Renal Case Studies - Cologne January 2011

NB. Creatinine clearance calculations, 1mg/dL = 88.4 μmol/L creatinine

Case 1.

Mr NT is a 40-year old man, diagnosed with testicular teratoma.

Weight	82kg (IBW = 78kg)	
Height	183cm	
CrCl = 112 ml/min		
eGFR = 117 ml/min		

Routine blood tests show:-

Urea	3.2 mmol/L	(2.1 – 7.1 mmol/L)
Creatinine	86 μmol/L	(49 – 92 μmol/L)
Sodium	142 mmol/L	(135 – 145 mmol/L)
Potassium	4.1 mmol/L	(3.5 – 5.1 mmol/L)
Magnesium	0.81 mmol/L	(0.7 - 1.0 mmol/L)
Corrected Calcium	2.32 mmol/L	(2.2- 2.65 mmol/L)

Before commencing treatment, a Cr-EDTA scan shows he has a GFR of 107 ml/min
He is subsequently treated with:
Prednisolone, Vincristine, Methotrexate, Bleomycin, Adriamycin, Cisplatin

One week later, a routine set of blood tests shows

Urea	15.1 mmol/L
Creatinine	200 μmol/L
Sodium	137 mmol/L
Potassium	2.8 mmol/L
Magnesium	0.2 mmol/L
Corrected Calcium	1.87 mmol/L

On his 4th admission, Mr. N.T. was given his chemotherapy as per protocol.
Two days later, he was pyrexial with a temperature of 39.8^{o} C.
His full blood count revealed that he was neutropenic,

WBC count = 1.3×10^{-9} (normal range $3.7 – 11.0 \times 10^{-9}$),
Neutrophil count = 0.1×10^{-9} (normal range $1.5 – 7.5 \times 10^{-9}$).

He was prescribed empirically the following drugs:-

Gentamicin	IV	560mg OD
Vancomycin	IV	1g BD
Ceftazidime	IV	2g TDS
Metronidazole	IV	500mg TDS

His biochemistry over the following days was as follows:-

	Day 2	Day 3	Day 4	(Normal Range)
Na^+	143	141	144	(135 – 145 mmol/L)
K^+	5.3	5.5	6.2	(3.5 – 5.1 mmol/L)
Ca^{++}	2.01	2.00	1.97	(2.2 – 2.65 mmol/L)
Mg^{++}	0.97	0.86	0.73	(0.7 – 1.0 mmol/L)
PO_4^-	1.29	1.57	2.01	(0.70 – 1.25mmol/L)
Urea	7.3	10.6	15.4	(2.1 – 7.1 mmol/L)
Creat.	155	235	481	(49 – 92 μmol/L)

Q1. What has happened now?

Mr. NT appears to have gone into acute renal failure, as indicated by rapidly rising and grossly elevated serum creatinine, hyperkalaemia, hyperphosphataemia and hypocalcaemia. Already had minor renal damage due to previous courses of chemotherapy, which has been exacerbated by cisplatin toxicity during this course of treatment. Also neutropenic and now septic, requiring broad spectrum antibiotics.

	Day 2	Day 3	Day 4
GFR(ml/min)	65	43	21

Q2. Comment on the antibiotic therapy he has been prescribed. Do you need to intervene??

Metronidazole - metabolised by liver, no dosage reduction necessary in renal impairment.

Vancomycin - renally excreted, and highly nephrotoxic. In severe renal impairment, need to drastically reduce dose. Suggest giving 1g IV stat, then wait 24 hours and do a random trough level before giving the next dose.

Ceftazidime - renally excreted, and toxic in overdose (mainly neurotoxicity). Must substantially reduce the dose in renal impairment – suggest 1g TDS or BD in Mr. NT and monitor response.

Gentamicin - exclusively renally excreted, and extremely nephrotoxic & ototoxic. Under no circumstances is once-daily dosing at 7mg/kg to be attempted, as has been prescribed. Suggest giving stat dose of 2mg/kg, waiting 24 hours and doing random trough level, then dosing again as necessary.

With all of the last 3 drugs, the patient's renal function is deteriorating rapidly, therefore Cockroft & Gault unreliable. Need to reassess patient's renal function each day, & adjust drug dosages accordingly.

Q3. What would you recommend?

See above

Case 2

Mr. D.K. is a 76 year-old man admitted to general surgical ward for repair of abdominal aortic aneurysm.

HPC One week history of intermittent abdominal pain, backache and breathlessness. Pulsating mass in abdomen.
Referred as an emergency by General Practitioner.
Angiogram shows dissecting aortic aneurysm - needs urgent repair.

PMH Hypertensive for the last 20 years.
Partial seizure epilepsy since childhood.
Declining renal function secondary to hypertension.

SOCIAL HISTORY
Retired company director
Married with 2 children - lives with wife
Smoked 30 cigarettes/day for 40 years.
Drinks alcohol socially

ON EXAMINATION
Hypertensive - BP 155/90
Height - 5'7"
Weight - 87kg
Serum Creatinine 140 μmol/L (49 - 92 μmol/L)
Serum Urea - 5.3 mmol/L
WBC count - 6.7 x 10^9/L

DRUGS ON ADMISSION
Furosemide 80mg BD
Enalapril 10mg BD
Nifedipine MR 20mg BD
Phenytoin 300mg OD

DAY 1

At operation Mr.D.K. experiences a major haemorrhage and collapses in theatre. He is resuscitated and taken to ITU where he is commenced on inotropes and cefotaxime IV 2g TDS.

DAY 2
Serum Creatinine 285 μmol/L
Urea 15 mmol/L
Serum Potassium 5.7 mmol/L

DAY 3
Serum Creatinine 482 μmol/L
Urea 22 mmol/L
Serum Potassium 6.9 mmol/L
Urine output has dropped to about 10 ml/hour
Weight - 91kg Height 178cm
Diagnosis of acute renal failure
Commenced on CVVHD

Also on Day 3:-

Temp 38^0C , BP 130 / 75, WBC count 15.8 x 10^9/L

Q1. Describe the factors which influence drug removal during haemodialysis and haemofiltration.

Factors Favouring Drug Removal by Dialysis.

1. Low molecular weight.
   - clearance increases proportionally as mol.wt. falls below 500 daltons.

2. Low percentage of drug bound to plasma protein.

3. Low apparent volume of distribution.
   If V_D < 1L/kg → significant drug removal.
   If V_D > 2L/kg → insignificant drug remonal.

4. High water solubility / low lipophilicity.

5. High degree of renal clearance in patients with normal renal function.

6. Low steric hindrance.

Dialysis Characteristics which affect drug clearance but are difficult to quantify:

1. Duration of dialysis procedure.
2. Blood flow rate in dialyser.
3. Type of dialyser membrane.
4. Flow rate + composition of dialysate.

CAVH & CVVH
- no dialysate involved.
- blood passes through filter.
- drugs + fluid removed by convection and ultrafiltration.
- haemofiltration solution used as fluid replacement either pre- or post-filter.
- no diffusion or osmosis involved.
- membrane more permeable than that used for intermittent HD.

CAVHD & CVVHD
- Combines ultrafiltration with solute convection + solute diffusion from the blood across a membrane into a dialysate.
- Haemofiltration solution used as dialysate.
- Relative pressure + flow rates of blood versus dialysate across membrane dictate amount of fluid removed from patient.
- Solute removal controlled by composition and flow rate of dialysate.

- Similar drug handling to conventional HD, but process removes drugs with mol. wt up to 10,000 daltons.

Mr.D.K.'s prescription is changed to:-

Ranitidine 50mg TDS IV
Amikacin 750mg OD IV
Teicoplanin 400mg OD IV
Phenytoin 100mg TDS IV
Diclofenac IM 75mg BD
Morphine IV Infusion @ 2mg/hr
Dopamine IV 2.5mcg/kg/min

Q2. Comment on the patient's prescription above. What changes you would recommend for the prescription?

Pre-Op.
Ideal body wt = 66kg.
At 87kg, is 32% overweight, counts as obese.

Using Cockcroft & Gault,
Creatinine Clearance = 37 ml/min.

Post Op Day 1.
Although data sheet says dose of cefotaxime need only be reduced when GFR < 5ml/min because of extra-renal clearance, in view of Mr. D.K.'s poor renal function, may be wise to reduce dose of cefotaxime to 1g tds.

Day 2.
Rapidly changing renal function Cockcroft & Gault no longer valid.
However, using it as rough guide, GFR = approx 17ml/min.

Day 3.
Creatinine now 482, Cockcroft & Gault definitely not valid.
GFR probably approx. 10 – 11 ml/min.
CVP 10cm H_20 → patient is adequately filled intravascularly. → Definitely acute renal failure.
CAVHD - dose as for moderate renal impairment.

Drugs

(a) **Amikacin** - dose must be reduced as will accumulate → ototoxicity & nephrotoxicity. Give eg. 7.5 mg/kg OD and measure random trough levels (must get to < 5 mg/L) before giving next dose.

(b) **Teicoplanin.**
- normally renally excreted but **not** cleared that well by CVVHD due to high protein binding
∴ it will accumulate.

Ideally, still give same loading dose as for normal renal function, ie, 400mg 12-hourly for 3 doses, then reduce the maintenance dose. At this level of renal function, teicoplanin dose should be 400mg every 2nd or 3rd day.

(c) **Ranitidine** - should reduce the dose in severe renal impairment.
Ideal dose would be 50mg BD IV – however most units may give 50mg TDS regardless of renal function.

(d) **Dopamine.**
Has a very short half-life, so if any is removed by the filter, probably won't have a significant clinical effect. Need to titrate dose to end-point, ie. maintain adequate CVP, dose is independent of renal function.

(e) **Morphine.**
Not the ideal analgesic for someone with acute renal failure. Morphine + diamorphine rapidly accumulate (the metabolites are pharmacologically active and are renally excreted) → excessive sedation + respiratory depression, ie. Very poorly tolerated in patients with moderate to severe renal impairment.
Ideal drug would be fentanyl or alfentanyl - metabolised by the liver, metabolites either inactive, or hepatically excreted.
→ Does not accumulate in renal failure.
Very short t½ → effects wear off quickly when infusion stopped, and less chance of accumulation.
If fentanyl can't be used, then morphine/diamorphine may be but in extremely low doses + monitor patient carefully. (NB. If the patient is on ITU and being artificially ventilated, respiratory depression is not a problem, so morphine or diamorphine may be used safely).
Another alternative is oxycodone, which does not have very active metabolites like morphine, so is much better tolerated. Still start with small doses and increase the dosing interval to every 6-8 hours. Works well in a patient-controlled-analgesia pump.

(f) **Diclofenac.**
Not ideal in a patient with ATN, as it interferes with prostaglandin mediated afferent arteriolar blood supply to the glomerulus. → could compromise the kidneys' attempt to recover from ATN.
If NSAID is required, ideally use one said to be more renally sparing, eg. sulindac or etodolac. Otherwise, simple analgesia (paracetamol, co-dydramol, tramadol, etc) may suffice.

(g) **Phenytoin**
99% protein bound, therefore not removed by CVVHD. Dose as per normal renal function.
NB. Watch patient's serum albumen level. ↓ albumen level = ↑ free fraction. Need to either measure total and free phenytoin levels, or use pharmacokinetic calculations to correct for low albumen.

DAY 7

Mr. D.K. is well enough to be discharged from ITU. He has not recovered any renal function so is transferred to a renal ward to receive intermittent haemodialysis.

Q3. Do you need to amend his drug doses again?

Intermittent haemodialysis has a much lower clearance than CVVHD, ie. 10 ml/min vs 20 – 35 ml/min.
Therefore the doses of some drugs will need to be reduced and the doses times around dialysis sessions.

Amikacin – reduce dose to 3mg/kg after dialysis, and monitor levels. Ideally, take level immediately pre-dialysis, and if a suitable trough level has been reached, dose again after dialysis.
Teicoplanin – reduce dose to either 400mg every 3 days, or can give 400mg 3 x/week after dialysis.
Morphine – avoid if at all possible. Use fentanyl or oxycodone instead.

Case 3

Mrs BH is a 43 year old woman, admitted with a 3 day history of fever, rigors, night sweats, and general malaise. On examination she was noted to have splinter haemorrhages under her fingernails and she had developed a new heart murmur. She had recently had a tooth extracted.

Previous Medical History
Diagnosed with lupus nephritis at age 31.
Reached end stage renal failure 3 years ago.
She now has haemodialysis, for 4½ hours, 3 times a week.

Temperature 38.2^{o}C BP = 135/90 mmHg Pulse = 66/min

Serum biochemistry	Value	Normal range
WCC	11.6 x 10^9 /L	(3.5 – 11.0 X 10^9 /L)
C Reactive Protein	65 mg/L	(0 – 5 mg/L)

An echocardiogram revealed vegetation on the mitral valve.
Blood cultures were taken, which subsequently grew *Streptococcus viridans.*

A diagnosis of infective endocarditis was made, and Mrs BH was admitted to the medical ward for intravenous antibiotics.
She was empirically prescribed:-

Benzylpenicillin IV 1.2g every 4 hours +
Gentamicin IV 80mg every 12 hours.

When the results of the blood cultures were known, amoxicillin 2g every 8 hours was added to her antibiotic regimen.

Q1. Do you want to make any dosage adjustments for this patient?

A patient on intermittent haemodialysis (HDx) has an effective GFR of less than 10ml/min, (even though clearances of up to 200ml/min are achieved during the 4 hour dialysis session), and so should be dosed as though having SEVERE renal impairment.

- Penicillins are generally non-toxic (unless the patient is actually allergic to penicillin), so for oral therapy, normal doses may be used. However, with high-dose IV therapy, they may accumulate in patients with ESRF, leading to grand-mal fits. Hence it is advisable to reduce the doses a little.
- Benzylpenicillin – suggest the dosing frequency is reduced from 4-hourly to 6-hourly, ie. give 1.2g four times a day.
- Amoxicillin – given that the patient is also on high-dose benzylpenicillin, being on amoxicillin as well increases the risk of penicillin accumulation, with associated fitting. Suggest reducing the dose to 1g three times a day.
- Gentamicin is a highly toxic drug and the dose needs to be greatly reduced in severe renal impairment. In effect, it will only be cleared from the body during dialysis sessions, so the usual rule is to dose after each dialysis session. For normal systemic infections, a dose of 2mg/kg should be prescribed, and then levels monitored until they are < 1.5 mg/L, when another dose can then be given.

- For bacterial endocarditis, lower doses of gentamicin are used even in the normal population. In order to achieve similar levels, a dose of 40-80mg after each dialysis session in probably required, and monitor levels.

NB. No need to monitor the patient's renal function as she has none!
However, must monitor for other toxic effects of aminoglycosides, eg. ototoxicity, vestibular problems, etc

Sensitivities showed Mrs. BH had acquired a resistant strain of *Strep. viridans*, and the microbiologists advise that a new antimicrobial agent, "Streptoban", be added to her current drug therapy.

There is no immediate data on appropriate dosing in haemodialysis but the following information about Streptoban is available:-

- The molecular weight is 370 daltons,
- 85% of the oral dose is excreted unchanged in the urine,
- Plasma protein binding is about 15%,
- The normal intravenous dose for a healthy adult is 1g BD.

Q2. What is the likely clearance of Streptoban by intermittent haemodialysis?
Can you suggest a dose for Mrs. BH?

Haemodialysis gives an effective GFR of approximately 10 ml/min

Dosing in Renal Failure = Daily Dose x [(1 - Feu) + (Rf x Feu)]

Feu - Fraction excreted unchanged in the urine.
Rf - Extent of renal impairment as a fraction of renal function.

Streptoban has a low molecular weight (370 daltons), low degree of protein binding (15%), and is known to be largely excreted unchanged in the urine (85%). Hence it fulfils the criteria for being well removed by haemodialysis.

Dose in renal failure = Daily dose x [(1 - Feu) + (Rf x Feu)]

Usual total daily dose = 2000mg (1g BD)

Fraction excreted unchanged in urine (Feu) = 85% = 0.85

Extent of renal impairment as fraction of renal function (Rf):-

.

The patient is anuric and renal function is totally dependent on intermittent haemodialysis, therefore treat as if the GFR is effectively 10mls/min, ie. Extent of renal impairment Rf = 0.1

Dose in severe renal impairment = 2000 x [(1 - 0.85) + (0.1 x 0.85)]
= 2000 x (0.15 + 0.085)
= 2000 x 0.235
= 470mg OD

In practice, would probably recommend 500mg OD, and monitor levels if possible.

Case 4

Mrs. N.R. is a 43-year old woman, admitted for treatment of a severe case of shingles (herpes zoster).

PMH
Diagnosed as having adult polycystic kidney disease at age of 39.
Reached end stage renal failure 4 years ago.
Has been on automated peritoneal dialysis, 10 hours overnight, 5x / week, ever since.

BP = 135/84 Pulse = 66/min Dry weight = 72kg
Daily fluid allowance = 500ml

Her initial serum biochemical and haematological profile is:-

Sodium	138 mmol/L
Potassium	5.0 mmol/L
Urea	16.0 mmol/L
Creatinine	624 mmol/L
Phosphate	1.8 mmol/L
Bicarbonate	22 mmol/L
Haemoglobin	9.2 g/dL
WCC	6.6 x 10^9 /L

It is decided she requires intravenous aciclovir.

Q1. What dose would you recommend, and how would you administer it?

The recommended dose of aciclovir for a patient with GFR < 10 ml/min is 2.5 – 5.0 mg/kg ONCE a day.
One point to note is that aciclovir does NOT cross the peritoneum, therefore will accumulate in patients on peritoneal dialysis.
Therefore, it is advisable to use the lowest possible dose, ie. 2.5 mg/kg OD.
Typical method of administration is in 100ml sodium chloride 0.9% over 1 hour.
NB. If the patient is very fluid restricted, aciclovir may be given undiluted via a CVC.

Q2. If Mrs. NR was on intermittent haemodialysis, what dose of aciclovir would you recommend?

Aciclovir is removed by haemodialysis very easily.
Therefore, although you still dose for GFR < 10 ml/min, it is OK to use the higher dose, ie. 5 mg/kg OD.
NB. Time the dose to be given in the evening. If it is given in the morning, and then the patient has dialysis, all the aciclovir will be removed.

Q3. If Mrs. NR was on CRRT, what dose of aciclovir would you recommend?

CVVH – dose as for GFR = 10 – 25 ml/min, ie, 5 – 10 mg/kg OD (typically 7 mg/kg OD)
CVVHD – dose as for 20 – 35 ml/min, ie. somewhere between 5-10 mg/kg OD and 5-10 mg/kg BD. Typically give 10 – 12 mg/kg OD.