Dialysis Overview

- Basics – when, which, who,....what (PD)
- Complications (PD)

Dialysis Case 1

- 13 year old girl presents with a month of nausea and tiredness and 2kg weight loss (40kg)
- She has always been small compared to her siblings
- She drinks and passes urine in the night
- She was diagnosed with retinitis pigmentosa 3 years before presenting to you

- Hb 50g/L Urea 45mmol/L Creat 800umol/L PTH 50pmol/L
- BP 90/60
- Passing around 3 litres of urine a day with 0.1g/l protein, no red or white cells
- Ultrasound shows 2 small smooth echogenic kidneys
Q1 What is the most likely diagnosis?

A) Autosomal dominant polycystic kidney disease  
B) Autosomal recessive polycystic kidney disease  
C) Nephronophthisis  
D) FSGS  
E) Typical HUS

Answer C

- ADPKD – kidneys not large, no macroscopic cysts noted, renal failure uncommon in childhood  
- ARPKD - would expect large kidneys & HTN  
- FSGS – no history of nephrotic syndrome or substantial proteinuria  
- Typical HUS - growth failure, 1 month history, bland urine sediment, polyuria, small kidneys don’t fit  
- Nephropathology – all of the above plus retinitis pigmentosa typical for this dx

Q2 What is your management plan?

- A. Bolus her with 20ml/kg N saline, then reassess bloods  
- B. Start EPO, dietician to see re a low protein diet, follow-up in clinic in 2 weeks  
- C. Blood transfusion, IV fluids and commence plans for dialysis  
- D. Blood transfusion and fluids then renal biopsy  
- E. Blood transfusion, fluids, EDTA GFR.

Who? – Contraindications to chronic dialysis

- Severe neurological compromise  
- Severe life limiting comorbidities  
- Technically impossible (center and equipment dependent, ~ <2kg)
When?
- Initiation of Chronic Dialysis

1. **Severity of renal dysfunction (GFR<15)**
   - Measured GFR – DTPA, EDTA
   - eGFR (ml/min/1.73m²) = 36.5 x height (cm) / serum creat (umol/L)
   - CrCl (ml/min/1.73m²) = \( \frac{24\times \text{Uvol} \times \text{Ucr} \times 1.73}{1440 \times \text{Scr} \times \text{BSA}} \)

2. **Clinical Factors** – most important aspect
   - Fluid overload & hypertension
   - Gastrointestinal sx – nausea and vomiting
   - Nutrition – poor linear growth, anorexia, malnutrition
   - Neurological concerns/ school performance

3. **Biochemical Parameters** - not easily controlled medically
   - ↑ PO4, ↑ K, acidosis

   **Dialysis should be started before the clinical condition deteriorates so that post-initiation, a significant clinical improvement should NOT be observed.**

You explain to the family that she needs to start dialysis which will be continued until she is fit enough for potential transplant.

Q3 You recommend to them:
- A. She must start HD as she is an adolescent and they have better outcomes and clearance with HD.
- B. She must start PD as it is a home based therapy and she won’t miss so much school.
- C. She must start PD so that she will still be able to go swimming at the beach.
- D. She must start HD as there’s not so much strain on the family and improved adherence in adolescents.
- E. None of the above.

Which modality - PD or HD?
Factors to consider:
- **Size / Age**
  - < 10kg / 2 years – HD difficult – access/ CV instability
  - Large / high BMI – HD improved clearance
- **Medical**
  - CI to PD – PD failure/ intra-abdominal adhesions/ gastroscerosis/ pleuro-peritoneal fistulae
  - CI to HD - systemic anticoagulation CI / prothrombotic condition / ltd vascular access
  - Residual renal function – better preserved on PD
- **Home** – proximity to hospital, small home space & poor living conditions, family (ability/understanding of caregiver to perform PD, supports - likelihood burn-out on PD)
- **Activities** – SCHOOL, sporting activities (swimming), holidays
- **Other** – power outages, body-image

**PD generally preferred for children but ALWAYS case by case decision**
You, your patient and their family think PD is the best option.

Her Dad has been googling PD and asks you will she be on CCPD or CAPD?

PD Terminology

- **CAPD**: Continuous Ambulatory Peritoneal Dialysis
- **CCPD**: Continuous Cyclic Peritoneal Dialysis

**PD Terminology**

- **Fill**: A prescribed volume of dialysis solution that is infused into the peritoneal cavity. Generally ~ 40ml/kg or 1100ml/m² once established.
- **Dwell**: The length of time the dialysis solution remains in the peritoneal cavity.
- **Drain**: The dialysate is drained from the peritoneal cavity.
- **Exchange/Cycle**: Fill, dwell, and drain.
- **Ultrafiltration**: Net fluid removed from patient

**What? – Principles of PD: The Peritoneum**

- Semi-permeable membrane, size ≈ to the BSA
- Protects the abdominal wall
- Closed sac consisting of a parietal layer and a visceral layer
- Space between the layers = the peritoneal cavity
**What? - Principles of PD**

- **Fluid removal (Ultrafiltration)**
  - Osmosis (H₂O molecules pass thru semi-permeable membrane along concentration gradient)
  - Osmotic agent (usually glucose/dextrose) in dialysate creates osmotic gradient

- **Solute removal (Clearance)**
  - Diffusion (concentration gradient)
  - Convection ("solute drag" via ultrafiltrate)

---

**Fluid Removal - Ultrafiltration**

**OSMOSIS**

The movement of water from a dilute area to a concentrated area. Dextrose, amino acid or icodextran can be the osmotic agent.

![Diagram](image)

**Ultrafiltration response to dextrose**

![Graph](image)
Factors Affecting Ultrafiltration

Membrane properties
1. Effective peritoneal surface area (> in infants)
2. Membrane resistance (permeability)
   - Peritonitis increases peritoneal membrane permeability acutely (increased dextrose transport, loss of osmotic gradient)
   - Fibrotic thickening or peritoneal sclerosis reduces permeability (decreased transport water – UF failure)

Prescription
- Dialysate dextrose concentration
- Dwell time, fill volume, number of cycles/hrs of dialysis

Patient clinical factors
- Blood pressure
- Blood flow rate
- Blood viscosity
- Serum albumin

Factors Affecting Diffusion
1. Concentration gradient between blood & dialysate
   - Concentration gradient decreases with time.
   - Initial movement from blood to dialysate of these solutes over the first two hours is quite rapid, tapering off after that.
   - Rapid diffusion requires frequent exchanges.

2. The molecular weight of the solute
   - Smaller molecules move across peritoneum more rapidly than large, heavy molecules.
   - Urea with a mol wt 60 diffuses more quickly than creatinine with mol wt 113.

3. Effective peritoneal SA
4. Membrane resistance
   - Fibrotic thickening or peritoneal sclerosis – decreased solute transport

Solute Removal

Diffusion
Movement of solute from area of high concentration to low concentration

Dialysis Case 2
6 year old boy started on cycler peritoneal dialysis 6 mo. ago for ESRF secondary renal hypoplasia

- He dialyses during the evening from 8pm to 6am.
- There have been no technical problems with his therapy.
- His present dialysis prescription is 10hrs, 1.5% dextrose, 800ml fill vol, 5 cycles and a 400ml last fill (ie. daytime volume).
Case contd

- His weight has been stable, 19 – 19.5kg
- Height 110cm (BSA 0.8m2)
- His daily urine output is usually 500-600ml
- His daily fluid restriction is 1L/day
- His overnight UF volume varies from 400-550mls
- His BP is usually normal for age/gender/height

Case contd

- His parents phone the children’s ward one morning concerned that their son was not wanting to go to school, and looking puffy and pale.
- You review the child to find that his weight is now 20.7kg, BP 125/88, afebrile
- No apparent neurological symptoms or signs

Question 4

What treatment would you initiate?

A. Restrict his fluid intake to 500mls daily
B. Increase the number of PD cycles to 10
C. Increase the dextrose concentration of each cycle to 2.36% and fluid restrict him.
D. Increase his dwell volume to 1000mls each cycle
E. Start an antihypertensive

Option A:
- PD 500, UO 500, Insensibles (400ml/m2) 300 = 1.3kg neg
- Fluid intake (if sticks to it) = 0.5 kg pos
- Net weight loss 0.8kg = 19.9kg

Option B:
- PD ?x500 = 1000ml, UO 500, Insens 300 = 1.8kg neg
- Fluid intake = 1kg pos
- Net weight loss 0.8 kg = 19.9kg
- Plus doubled time on dialysis

Option C:
- PD ? x 500 = 1000, UO 500, Insens 300 = 1.8kg neg
- Fluid intake = 0.5kg pos
- Net weight loss 1.3kg = 19.4kg

Option D:
- 1250ml/m2 fill volume too high

Option E:
- Fluid balance is the cause of the hypertension and thus is the solution!
Question 5

- Your 6 yr old patient on PD arrives in ED with abdominal pain and fever
- PD effluent is cloudy
- Microscopy shows 14000 white cells, 80% polymorphs and few gram +ve cocci

What is best initial therapy?

A) Oral flucloxacillin
B) IV flucloxacillin
C) IV Vancomycin
D) IP Cefazolin
E) IP Cefazolin & Ceftazidime

IP Abx to cover G+ and G- organisms

- Dx PD peritonitis = WBC >100, neut >50% (need fluid spec from min 2 hr dwell time before can exclude)
- IP antibiotics are first line therapy
- First line empirical therapy must include coverage for gram pos and neg organisms irrespective of the gram stain until culture result is available
- Usual tx duration 2-3 weeks, organism dependent
- Peritonitis alters membrane function acutely and in some cases chronically. Decreases membrane longevity.

Figure 1. Distribution of causative organisms.

Largest Paediatric PD Peritonitis Study (IPPR), organisms in 501 cases. Warady et al. JASN 2007.

Note, for spontaneous bacterial peritonitis (eg in nephrotic patients, *strept pneumonieae* is classically most common organism followed by E coli, this however may change with changing vaccination schedules).
Question 6

What is the most unlikely root cause of this episode of PD Peritonitis?

A) Touch contamination
B) Use of high glucose concentration dialysate
C) Swimming in a farmland stream
D) Invasive dental work
E) Severe gastroenteritis
Strategies to minimise peritonitis risk:

- PD catheter insertion techniques
- Equipment/technical advances
- Training
- Exit site care
- Rx Staph aureus/Pseudomonas colonization
- Antibiotic prophylaxis peri:
  - Invasive dental/GU or GI procedures
  - Any accidental intraluminal contamination episode
  - Antifungal prophylaxis for patients on abx course
- Reduce environmental risks – swimming/pets

Complications of PD

- Infection
  - exit site
  - tunnel infection
  - peritonitis
- Hernia
- Catheter malfunction
  - catheter migration
  - fibrin blockage lumen
  - omentum wrap – poor outflow
  - constipation
- Leak
  - exit site
  - subcutaneous (abdominal wall)

Renal Transplant Overview

- Why
- Sources allografts
- Who
- Meds
- Complications
  - Graft dysfunction
  - Hypertension
  - Infection
  - Malignancy

Transplant Case 1

- A 15 year old boy with ESKD since neonatal period due to cortical necrosis.
- On PD as an infant. Transplanted age 3 (LRD from mum). Lost graft age 5 due to severe CNI induced haemolytic uremic syndrome.
- He is back on PD.
- Father is keen to donate but is blood group incompatible.
Question 7

What is the best choice of treatment for his long term life expectancy?

A. Stay on dialysis
B. Living related donor – ABO incompatible
C. Paired kidney exchange
D. Deceased donor
E. Extended criteria donor or Donation after cardiac death donor
Long-term outcomes post transplantation superior to dialysis:

- Mortality
- Cardiovascular disease
- Growth
- Neurodevelopment
- Quality of life

PRE-EMPTIVE renal transplant (pre dialysis, ie at GFR <15-20) results in improved outcomes in all of these domains.

Survival on Dialysis

Cf to healthy age matched popn mortality rates ~ 30X higher
Cf to age matched transplant recipient mortal ~ 4x higher

Treatment Options ESKD
"Renal Replacement Therapy" (RRT)

- Transplant
- Dialysis
  - PD
  - HD

Dialysis considered "bridge to transplantation" in children

Sources of Kidneys

LURD
LRD
DCD
Brain Dead
Living Donation (LD)

18-~55 yrs age for paediatric recipients

Allows for a planned, scheduled transplant

- Living related donor (LRD)
- Living unrelated donor (LURD)
- Altruistic/Non-directed donor: no intended/known recipient

Deceased Donor (DD)

1. Brain dead, circulatory system intact on life support.
   nb. Terms “cadaveric” and “harvest” (for procurement/organ recovery) now avoided.

2. DCD: Donation after Cardiac Death
   - Uncontrolled: post failed resuscitation (Japan, Europe)
   - Controlled: non-recoverable irreversible neurological injury resulting in ventilator dependency but not fulfilling brain death criteria.
     [May also incl end stage musculoskeletal disease, pulmonary disease & high spinal cord injury]

Pre-requisites for directed living donation

- Medically and psychologically fit
- Blood group compatible – O “universal donor”, AB “universal recipient”
- Cross match compatible – no preformed antibody to donor HLA
ABO Incompatible Transplantation

- LD transplants only
- Specialized IS protocol to deplete anti-A/B titres
  - Rituximab
  - Plasmapheresis
  - Hence at risk of complications assoc with incr IS
- Worse graft survival than ABO compatible tpx

Living Donor Paired Exchange

Domino Exchange

Longest organ donor chain links 60 people in US

Took 4 months, involved 17 hospitals across 11 states.
Back to the Case

- Boy received a living unrelated renal tpx via paired kidney exchange program.
- At age 15 graft is lost from severe antibody mediated rejection. There is proven non-adherence (undetectable tac levels, delayed prescription refills) and recreational drug use. He has also developed bronchiectasis, which is currently under good control.
- Should he be re-listed for a third transplant?

Q 8 Should he be put back on DD wait list now for a third transplant?

A. Yes
B. No because he has a chronic infective illness (bronchiectasis)
C. No because he is a recreational drug user
D. No because he has already had 2 transplants (where would the third go?)
E. Not at present because he is non-adherent

Who do we transplant?

- ESRD (=CKD 5/ GFR<10-15ml/min/1.73m2*)
- At least ~ 6.5-10kg (centre dependent)
- No contraindications

* May consider pre-emptive at 15- 20ml/min/1.73m2 in certain cases

Contraindications

- Absolute
  - Active malignancy
  - Severe neurological dysfunction
  - Terminal illness/multiorgan failure

- Case-by-case
  - Chronic infections
  - Co-morbid immunosuppressed state
  - High recurrence risk of native disease
  - Recreational drug abuse
  - Non adherence
Correctable/Temporary Contraindications

- Size
- Poor nutritional status
- Untreated infection
- Need for native nephrectomy pre tpx:
  - congenital nephrotic syndrome
  - tubulopathies with profound polyuria
  - corrective urological surgery (need competent, low pressure, functional or catheterisable bladder equivalent)

Transplant Case Two

- You see a 5 year old who is 2 months post renal transplant in routine weekly OPC.
- Baseline creatinine has been 40µmol/L.
- Drugs include tacrolimus, mycophenolate and prednisone. Cotrimoxazole and Valganciclovir prophylaxis.
- He looks well, no fevers, weight 0.5kg less than that of 1 week ago, BMs 4 times daily.

Exam unremarkable, no graft tenderness, no bruit.
BP 130/84, confirmed to be elevated on 3 repeated measurements in clinic.
Lab results
- Creatinine 70µmol/L, urea 12mmol/L
- Tacrolimus level is pending
- Hb 120g/L, WBC and platelets normal

Question 9

What is your next course of action?
A. Review with bloods in clinic in one week.
B. Repeat bloods tomorrow and clinical review.
C. Increase his amlodipine dose
D. Hold the tacrolimus
E. Repeat serum creatinine urgently, send urine for MC&S and chase pending tac level
Question 10
What are 5 causes of allograft dysfunction you need to consider?

Causes of allograft dysfunction
- Dehydration
- Medication (or other nephrotoxin)
- Infection
- Obstruction
- Rejection
- Perfusion problem

Approach to allograft dysfunction
- Check patient’s state of hydration carefully – weight most useful – usually admit for IV fluids pending IX’s
- Rule out exposure to nephrotoxic meds/ OTC drugs/ herbal. Check tac level.
- Look for infection – hx and exam, check urine MC&S, CMV, BK and EBV PCR
- +/-Transplant doppler USS if no cause determined or improvement with rehydration
- +/- Biopsy if no cause determined or improvement with rehydration

Acute rejection (AR)
- May occur at any time, most common in 1st 6 months post tx
- Newer IS agents have resulted in lower incidence of AR. Now 10-20% have AR in 1st year.
- May occur concomitantly with ATN or infection – may only be recognised with transplant biopsy
- Acute rejection should be confirmed by biopsy where practicable
- Type of treatment determined by histological severity (Banff grading) and clinical progress
- Other causes of dysfunction may simulate AR
  - Viral infections (BKV, CMV, EBV)
Case continued

- Repeat creatinine 80umol/L
- Urine negative for cells/bacteria
- Tacrolimus level 18
- You admit for IVF rehydration and manipulation of his tacrolimus dosing

Question 11

With regards to his blood pressure (130/84):

A. He is asymptomatic and this is normal 2 months post kidney transplant, no action required
B. Should start ACE-inhibitor
C. Should start long acting calcium channel blocker
D. Should do a 24hr ABPM during this admission
E. You will monitor his BP during admission and consider short acting treatments in the first instance

Post Transplant Hypertension

- Common post transplant problem, even in those who were normotensive pre tx, usually improves with time
- due to high fluid intake, steroids, calcineurin inhibitors
- Be aware of possible RA stenosis

- Need to control BP early in course of transplant
  - Use vasodilators (Ca channel blockers) in early post tx period, diuretics if hypervolaemic, ACE inhibitors preferred BUT only once graft function is stable (>2-3/12 post tx)

- Persistent post tx hypertension associated with lower graft survival, requires investigation and treatment – doppler uss, ABPM, echo.
- Target BP should probably be 50th percentile

Case 2 Continues

- On further history he complains of “tingly feelings” of his tongue & lips and on exam you note a tremor.
- You check a serum Magnesium which is 0.3 mmol/l ( n 0.7-1.2).
Q12  Which of his drugs is most likely to have led to this?

A) Prednisone  
B) Mycophenolate mofetil  
C) Tacrolimus  
D) Felodipine  
E) Valganciclovir

Answer C

- High tacrolimus levels
- Other SEs CNI: nephrotoxicity, HTN, headache, tremor, hepatic dysfn, glucose intol, hyperkalemia, cyclosporin – hirsuitism, gingival hyperplasia.
- You talk more to his family and find that he’s on an antibiotic from the GP for a sore throat.

Q13  Which of the following increases CNI levels?

A) Rifampicin  
B) Gentamicin  
C) Phenytoin  
D) St Johns Wort  
E) Erythromycin

Answer E

Increase CNI level (P450 CYP3A4 Inhib):  
- Grapefruit, starfruit, pomegranate  
- Erythromycin  
- Clarithromycin  
- Chloramphenicol  
- Doxycycline  
- Ciprofloxacin  
- Metronidazole

Decrease CNI level (P450 CYP3A4 inDuc):  
- St Johns Wort  
- Rifampicin  
- Isoniazid  
- Fluconazole/Ketoconazole/voricon  
- HIV protease inhibitors  
- CCBs nifedipine/verapamil/diltiazem  
- Carbamazepine/phenobarb/phenytoin
Immunosuppressive Therapy

- Renal transplant pts require lifelong immunosuppression to prevent rejection.
- Intense IS early, tapered over 6/12
- Predominately suppressing T cell function
- Induction IS (immediately pre op)
  - Basiliximab
  - (IV methylpred intraop)
- Maintenance IS
  - Standard “triple” regime calcineurin inhibitor, mycophenolate mofetil and corticosteroids.

Tacrolimus

- Produced by a type of soil bacterium, *Streptomyces tsukubaensis*
- “Calcineurin Inhibitor” (CNI)
- Binds to intracellular T cell proteins, this complex blocks calcineurin, & ultimately inhibits nuclear activation of genes coding for IL-2 & related cytokines

Relative toxicity of calcineurin inhibitors

<table>
<thead>
<tr>
<th></th>
<th>CsA</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>nephrotoxicity</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>hypertension</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>tremors</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>gingival hyperplasia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>hirsutism</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>hyperuricaemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>hypercholesterolaemia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>hypomagnesemia</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Mycophenolate mofetil (MMF)

- Inhibition of lymphocyte proliferation (“antimetabolite”) & other effects
  - blocks an enzyme (IMDPH) reqd for purine (DNA) synthesis specifically in lymphocytes (B & T).
- Replaced azathioprine in many centres
- Much lower incidence of acute rejection
- GI side effects most common, may improve with mild dose reduction
- Leukopenia, thrombocytopenia, anorexia other side effects
- Significant interactions with CyA and tacrolimus
**Corticosteroids**

- Potent immunosuppressants
- Wide range of effects on immune system specifically the T lymphocytes and numerous cytokines
- High daily dose can impair growth, glucose intolerance, HTN, weight gain, cataracts, acne, osteoporosis, gastritis, mood/behaviour, hirsutism, hyperlipidemia, impaired wound healing.
- Initially IV methylprednisone (first dose intra-operative) then PO
- Dose weaned over initial 6 months to low dose EOD
- Some centres use steroid free protocols

**Case 2 continued**

- You see him again a month later with a sore throat, and weight loss.
- His renal function is stable, normotensive.
- Urine is clear
- Widespread lymphadenopathy and splenomegaly on examination

**Q14 What is the most likely cause?**

A) Post transplant lymphoproliferative disease  
B) CMV infection  
C) BK infection  
D) UTI  
E) TB

**Answer A**

- BK infection presents with graft dysfunction and haematuria
- CMV is associated with fever, colitis, deranged LFTs but is possible
- Most likely is EBV infection or reactivation leading to PTLD, need node biopsy to confirm. Symptom of over-immunosuppression.
Post Transplant Malignancies

- Uncommon in children
- Most common - lymphomas, skin cancers- sun protection advice
- Related to intensity of immunosuppression
- Post transplant lympho-proliferative disease (80%)
  - EBV driven in many but not all forms
  - EBV naive recipient
  - Some correlation to overall intensity of immunosuppression
  - Wide range of symptomatology

Post Transplant Infection

- Extensive pre & post transplant vaccinations required – annual flu. NZ guideline accessible via SSH clin guidelines website.
- Live vaccines - VZV and MMR important to administer pre Tpx (minimum 4 weeks prior). LIVE vaccines contraindicated post transplant.

- Signs and symptoms of infection can be muted by immunosuppression
- Specific, predictable risk periods for specific pathogens
- Link between degree of immunosuppression and infection risk
- Consider the possibility of donor-derived infection (viral, fungal, bacterial, mycobacterial, etc.)
Post Transplant Infection Prophylaxis

CMV: 3 months of antiviral (valganciclovir) for any D+ or R+

PJP: 6 mo TMP/SMX (or dapsone, pentamidine)

UTI: 3 mo TMP/SMX

Candida: 1mo nilstat

Growth after transplantation

- A well functioning graft should enable a child to attain catch-up growth
- BUT long term follow up data does not support this in > 6 yr olds or after first 2 yrs post tpx
- Loss of graft function is associated with loss of height potential
- GH can be used after first 6-12 mo if other factors corrected (nutrition/PTH/Ca & PO4/acidosis/lowest poss steroids)

Questions?