Renal Therapeutics for Beginners

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Kongress für

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What will we cover?

- Look at the different methods of calculating GFR
- Look at the influence of renal impairment on pharmacokinetics and pharmacodynamics of drugs
- Tips on adjusting the doses of common drugs in acute and chronic kidney injury.

Normal Renal Function

- Approximately 1 million nephrons per kidney, receiving 25% of the cardiac output
- Kidneys filter about 180 litres per day, filtrate consists of low molecular weight compounds, water, amino acids, waste products, electrolytes & glucose.
- Large molecular weight compounds, plasma proteins, lipids, and avidly bound compounds are not filtered.
- About 99% of water, electrolytes & amino acids are reabsorbed, $\Rightarrow$ about 60mls of urine produced per hour (1.5L per day).
- Glomerular Filtration Rate (GFR) is a measure of the rate at which the kidney filters, $\Rightarrow$ used as a measure of the excreting function of the kidney.

General Functions of the Kidney

- regulation of salt & water balance
- regulation of blood pressure (renin-angiotensin system)
- regulation of acid-base balance
- elimination of waste products including urea and creatinine, arising from nitrogenous metabolism
- produces erythropoietin $\Rightarrow$ stimulation of erythrocyte production
- activation of vitamin D
- metabolism of insulin
- normal adult urine output = 1000 – 2000 mls/24 hrs

Creatinine

- production rate varies widely between individuals
- higher in men than women
- declines after middle age
- decreased in wasted patients
- decreased during pregnancy
- less affected by diet than urea
- plasma creatinine doubles for every 50% fall in GFR
- time-lag for equilibration to occur after changes in renal function
- inaccurate in unstable, rapidly changing renal function, such as in AKI

Example 1 – patient with creatinine 105micromols/L

- 44 year old male
- Serum creatinine 105micromols/l
- 100kg
- C&G **112mls/min/1.73m^2**
- MDRD **71mls/min/1.73m^2**
- Over estimate with C&G, underestimate with MDRD

Example 2 – same creatinine 105micromols/L

- 78 year old lady
- Serum creatinine 105micromols/l
- 50kg
- C&G = 30mls/min
- MDRD = 47mls/min/1.73m^2
- underestimate with C&G, overestimate with MDRD

Monitoring Renal Function

- Can calculate either glomerular filtration rate (GFR) or creatinine clearance (Clcr)

- 24-hour urine collection
- Cockcroft & Gault equation
- MDRD equation (eGFR)
- CKD-EPI equation

24 hour urine collection

- Collect urine over 24 hours to measure urinary creatinine

- Measure plasma creatinine level sometime during the 24 hour period

- $\text{CREATININE CLEARANCE} = \left(\frac{UV}{P}\right)\left(\frac{1.73}{A}\right)$

U = Creatinine concentration of the 24 hour urine (mg / dl)
V = 24 hour urine volume (mls) **per minute - V / 1440 = mls / minute**
P = Plasma creatinine concentration (mg / dl)

A = Correction factor accounts for differences in body surface area obtained from a height – weight chart

(Ranges: 90-140 (m); 80-125 (f) ml / min)

Cockcroft and Gault (1973)

$$Clcr = \frac{[140 - Age\ (years)\ ] \times Weight\ (kg)}{Plasma\ creatinine\ (\mu mol/L)}$$

- For males, multiply above equation by 1.23
- For females, multiply above equation by 1.04
- Use ideal body weight in obesity (ie. If patient's weight is > 15% over IBW)
- Equation can only be used if the plasma creatinine is stable (ie. Not varying by > 40μmol/L per day).

Cockcroft and Gault

Not accurate if:-

- patient is < 15 years or > 90 years of age
- patient has rapidly changing renal function
- patient has a serum creatinine > 350 μmol/L
- patient is pregnant
- patient has burns / liver cirrhosis
- patient is an amputee
- patient is a body builder
- patient is severely wasted / has muscle disorder
- not adjusted for body surface area

MDRD equation (1999)

GFR (mL/min/1.73m^2) =

170 x (serum creatinine) $^{-0.999}$

x (age) $^{-0.176}$

x (0.762 if female)

x (1.180 if African American)

x [Serum Urea Nitrogen] $^{-0.170}$

x [Alb] $^{+0.318}$

Normalised value ∴ may need to correct for actual surface area

Limitations: only useful in estimating GFR in stable chronic kidney disease; not suitable in AKI, less accurate when GFR > 60ml/min/1.73 m^2

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009)

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

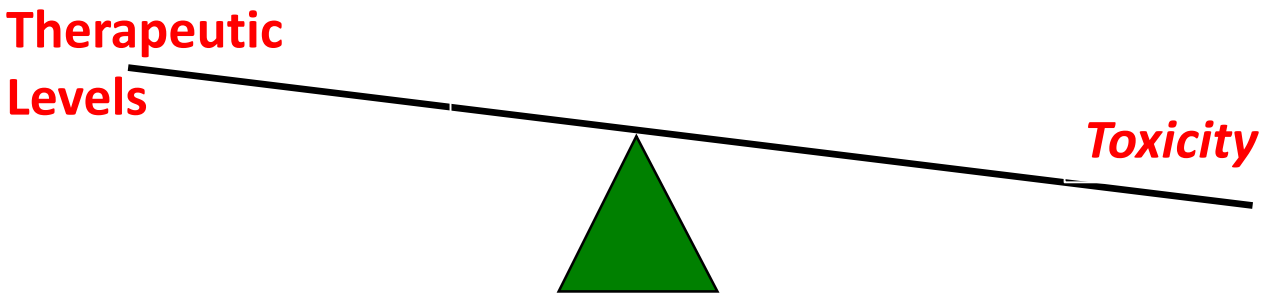
Scr = serum creatinine (mg/dL)

CKD EPI

- It was developed by Levey AS, et al in an effort to create a formula more accurate than the MDRD formula, ***especially when actual GFR is greater than 60 mL/min per 1.73 m^2.***
- Need to adjust for ***age, gender, race (black ethnicity) and BSA.***
- Larger cohort n=16,032 from various studies. Few elderly patients - limitation
- Greater precision, accuracy and less bias

Assessing Renal Function in Practice

- Above EQUATIONS have not been validated in ACUTE KIDNEY INJURY – the GFR/CrCl values may not represent true clearance
- Equations will - **overestimate** clearance when **creatinine is increasing**
  - underestimate clearance when **creatinine is decreasing**
- Overall trend is much more important than the absolute value
- Best Guess Approach needed in terms of estimating function
- Drug Dosing based on assessment of Toxicity Risk vs Need for Therapeutic Levels



Chronic Kidney Disease

- Chronic kidney disease (CKD) insidious in onset, with gradually deteriorating renal function.
- Symptoms seldom present before GFR is < 10 ml/min.
- Clinical features are non-specific, with a general feeling of weakness, fatigue and “not well”.
- The progression to end stage renal failure may takes months, or more usually, years, at which point, renal damage is irreversible.

Symptoms of CKD

- Hypertension
- Fluid & Electrolyte imbalance (Na, K, Mg)
- Metabolic acidosis
- Anaemia (EPO)
- Metabolic bone disorder (Ca, PO4, PTH)
- Uraemia (nausea, itching, peripheral neuropathy, restless legs)

CKD

Most common causes of CKD:-

- Chronic damage due to eg. pyelonephritis, glomerulonephritis, interstitial nephritis.
- Autoimmune: SLE, Wegener's granulomatosis, vasculitis,
- Genetic: adult polycystic kidney disease
- Systemic diseases such as diabetes mellitus hypertension, hyperlipidaemia.

Staging of CKD *(K-DOQI)*

Am J Kidney Dis 2002;39(suppl 1):S17-S31

Stage	Description	GFR ml/min/1.73m^2
1 +/-(p)	Kidney damage with normal or ↑GFR	≥ 90
2 +/-(p)	Kidney damage with mild ↓GFR	60-89
3A +/-(p) 3B +/-(p)	Moderate ↓GFR	45-59 30-44
4+/- (p)	Severe ↓GFR	15-29
5+/- (p)	Kidney failure	≤ 15

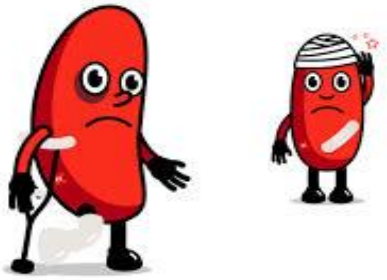
P= proteinuria 1g/day or PCR 100g/mol or ACR 70mg/mmol

Definition of AKI

- A significant deterioration in renal function occurring over hours or days, clinically manifesting as an abrupt and sustained rise in serum urea and creatinine

Divided into:-

- Pre-Renal
- Post-Renal
- Intra-Renal



Oxford handbook of Clinical Medicine 8th edition.

Pre-Renal AKI - decreased perfusion of the kidneys:-

- Volume depletion (excessive diuresis, haemorrhage (shock), burns, severe trauma)
- Cardiovascular disorders (congestive cardiac failure & acute MI)
- Obstruction of renal arteries (renal thrombosis, renal artery stenosis)

Post-Renal AKI - obstruction to urine outflow, from the collecting ducts in the kidney down to the urethra.

- Deposition of crystals in the tubules, eg. uric acid, sulphonamides, aciclovir, cisplatin.
- Renal stones in the ureter or bladder
- Tumour, either within the tract or pressing on it from another pelvic organ, eg. prostate hypertrophy, bladder cancer, bowel cancer.

Intra-Renal AKI (Acute Tubular Necrosis) – Sustained hypoperfusion, or exposure to nephrotoxic agents

- Antibiotics - aminoglycosides, amphotericin.
- Analgesics - paracetamol, salicylates
- Ethylene glycol (antifreeze)

Autoimmune Renal Disease – SLE, vasculitis, interstitial nephritis, glomerulonephritis

Staging of AKI (*K-DIGO*)

KDIGO Staging System for Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	rise ≥ 26 µmol/L within 48hrs or rise ≥1.5- to 1.9 X baseline SCr	<0.5 mL/kg/hr for > 6 consecutive hrs
2	rise ≥ 2 to 2.9 X baseline SCr	<0.5 mL/kg/hr for > 12 hrs
3	rise ≥3 X baseline SCR or rise 354 µmol/L or commenced on renal replacement therapy (RRT) irrespective of stage	<0.3 mL/kg/hr for > 24 hrs or anuria for 12 hrs

Pharmaceutical input for patients with AKI

- Identify potential drug causes of AKI
- Review medications and ensure medicines are appropriately withheld/ stopped and suggest suitable alternatives
- Advise on the use of fluids if required in the management of AKI
- Provide recommendations around fluid restriction and minimum volumes of drugs used in fluid-overloaded patients
- Fluid balance chart
- Advise prescribers about drug dosing in AKI
- Counsel patients regarding medication changes
- Avoid nephrotoxic drugs eg. aminoglycosides
- Amend drug doses according to level of renal function

Clinical Pharmacist, 2012, vol 2, p.103-106

Medications optimisation

- Is the patient on any medication that should be stopped or avoided?
  - ACE inhibitors
  - ARBs
  - NSAIDs
  - Diuretics
  - Metformin
  - Aminoglycosides
  - Contrast media

Before holding or stopping any medication, review the indication for the medication, review renal function, co-morbidities, blood pressure, other medications for similar indications, discuss with medical team if necessary

Handy Tips for Prescribing in Renal Impairment

- Most drugs have a wide therapeutic index, so don't worry about amending doses.
- If in doubt, start at a low dose and increase slowly according to response versus adverse effects.

  e.g. analgesia, anti-diabetic medication, antihypertensives.
- Antibiotics – don't be afraid to start with a large dose, then reduce to a smaller maintenance dose

Handy Tips for Prescribing in Renal Impairment

- Check the pharmacokinetics
- How is the drug usually excreted?
- Does it undergo metabolism?
- Are the metabolites active or inactive?
- How are the metabolites excreted?
- Can you monitor drug levels if necessary?

Morphine

% excreted unchanged in urine	10
Half life (normal)	2 – 3 hours (M6G metabolite 3-5 hours)
Half life (ESRD)	Unchanged (M6G metabolite 50 hours)
Volume of distribution (L/Kg)	3 - 5
% plasma protein binding	20 - 35
Metabolism issues	Main metabolites are M6G (active and 6 x more potent than morphine) and M3G (no analgesic activity but potentially neurotoxic) Both metabolites excreted in the urine
Comments	M6G crosses BBB ⇒ prolonged CNS effects. Toxicity from metabolites – significant narcosis, toxic agitation, profound respiratory depression. M3G may decrease seizure threshold Can be used in PCA

Oxycodone

% excreted unchanged in urine	<10%
Half life (normal)	2 – 4 hours
Half life (ESRD)	3 to 5 hours
Volume of distribution (L/Kg)	1.2 – 6.3
% plasma protein binding	45%
Metabolism issues	Metabolites inactive (noroxycodone) or weakly active (oxymorphone)
Comments	Pharmacokinetically a clean drug for renal patients with similar flexibility in formulation choice to morphine. Reports of increased sedation. Preferred strong opiate in many UK renal units

Low Vd (<1L/kg)

HYDROPHILIC Drugs

- Water soluble – do not distribute widely into fatty tissue
- Do not require hepatic metabolism
- Excreted unchanged by kidneys
- Dose Adjustments required in renal dysfunction & RRT

Examples:
- Aminoglycosides
- Beta Lactams
- Colistin
- Glycopeptides
- Daptomycin
- Fluconazole
- Flucytosine

High Vd (>1L/kg)

LIPOPHILIC Drugs

- Fat soluble – distribute widely into fatty tissue
- Require hepatic metabolism
- Excreted in bile, faeces or as water soluble metabolites
- Dose Adjustments **not** required in renal dysfunction & RRT

Examples:
- Fluoroquinolones
- Macrolides
- Lincosamides
- Tigecycline
- Tetracyclines
- Echinocandins
- Ambisome
- Vori/Posa/Isavu-conazole

Drug Removal by Renal Replacement Therapy

Influenced by: *Drug Characteristics*

- Low molecular weight (up to 20,000 daltons)
- Low % protein binding.
- Low volume of distribution - < 1L/kg -> generally dialysable
- High degree of water solubility
- Relatively short half-life
- Usually excreted via the kidneys – If CL_R - >25% - likely to be significantly dialysed

- Remember metabolites!

Drug removal in Renal Replacement Therapy

Influenced by: *System Characteristics*

- Membrane characteristics – flux potential; acute vs chronic; membrane thickness + surface area,
- Flow rates – blood and dialysate

  Generally faster – higher clearances (plateau effect)
- PD – volume and dwell times used influence drug removal
- Peritonitis – increases removal across inflamed membrane

Drug removal in Renal Replacement Therapy

Renal Replacement Technique	Principle of Removal	Typical Creatinine Clearance Achieved (mL/min)
CAPD	Dialysis and ultrafiltration	5 to 8
Intermittent HD	Dialysis and ultrafiltration	150 to 300
CAVH	Ultrafiltration only	10 to 20
CVVH	Ultrafiltration only	Up to 50
CAVHD or CVVHD	Dialysis and ultrafiltration	20 to 35

Calculating Drug Doses

- CRRT is a continuous process
- Dose as if a patient has renal function with the GFR according to the CRRT system used.

  Eg. CVVH = 15 – 30 ml/min.

  CVVHD = 20 – 35 ml/min
- No need to give supplementary doses
- Use published dose recommendations if available
- Otherwise, seek specialist advice.

Calculating Drug Doses

- Intermittent HDx – excellent clearance of small water-soluble molecules whilst on dialysis.
- No clearance when not on dialysis.
- Time doses around dialysis sessions rather than give supplementary doses
- Look at pharmacokinetics of drug
- If renally excreted and t½ prolonged in ESRF –> can dose 3 x/week on HDx

Eg. Ertapenem, Normal dose = 1g OD

Dose in ESRF = 50% normal dose

⇒ 500mg OD, AFTER dialysis on HDx days

Antibiotics on 3 x/week HDx

	t ½ normal renal function (hours)	t ½ ESRD (hours)	Dose on Intermittent HDx (3 x/week)
Vancomycin	6	120 - 216	750mg – 1.25g
Gentamicin	2-3	20	2 mg/kg
Amikacin	2-3	17 - 150	5 mg/kg
Meropenem	1	6 - 14	2g
Ertapenem	1	14	1g
Ceftazidime	2	13 - 25	2g
Cefazolin	1.8	40 - 70	2g/2g/3g
Temocillin	3 - 5	28	2g /2g/3g
Teicoplanin	150	62–230	Max 1000mg

Changes in Pharmacokinetics

- Absorption

  can be reduced (gut oedema & changes in pH)

- Distribution

  altered by state of hydration

  decreased protein binding of some drugs, eg. phenytoin

  decreased tissue binding of some drugs, eg digoxin

Changes in Pharmacokinetics

- Metabolism

  liver metabolism generally unchanged in renal impairment

- Excretion

  50% reduction in GFR suggests a 50% decline in excretory renal function.

  Assume that non-renal clearance will remain unaltered in renal disease

Altered Elimination in renal impairment

- Highly significant for drugs (or metabolites) where renal function is the main organ of clearance
  e.g. penicillins, cephalosporins, ciprofloxacin

- Significant where drugs have narrow therapeutic index
  e.g. aminoglycosides, vancomycin digoxin, ciclosporin

- May need to be careful even with “safe” drugs
  e.g. benzylpenicillin

- Need to be aware of accumulation of active metabolites
  e.g. morphine and midazolam, allopurinol, pethidine,

Case Study - SS

- 27 yrs old
- Male
- PC – oedema
- HPC – increasing oedema to scrotum and abdomen over last month
- SOB on walking
- Weight gain 12kg in 3 months

SS

- PMHx: type 1 DM for 22 years
- PMHx: asthma

- Diabetic retinopathy – recent laser therapy

Hospital history

- Attended clinic 3/12 ago
- Hypertensive
- DNA: - last 3 appointments

Referral from GP to Clinic

- “he’s very unwell can you see him”

- BP 208/105 mmHg
- Hb 8.5 g/dl
- SrCr 824micromols/l

Drug history

- Novorapid
- Insulin glargine
- Symbicort 200/6 inhaler
- Salbutamol inhaler

Questions:

- What further information do you want/ need?
- What test results and investigations do we need?
- How should we manage him initially? Anything urgent?
- Suggest a management plan for anaemia
- Suggest a management plan for renal bone disease
- Suggest a management plan for hypertension

Tests

- Full set of U & Es
- Full autoimmune panel

  (proteinuria & haematuria not common with diabetic neuropathy)
- Renal ultrasound / CT scan
- Renal biopsy

Test results

- Na 141
- K+ 6.4
- HCO3 18.4
- Urea 24.1
- Cr 515
- PO4 1.9
- Cholesterol: 5.9
- Alb 24

- Hb 86
- MCV 84
- Ferritin 72
- Iron Sats 18.1%
- APTT 27.6
- PT 12.6
- Dipstick +++blood
- Dipstick +++protein
- Kidneys right=left=11.4cm

Test results

- Na 141
- K+ 6.4
- HCO3 18.4
- Urea 24.1
- Cr 915
- Ca_{corr} 2.09
- PO4 1.9
- Cholesterol: 5.9
- Albumen 24
- Hb 76
- MCV 84
- Ferritin 72
- Iron Sats 18.1%
- APTT 27.6
- PT 12.6
- Dipstick +++blood
- Dipstick +++protein
- Kidneys right=left=11.4cm

Urgent points

- Hyperkalaemia – K 6.4. Risk of cardiac arrhythmia or cardiac arrest
- Treat with Insulin/Dextrose or K-Binder (Lokelma/Patiromer) or Haemodialysis

- Metabolic Acidosis – HCO3 18.4
- Treat with Sodium Bicarbonate PO or IV or Haemodialysis

Anaemia

- Caused by inability of failing kidneys to produce erythropoietin.

- SS – Hb 76
- Treat with IV Iron (why not oral iron?)
- Start ESA (epoetin, darbepoetin, Mircera)
- If symptomatic, consider urgent transfusion

Renal bone disease

- Vitamin D analogue – Alfacalcidol or Calcitriol

- Phospate binders – taken with meals
  - Calcium Carbonate / Acetate
  - Magnesium Carbonate
  - Lanthanum Carbonate
  - Sevelamer Carbonate

Hypertension

- Often need multiple agents
  - β-blockers
  - α-blockers
  - Ca antagonists
  - ACEI / ARB
  - Loop diuretics

- Can usually reduce the medication as the patient becomes euvolaemic.

Case Study - PG

- Mr. PG is a 76-year-old male with Stage 3 chronic kidney disease and hypertension. He has presented to the Emergency department after being unwell with diarrhoea and vomiting for more than 24 hours. He had a urinary tract infection diagnosed by his GP 2 days ago.
- Medication on presentation:
- Bendroflumethiazide 2.5mg OM
- Ramipril 10mg ON
- Simvastatin 40mg ON
- Trimethoprim 200mg BD for 3 days – for the UTI

The Questions

- **Q1.** What are Mr PG's risk factors for AKI?
- **Q2.** How would you manage this case?
- **Q3.** What advice might you give to Mr. PG to reduce his risk of developing AKI in the future?

Case Study - JD

- Known paranoid schizophrenic. 31 years old
- Admitted on the 26th Dec with neuroleptic malignant syndrome secondary to his zuclopenthixol depot
  Admitted to ICU from Resus. Peri-arrest. I+V in resus for severe agitation
- His zuclopenthixol depot dosing schedule was 4-weekly from August, but uptitrated to 2-weekly in November.
  His last dose was 17/12/24. The elimination half-life of zuclopenthixol is 19-29 days.
- Severe rhabdomyolysis (CK 827,000) resulting in a severe AKI3 initially rendering him anuric.

JD

- Meds on admission:

  Atorvastatin 20mg OD

  Zuclopenthixol 200mg every 2 weeks IM

Any thoughts?

JD

- Meds on admission:
  Atorvastatin 20mg OD
  Zuclopenthixol 200mg every 2 weeks IM

Any thoughts?

- Stop Atorvastatin, given CK > 800,000
- Stop Zuclopenthixol
- Ensure absolutely no antipsychotics, haloperidol, metoclopramide, dopaminergic antagonists are given

JD

- Started on CVVH
- Initially Rx Piperacillin/Tazobactam 4.5g QDS
- 2 weeks later, developed sepsis -> Rx Meropenem 1g TDS

- Q1. Are you happy with these doses?
- Q2. What would you do if he was transferred to the ward on these antibiotics and switched to intermittent HDx?
- Q3. What would you do if he needed to be discharged on Meropenem?

Meropenem

DOSE IN NORMAL RENAL FUNCTION	500 mg – 1 g every 8 hours Up to 2 g every 8 hours in cystic fibrosis and meningitis
PHARMACOKINETICS	
Molecular weight (daltons)	437.5
% Protein binding	2
% Excreted unchanged in urine	70
Volume of distribution (L/Kg)	0.35
Half-life – normal/ESRF (hrs)	1 / 6 – 13.7
METABOLISM	Meropenem is more stable to renal dehydropeptidase 1 than imipenem but undergoes some renal metabolism, and is mainly excreted in the urine by tubular secretion and glomerular filtration. It is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.
DOSE IN RENAL IMPAIRMENT	
GFR (mL/min)	
26–50	500 mg – 2 g every 12 hours.
10–25	500 mg – 1 g every 12 hours or 500 mg every 8 hours.
<10	500 mg – 1 g every 24 hours.
DOSE IN PATIENTS UNDERGOING RENAL REPLACEMENT THERAPIES	
APD/CAPD	Dialysed. Dose as in GFR<10 mL/min.
HD	Dialysed. Dose as in GFR<10 mL/min or 1–2 g post dialysis.
HDF / High flux	Dialysed. Dose as in GFR<10 mL/min.
CAV/VVH/HD	Dialysed. 0.5–1 g every 8 hours or 1 g every 12 hours.
CVVHDF	1 g every 12 hours.

Amikacin

DOSE IN NORMAL RENAL FUNCTION	15 mg/Kg/day in 1-2 divided doses In severe infections increased to 22.5mg/Kg /day
PHARMACOKINETICS	
Molecular weight (daltons)	585.6
% Protein binding	<20
% Excreted unchanged in urine	94–98
Volume of distribution (L/Kg)	0.22–0.29
Half-life – normal/ESRF (hrs)	2–3 / 17–150
METABOLISM	Amikacin is excreted in the urine unchanged, primarily by glomerular filtration.
DOSE IN RENAL IMPAIRMENT	
GFR (mL/min)	
20–50	5–6 mg/Kg every 12 hours or as per local protocol.
10–20	3–4 mg/Kg every 24 hours or as per local protocol.
<10	2 mg/Kg every 24–48 hours or as per local protocol.
DOSE IN PATIENTS UNDERGOING RENAL REPLACEMENT THERAPIES	
APD/CAPD	Dialysed. Dose as in GFR<10 mL/min.
HD	Dialysed. Give 5 mg/Kg after dialysis.
HDF / High flux	Dialysed. Give 5 mg/Kg after dialysis.
CAV/VVHD	Dialysed. 7.5 mg/kg every 24 hours and monitor levels.[1] See other information.

Piperacillin/Tazobactam

DOSE IN NORMAL RENAL FUNCTION	4.5 g every 6 hours
PHARMACOKINETICS	
Molecular weight (daltons)	Piperacillin: 539.5, Tazobactam: 322.3 (as sodium)
% Protein binding	Piperacillin: 20–30, Tazobactam: 20–30
% Excreted unchanged in urine	Piperacillin: 60–80, Tazobactam: 80
Volume of distribution (L/Kg)	Piperacillin: 0.18–0.3, Tazobactam: 0.18–0.33[1]
Half-life – normal/ESRF (hrs)	Piperacillin: 1 / 4–6, Tazobactam: 1 / 7
METABOLSIM	Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.
DOSE IN RENAL IMPAIRMENT	
GFR (mL/min)	
40–50	Dose as in normal renal function.
20–40	4.5 g every 8 hours.
<20	4.5 g every 12 hours.
DOSE IN PATIENTS UNDERGOING RENAL REPLACEMENT THERAPIES	
APD/CAPD	Not dialysed. Dose as in GFR<20 mL/minute.
HD	Dialysed. Dose as in GFR<20 mL/minute.
HDF / High flux	Dialysed. Dose as in GFR<20 mL/minute.
CAV/VVH	Dialysed. Dose as in GFR=20–40 mL/minute, or 2.25 g every 6 hours,[1] or 4.5 g every 12 hours.
CVVHD/HDF	Dialysed: Dose as in GFR=20–40 mL/minute or 2.25–3.375 g every 6 hours[1].

Antibiotics on 3 x/week HDx

	t ½ normal renal function (hours)	t ½ ESRD (hours)	Dose on Intermittent HDx (3 x/week)
Vancomycin	6	120 - 216	750mg – 1.25g
Gentamicin	2-3	20	2 mg/kg
Amikacin	2-3	17 - 150	5 mg/kg
Meropenem	1	6 - 14	2g
Ertapenem	1	14	1g
Ceftazidime	2	13 - 25	2g
Cefazolin	1.8	40 - 70	2g/2g/3g
Temocillin	3 - 5	28	2g /2g/3g
Teicoplanin	150	62–230	Max 1000mg

Case Study GF

- GF is a 70-yr old lady admitted to the orthopaedic ward for a total hip replacement.

- Weight = 55kg
- Height = 162cm

Medication

On admission:-

- Bendroflumethiazide 2.5mg OD
- Aspirin 75mg OD
- Ramipril 5mg OD
- Simvastatin 40mg OD
- Metformin 500mg BD

Post Op Analgesia:-

- Paracetamol 1g QDS prn
- Diclofenac 50mg TDS prn
- Oramorph 10mg 4-hourly prn

Thromboprophylaxis:- Enoxaparin 40mg OD

Diabetes:- Sliding scale insulin whilst nil by mouth

Day 2 Post-Op

- GF develops a temperature
- She has a raised CRP and WCC
- Feels unwell
- On examination, crackles on her lungs are heard.
- Diagnosis of hospital-acquired pneumonia.

In accordance with hospital protocol, Rx

- Gentamicin 5mg/kg OD IV
- Co-amoxiclav 1.2g TDS IV

Day 4 Post-Op

- The nurse attending to GF notes that her urine output has decreased.
- She mentions this to the FY1.

- PANIC !!!

U & Es

Day	Creatinine (µmol/L)	Urea (mmol/L)	K+ (mmol/L)	Na+ (mmol/L)	Trough Gentamicin (mg/L)	Urine Output (ml/hr)
Pre-op Clinic	90	5.3	3.5	142		
3	90	5.4	3.2	140	1	
4	140	14	4.9	144		
5	362	29	5.7	141		20 (for 16 hours)

The Questions

- **Q 1.** What are the factors that have contributed to Gillian developing AKI. What stage of AKI does she currently have? At what point should Gillian's risk factors for AKI have been assessed?
- **Q2.** Which drugs should be stopped at this point? Are there any other drugs you would consider withholding?
- **Q3.** Which drugs should have doses adjusted?
- **Q4.** What pain relief would be appropriate?
- **Q5.** Comment on the antibiotic regime
- **Q6.** What are the issues around her post-operative fluid management?

What went wrong??

- GF became dehydrated and this was not managed soon enough
- She was Rx a nephrotoxic antibiotic (gentamicin)
- She was already taking a diuretic & an ACEI which can potentially compromise renal function especially if the patient is hypovolaemic.

- The combination led to her developing AKI stage 3

  Urine output = AKI stage 2

  Creatinine = AKI stage 3

Which drugs should be stopped at this point?

- Bendroflumethiazide & Ramipril should be withheld
- If she had started eating and had restarted her Metformin, that should be withheld.
- Simvastatin - Withhold or not?
- Gentamicin & Diclofenac should be stopped.

Which drugs should have doses adjusted?

- The dose of enoxaparin should be decreased to 20mg OD.
- The dose of Oramorph® should be reduced to 2.5-5mg & the dosage interval increased to 8-hrly. Morphine is metabolized to the 3- and 6-glucuronides, which are 6 times more potent than morphine, and are cleared via the kidneys. In severe renal impairment, metabolites accumulate → respiratory depression.
- Or switch to an alternative opiate without active metabolites, eg. oxycodone, hydromorphone, fentanyl.
- Monitor blood glucose ⇒ in severely impaired renal function, less insulin is required.

How about her Antibiotics?

- Gentamicin is nephrotoxic & should be avoided in all stages of AKI if possible.
- 1st level not toxic but no further levels done as renal function deteriorated.
- If gentamicin is the only choice of Ab available, ⇓ dose & ⇑ dosing interval.

  Monitor levels!!
- Co-amoxiclav - ⇓ dose to 1.2g BD
- Remember to re-calculate renal function EVERY day

How about her post-op fluid management?

- Her U&E's & reduced urine output suggest that GF became dehydrated around Day 3-4.
- This was not managed (encouraging oral fluids or Rx-ing IV fluids)
- Dehydration + Nephrotoxic drugs = AKI
- Now need to assess volume status.
- Likely hypovolaemic $\Rightarrow$ fluid challenge
- ? High-dose furosemide?

Assuming she gets better?

- Continue to monitor renal function and adjust medication doses accordingly.

- As her renal function returns to normal, remember to re-instate her medications (ramipril, bendroflumethiazide, metformin)

- Discuss “drug holidays” with her, eg, in case of vomiting/diarrhoea.

Pain management

Pain management in patients with kidney disease often goes something like this:

- NSAIDs are evil,
- Paracetamol hardly works,
- Opioids are dangerous,
- All the rest (tramadol, gabapentinoids, antidepressants, etc) are messy.

NSAIDs

NSAIDs and nephrotoxicity

- Reduce renal perfusion via effects on renal prostaglandins E2 & I2.
- Notorious for triggering interstitial and glomerular reactions in the kidney, manifesting as interstitial nephritis and nephrotic syndrome.
- Patients at risk are those with existing CKD (renovascular disease, volume depletion, nephrotic syndrome, ACEIs/ARBs,)
- Prostaglandin-mediated afferent arteriolar vasodilation is a must in these individuals; without it, the kidney vascular supply is inadequate

Is the drug nephrotoxic?

- NSAIDs and nephrotoxicity
  - Third of drug induced AKIs have link to NSAID
  - Degree of toxicity accepted as being linked to potency of individual NSAIDs
  - Less clear on any link to dose of the NSAID
  - No reduction in risk with COX-II inhibitors
- But NSAIDs potentially useful in CKD patients?
  - Gout, bone pain, pericarditis

Opioid analgesics

- Look at metabolism
- Are metabolites active?
- How are they excreted?
- Morphine vs Oxycodone
- Also useful: Fentanyl, Buprenorphine
- Start with very low doses & extended intervals between doses

Neuropathic pain

- Gabapentin, Pregabalin, Amitriptyline all useful
- Start low and increase according to response vs side effects

Any Questions???