns
  - CMV
  - PCP (now *Pneumocystis jiroveci*)
  - herpes
  - oral thrush
- Goal is prevention

PCP Prophylaxis

- TMP/SMX – drug of choice
  - many regimens
  - excellent efficacy at very low doses (*e.g.* 1 SS tab PO 3x/week)
- Dapsone – if mild documented sulfa allergy
  - 50 – 100mg PO 5 - 7x/week
- Pentamidine – if severe documented sulfa allergy
  - 300mg inhaled q 4 weeks
- Variable duration (usually at least 6 mos)

Am J Transplant 2009; 9(Suppl 4):S227

Cytomegalovirus (CMV)

- Member of herpesvirus family
- Most common post-transplant opportunistic infection
- ↑ morbidity and mortality, ↑ risk of graft loss
- Previous exposure to virus important
  - immunologically naïve patients at highest risk
- Different approaches to prevention
  - prophylactic therapy (most common)
  - 'pre-emptive' therapy

CMV Prophylaxis

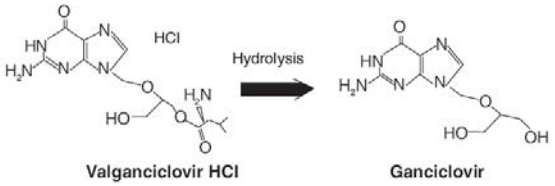
Risk assessment

1. Transplant type (lung > heart > liver > kidney)
2. CMV donor and recipient serology:
   D+R- > D+R+ > D-R+ > D-R-
3. Net state of immunosuppression (esp. use of anti-thymocyte globulin)
4. Previous CMV infection

Variable duration (usually 3 – 6 mos)

Am J Transplant 2009; 9(Suppl 4):S78

Anti-CMV Therapy: Ganciclovir and Valganciclovir



Lake KD. Am J Health-Syst Pharm; 2003; 60 (Suppl 8):S13-S16

Anti-CMV Therapy

- Ganciclovir (IV) or valganciclovir (PO)
- Inhibit viral DNA polymerase
- Prophylaxis: valganciclovir
- Treatment: ganciclovir or valganciclovir
- NPO or poor GI absorption: ganciclovir
- Do NOT dose-reduce for toxicity (*e.g.* ↓ WBC or platelets)

Am J Transplant 2009; 9(Suppl 4):S78

Anti-Infective Dosing in CKD

- TMP/SMX, dapsone
  - extensive hepatic metabolism, renal elimination
  - no adjustment at low prophylaxis doses
  - TMP/SMX → dose post-HD
  - dapsone → dose post-HD
- Valganciclovir OK for use in hemodialysis
- Current guidelines for ganciclovir and valganciclovir may underdose in hemodialysis (?)

Valganciclovir Dosing

Calculated Creatinine Clearance	Prophylaxis*	Treatment*
> 60 mL/min	900 mg PO daily	900 mg PO BID
40 - 59	450 mg PO daily	450 mg PO BID
25 – 39	450 mg PO every other day	450 mg PO daily
10 - 24	450 mg PO twice weekly	450 mg PO every other day
hemodialysis	100 mg PO three times weekly post-HD*	200 mg PO three times weekly post-HD*

*must use Valcyte oral solution

Valcyte® product monograph, 2008

Ganciclovir Dosing

Calculated Creatinine Clearance	Prophylaxis	Treatment
≥ 70 mL/min	5 mg/kg IV q24h	5 mg/kg IV q12h
50 – 69	2.5 mg/kg IV q24h	2.5 mg/kg IV q12h
25 – 49	1.25 mg/kg IV q24h	2.5 mg/kg IV q24h
≤ 24	0.625 mg/kg IV q24h	1.25 mg/kg IV q24h
hemodialysis	0.625 mg/kg IV post-dialysis on dialysis days only	1.25 mg/kg IV post-dialysis on dialysis days only

CYTOVENE-IV® product monograph, 2008

Infection Prophylaxis for NRSOTR (UHN)

	Liver	Heart	Lung
PCP -TMP/SMX -dapsone	6 – 12 mos	indefinite	indefinite
CMV (per risk assmt) -valganciclovir -IV ganciclovir	3 – 6 mos	3 – 6 mos	6 – 12 mos
Herpes (if no CMV Px) -acyclovir, famciclovir, valacyclovir	usually none	3 mos	3 mos

Follow established guidelines where they exist. Duration may be prolonged if net state of immunosuppression is intensified.

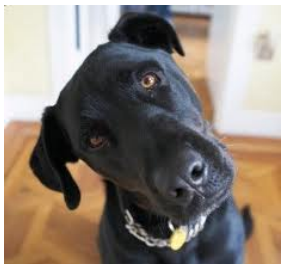
UHN Toronto General Hospital

Summary

- CKD in NRSOTR is a growing problem and complicates therapy of both conditions
- TDM is an important tool to optimize dosing of immunosuppressants
- Vigilance and careful management of drug interactions is important to avoid unnecessary drug toxicity
- Infection is common but may be more difficult to recognize and manage; goal is prevention

UHN Toronto General Hospital

Questions?



UHN Toronto General Hospital