Medicines and renal impairment

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Why should pharmacists be interested in patients with renal impairment?

Why should pharmacists be interested in patients with renal impairment?

- Some drugs are excreted renally (could accumulate and cause harm)
- Some drugs are harmful to the kidneys
- Patients with Chronic Kidney Disease will need medicines to treat symptoms (and are probably already on lots of medicines for co-morbidities)
- And may need dialysis or a transplant
- Want to improve patient's quality of life and longevity
- Dialysis and Transplants are expensive!

Drug use in renal impairment tutorial

Objectives:

- Identify patients at risk of (or who have) renal impairment
- Describe how patients' renal function should be monitored and role of pharmacist
- Classify renal function
- Describe the influence of renal impairment on drug pharmacokinetics
- Identify drugs (and other factors) commonly associated with acute and chronic renal impairment
- Describe the treatment of the complications of chronic renal failure including transplantation

Terminology

- Renal Impairment is a more favoured term for renal failure
- Chronic renal failure is now called Chronic Kidney Disease (CKD)
- Acute renal failure is now called Acute Kidney Injury (AKI)

“a significant % of patients with renal impairment are admitted to hospital on inappropriately high doses of drugs, with a high fractional renal excretion and low therapeutic index”

(Pillans et al 2003)

Identifying patients at risk of chronic renal impairment

- Elderly patients– Glomerular Filtration Rate (GFR) may be significantly reduced despite serum creatinine being in the normal range due to ↓ muscle mass and protein intake
- Patients with diabetes
- Patients with Congestive Heart Failure, high blood pressure, high cholesterol
- Smokers
- Obese patients
- Family history of kidney disease
- Transplant patients

Consideration

Multiple co-morbidities & complex frequently changing medication regimens

=

unwanted effects drug interactions and confusion

CKD of unknown aetiology (CKDu)

- CKD usually caused by hypertension, diabetes mellitus and glomerulonephritis
- Sri Lanka has patients presenting with CKD without any of these underlying diseases
- Increasingly common cause of death
- Endemics of CKDu in other low and middle income countries, share features - affect rural populations, men more than woman, countries have a hot climate.
- Being investigated
- Maybe linked to exposure to pesticides, fertilisers, heavy metals, water hardness and infections.

Acute Kidney Injury (AKI)

- Will cover in more detail later (not a physical injury but an assault on the kidneys!)

- In Sri Lanka, like other less developed countries, AKI, is more common than in developed countries
- The AKI seen is mainly due to snake bites (envenomation) and poisoning, sometimes deliberately, by chemicals and plants

Describe how patients' renal function should be monitored and the role of the pharmacist

How to monitor patients' renal function

Review:

- **Patient's clinical condition:**
  - Observations e.g. PR, BP, Oxygen sats
  - Fluid status
  - Signs of oedema
- **Biochemical Data**
  - Creatinine
  - Urea
  - Albumin
  - Iron studies
  - Vitamin D studies
  - Phosphate
  - Calcium

Why do we monitor renal function

- To ensure appropriate drug dosages for renal function e.g. antibiotics
- To ensure drug efficacy e.g.
  - Diuretics and weight
  - Anti-hypertensives and blood pressure monitoring
- To avoid further deterioration of renal function e.g. with nephrotoxic drugs
- To reduce toxicity of drugs especially in drugs with narrow therapeutic index
- To reduce incidence of side effects

Role of the pharmacist

What does the pharmacist need to review?

Role of pharmacist

What does the pharmacist need to review?

- What level of renal function does the patient have?
- Does patient have acute or chronic renal impairment
- Are they on dialysis? If so what? (Haemo/CAPD/CVVHD)
- Are the doses charted correctly?
- Get a good Med Hx – remember EPO/iron (Dialysis charts)
- Review timing of medication in relation to dialysis
- Review timing of medication for efficacy
- Is patient switching from one form of dialysis to another?
- Is the patient commencing dialysis?
- Check relevant bloods (remember microbiology)

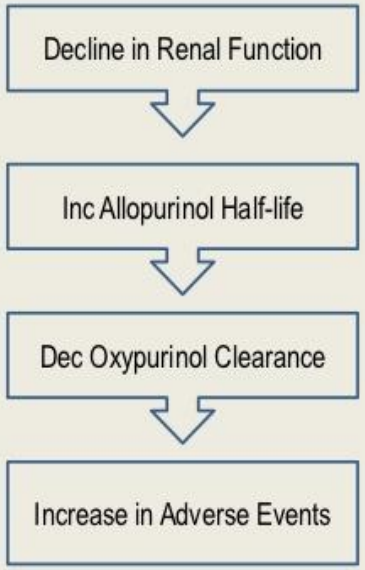
Signs and symptoms of renal abnormalities

Basic Function	Sign	Symptom
Fluid Balance	Oedema, raised JVP	Breathlessness
Electrolytes K, Na, PO_4, Ca regulation	Abnormal ECG eg Absent P waves, Broad QRS complex, Peaked T waves	Probably none
EPO (erythropoietin) production	Pallor	Fatigue
Vitamin D	Osteomalacia	Bone pain
Excretion	Raised urea concentration in blood	Pruritis Nausea & Vomiting
Acid-base balance	Low pH and bicarbonate	Deep & rapid respiration

Dosing in renal impairment

What dose should I use??

Allopurinol in Renal Disease



Maximum Recommended Allopurinol Dose Based on Crea Clearance

Crea Cl (ml/min)	Dose
0	100 mg q 3 days
10	100 mg q 2 days
20	100 mg/day
40	150 mg/day
60	200 mg/day
80	250 mg/day
100	300 mg/day
120	350 mg/day

Hande KR, et al. Am J Med, 1984

Classify renal function

Table 1. **Definition of CKD Stages Based on GFR***

CKD Stage	Definition
1	Kidney damage with GFR ≥90 mL/min/1.73 m^2
2	Kidney damage with GFR of 60–89 mL/min/1.73 m^2
3	GFR of 30–59 mL/min/1.73 m^2
4	GFR of 15–29 mL/min/1.73 m^2
5	GFR <15 mL/min/1.73 m^2, or kidney failure treated by dialysis or transplantation

CKD = chronic kidney disease; GFR = glomerular filtration rate.
* Adapted from reference 3. The Kidney Disease: Improving Global Outcomes Work Group recently updated its definition of CKD progression to include consideration of both GFR and albuminuria stages (2).

Medication Resources – Dosing in Renal Impairment

www.medicines.org.uk

SPC

Augmentin 625mg Tablets

Last Updated on eMC 01-Sep-2015 View changes | GlaxoSmithKline UK Contact details

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

BNF

71

March – September 2016

bnf.org

Renal impairment risk of crystalluria with high doses (particularly during parenteral therapy).

Co-amoxiclav 250/125 tablets or 500/125 tablets: if eGFR 10–30 mL/minute/1.73 m^2, one *250/125* strength tablet every 12 hours *or* one *500/125* strength tablet every 12 hours; if eGFR less than 10 mL/minute/1.73 m^2, one *250/125* strength tablet every 24 hours *or* one *500/125* strength tablet every 24 hours.

Co-amoxiclav 400/57 suspension: avoid if eGFR less than 30 mL/minute/1.73 m^2.

Co-amoxiclav injection (expressed as co-amoxiclav): if eGFR 10–30 mL/minute/1.73 m^2, 1.2 g initially, then 600 mg every 12 hours; if eGFR less than 10 mL/minute/1.73 m^2, 1.2 g initially, then 600 mg every 24 hours

GFR and Creatinine Clearance

- Glomerular filtration rate (GFR) mLs/min
- Creatinine Clearance (CrCl) - mLs/min - calculate
- eGFR – mLs/min/1.73m^2 - reported by the laboratory

Based on

- Modified Diet in Renal Disease (MDRD) from the USA

Equation was developed in patients with CKD considered more accurate

$$eGFR = 170 \times (P_{Cr})^{-0.999} \times (age)^{-0.176} \times (0.762 \text{ if female}) \times (SUN)^{-0.170} \times (Alb)^{+0.318}$$

GFR by 24 hour urine collection

- Urine is collected over 24 hours (or 12 hours)
- Blood sample taken at the midpoint of the collection period and creatinine measured

$$\text{GFR (mls/min)} = \frac{UV}{P}$$

Where:

U = urine creatinine concentration (micromol/L)

V = volume of urine collected (ml)

P = serum creatinine concentration (micromol/L)

Predicting CrCl using serum creatinine concentrations

Cockcroft and Gault Equation

$$CrCl = \frac{F\,(140 - \text{age [yrs]}) \times \text{Ideal Body Wt (kg)}}{\text{serum creatinine } (\mu\text{mol/L})}$$

Where:

F = 1.23 for males and 1.04 for females

OR

$$CrCl = \frac{F\,(140 - \text{age [yrs]}) \times \text{Ideal Body Wt (kg)}}{0.815 \times \text{serum creatinine } (\mu\text{mol/L})}$$

F=1 for men and 0.85 for women

Ideal Body Weight

IBW = 50 kg + 0.9kg/cm >152cm (male)

IBW = 45.5 kg + 0.9kg/cm >152cm (female)

HEIGHT	WEIGHT	KGS	HEIGHT	WEIGHT	LBS
(CMS)	MEN	WOMEN	INCHES	MEN	WOMEN
147	-	45-59	58	-	100-131
150	-	45-60	59	-	101-134
152	-	46-62	60	-	103-137
155	55-66	47-63	61	123-145	105-140
157	56-67	49-65	62	125-148	108-144
160	57-68	50-67	63	127-151	111-148
162	58-70	51-69	64	129-155	114-152
165	59-72	53-70	65	131-159	117-156
167	60-74	54-72	66	133-163	120-160
170	61-75	55-74	67	135-167	123-164
172	62-77	57-75	68	137-171	126-167
175	63-79	58-77	69	139-175	129-170
177	64-81	60-78	70	141-179	132-173
180	65-83	61-80	71	144-183	135-176
182	66-85	-	72	147-187	-
185	68-87	-	73	150-192	-
187	69-89	-	74	153-197	-
190	71-91	-	75	157-202	-

Serum Creatinine (40-120 µmol/L)

Increased by:

- Large muscle mass, high meat intake
- Drugs- Interfere with analysis e.g. methyldopa, levodopa, dexamethasone, cephalosporins
- Drugs - Inhibit tubular secretion e.g. cimetidine, trimethoprim, aspirin
- Ketoacidosis

- **Decreased by:**
- Reduced muscle mass (elderly)
- Severe renal disease (increased secretion)
- Cachexia / starvation
- Immobility
- Pregnancy

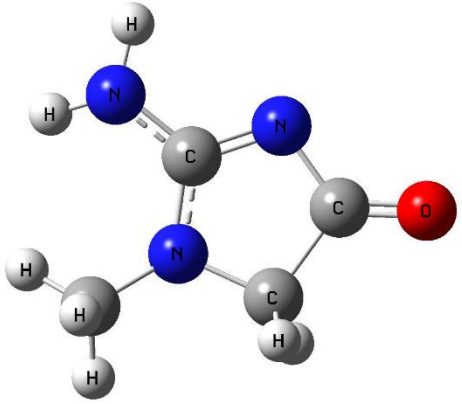
Limitations of Cockcroft-Gault equation

1. Accurate only when renal function is stable
2. Inaccurate when serum creatinine values > 450 μmol/L
3. Becomes inaccurate when GFR < 20 ml/min
4. Not valid in pregnancy

Limitations of creatinine as a marker:

1. Retrospective indicator of renal function
2. May only increase when < 50% of nephrons not functioning

Misleading results using eGFR (MDRD and CKD-EPI)



- Acute changes in renal function
- Dialysis
- Extremes of body size
- <18 years of age
- Severe liver disease
- Dietary intake e.g. vegetarian diet, high protein diet
- Drugs interacting with creatinine excretion e.g. trimethoprim

- NB equation uses GFR/1.73m ^{2} Need to adjust for BSA

What is used in Sri Lanka

- CKD/EPI Creatinine 2009 equation
- eGFR is given in ml/min/1.73 m^2
- mg/dL

2009 CKD-EPI creatinine (Levey et al[16])

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

If female: $\kappa = 0.7$, $\alpha = -0.329$

If male: $\kappa = 0.9$, $\alpha = -0.411$

2012 CKD-EPI cystatin C (Inker et al[20])

$$eGFR = 133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

2012 CKD-EPI creatinine–cystatin C (Inker et al[20])

$$eGFR = 135 \times \min(SCr/\kappa, 1)^{-\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age} [\times 0.969 \text{ if female}] [\times 1.08 \text{ if black}]$$

If female: $\kappa = 0.7$, $\alpha = -0.248$

If male: $\kappa = 0.9$, $\alpha = -0.207$

Calculating a CrCl usingCockcroft-Gault

Using Cockcroft and Gault Equation:

$$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{Ideal body weight in kg}}{\text{Serum creatinine in micromol/L}}$$

For males multiply by 1.23

For females multiply by 1.04

Calculating a CrCl using Cockcroft-Gault for Mr JB

Mr JB is a 75 year old gentleman with history of NIDDM and hypertension.

Ideal body weight = 80 kg

Serum creatinine = 400 micromol/L,

Using Cockcroft and Gault Equation:

$$GFR = \frac{(140 - \text{age}) \times \text{IBW in kg}}{\text{Serum creatinine in micromol/L}}$$

For males multiply by 1.23

For females multiply by 1.04

Calculating a CrCl using Cockcroft-Gault for Mr JB

Mr JB is a 75 year old gentleman with history of NIDDM and hypertension.

Ideal body weight = 80 kg

Serum creatinine = 400 micromol/L,

Using Cockcroft and Gault Equation:

$$GFR = \frac{(140 - 75) \times 80}{400} \times 1.23$$

= 16 ml/min/1.73m^2 (CKD Stage IV)

Dosage Adjustment

For Mr JB, what dose of:

1. Ciprofloxacin would you recommend?
2. Would you recommend Metformin as a treatment for his NIDDM?

Dosage Adjustment

For Mr JB, what dose of:

1. Ciprofloxacin would you recommend?
   - 250-500mg every 24 hours (BNF)
   - 50-100% dose every 12hours (PAH)
   - Accumulation can cause seizures

2. Would you recommend Metformin for NIDDM?
   - Avoid if eGFR less than 30 mL/minute/1.73m^2 (BNF)
   - Avoid if eGFR is less than 30mL/minute/1.73m^2(PAH)
   - Accumulation can cause lactic acidosis

Other biochemical abnormalities seen in renal impairment

Serum Urea (BUN – blood urea nitrogen) (7 to 20 mg/dL or 2.5 – 7.5 mmol/Litre)

Limitations as a marker:

It varies with the dietary protein intake

Reabsorbed by the tubules

Reabsorption varies with urine flow. Its clearance is independent of GFR at low urine flow rates

Factors increasing serum urea

High protein diet

Hyper-catabolic conditions e.g. severe infection, burns, hyperthyroidism

Gastrointestinal bleeding

Muscle injury

Drugs e.g. Glucocorticoids (with catabolism) Tetracycline

Hypovolaemia

Factors decreasing serum urea Malnutrition, liver disease, sickle cell anaemia

Other biochemical abnormalities seen in renal impairment

Raised Serum **Potassium** (3.5 to 5 mmol/L)

When GFR < 5 ml/min – hyperkalaemia develops

When serum potassium > 7 mmol/L – life threatening

Raised Serum **Phosphate** (0.8 to 1.2 mmol/L)

Chronic Renal Failure leads to hyperphosphataemia

Decreased Serum **Calcium** (2.2 to 2.6 mmol/L)

Linked to vitamin D production

Patients with CRF are typically hypocalcaemic

Describe the influence of renal failure on drug pharmacokinetics

- Absorption can be affected by nausea and vomiting, and bowel oedema
- Hypoalbuminaemia -↓protein binding ↑free drug levels -can cause drug accumulation
- Dehydration - ↑levels of water soluble drugs
- Increased bioavailability of drugs showing first pass metabolism when the function of the drug metabolising enzymes is affected (eg morphine)
- Reduced clearance increases half life and volume of distribution
- Reduced drug elimination can lead to accumulation of some drugs or metabolites -need to adjust dose to avoid accumulation and toxicity

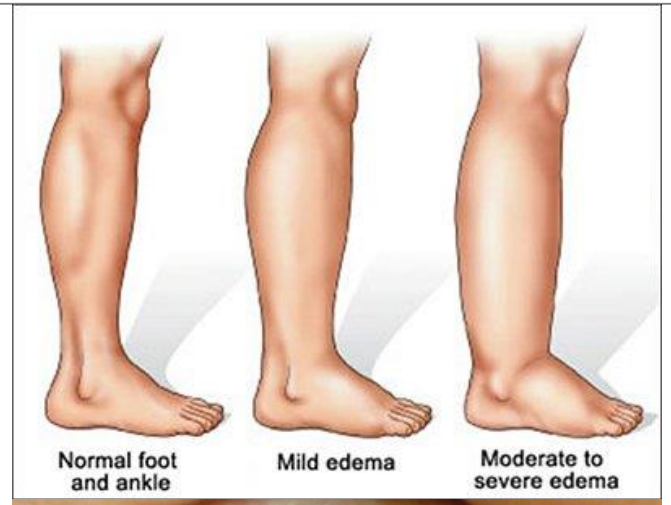
Some dosing principles

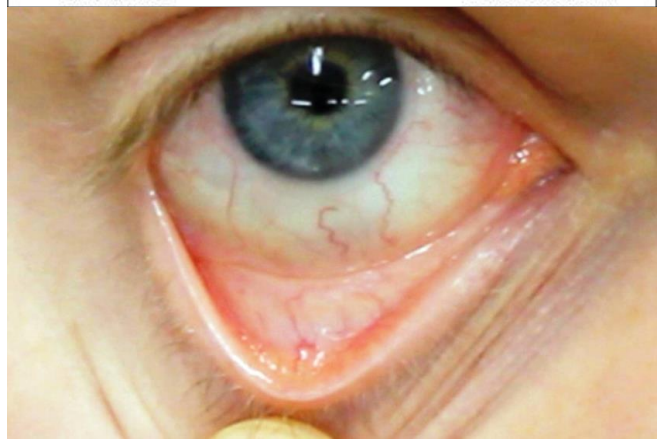
- Drug dosing is complicated so clinical judgement is important
- Patient response must be constantly re-evaluated
- GFR using MDRD or CKD/EPI is probably the most accurate but still only an estimate
- Correct for BSA when patient is either very small or big
- Can be variation in results between CrCl and GFR - care with drugs with narrow therapeutic index

Describe treatment of complications of chronic renal impairment

Complications:

- Hypertension
- Fluid retention
- Electrolyte control
  - Potassium
  - Calcium & Phosphate
- Anaemia

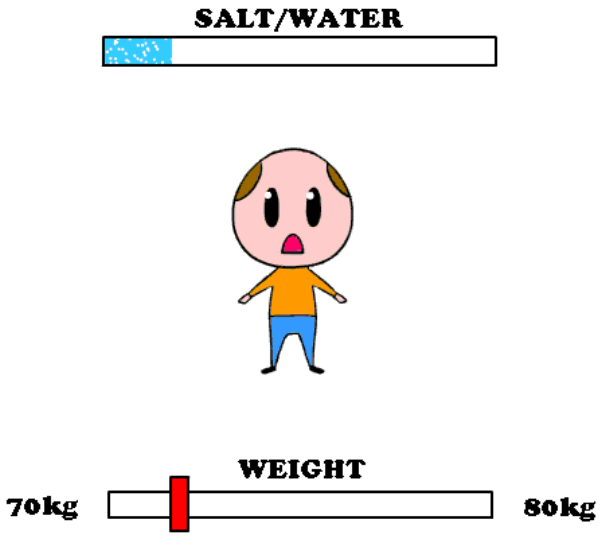




Treatment of Hypertension

- Diuretics (thiazides??)
- Beta blockers
- ACE-I
- AT II receptor antagonists
- Calcium channel blockers
- Alpha adrenergic blockers

Fluid retention



Fluid restriction - 800 to 1000 ml/day

Low salt diets

Loop diuretics

Oral Frusemide (furosemide)

Effective when GFR as low as 5 mL/min

Thiazides – ineffective (as a diuretic) if GFR < 25 mL/min

Metolazone – synergism with loop diuretics – short term therapy

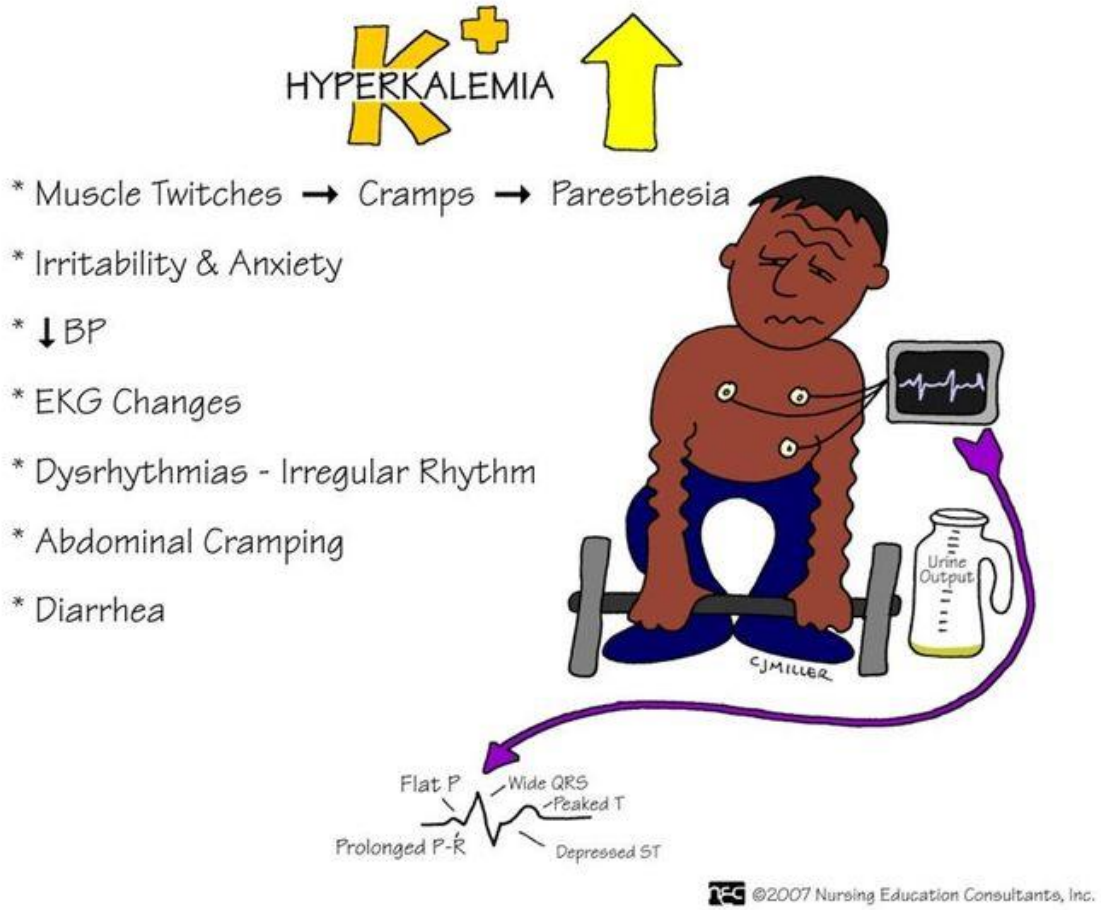
Avoid potassium sparing diuretics - hyperkalaemia

Electrolyte disturbances

Hyperkalaemia (Normal serum concentration 3.5 to 5.0 mmol/L)

- Mainly excreted by active tubular secretion
- Small contribution from aldosterone
- When GFR < 5 mL/min potassium raises rapidly
- Life-threatening condition when > 7 mmol/L – cardiac arrhythmias (peaked T-waves)

Symptoms of hyperkalaemia?



Treatment of hyperkalaemia

- **Diet** -avoid foods high in K eg coffee, nuts, grapes, bananas, spinach

- **Medication**
  - stop K raising drugs where possible e.g. ACEi, ARBs
  - K 5.5 to 6.5mmol/L -Sodium/Calcium polystyrene 15 to 30g
  - K>7mmol/L or severe muscle weakness or ECG changes
    - Ca Gluconate 10% 10mL over 2-3 minutes for cardiac protection
    - IV Glucose 50% 25 to 50mL with short-acting insulin 5 to 10 units over 5-10 minutes (pushes potassium into cells)
    - Nebulised salbutamol 10mg
    - Sodium bicarbonate 8.4% 50mL over 5 to 10 minutes if patients has metabolic acidosis
    - Sodium/Calcium polystyrene 15 to 30g
    - Dialysis

Electrolyte Disturbances

Calcium and phosphate balance

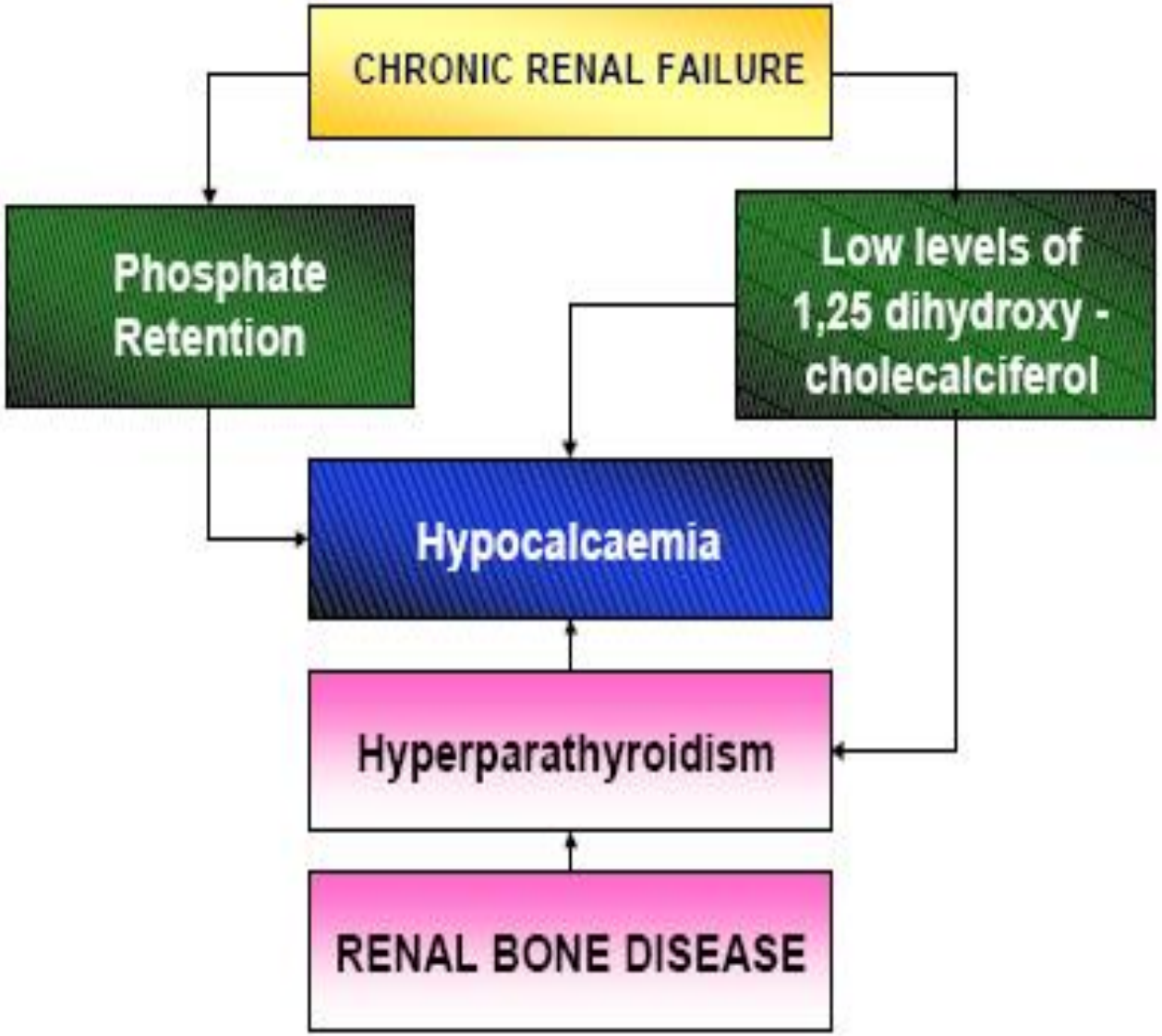
Normal serum values :

- Calcium 2.2 to 2.6 mmol/L
- Phosphate 0.8 to 1.2 mmol/L

Deficiency in vitamin D synthesis – hypocalcaemia

Decreased phosphate clearance – hyperphosphotaemia- deposits on coronary arteries

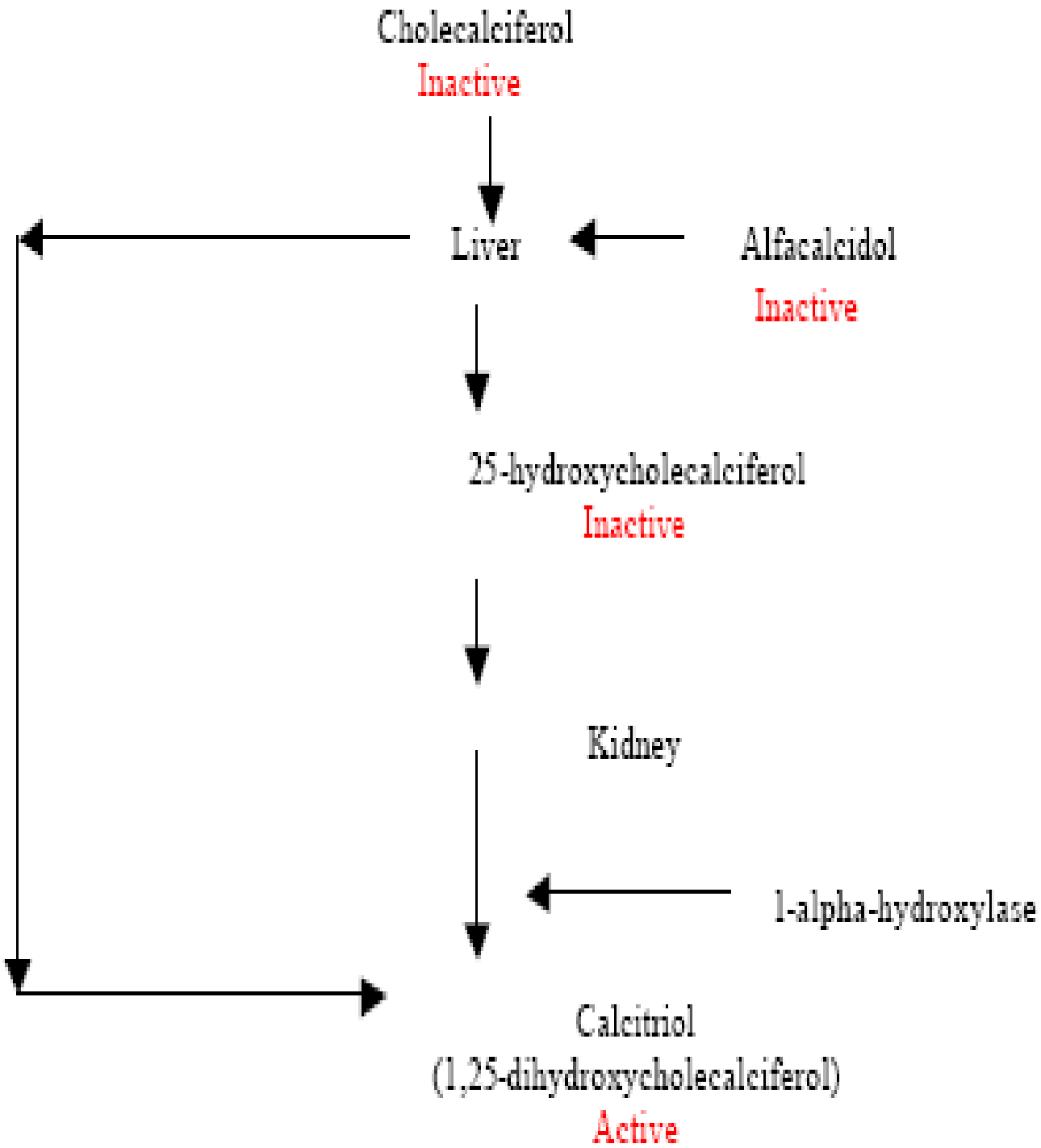
Renal Osteodystrophy



Phosphate Binders

- Calcium-containing
  - Calcium carbonate (Calcichew®) – chewable
  - Calcium acetate (Phosex®) – swallow whole
- Non-calcium containing
  - Sevelamer tablets – swallow whole
  - Lanthanum tablets – chewable
  - Sevelamer/lanthanum powder – dissolve in water
  - Velphoro® (contains iron) – chewable

All must be taken with MEALS/SNACKS


Cholecalciferol
Inactive
Liver
Alfacalcidol
Inactive
25-hydroxycholecalciferol
Inactive
Kidney
1-alpha-hydroxylase
Calcitriol
(1,25-dihydroxycholecalciferol)
Active

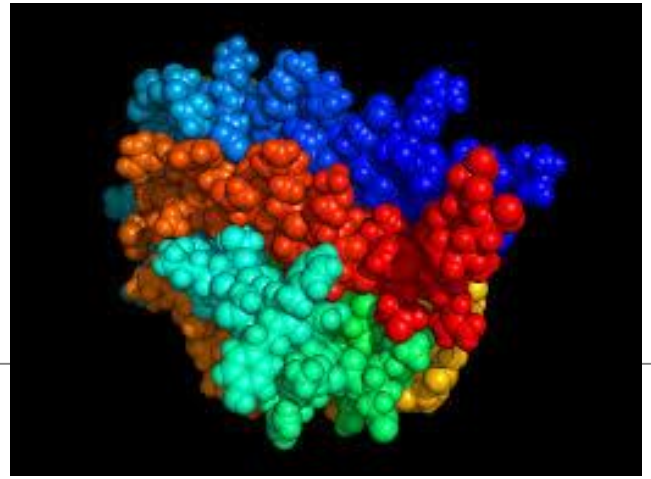
Electrolyte Disturbances

Calcium and phosphate balance

Treatment

- Active Vitamin D alfacalcidol or calcitriol
- Oral phosphate binders – complex phosphate in gut eg Calcium Carbonate or Aluminium Hydroxide
- Dietary control

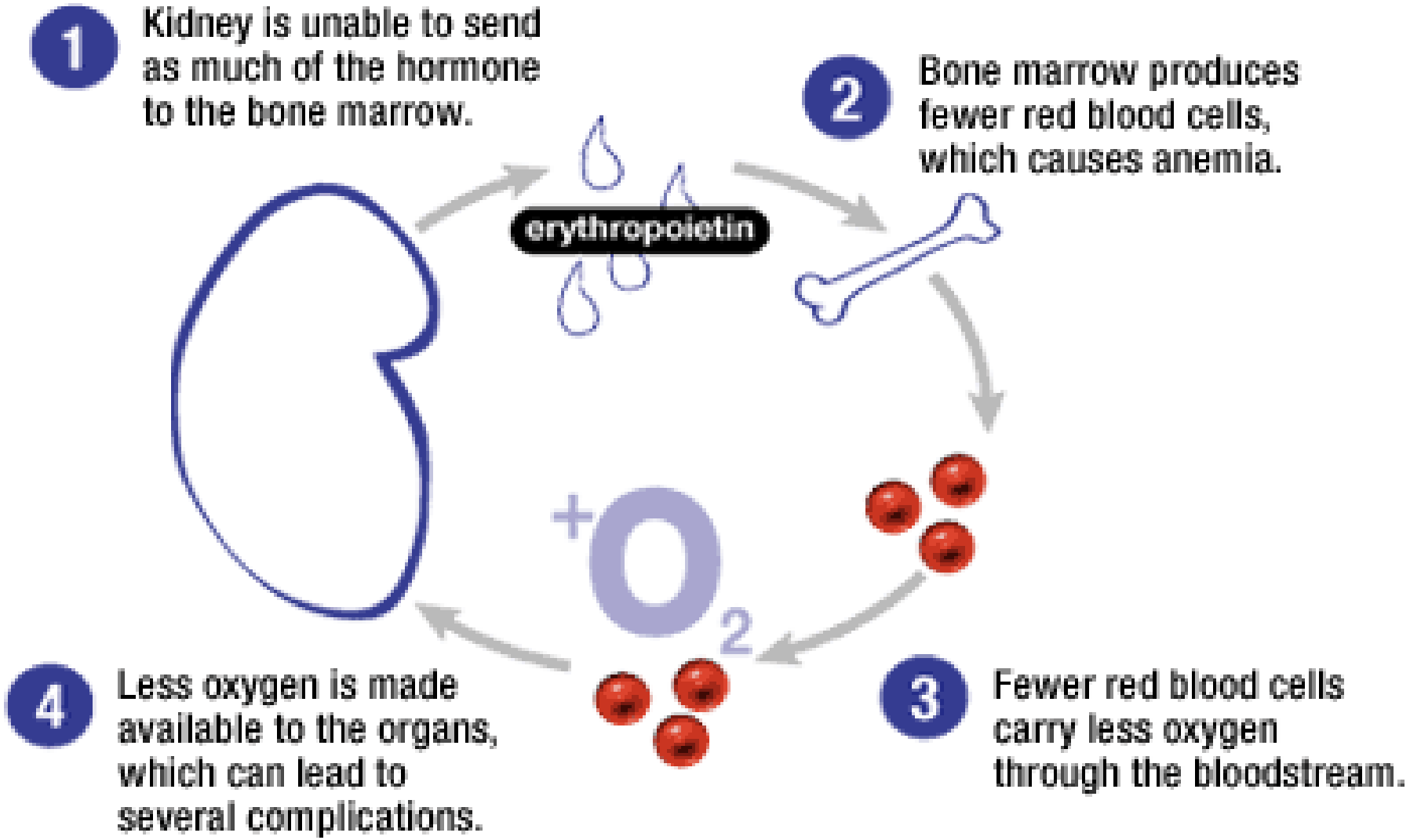
Anaemia - Epoetin



- Recombinant human erythropoietins
- Used to treat symptomatic anaemia associated with erythropoietin deficiency in chronic renal failure to avoid blood transfusions
- Darbepoetin and epoetin are used
- Iron or folate deficiency need to be corrected
- Haemoglobin concentrations higher than 12 g/100mL should be avoided
- Can rarely cause pure red cell aplasia

Reduced Kidney Function

EPO THERAPY WHEN
Hb<11-12g/dl
Hct <33-37%



Chronic Kidney Disease (CKD) – a typical prescription

- Antihypertensive – often needed (ACEI should be considered early)
- Loop diuretic – control fluid balance (especially as disease progresses)
- Phosphate binder – beware of binding of prescribed drugs (care with timing of doses)
- Active Vitamin D – calcitriol or alfacalcidol
- Iron supplementation – according to degree of anaemia
- EPO – according to degree of anaemia
- Ion-exchange resins – to bind potassium (usually end-stage renal impairment only) – avoid potassium sparing drugs and consider the influence of the resin on bioavailability
- Oral hypoglycaemic or insulin – often renal patients are also diabetic

What is a nephrotoxic medicine?

It is a medicine that:

Adversely effects renal function

Either

Through direct toxicity

Or

By impairment of renal function

And an added risk of toxicity during inter-current illness

Identify drugs commonly associated with renal failure

How do they cause renal failure:

Interstitial nephritis	**inflammation in interstitial cells**
Rhabdomyolysis	**breakdown of muscle cells**
Glomerular nephritis	**inflammation of glomerulus**
Acute tubular necrosis	**death of tubular epithelial cells**
Crystal nephropathy	**obstruction caused by intratubular precipitation of crystals**

Identify drugs commonly associated with renal failure

Interstitial nephritis	
Rhabdomyolysis	
Glomerular nephritis	
Acute tubular necrosis	
Crystal nephropathy	

Drugs causing renal impairment

- **Interstitial nephritis:** loop & thiazide diuretics, PPIs, allopurinol, phenytoin, NSAIDs
- **Rhabdomyolysis:** benzodiazepines, statins, cocaine, heroin, ketamine, methadone, methamphetamine
- **Glomerular nephritis:** pamidronate, beta lactams, lithium, gold
- **Acute tubular necrosis:** aminoglycosides, statins, cisplatin, amphotericin, cyclosporine, tacrolimus, sulphonamides, NSAIDs
- **Crystal nephropathy:** Foscarnat, ganciclovir, methotrexate, sulfonamides

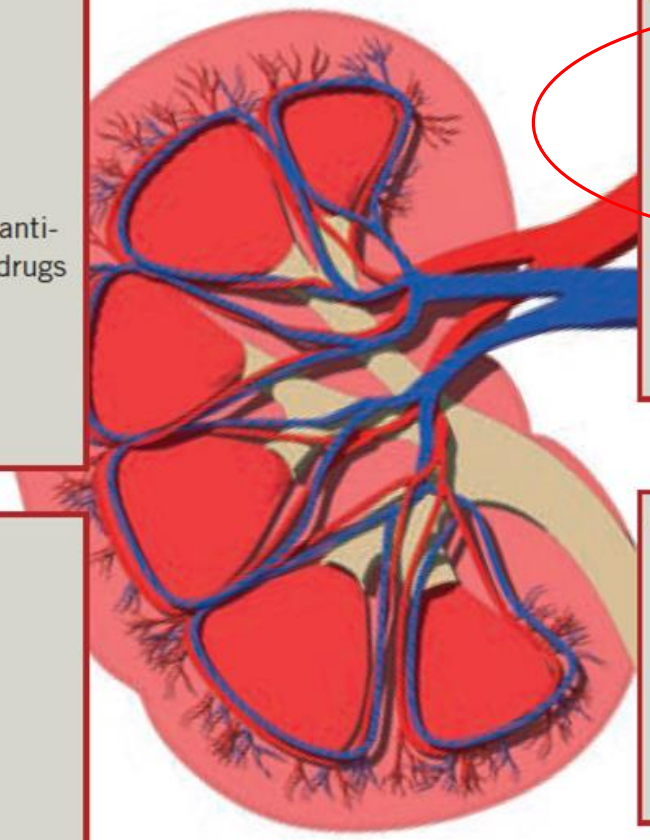
Figure 1: Medicines that can cause acute kidney injury

Intrinsic: acute tubular necrosis

- Aciclovir
- Aminoglycosides
- Amphotericin
- Calcineurin inhibitors
- Cephalosporins
- Cisplatin
- Contrast media
- Ciprofloxacin
- Ethylene glycol
- Foscarnet
- Furosemide
- Gold
- Ifosfamide
- Lithium
- Methotrexate
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Paracetamol
- Rifampicin
- Vancomycin

Intrinsic: acute interstitial nephritis

- Allopurinol
- Aminoglycosides
- Aminosalicylates
- Amlodipine
- Azathioprine
- Beta-lactams
- Captopril
- Carbamazepine
- Diltiazem
- Erythromycin
- Gold
- Interferon
- Isoniazid
- Lithium
- Loop diuretics
- Methyldopa
- Minocycline
- NSAIDs
- Phenobarbital
- Phenytoin
- Proton pump inhibitors
- Pyrazinamide
- Quinolones
- Ranitidine
- Rifampicin
- Sulfonamides
- Thiazide diuretics
- Vancomycin



Pre-renal

- Diuretics
- NSAIDs
- Angiotensin-converting enzyme inhibitors
- Angiotensin-II receptor blockers
- Antihypertensives
- Laxatives (abuse)
- Calcineurin inhibitors (high blood levels)

Post-renal

- Anticoagulants
- Cytotoxic chemotherapy
- Beta-blockers
- Bromocriptine
- Methyldopa
- Methysergide
- Pergolide

Intrinsic: rhabdomyolysis

- Amphotericin
- Barbiturates
- Benzodiazepines
- Colchicine
- Co-trimoxazole
- Fibrates
- Lithium
- Monoamine oxidase inhibitors
- Opioids
- Phenothiazines
- Retinoids
- Theophylline
- Statins

Picture credit: Sebastian Kaulitzki / Dreamstime.com

Acute Kidney Injury (AKI)

- In Sri Lanka, like other less developed countries, AKI, is more common than in developed countries
- The AKI seen is mainly due to:
- Snake bites (envenomation) - Russell's Viper 10-40% chance of developing AKI and is fatal for 1-20%
- Deliberate self-poisoning with paraquat >50% incidence AKI and 40-50% mortality
- Plants rates variable – Gloriosa superba (Flame Lily) – 25% incidence AKI and 6% mortality

Treatment of AKI

- Stop cause
- Rehydrate but need to balance against fluid overload
- Care when re-introducing drugs – need to ensure correct doses
- May go on to develop CKD

(*Note In Western Countries patients who have an AKI often already have CKD, are frequently elderly, with nephro-toxic drugs contributing and may have sepsis)*

Treatments other than medicines
Is the patient on dialysis?

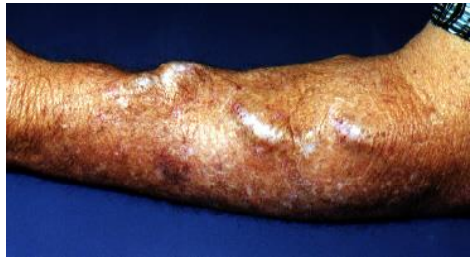
What type of dialysis are they on?

- Haemodialysis
- Continuous Ambulatory Peritoneal Dialysis (CAPD)*
- CVVHD or Haemofiltration (usually in hospitalised patients on intensive care units)

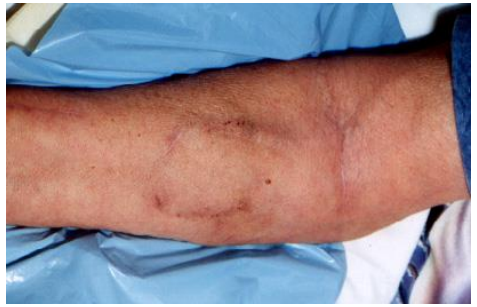
Haemodialysis Access

Access is the term used to describe the way staff “tap” into the patient’s blood stream

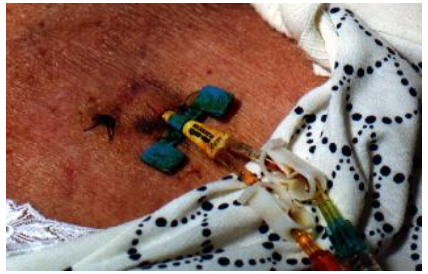
- **Fistula** - the most common access used. Created by joining an artery and vein together under the skin.



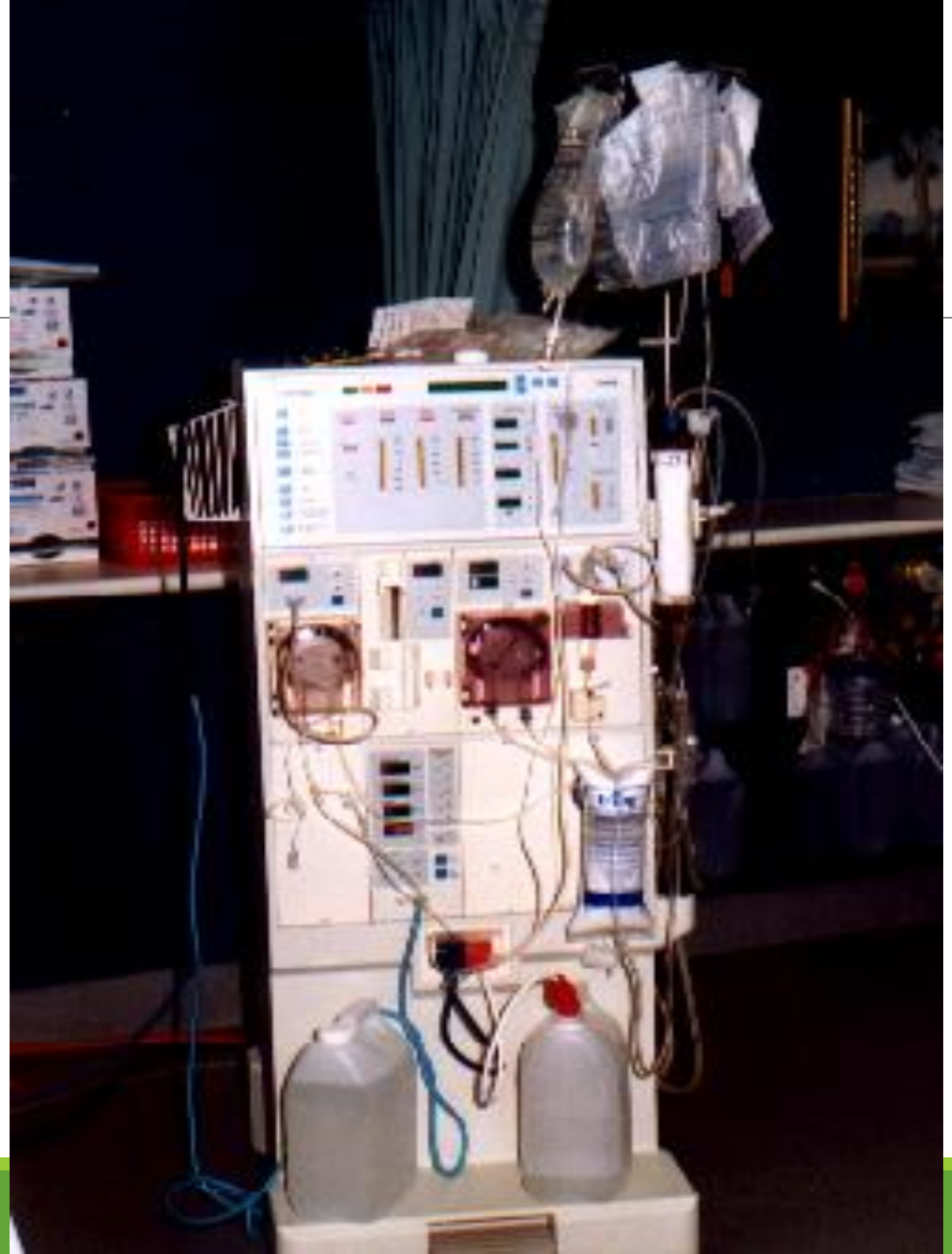
- **Graft** - the use of synthetic material to join an artery to a vein.



- **Vascath or Permacath** - a catheter surgically placed in a neck or leg vein



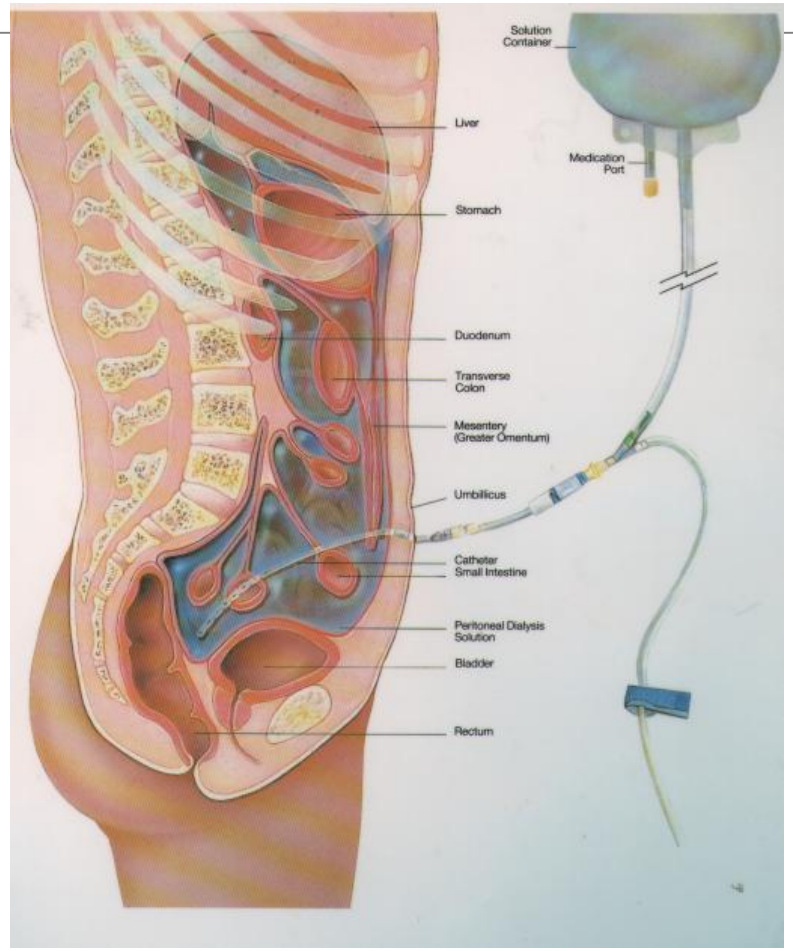
Dialysis machine



Peritoneal Dialysis
How does it work?

1. Sterile dialysis fluid is drained into the peritoneal cavity

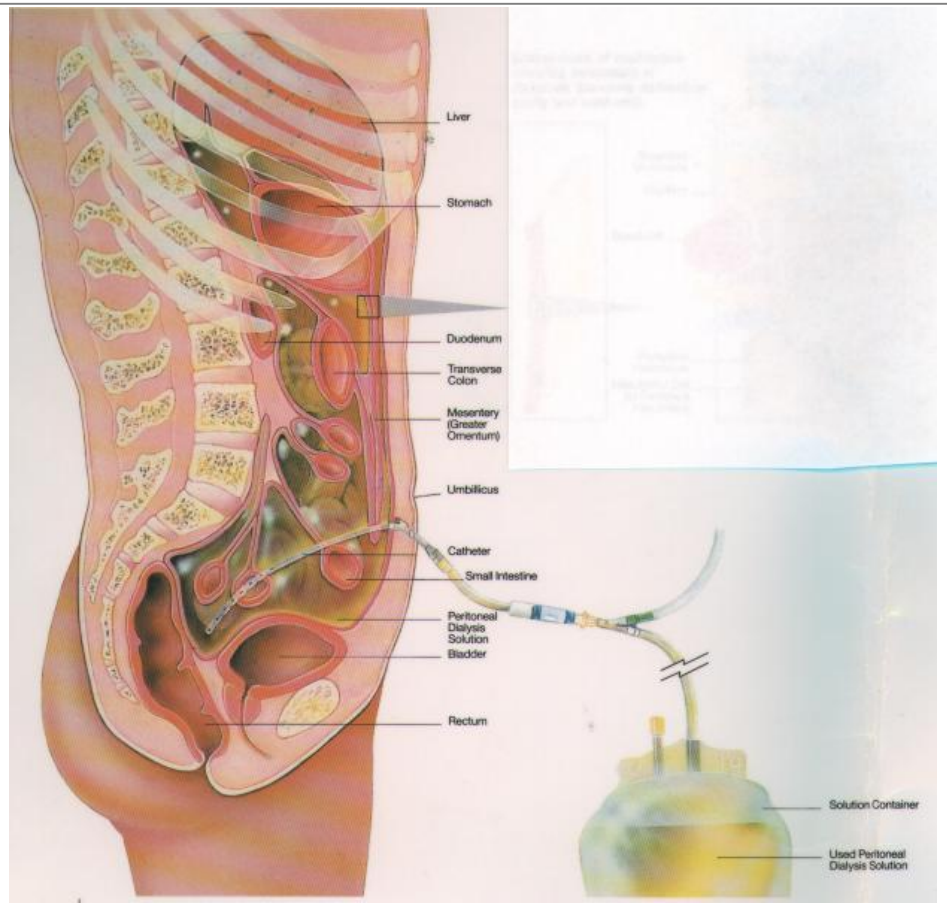
2. Glucose (sugar) in the dialysis fluid attracts excess water from the blood into the peritoneal cavity



How does it work?

3. Waste products such as creatinine and urea also filter into the dialysis fluid.

4. Drain out the old fluid and re-fill.



Drug clearance - RRT

Drug/active metabolite characteristic	Clearance on HD	Clearance on PD	Clearance on HF
MW	Diffusion <500 Da = likely 500-20000 = Variable (low flux < high)	Diffusion and convection Generally poor drug clearance	Convection Increased clearance up to 30,000 Da
Protein Binding	Low = more drug available for clearance High = not generally removed		
Vd	Small (<1L/kg) = mostly in plasma, more likely Large (>2L/kg) = less in plasma, less likely		
Water/lipid solubility	Higher water solubility = higher clearance Higher lipid solubility = lower clearance		
Renal Clearance	High = more likely to be cleared		

What properties would an ideal drug for use in renal impairment have?

What properties would an ideal drug for use in renal impairment have?

- Not nephrotoxic
- Have a large volume of distribution
- Does not require renal metabolism to an active form
- Does not require renal excretion for active drug or active metabolites
- Has a low adverse effect profile
- Is not highly protein bound
- Has an action unaffected by altered tissue sensitivity
- Is unaffected by fluid balance changes
- Is able to reach the site of action in high enough concentrations in the presence of renal impairment
- When given intravenously needs a small volume of fluid and is low in Na^+

Transplantation

- Multiple medication changes post transplant
- Which drugs to stop?
  - Renal drugs: phosphate binders, alfacalcidol, EPO, cinacalcet
  - Antihypertensives (except beta blockers)
- Immunosuppressants start
- Adjuvant therapy to prevent infections

  Eg Co-trimoxazole 480mg bd for 1 year

  Nystatin 1ml qds for 6 months

Maintenance Immunosuppression

Calcineurin Inhibitors	Antimetabolites	Steroids	mTOR inhibitor
Suppress T cell and T cell dependant B-cell activation	Inhibits proliferation of activated T cells and B cells	Many immune system lowering effects	Block proliferation of T cells and B cells (not used immediately as impairs wound healing)
Tacrolimus	**Azathioprine**	**Prednisolone**	**Sirolimus**
Ciclosporin	**Mycophenolate**		

- Two or three drugs
- Different modes of action
- Use lowest effective dose of each

In summary

In the classroom

- Identified at risk patients
- Know which drugs are renally cleared
- Reduced doses accordingly
- Checked for drug interactions

On the wards and in clinics will

- Educate and empower the patient
- Raise queries with doctors

Thank you for your attention


Tutorial

Case 1

Mr HB 65 years admitted with swollen ankles and shortness of breath.

PMHx: Hypertension, reflex, diabetes, mild renal failure

Medications:

- perindopril 8mg mane
- candesartan 16mg mane
- omeprazole 20mg mane
- metoprolol 50mg bd
- metformin 1g tds
- glibenclamide 10mg tds
- aspirin 100mg mane
- on questioning you find out that he also takes ibuprofen obtained from community pharmacy

- **What observations/test results would you like to know?**

Case 1

1. What results/observations would you like to know?

- Cr 500 micromol/L
- Blood Sugar Level (Glucose) 6 mmol/L
- Weight 77kg NB looks lean
- K 5.5mmol/L

- **What action would you take with the knowledge you now have?**

Case 1

2. What action would you take with the knowledge you now have?

- Calculate CrCl or GFR –approximately 14mL/min
- Discuss with doctor –last recorded CrCl was 50mL/min –acute renal failure caused by ibuprofen
- Discuss risk of lactic acidosis with metformin and consider ceasing
- Withhold perindopril and candesartan until Cr normalises
- Watch K
- Consider changing from glibenclamide to gliclazide in older patient to reduce risk of hypos and accumulation
- **What counselling would you give to any patient who is prescribed metformin or NSAID's?**

Case 1

3. What counselling would you give to any patient who is prescribed metformin or NSAID's?

Patients should cease NSAIDS/metformin if they are in a situation where they may become dehydrated:

- vomiting
- diarrhoea
- sepsis
- pre-surgery
- excessive exercise

If on metformin they should seek medical advice -risk of lactic acidosis

In patients with renal failure, consider options other than NSAIDs

Metformin induced lactic acidosis

Metformin

- Largely eliminated via kidneys
- Increases production and decreases clearance of lactate
- Impaired ability of liver to remove lactate as pH falls
- Hepatic conversion of lactate to glucose impeded.

Case 2

Mrs SR is a 43 year old haemodialysis patient who was admitted to hospital with a leg ulcer infected with pseudomonas aeruginosa.

Current Medical History:

- End Stage Renal Disease
- Hypertension

Case 2

Medication on admission:

Calcium carbonate 2 tds

Aluminium hydroxide 1 tds

Folic acid 5mg mane

Vitamin B 1 mane

Perindopril 4mg mane

Aspirin 100mg mane

Darbepoietin 40micrograms sc weekly on dialysis

Iron polymaltose 50mg weekly on dialysis

Case 2

During admission:

Piperacillin and tazabactam 4.5g tds and gentamicin 240mg stat were started on admission

While in the ward she develops AF and is put on digoxin 125 micrograms mane.

For discharge she is changed to ciprofloxacin 500mg bd

Explain why patient is on each medication

Case 2

1.Explain why the patient is on each medication?

Calcium carbonate 2 tds with meals	Phosphate binder
Aluminium hydroxide 1 tds with meals	Phosphate binder
Folic acid 5mg mane	Supplement (lost in HD)
Vitamin B 1 mane	Supplement (lost in HD)
Perindopril 4mg mane	Antihypertensive
Aspirin 100mg mane	Anti-platelet
Darbepoietin 40mcg weekly on dialysis	Anemia
Iron polymaltose 50mg weekly on dialysis	Anemia
Piperacillin/tazabactam 4.5g tds	Antibiotic for pseudomonas
Gentamicin as per levels	Antibiotic for pseudomonas
Digoxin	Atrial fibrillation

2.Are you are unhappy about any doses? If so what suggestions do you have?

3. What times would you recommend medications be dosed at?

Case 2

2.Are you are unhappy about any doses? If so what suggestions do you have?

Piperacilin/tazabactam dose is too high. Dose in renal failure is 4.5g bd

- penicillins can cause seizures in accumulation
- tazabactam ↑LFT's

Ciprofloxacin dose is too high. Maximum dose 500mg daily

- Risk of achilles tendon rupture

Digoxin dose is too high. Maximum dose is 62.5micrograms daily

- renally cleared, not dialysed, highly tissue bound

Case 2

3. What times would you recommend medications be dosed at?

- Take calcium and aluminium with meals
- Take folic acid and vitamin B post dialysis (nocte), as it is cleared
- Gentamicin if further doses are needed should be given post dialysis if possible
- Metoprolol and perindopril should not be given prior to dialysis on dialysis days. As dialysis removes fluid which could cause a drop in blood pressure
- Take ciprofloxacin 500mg nocte away from binders which can reduce absorption

Case 2

4. Should renal patients receive a loading dose of digoxin, if so what?

5. How would you dose gentamicin in this patient?

6. Mrs SR is in considerable pain what analgesic(s) would you suggest?

Case 2

4. Should renal patients receive a loading dose of digoxin, if so what?

Normal loading dose

5. How would you dose gentamicin in this patient?

1st dose 2-3mg/kg redose level <2 at 1-2mg/kg

6. Mrs SR is in considerable pain what analgesic(s) would you suggest?

Fentanyl, oxycodone

(Morphine – respiratorydepression, pethidine – seizures, codeine - hallucinations)

Case 3

Mrs ST is 67 year old diagnosed with herpes zoster. She weighs 57kg. She has chronic renal failure with CrCl 20mL/minute. She was prescribed valaciclovir 1g tds

1. Comment on dose. Does it need adjustment?

2. What side effects could be expected with too high a dose?

3. What other issues should be considered

Case 3

Mrs ST is 67 year old diagnosed with herpes zoster. She weighs 57kg. She has chronic renal failure with CrCl 20mL/minute. She was prescribed valaciclovir 1g tds

1. **Comment on dose. Does it need adjustment?**

Dose is too high - Suggest 1g d - bd (varies in different texts)

2. **What side effects could be expected with too high a dose?**

Increased risk of nephrotoxicity and neurological adverse effects (confusion)

3. **What other issues should be considered**

Adequate hydration is required to avoid to prevent crystals precipitating in renal tubules - fluid restrictions may need to be altered

Case 4

Mr DM 54 years 67kg

Admitted with gangrenous L foot (work up for Below Knee Amputation)

Chronic RF secondary to DM & reno-vascular disease

Cr 310 micromol/L

Medications:

- diltiazem CD 360mg mane
- simvastatin 80mg evening
- aspirin 150mg mane
- pantoprazole 40mg mane
- protaphane/Humalog insulin
- darbepoietin 30micrograms weekly

Can you identify any drug issues?

Case 4

- 6/7 later Creatinine Kinase (CK) 3770 and Cr 630 micromol/L
- Patient was admitted to ICU with hypotension, acidosis, and rhabdomyolysis
- CK peaked 126,000
- Patient died 4/7 following admission to ICU

What happened?

Case 4

- 6/7 later Creatinine Kinase (CK) 3770 and Cr 630 micromol/L
- Patient was admitted to ICU with hypotension, acidosis, and rhabdomyolysis
- CK peaked 126,000
- Patient died 4/7 following admission to ICU

What happened:

diltiazem/simvastatin combination caused rhabdomyolysis which caused renal failure

Risk factors for myopathy and rhabdomyolysis with statins

Substances inhibiting **metabolism** by CYP3A4	Cyclosporine, diltiazem, verapamil, macrolide antibiotics, azole antifungals, protease inhibitors, grapefruit juice.
Medicine inhibiting metabolism by other means.	gemfibrozil
Disease States	Diabetes, hypothyroidism, renal and hepatic disease.
Advanced Age	≥ 70 years
High statin dose	≥ 40mg/day

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