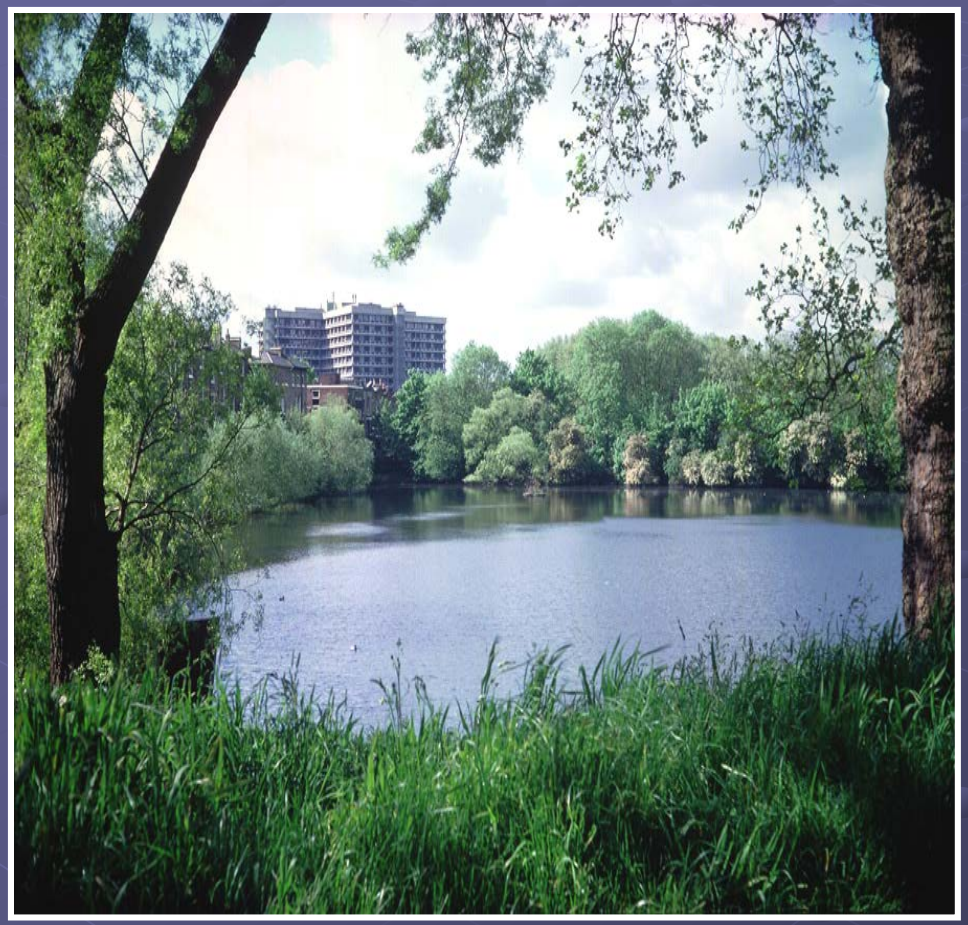
Update on Renal Therapeutics



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Kongress für

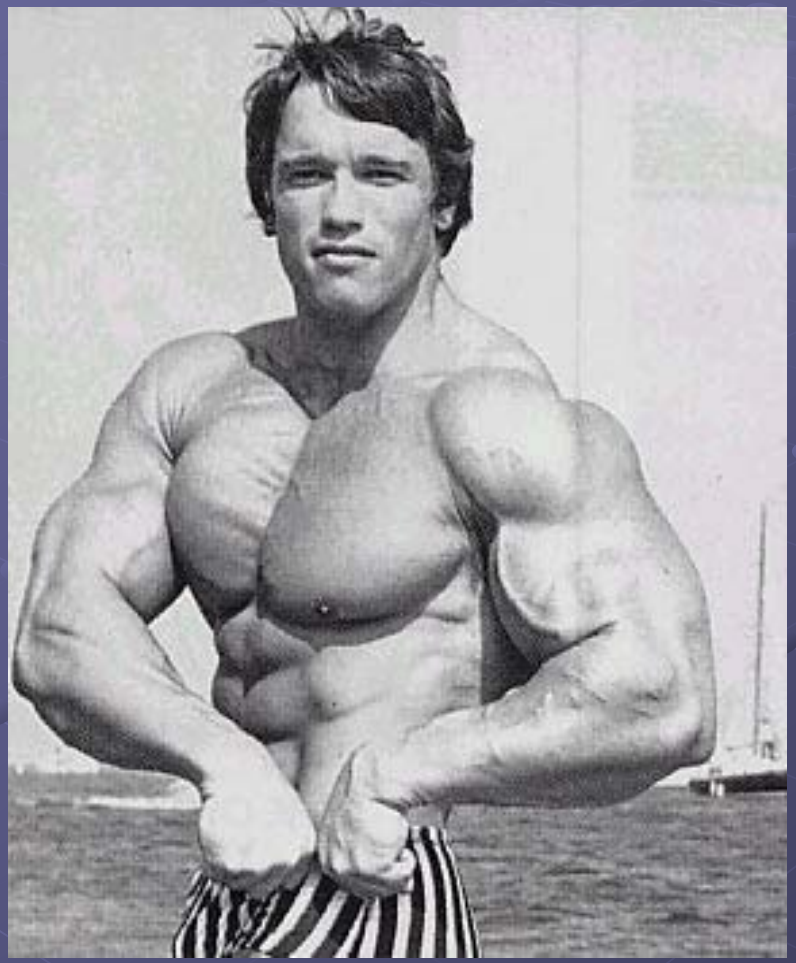
Arzneimittelinformation

January 2014

What are we going to discuss?

- How to calculate renal function
- Types of renal replacement therapy (RRT)
- How to adjust drug dosages according to type of RRT

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

Staging of CKD *(K-DOQI)*

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

Stage	Description	GFR ml/min/1.73 m^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

Old Classification of CRF

Grade	GFR (mL/min)	Serum creatinine (μmol/L)
Mild	20-50	150-300
Moderate	10-20	300-700
Severe	< 10	>700

How do we measure renal function?

Cockcroft & Gault

CrCl (ml/min) =

$$\frac{F \times (140 - age) \times weight\ (Kg)}{serum\ creatinine\ (\mu mol/L)}$$

Where F = 1.04 (female) and
1.23 (male)

Nephron 1976 16 (1) 31-41

Cockcroft and Gault

Do not use 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 is an amputee
- patient is severely wasted

MDRD equation

Modified Diet in Renal Disease

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 patient's actual body surface area

Nephrol Dial Transplant (2002) 17: 2036-2037

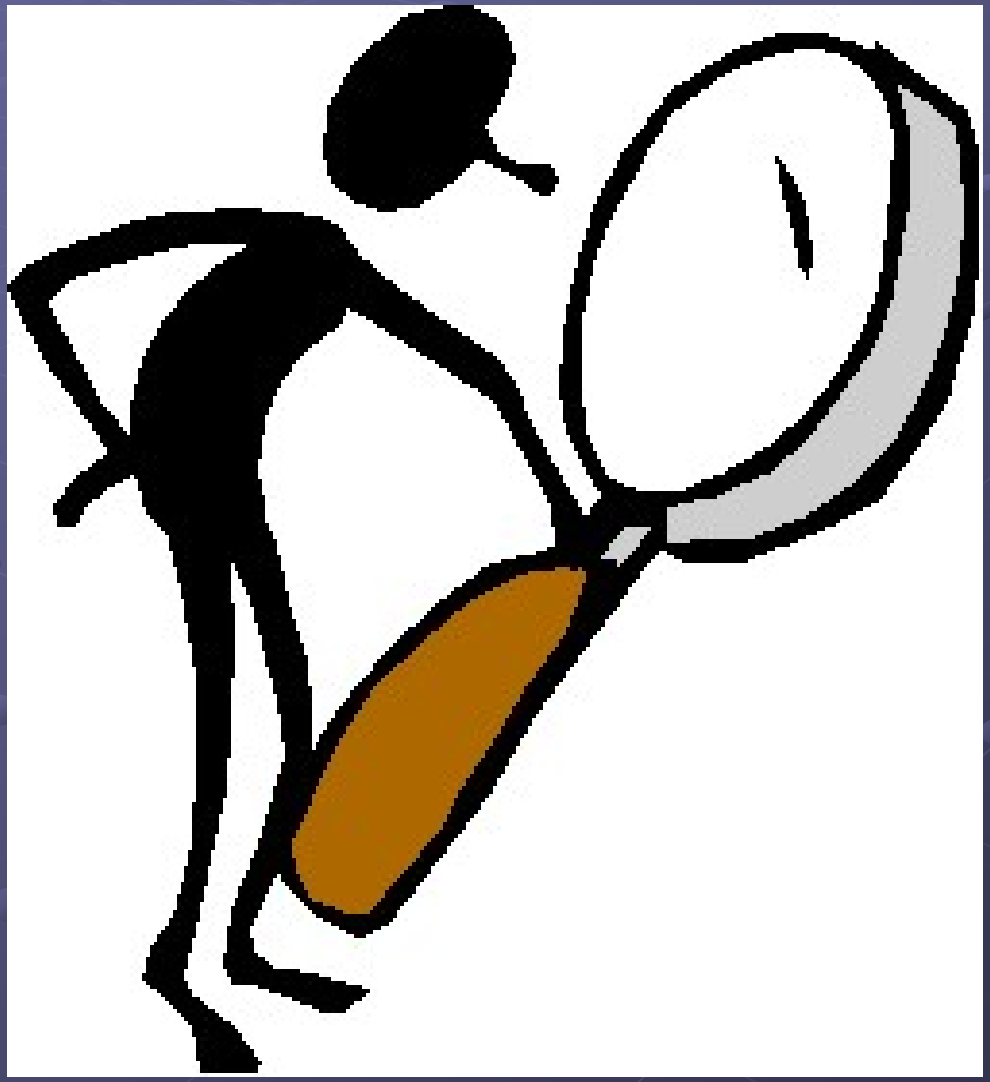
Cystatin C

- Serum concentrations of low molecular weight protein Cystatin C correlate inversely with GFR
- Concentration of Cyctatin C independent of height, weight, muscle mass, adult age or sex.
- Largely unaffected by meat vs vegetarian diets.
- Not currently in widespread use.

Other markers

- Inulin
- Iohexol
- Radio-isotopes – ^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-iothalamate.
- Too expensive and labour-intensive for widespread use.
- Inulin most accurate
- Radioisotopes validated reference standards.

So which one do we use?



Drug Dosing

- Cockcroft & Gault generally over-estimates
- People tend to use ABW rather than IBW
- Pharmacists use correctly!!

- MDRD said to be more accurate than C&G.
- Does not require patient's weight.
- Same restrictions / inaccuracies as C&G, eg. < 18 yrs, amputees, pregnant, malnourished.

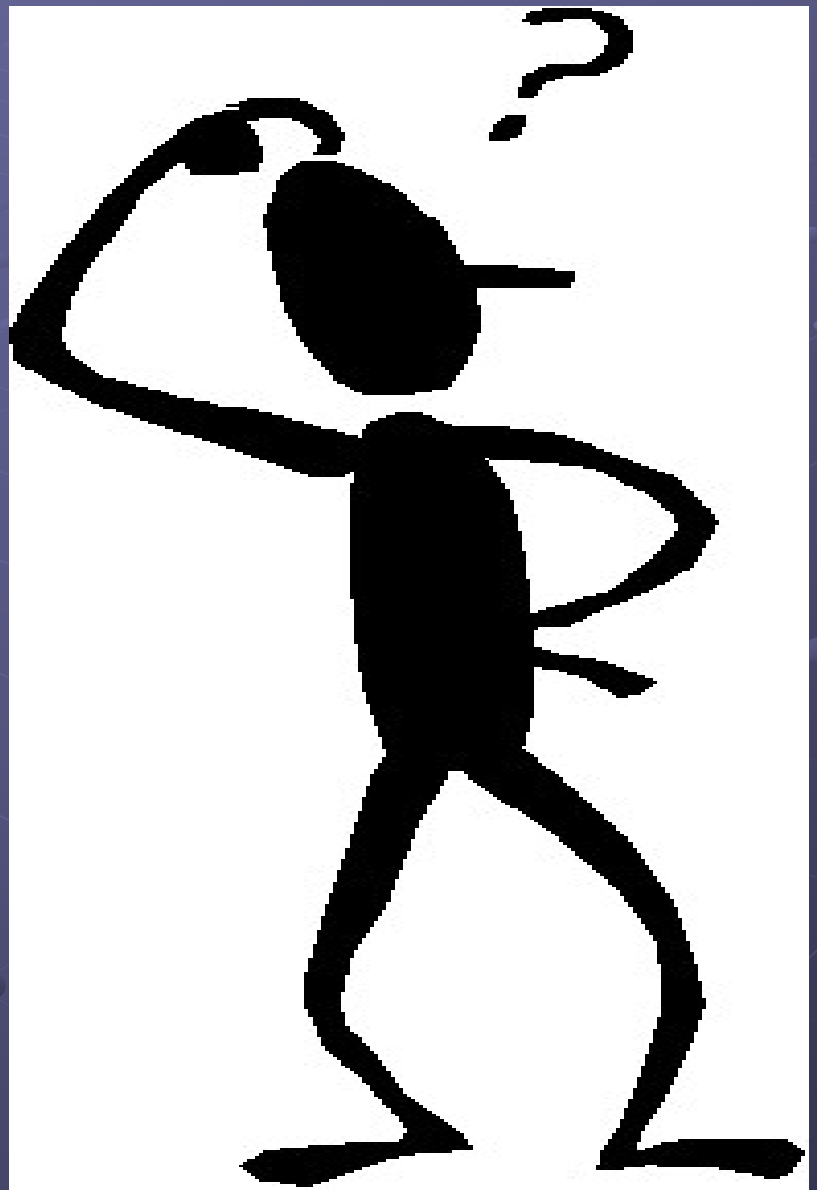
eGFR

- 90% confidence intervals are quite wide, e.g. 90% of patients will have a measured GFR within 30% of their estimated GFR.
- The MDRD equation tends to underestimate normal or near-normal function, so slightly low values should not be over-interpreted.

eGFR

	Serum Creatinine (μmol/L)	CrCl (mL/min) C&G	eGFR (mL/min/1.73m^2) MDRD
Young muscular black male (20yrs, 90Kg)	110	120	>90
Thin elderly female (75yrs, 50Kg)	110	29	40

Confused?? You will be……..



Drug Dosing

Practical suggestions:-

- For the majority of drugs, use MDRD eGFR.
- For drugs with narrow therapeutic index, use eGFR, BUT correct for pt's actual BSA

$$GFR_{Absolute} = \frac{eGFR \times Actual\ BSA}{1.73}$$

Or

If in doubt, and for narrow therapeutic index drugs,

- Use Cockcroft and Gault

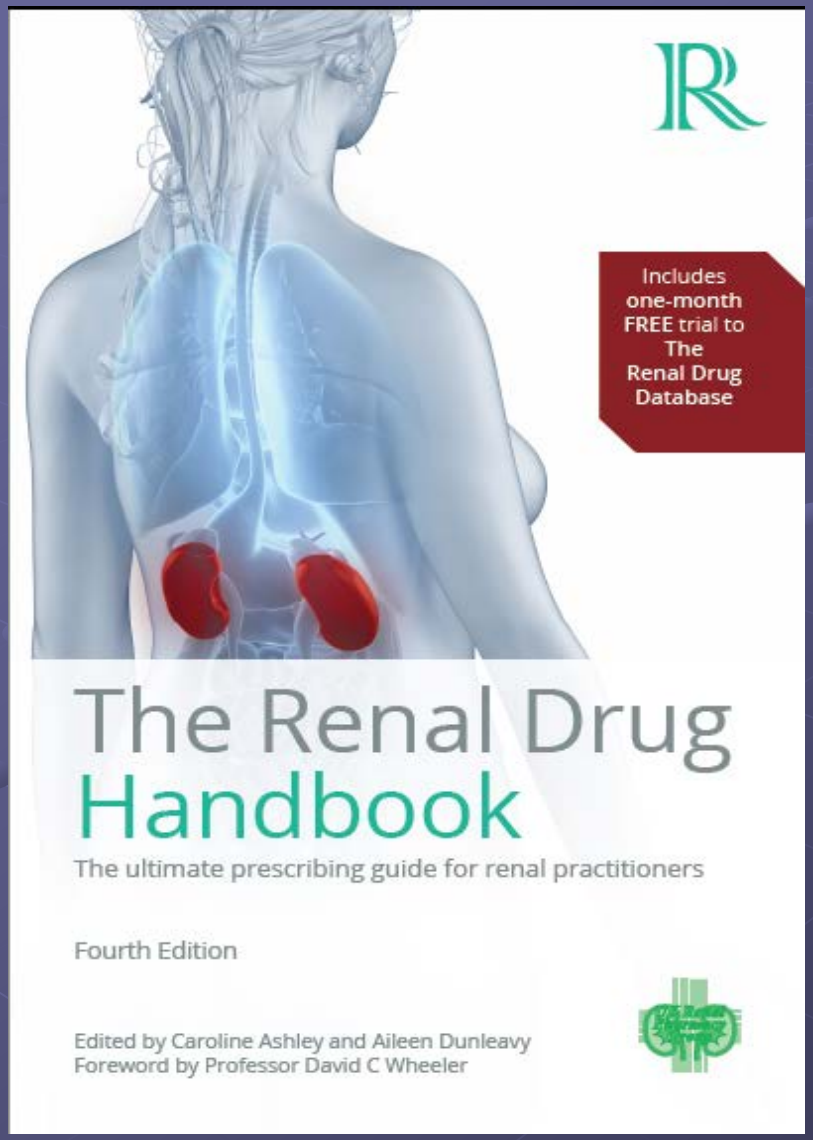
Bennett

- Also available on-line

http://www.kdp-baptist.louisville.edu/renalbook/

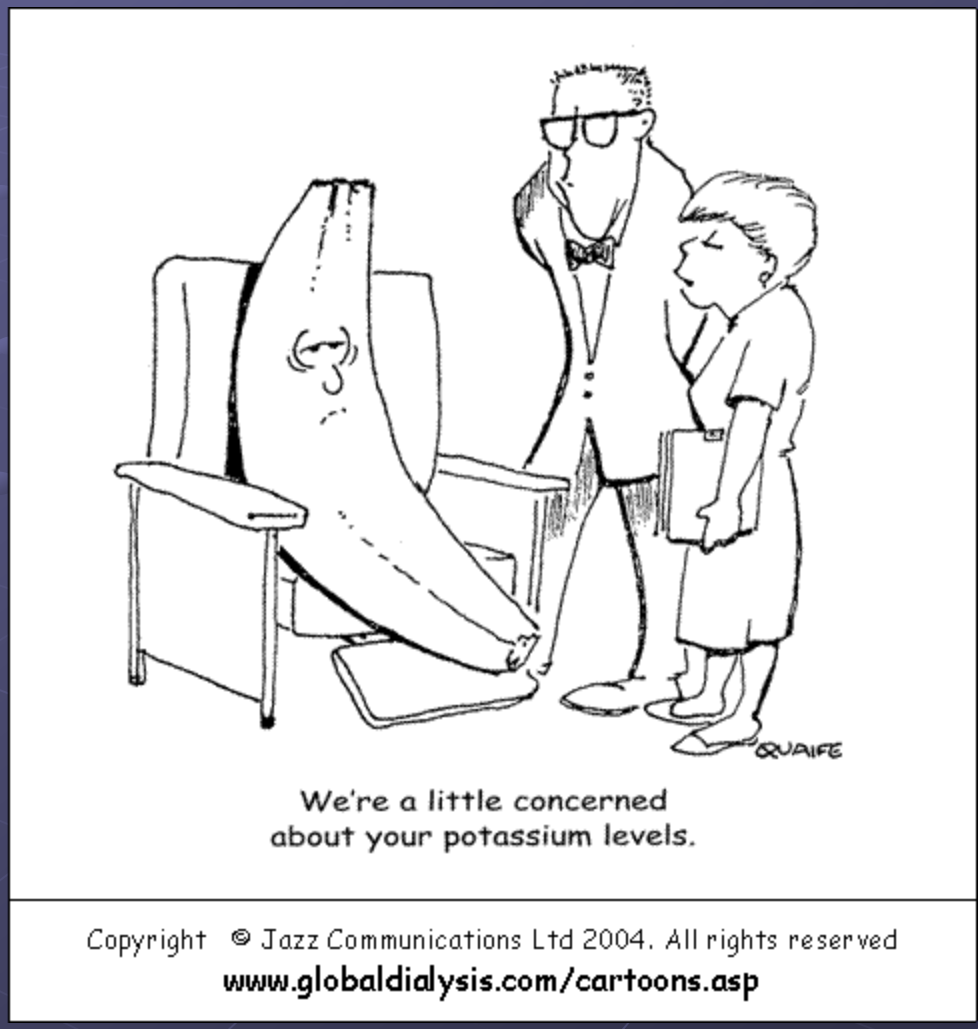
- Fully referenced
- Does not use K-DOQI classification
- Normal, >50ml/min, 10-50ml/min, <10ml/min

Renal Drug Handbook



- 4th edition published May 2014
- Nearly 1000 drug monographs
- New section on drug metabolism & excretion

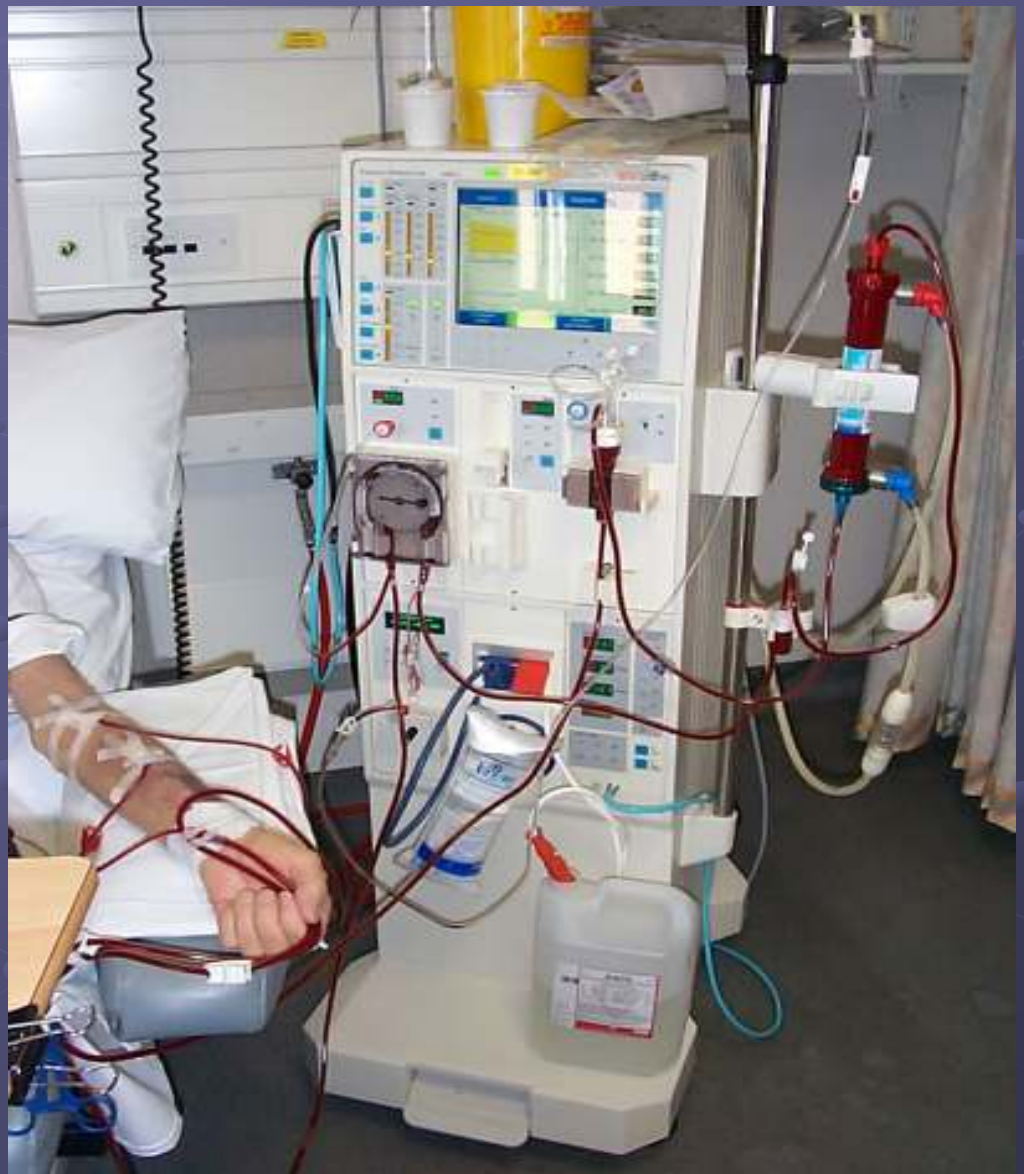
When do we start dialysis?



Nomenclature

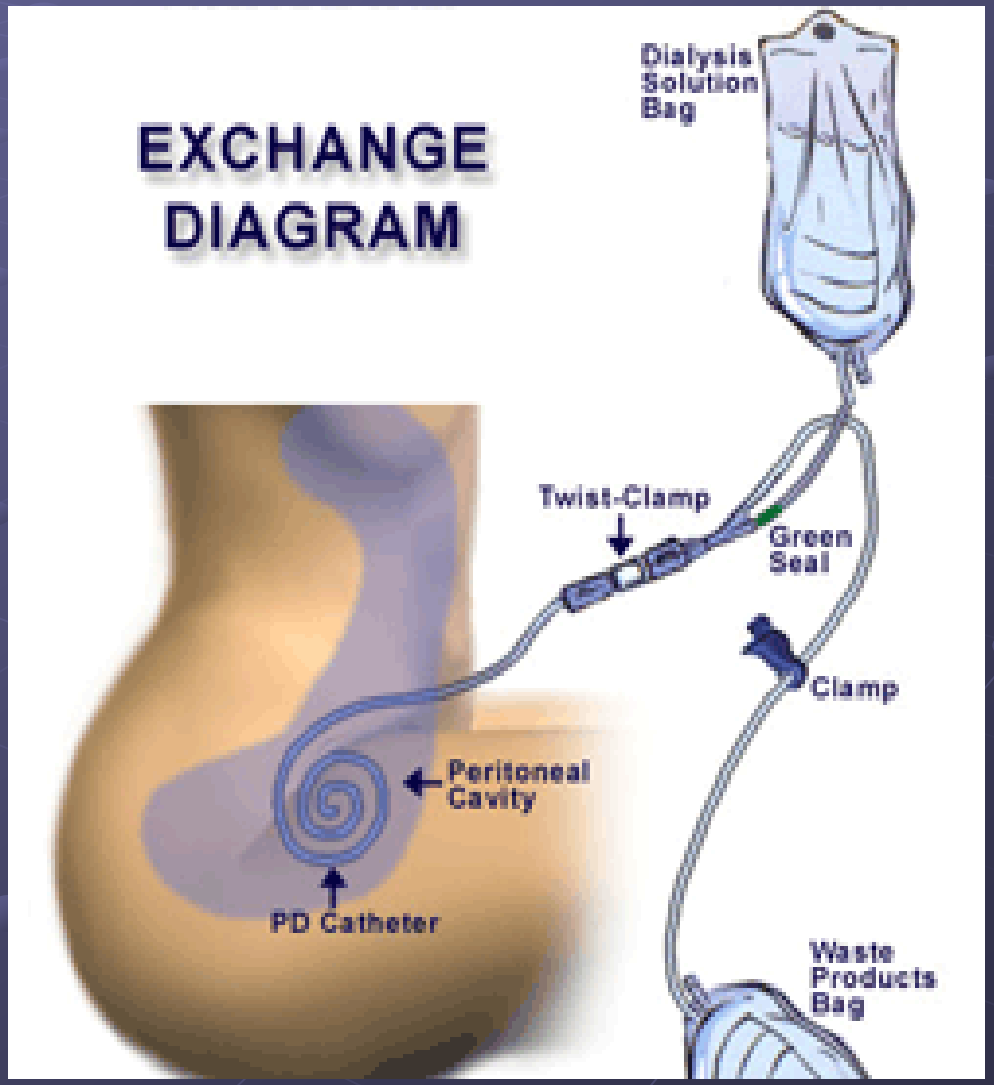
- Continuous Renal Replacement Therapy (CRRT)
- Continuous Arterio-Venous Haemofiltration (CAVH)
- Continuous Veno-Venous Haemofiltration (CVVH)
- Continuous Arterio-Venous Haemodiafiltration (CAVHD)
- Continuous Veno-Venous Haemodiafiltration (CVVHD)
- Intermittent Haemodialysis (IHD)
- Ultrafiltration (UF)

Intermittent Haemodialysis



Peritoneal Dialysis

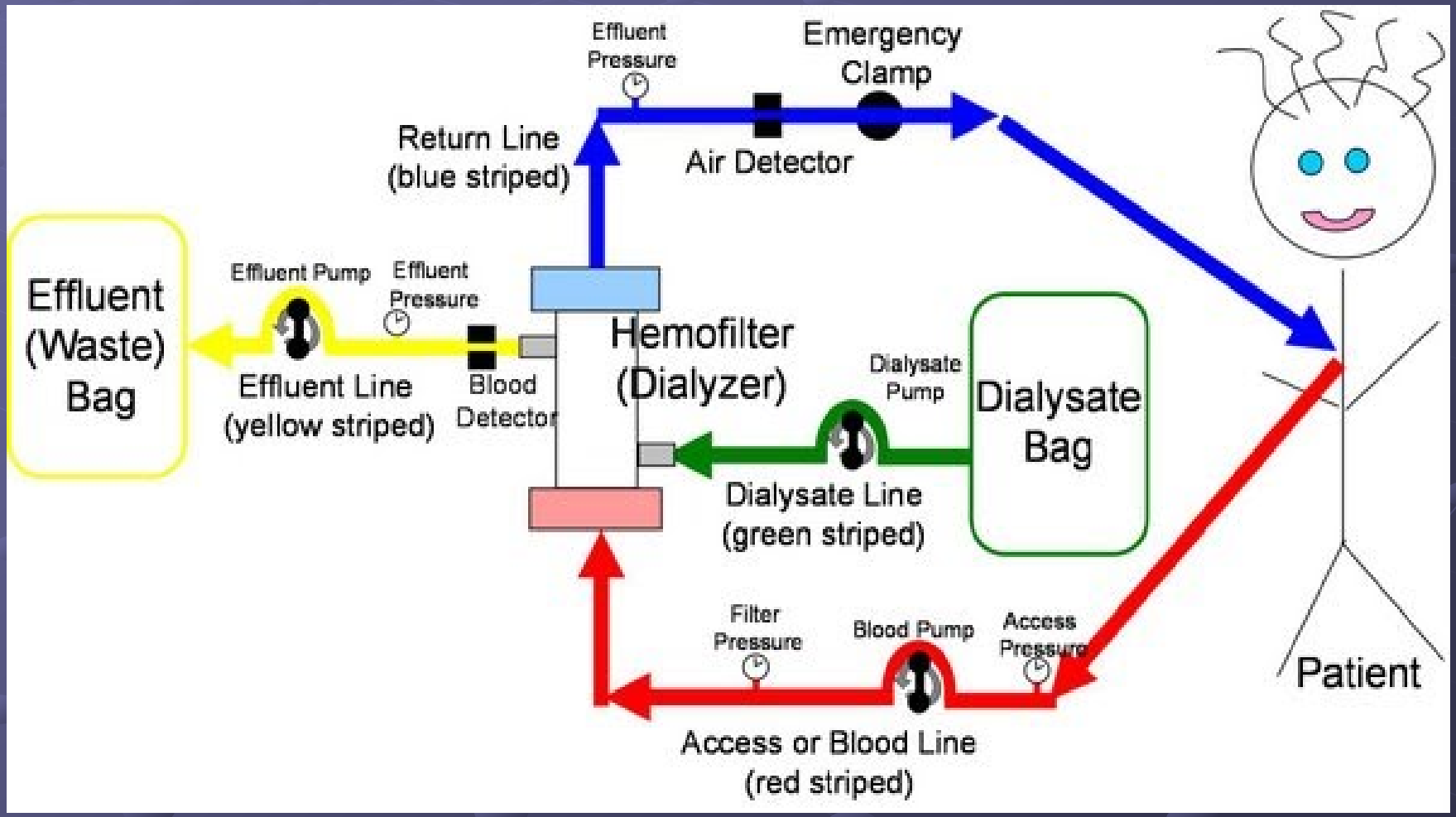
- CAPD
- APD



Indications for CRRT

- Metabolic acidosis (pH>7.3 & falling)
- Hyperkalaemia (K+ >6.0mmol/L & ↑)
- Fluid overload that compromises gaseous exchange
- Urea > 30 mmol/L
- Creatinine > 300 μmol/L
- Oliguria (< 200ml /12 hours) or anuria
- Haemodynamic instability (no IHDx)
- Pt has / at risk of cerebral oedema

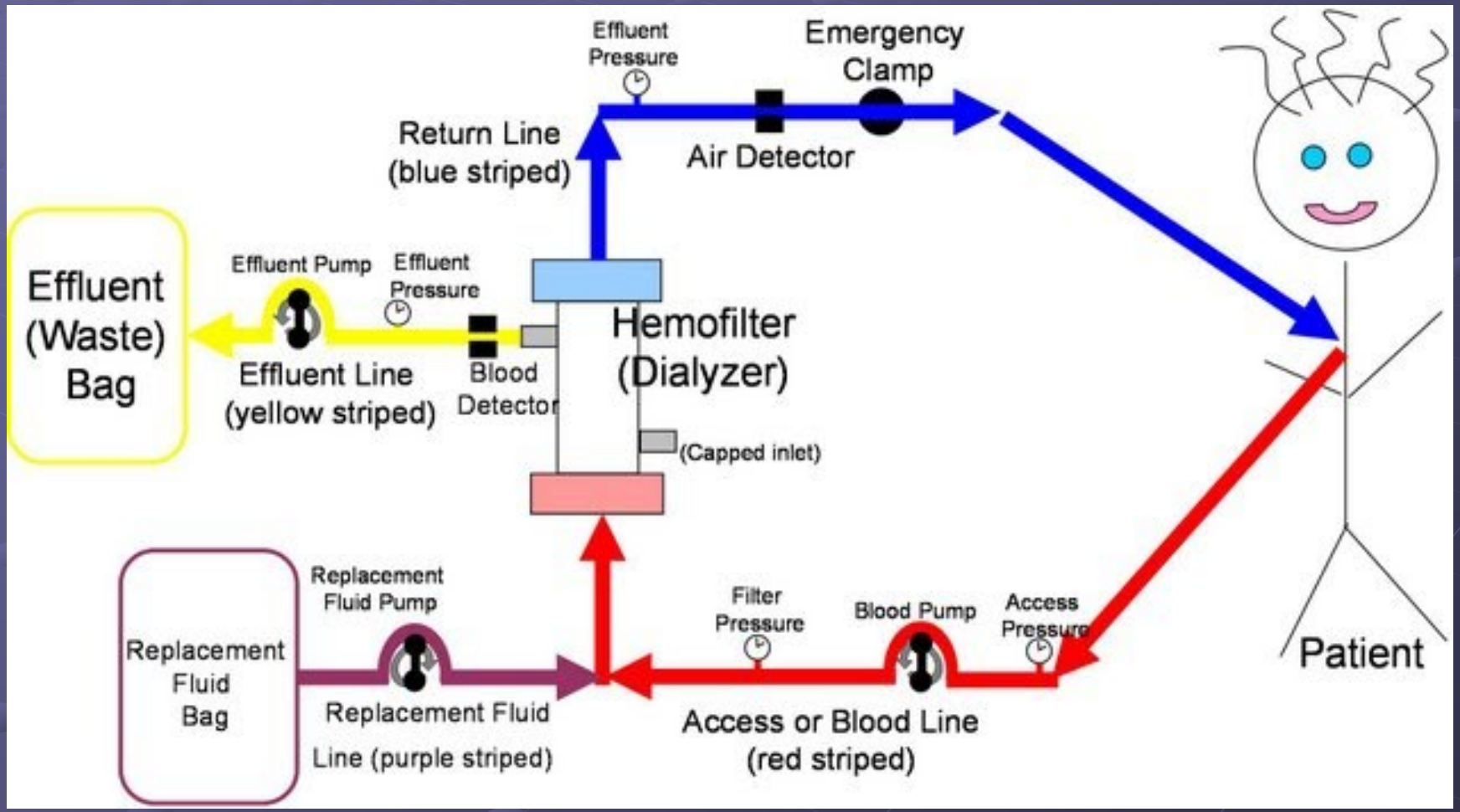
CVVHD


Effluent Pressure
Emergency Clamp
Return Line (blue striped)
Air Detector
Effluent (Waste) Bag
Effluent Pump
Effluent Pressure
Hemofilter (Dialyzer)
Effluent Line (yellow striped)
Blood Detector
Dialysate Pump
Dialysate Bag
Dialysate Line (green striped)
Filter Pressure
Blood Pump
Access Pressure
Patient
Access or Blood Line (red striped)

CVVHD

- Blood is passed along one side of a semi-permeable membrane.
- Crystalloid solution is pumped along other side of membrane in opposite direction.
- Solutes move across membrane by *convection* & *diffusion* at rate depending on concentration gradient & molecular size.
- More effective at clearing middle-size molecules
- Doesn't mirror physiological process in kidney

CVVH


Effluent Pressure
Emergency Clamp
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Effluent Pressure
Hemofilter (Dialyzer)
Effluent Line (yellow striped)
Blood Detector
(Capped inlet)
Replacement Fluid Pump
Filter Pressure
Blood Pump
Access Pressure
Patient
Replacement Fluid Bag
Replacement Fluid Line (purple striped)
Access or Blood Line (red striped)

CVVH

- Blood passed under pressure down one side of highly permeable membrane
- Water and solutes removed by *convection*, driven by the pressure gradient.
- Better for fluid removal
- Solutes present at low concentrations, large volumes of fluid must be removed to achieve adequate solute clearance
- Mirrors process of GF within kidney

Pre vs Post Dilution

- Post-dilution is recommended method of Acute Dialysis Quality Initiative
- Pre-dilution – only limited evidence that this method prolongs life of filter
- Pre-dilution results in reduction of solute clearance due to dilution of solutes as blood enters the artificial kidney

Drug Removal by CRRT

- Drug Factors

- Low molecular weight (up to 20,000 daltons)
- Low % protein binding.
- Low apparent volume of distribution
- High degree of water solubility
- Relatively short half-life
- Usually excreted via the kidneys

Drug Removal by CRRT

- System factors

- Size of treatment cycle will directly affect convective transport ⇒ higher treatment cycle volumes & blood pump speeds ⇒ more efficient drug removal

- Chemistry & SA of the dialysis membrane

- Majority of drug-membrane binding occurs in first hours of membrane life ⇒ clearance artificially high then.

Effective GFRs on Dialysis

RRT	GFR (ml/min)
Intermittent HD	250 - 300 (0-10 otherwise)
CAPD / APD	5 – 10
CAVH / CVVH	15 - 30
CAVHD / CVVHD	20 - 35

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.

Eg. Ertapenem, Normal dose = 1g OD

Dose in ESRF = 50% normal dose

Either 500mg OD, AFTER dialysis on HD days,

Or 1g 3 x/week after each dialysis

Calculating Drug Doses

- CRRT is a continuous process
- Dose as if a patient 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.

Example 1

- 25-year old male
- ESRD, dialysis-dependent

- Developed AML
- Prescribed Flag-X

  (Fludarabine, Cytarabine, GCSF, - Liposomal Daunorubicin)
- Help?!

Example 1

- Fludarabine
  * 40-60% excreted unchanged in urine
  * Protein binding 60%
  * Active metabolite also renally excreted
  * S/E include severe neurotoxicity
  * Single dose vs repeated dosing

- Liposomal Daunorubicin
  * 100% liver excreted

Example 1

Cytarabine ($3g/m^2$)

- Neuro & Cerebellar toxicity
- Elevated baseline serum creatinine independent risk factor
- Incidence of 8% in patients with GFR > 60ml/min
- Incidence of 86 - 100% in patients with GFR < 40ml/min
- Only 10-15% excreted in urine, inactive metabolites

Example 1

- Fludarabine - 50% dose
- Cytarabine - 50% dose
- Daunorubicin - 100% dose
- All in reduced volumes of IV fluids (cytarabine neat in syringe driver)

- Gave chemotherapy each afternoon / evening
- Dialysed each morning

Example 2

- 68 yr-old male, HDx dependent, diagnosed with small cell lung Ca.
- Oncologists decided single agent chemo.

- Cisplatin – very difficult to dose-reduce in renal impairment.
- Carboplatin – very easy to dose reduce.

Example 2

- Carboplatin Dose =

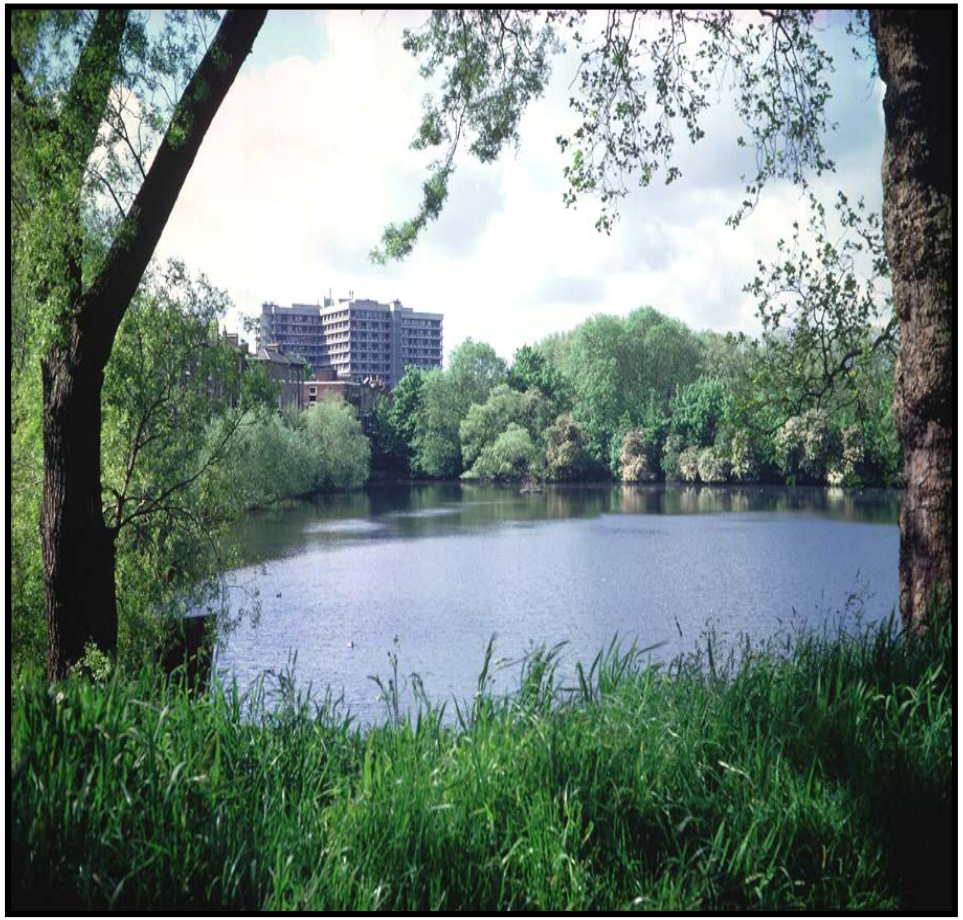
  Target AUC x [GFR (ml/min) + 25]

  where AUC = 5 (sometimes 6 or 7)

  GFR = ? For patient on HDx?
- Dosed on Day 0
- Consecutive dialyses on Days 1 & 2 to remove it.

Any Questions???

Acute Kidney Injury Case Study



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Definition of AKI

- A rapid deterioration in a patient's renal function over hours or days.

Epidemiology

- Estimated that 486 - 630 people per million of the population will develop AKI each year, equating to 750,000 people in England.
- In the hospital setting 20% of acute admissions will develop AKI.
- Up to 30% of all cases of AKI are thought to be due to drugs.
- 5% of inpatients develop drug-induced renal impairment.
- AKI has a high mortality rate, from 10-80% depending on complications that arise, the need for intensive care and renal replacement therapy.
- AKI has significant cost implications to the NHS - in 2009-2010 it is estimated that £434 - £620m was spent on managing this condition.

Pre-Renal AKI

Any condition that decreases perfusion of the kidneys:- eg.

- Volume depletion
  - excessive diuresis, haemorrhage, burns, severe trauma, surgery
- Cardiovascular disorders
  - congestive cardiac failure & acute MI (cardiogenic shock)
- Local obstruction of the renal arteries
  - renal artery stenosis/thrombosis

Post-Renal AKI

Obstruction to urine outflow, may occur anywhere along the urinary tract from the collecting ducts in the kidney down to the bladder or urethra. Causes include:-

- deposition of crystals in the tubules, eg. uric acid, sulphonamides, acyclovir, cisplatin.
- stones in the kidney, ureter or bladder
- a tumour, eg. prostate hypertrophy, bladder cancer, bowel cancer.

Intra-Renal AKI

- Acute Tubular Necrosis, Acute Pyelonephritis, Autoimmune Renal Disease

Sustained hypoperfusion, or exposure to nephrotoxic agents

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

And for starters, what is normal?

- Serum creatinine = 49 – 92 μmol/L

- Creatinine clearance or eGFR
  = > 90 ml/min (young adult)

- But, renal function declines with age
- Typically 40-60 ml/min in elderly
  (↓ GFR, but also ↓ muscle mass ∴ serum creatinine looks relatively normal)

Staging of CKD *(K-DOQI)*

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

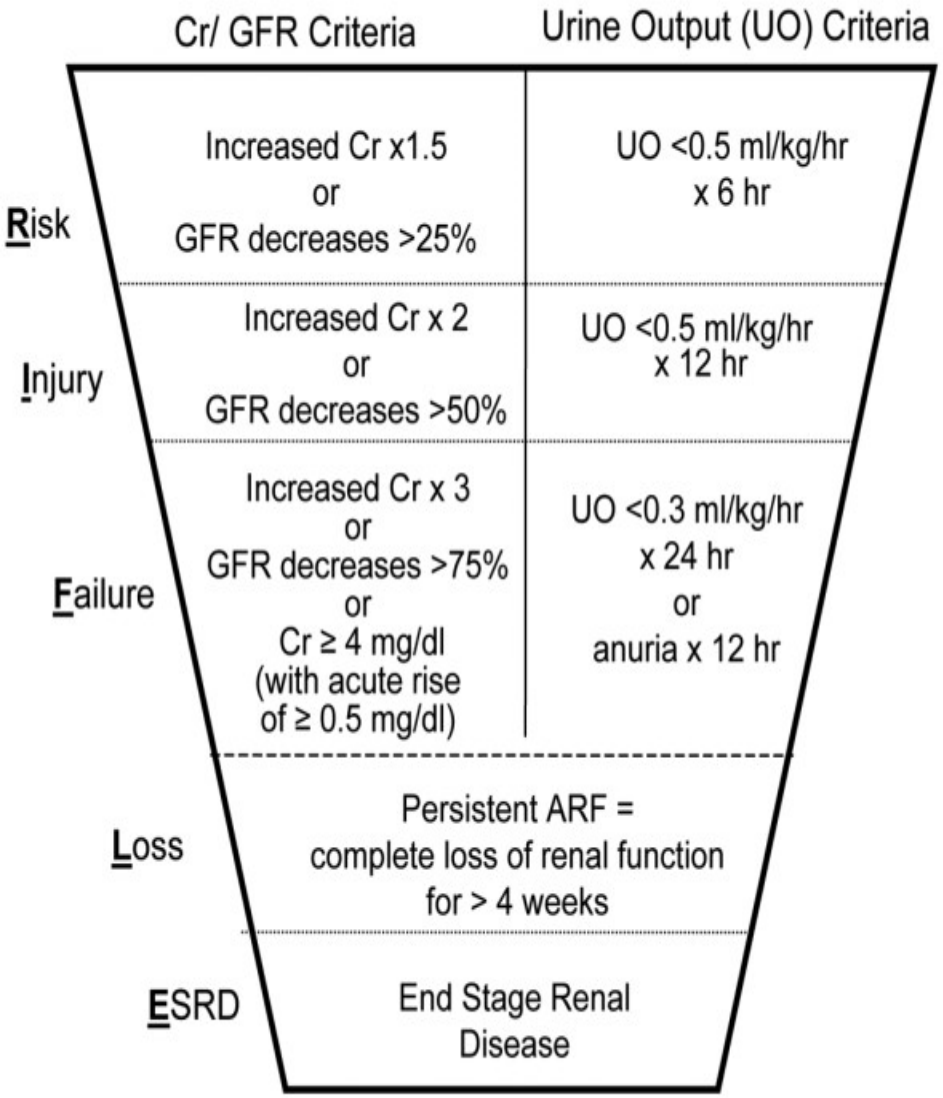
Stage	Description	GFR ml/min/1.73 m²
1 +/-(p)	Kidney damage with normal or ↑GFR	≥ 90
2 +/-(p)	Kidney damage with mild ↓GFR	60-89
3A +/-(p)	Moderate ↓GFR	45-59
3B +/-(p)		30-44
4+/- (p)	Severe ↓GFR	15-29
5+/- (p)	Kidney failure	≤ 15

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

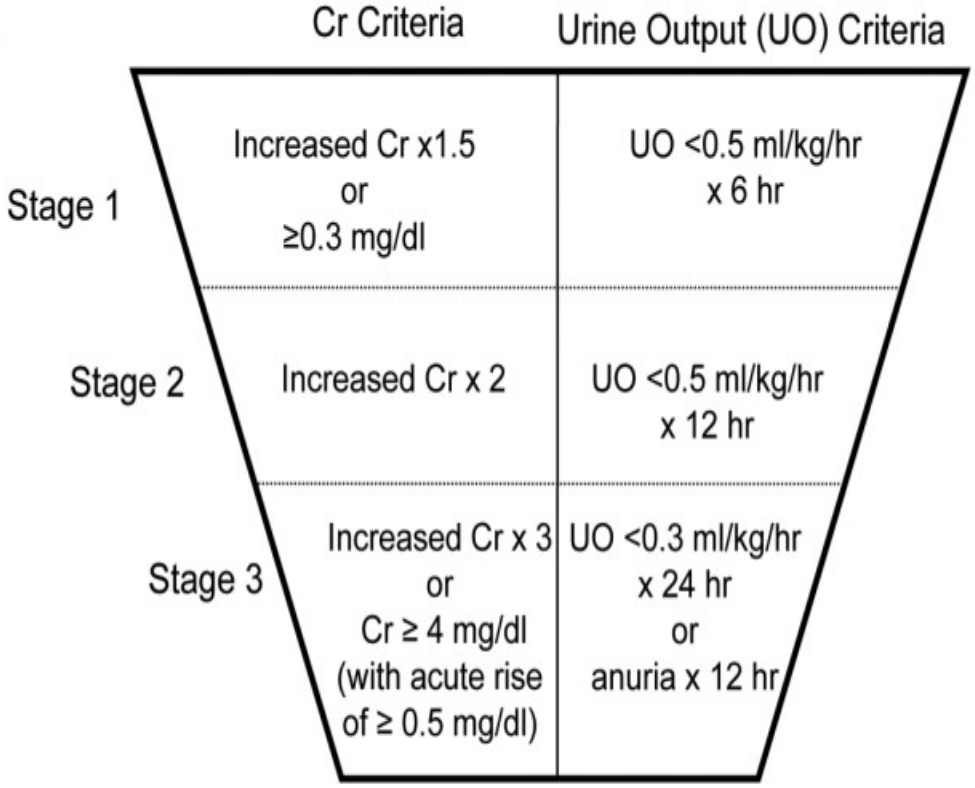
KDIGO Staging System for Acute Kidney Injury

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

RIFLE



AKIN



Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Differences between AKI and CKD

- **Acute**
- Unwell
- Good colour
- No pigmentation
- Hb Normal
- Normal kidney size
- Normal bone x-rays

- **Chronic**
- May seem well for level of function
- Hypertensive
- Clinically anaemic
- Skin pigmentation
- Bone disease
- ? Shrunken kidneys

Calculating CrCl or eGFR

CrCl (ml/min) =

$$\frac{F \times (140 - age) \times weight\ (Kg)}{serum\ creatinine\ (\mu mol/L)}$$

where F = 1.04 (female)
and 1.23 (male)

Nephron 1976 16 (1) 31-41

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

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Nephrol Dial Transplant (2002) 17: 2036-2037

NEITHER are very accurate in AKI

UK Renal Pharmacy Group has developed a **Pharmacists' Toolkit for AKI**

- Risk factors for developing AKI
- Diabetes Mellitus?
- Age > 75
- Congestive Cardiac Failure?
- Chronic kidney disease?
- Peripheral Vascular Disease?
- Liver disease?
- Sepsis?

Pharmacists' Toolkit for AKI

- How to recognise AKI when it occurs

- What to do with an AKI patient
  * Drugs to be stopped or avoided
    eg. ACEIs, ARBs, NSAIDs, Diuretics
  * Which drugs require dose modification
  * What to monitor

- When to restart drugs as AKI resolves

AKI Medicines Optimisation Toolkit

Is the patient receiving medication which may impair renal function?

Consider **A**cute **N**ephrotoxic **D**rug **A**ction

Contrast media

ACE Inhibitor

NSAIDs } **CONSIDER WITHOLDING**

Diuretics

Angiotensin receptor blocker

Other medications

Drugs to stop	Drugs to avoid	Drugs to reduce dose, monitor levels or withold
ACEI / ARB	**ACEI / ARB**	Allopurinol
Metformin	Analgesics e.g. opioid analgesics*	Antibiotics / antifungals / antivirals*
NSAIDs	**Contrast media***	Anticoagulants inc. LMWH, warfarin*
	DMARDs e.g. methotrexate	Antiepileptics (phenytoin, gabapentin, pregabalin
	Metformin	Antihypertensives
	NSAIDs	Chemotherapy – seek specialist advice
		Digoxin
		Diuretics
		Hypoglycaemic agents
		Immunosuppressants – advice Tx centre
		Lipid-lowering agents e.g. fibrates, statins

AKI Medicines Optimisation Toolkit

Drug	Problem	Action in presence of AKI	Patient education
Co-trimoxazole	Crystal nephropathy Hyperkalaemia	Reduce dose. Seek medical advice if patient is fluid restricted.	Encourage patient to drink plenty. Seek medical advice if at risk of dehydration.
Metformin	Lactic acidosis Accumulation	Avoid. Seek nephrologist advice if undergoing contrast procedure or at risk AKI.	Seek medical advice if at risk of dehydration.

AKI Medicines Optimisation Toolkit

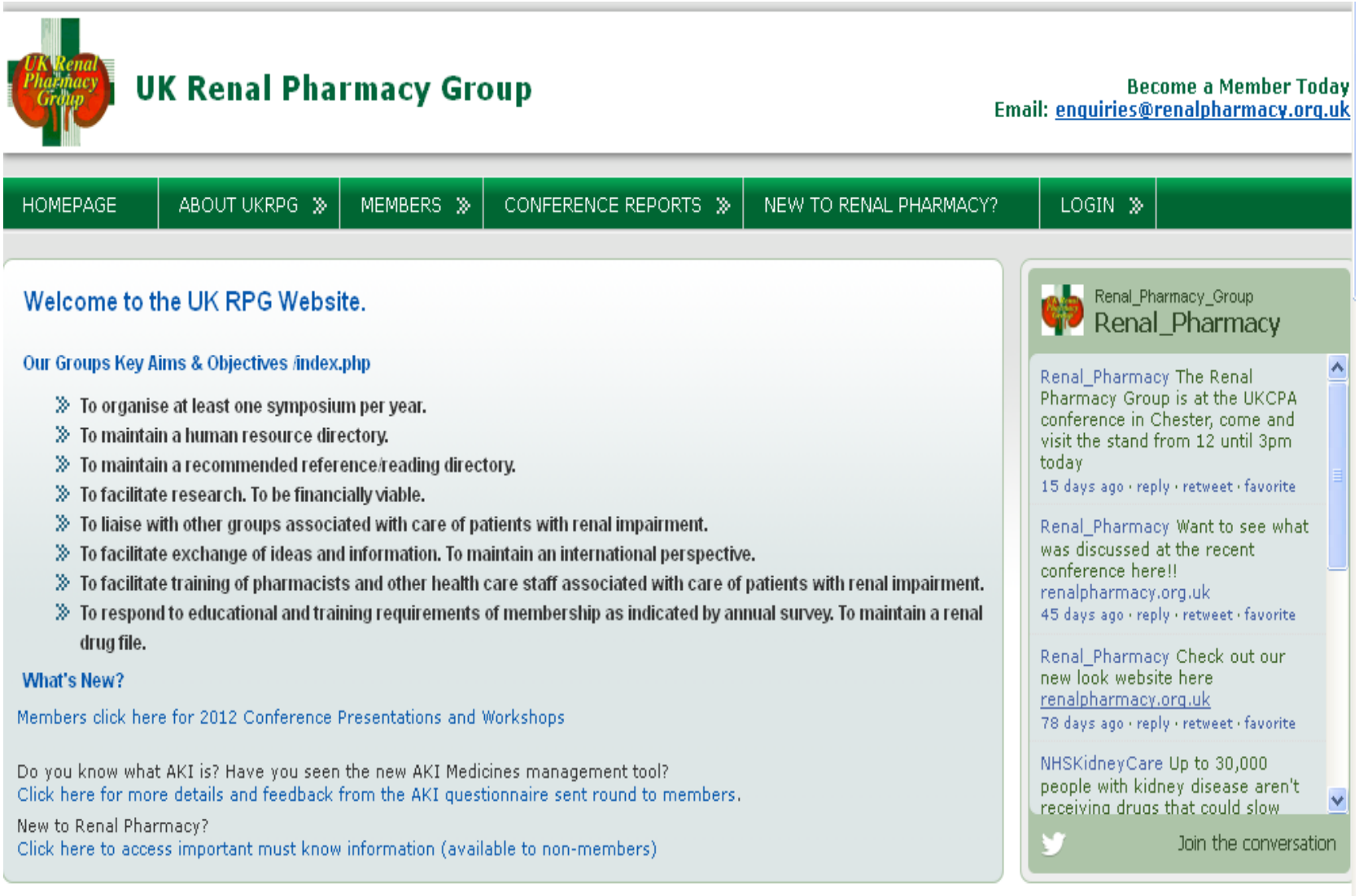
Educate the patient before discharge

- which medications to restart and when?
- what to avoid in future?
- Pass this information on to the GP / care home, etc.

? Drug holidays if ill in future

RPG website

www.renalpharmacy.org.uk



Case Study

- Mrs. 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 prn

Thromboprophylaxis:- Enoxaparin 40mg OD

Diabetes:- Sliding scale insulin whilst nil by mouth

Day 2 Post-Op

- Mrs. 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 Mrs. GF notes that her urine output has decreased.
- She mentions this to the FY1 (junior Dr.)

- PANIC !!!

U & E's

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)

What went wrong??

- GF became dehydrated and this was not managed soon enough

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- She was Rx a nephrotoxic antibiotic (gentamicin)

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- GF became dehydrated and this was not managed soon enough
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- She was already taking a diuretic & an ACEI which are potentially nephrotoxic.

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 are potentially nephrotoxic.
- The combination led to her developing AKI stage 3

NB. Urine output = AKI stage 2

Creatinine = AKI stage 3

Which drugs should be stopped at this point?

- Bendroflumethiazide & Ramipril should be witheld

- If she had started eating and had restarted her Metformin, that should be witheld.
- Simvastatin - Withold or decrease dose ?

- 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. Or switch to an alternative opiate, eg. oxycodone, hydromorphone, fentanyl.
- Monitor blood glucose $\Rightarrow$ in severe renal impairment, less insulin is required.

How about her Antibiotics?

- Gentamicin is nephrotoxic & should be avoided in all stages of AKI if possible.
- 1st gent level was not toxic but no further levels were done as her 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 & amend doses prn

How about her post-op fluid management?

- Her U&E's & reduced urine output suggest that Mrs. GF became dehydrated around Day 3-4.
- This was not managed adequately (pushing oral fluids or Rx-ing IV fluids)
- Dehydration + Nephrotoxic drugs = AKI
- 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-start her medications (Ramipril, bendroflumethiazide, metformin)
- Discuss “drug holidays” with her, eg, in case of vomiting/diarrhoea.

Any Questions?

Renal Transplantation Case Study

Case study and questions

Day 1 (am) Mr JO, a 38-year-old man, was urgently admitted from home for a cadaveric renal transplant. He had a 6-year history of renal impairment, having first presented to his general practitioner (GP) with persistent headaches. He had also complained of weakness, fatigue and generally 'not feeling well', and on investigation was found to have a markedly elevated serum creatinine. He had been diagnosed as having chronic kidney disease (CKD). For the 5 years prior to this admission he had been in end-stage renal failure (CKD5), receiving intermittent haemodialysis three times a week while awaiting a transplant. A donor kidney was now available.

His drug therapy on admission was:

- Lanthanum carbonate (Fosrenol) 1000 mg), one tablet three times daily
- Alfacalcidol 1 microgram three times a week
- Folic acid 5 mg daily
- Ketovite, one tablet daily
- Amlodipine 10 mg once daily
- Perindopril 4 mg daily
- Venofer 100 mg intravenously (IV) once a month
- Darbepoetin 60micrograms intravenously once a week

Mr JO was a non-smoker who rarely drank alcohol. He was married with an 8-year-old daughter and worked as a draughtsman, although he had recently been having difficulty maintaining his job owing to the frequent dialysis sessions.

On examination Mr JO was reported to be pale, but generally quite well. He was mildly hypertensive (blood pressure 135/85 mmHg) and had a pulse of 70 beats per minute (bpm), with no oedema or signs of cardiac failure. His urine output was <50 mL/day and he weighed 72 kg.

His serum biochemistry and haematology results were:

- Creatinine 672 micromol/L (reference range 60–120)
- Potassium 4.0 mmol/L (3.5–5.0)
- Calcium 2.44 mmol/L (2.1–2.6)
- Urea 12.8 mmol/L (3.0–6.5)
- Haemoglobin 10.2 g/dL (13.5–18.0)
- Phosphate 1.66 mmol/L (0.8–1.4)
- Sodium 140 mmol/L (135–146)
- White blood cells (WBC) $5.2x10^9$/L ($4–10x10^9$)
- Liver function tests within normal limits

Day 1 (pm) Mr JO was prepared for transplant. One hour before the operation he was given 20 mg basiliximab IV, 5.5 mg tacrolimus (approximately 0.075 mg/kg) orally, 1 g mycophenolate mofetil orally, 500 mg methylprednisolone IV, and 1.2 g co-amoxiclav IV. The latter was given to cover the surgery and insertion of a central line.

Q1 What are the therapeutic aims on return from theatre?

Q2 Which immunosuppressant(s) would you recommend be prescribed subsequently, and why?

On return to the renal unit later that evening, Mr JO was started on:

- Tacrolimus 5.5 mg orally, to be repeated every 12 hours
- Mycophenolate mofetil 1 g orally, to be repeated every 12 hours
- Prednisolone 20 mg orally, to be repeated once each day

Q3 How should therapy with a calcineurin inhibitor be prescribed?

O4 How should therapy with a calcineurin inhibitor such as ciclosporin or tacrolimus be monitored?

Q5 Are there any parameters that should be monitored when mycophenolate mofetil (MMF) is prescribed?

Hourly fluid balance charts, temperature, blood pressure and respiration rate monitoring were started. Mr JO initially had a urine output of 40 mL/h. He was given Hemosol (an electrolyte replacement solution containing glucose, calcium, sodium, magnesium, chloride and lactate), 1 L IV, plus the replacement volume to match his urine output each hour, using the central venous pressure (CVP) as a guide to fluid balance. The kidney initially failed to diurese, so an infusion of furosemide (10 mg/h) was set up.

Mr JO's blood pressure was noted to be 125/95 mmHg, but in order to keep the transplanted kidney well perfused, it was decided that antihypertensive therapy was not necessary. He was, however, started on omeprazole to prevent stress ulceration.

Two hours postoperatively, serum biochemistry and haematology results were:

- Sodium 139 mmol/L (135–146)
- Urea 8.3 mmol/L (3.0–6.5)
- Creatinine 412 micromol/L (60–120)
- Potassium 3.6 mmol/L (3.5–5.0)
- Haemoglobin 9.0 g/dL (13.5–18.0)
- WBC 5.8×10^9/L ($4.0–10.0 \times 10^9$)

Q6 What other medications should be prescribed for Mr JO and why?

Day 3 Mr JO was well, apyrexial, and his urine output was good (approximately 150 mL/h). Serum biochemistry and haematology results were:

- Creatinine 208 micromol/L (60–120)
- WBC 6.5×10^9/L ($4.0–10.0 \times 10^9$)
- Tacrolimus 10.2 nanograms/mL (target level 5–15 by HPLC of whole blood)

Amlodipine 10 mg orally when required was prescribed as an antihypertensive, to be used if Mr JO's diastolic blood pressure was >100 mmHg.

Q7 Would you have recommended amlodipine as an antihypertensive for Mr JO?

Day 4 Serum biochemistry and haematology results were:

- Creatinine 215 micromol/L (60–120)
- WBC 6.1×10^9/L ($4.0–10.0 \times 10^9$)

Day 5 Mr JO became pyrexial with a temperature of 37.5°C and the kidney site was slightly tender. His blood pressure was 130/100 mmHg.

Serum biochemistry and haematology results were:

- Creatinine 270 micromol/L (60–120)
- Lymphocytes 3.2×10^9/L (1.0–3.5)
- WBC 6.4×10^9/L (4.0–10.0)
- Tacrolimus 9.9 nanograms/mL (5–15)

A MAG3 (^{99m}Tc mercapto acetyl triglycene) scan showed reduced perfusion of the kidney, and it was decided that Mr JO was suffering from an episode of acute rejection, which was confirmed by renal biopsy.

Q8 How should Mr JO's acute rejection episode be managed?

Day 8 Mr JO was looking better. His serum creatinine level had fallen to 143 micromol/L and the graft site was no longer tender. His tacrolimus level (trough) was 10.3 nanograms/mL.

Day 12 Mr JO again became pyrexial, and the transplant had become tender and increased in size. There was no obvious infection.

Serum biochemistry and haematology results were:

- Creatinine 378 micromol/L (60–120)
- Lymphocytes 3.9×10^9/L ($1.0–3.5 \times 10^9$)
- WBC 5.6×10^9/L ($4.0–10.0 \times 10^9$)
- Tacrolimus 10.1 nanograms/mL (5–15)

Renal biopsy showed severe acute vascular rejection, and it was decided that Mr JO required further immunosuppression with anti-thymocyte immunoglobulin (ATG).

Q9 What precautions should be taken when starting ATG?
Q10 How should the dose be calculated?
Q11 How should ATG be administered?
Q12 Should the doses of his other immunosuppressants be adjusted during ATG therapy?

Day 12 A subclavian line was inserted and a 7-day course of ATG started. The initial dose was 125 mg (approximately 1.5 mg/kg).

Day 13 Lymphocytes 1.09×10^9/L, dose of ATG = 125 mg.

Day 14 Lymphocytes 0.31×10^9/L, dose of ATG = 75 mg.

Day 15 Lymphocytes 0.15×10^9/L, dose of ATG = 75 mg.

Day 16 Lymphocytes 0.07×10^9/L, dose of ATG omitted.

Day 17 Lymphocytes 0.14×10^9/L, dose of ATG = 75 mg.

Day 18 Lymphocytes 0.26×10^9/L, dose of ATG = 125 mg.

Day 19 Mr JO was showing a marked improvement, with increased renal perfusion shown by a MAG3 scan.

His serum biochemistry and haematology results were:

- Creatinine 131 micromol/L (60–120)
- Tacrolimus 9.8 nanograms/mL (5–15)

• WBC 3.1x10^9/L (4.0–10.0)

Mr JO was now well, with good renal function, and so he was discharged home. He was to attend outpatients twice a week initially so that his progress could be closely monitored.

Mr JO was discharged on the following medication:

- Tacrolimus 4 mg orally twice daily
- Prednisolone 15 mg orally each morning
- Omeprazole 20 mg orally once daily
- Valganciclovir 450 mg once daily
- Mycophenolate mofetil 1 g orally twice daily
- Nystatin liquid 1ml (100,000 IU) four times daily
- Aspirin 75 mg once daily
- Co-trimoxazole 480 mg once Daily

Q13 How long should Mr JO remain on immunosuppressants?
Q14 How long is Mr JO likely to require concomitant prophylactic therapy?

Day 35 Mr JO became pyrexial again, but this time the transplant site was not tender. He had developed a fever, cough and sore throat, headache and generalised muscle and joint aching.

His serum biochemistry and haematology results were:

- Creatinine 128 micromol/L (60–120)
- WBC 4.9x10^9/L (4.0–10.0x10^9)
- Platelets 329x10^9/L (140–400)
- Tacrolimus 9.2 nanograms/mL (5–15)

Blood and midstream urine samples and nasal aspirates were sent to microbiology and virology for culture.

Q15 What has predisposed Mr JO to infection?
Q16 What types of infection is Mr JO susceptible to?

Mr JO was diagnosed as having influenza A..

Q17 What course of treatment would you recommend?

Over the next 7 days Mr JO's temperature returned to normal and he appeared to be progressing well. His urine output was approximately 2 L/24 h and his generalised symptoms were improving.

At 3 months post transplant Mr JO was discharged back to the care of his GP, attending the hospital for transplant outpatient appointments every 3 months.

Day 192 Approximately 6 months post-transplant, Mr JO presented to the renal unit as an emergency. He mentioned that he had recently been treated by his GP with clarithromycin for a chest infection. His urine output had fallen to 750 mL in the last 24 hours and he had become oedematous. He was prescribed IV furosemide 40 mg twice daily to relieve the oedema. A MAG3 scan showed deterioration of renal perfusion, but a biopsy of the transplant showed no evidence of rejection. Tacrolimus nephrotoxicity was diagnosed.

Serum biochemistry and haematology results were:

- Creatinine 380 micromol/L (60–120)
- Tacrolimus level 27 nanograms/mL (5–15)
- WBC 5.3x10^9/L (4.0–10.0x10^9)

Q18 What could have caused tacrolimus toxicity?
Q19 Which drugs interact with tacrolimus?
Q20 How can tacrolimus nephrotoxicity be differentiated from rejection?

Day 540 Nearly 2 years post-transplant, Mr JO attended the transplant outpatient clinic for a routine 3-monthly check-up.

Serum biochemistry results were:

- Creatinine 197 micromol/L (60–120)
- Tacrolimus level 6.5 nanograms/mL (5–15)

He was admitted for a renal transplant biopsy, which showed evidence of chronic allograft nephropathy (CAN). The decision was made to change Mr JO's immunosuppression regimen and convert him from tacrolimus to sirolimus.

Q21 Why is sirolimus an appropriate immunosuppressive agent to use now?

Mr JO was prescribed a dose of 3 mg sirolimus once daily. Concurrently, his tacrolimus dose was halved for 1 week, then stopped completely.

Q22 When should blood levels of sirolimus be measured?

Renal Transplant Case Study - Answers

What are the therapeutic aims on return from theatre?

(a) Volume expansion using a combination of crystalloid fluids and blood/colloids.

The latter are given to maintain a high central venous pressure (CVP). Clear fluids are given to replace the urine output volume for volume. HSA (human serum albumin) or Gelofusine are usually given as the colloid.

(b) Maintain good renal perfusion, using furosemide (10 mg/h) if the urine output is <50 mL/h and ensure Mr JO is volume replete.

Mannitol has been used in the past to obtain a diuresis, but it has been shown to have an osmotic effect on renal tubules, is itself nephrotoxic, and exacerbates the nephrotoxicity of tacrolimus and ciclosporin.

(c) Control any post-operative hypertension.

This will reduce the risk of fitting and/or renal damage.

(d) Treat any systemic vasoconstriction using vasodilators.
(e) Maintain adequate immunosuppression to prevent rejection.
(f) Avoid infection.
(g) Recheck plasma electrolytes (risk of rapidly rising potassium levels) and haemoglobin (to ensure Mr JO is not bleeding) on return from theatre.

Which immunosuppressant(s) would you recommend be prescribed subsequently, and why?

Mr JO should receive combined immunosuppressive therapy with tacrolimus, mycophenolate mofetil (MMF) and corticosteroids.

Combining immunosuppressants provides a synergistic effect, allowing lower doses of each agent and a lower incidence of toxicity and rejection. Most centres use 'triple therapy' according to NICE guidelines, employing a combination of immunosuppressive agents, typically a calcineurin inhibitor (ciclosporin or tacrolimus) plus an anti-proliferative agent (azathioprine or MMF) plus steroids (prednisolone).

Rejection occurs when Mr JO's grafted kidney is recognised as 'foreign' and is attacked by his immune system. On recognition of the 'foreign' tissue, the lymphokine interleukin (IL-2) causes T lymphocytes in his lymph nodes to differentiate into T helpers (lymphocytes that provide information to B lymphocytes about the antigens), T-cytotoxic cells (killer lymphocytes that cause direct damage to 'foreign' cells) and T suppressors (which suppress B lymphocytes and prevent multiplication and antibody formation). Sensitised lymphocytes return to the graft site in large numbers, reacting with the antigenic material and releasing lymphokines ('messenger' substances), which attract macrophages to the site. These, together with T-cytotoxic cells, destroy the grafted kidney.

The risk of acute rejection is greatest in the first 3–6 months. After this period some kind of adaptive process appears to occur, although a patient may experience a rejection episode any time during the life of the transplant, especially if they omit to take their

immunosuppressive medication. Once the risk of acute rejection is less, the doses of the immunosuppressive drugs are usually reduced down to maintenance levels. This reduces the incidence and severity of side-effects without compromising graft function.

Immunosuppression either reduces to ineffectiveness the number of cells reacting against the transplanted organ or it inhibits their normal function.

Prophylactic regimens against rejection vary between transplant centres. The main immunosuppressants used are ciclosporin; tacrolimus; azathioprine; prednisolone; MMF; sirolimus; polyclonal antibodies such as anti-thymocyte globulin (ATG); monoclonal antibodies such as basiliximab, alemtuzumab and OKT_3.

(a) **Ciclosporin.** This appears to act primarily by blocking the production of IL-2 by T-helper (Th) cells through inhibition of their messenger RNA. Unlike azathioprine it is not myelosuppressive. Ciclosporin is used initially at oral doses of 5–10 mg/kg/day (it has an oral bioavailability of the order of 30%), reducing over several months to maintenance doses as low as 3 mg/kg/day without an apparent increase in graft rejection. Individual patient handling of ciclosporin is very variable and doses must be tailored according to ciclosporin levels. Toxic effects include nephrotoxicity and hypertension as well as hirsutism, acne and gum hypertrophy.

(b) **Tacrolimus (FK506).** This is a macrolide immunosuppressant that suppresses T-cell activation and T-helper cell-dependent B-cell proliferation, as well as the formation of lymphokines such as IL-2 and IL-3, and beta-interferon through similar mechanisms to ciclosporin. Oral absorption is estimated to be approximately 20% in kidney transplant patients. An initial dose of 0.1 mg/kg/day in two divided doses is generally used, again with the dose being adjusted according to blood levels. As with ciclosporin, the side-effects of tacrolimus include nephrotoxicity and hypertension; however, it does not cause the other more cosmetic side-effects of ciclosporin, and if anything may be associated with causing alopecia.

Studies comparing ciclosporin with tacrolimus as primary immunosuppressants following renal transplantation have shown tacrolimus to be the more potent of the two, and to be associated with a lower incidence of acute allograft rejection. Tacrolimus has been shown to cause nephrotoxicity, neurotoxicity and cardiotoxicity, although the incidence of these side-effects is much less with the lower doses now used in clinical practice.

(c) **Azathioprine.** This is metabolised to 6-mercaptopurine, which disrupts purine metabolism and consequently interferes with DNA synthesis and cell proliferation, thereby reducing lymphocyte function.

(d) **MMF.** This is a prodrug of mycophenolic acid, and acts by inhibiting the intracellular *de novo* pathway for purine synthesis. Most cells also possess a salvage pathway, but T lymphocytes do not, thereby rendering them unable to synthesise purines, which in turn prevents successful cell replication. MMF is therefore similar to azathioprine, but is more selective in its pharmacological effect. Its main side-effects are gastrointestinal upsets and increased susceptibility to infections, especially viral illnesses. Another formulation, -mycophenolate sodium EC, is now available. It is purported to have a lower incidence of gastrointestinal side-effects, although the evidence does not support this claim.

(e) **Corticosteroids.** These have several possible mechanisms of action, which include anti-inflammatory activity (which profoundly alters the effector phases of graft rejection, including macrophage function), blocking the production of IL-1 and IL-2 (lymphokines), and causing the sequestration of circulating lymphocytes and monocytes in lymphoid tissue, particularly the bone marrow.

Adverse effects are commonly encountered and include cushingoid appearance,

hypertension, hyperglycaemia, weight gain, increased susceptibility to infection and personality changes. Long-term complications include skin and muscle atrophy and avascular necrosis of bone.

(f) **Sirolimus** is a novel immunosuppressive agent that inhibits T-cell proliferation by inhibiting cytokine-mediated signal transduction pathways. It has been used in combination with ciclosporin and prednisolone to lower the incidence of early acute rejection. However, its place in therapy has now been defined by NICE guidelines as in the treatment of chronic rejection, or CAN. Side-effects include hyperlipidaemia, anaemia and severe aphthous ulceration.

(g) **Monoclonal antibodies**, e.g. basiliximab (chimeric) and alemtuzumab (humanised). Basiliximab binds to the CD25 antigen on human T lymphocytes to prevent them from expressing IL-2, thereby inhibiting the activation of T-cytotoxic cells and hence effectively hiding the graft from the recipient's immune system, resulting in a reduced incidence of acute rejection. It is relatively expensive, but NICE guidelines recommended that it be given to all renal transplant recipients. OKT3 is a murine monoclonal antibody used only for the treatment of severe acute rejection unresponsive to other therapies. It is associated with side-effects such as rigors, high fever, abdominal pain and pulmonary oedema, and is rarely used nowadays. Alemtuzumab, a drug originally developed for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL), has also been used as part of the pre-conditioning regimen for bone marrow transplantation. There is now increasing evidence that it can be successfully used at a low dose as induction therapy prior to solid organ transplantation, and is used routinely in several transplant units in the UK. It is associated with side-effects such as infusion reaction and profound immune system suppression, with an increased susceptibility to infection.

(h) **Polyclonal antibodies**, e.g. ATG (rabbit). ATG removes circulating T lymphocytes and blocks their formation and proliferation in response to antigenic stimuli. It reacts with a wide variety of receptors on T cells. Before the advent of the newer monoclonal antibodies a 10-day course of low-dose ATG was given as induction therapy after a 'high-risk' transplant, but its use now tends to be reserved for salvage therapy in patients whose acute vascular rejection episodes are not responding to high-dose steroids.

How should therapy with a calcineurin inhibitor be prescribed?

All calcineurin inhibitors should be prescribed by brand name. Since the patent for tacrolimus expired in 2010, numerous generic preparations have become available. The same has happened for ciclosporin. Evidence suggests that the generic versions may not have identical pharmacokinetic and pharmacodynamic properties to the original branded versions. As it is critical that the plasma levels of these drugs be kept as steady as possible to prevent toxicity or rejection, it is not desirable for patients to switch between brands in an uncontrolled fashion. To support this, the MHRA has issued a statement saying that

(i) all calcineurin inhibitors (ciclosporin and tacrolimus) must be prescribed by brand name, and

(ii) patients may only be switched between brands by a specialist transplant unit, with appropriate drug monitoring.

How should therapy with a calcineurin inhibitor such as ciclosporin or tacrolimus be monitored?

By regular review of blood levels of the drug itself, glucose and potassium levels, liver function tests, plasma lipid levels, and blood pressure.

(a) **Drug level monitoring.** Ciclosporin levels may be monitored in two ways:

(i) Trough levels should be taken before the morning dose every 2–3 days until therapy is stabilised, then monthly, or 2–3 days after any dosing change. Times to achieve peak levels are variable (1–6 hours after oral dosing); 12-hour trough levels provide more consistent results. The risk of rejection is greatest shortly after transplant, and pathophysiological changes occur rapidly. The half-life of ciclosporin has been reported to be 5–20 hours, and hence 2–3 days is the time usually required to achieve steady-state concentrations.

(ii) Profiling of the absorption of ciclosporin is a concept of therapeutic drug monitoring designed to further optimise the clinical efficacy of the drug while at the same time minimising adverse effects. A trough (C_0), followed by a single blood concentration measured 2 hours after ciclosporin administration (C_2) to determine the area under the curve (AUC) has been shown to be a significantly more accurate predictor of total drug exposure than trough concentrations alone. Although this would be the ideal way to monitor exposure to ciclosporin in all transplant patients, in practice it is difficult to achieve this in the outpatient clinic as it requires two blood samples to be taken exactly 2 hours apart. Hence its use is often restricted to the inpatient setting when initiating therapy.

Ciclosporin in blood distributes between erythrocytes (50%), leukocytes (10%) and plasma (40%). Whole blood, plasma or serum samples may be used, but quoted therapeutic ranges differ depending on the sample type and the assay method. Several assay techniques are available: high-performance liquid chromatography (HPLC) is regarded as the gold standard, but is laborious and costly. Immunoassays such as EMIT and ELISA have been developed in order to measure microamounts of drugs in human biological fluids. Using a standard triple-therapy immunosuppression regimen, it is usual to aim for 12-hour ciclosporin trough levels of 250–350 nanograms/mL for the first 2 months, reducing to a target level of 150–250 nanograms/mL for the next 4–6 months. Thereafter, in a stable graft, levels of 100–150 nanograms/mL or less are acceptable. These levels vary according to local protocols.

(iii) Tacrolimus trough level (C_0) monitoring provides a good correlation with the AUC, although research has also been carried out to see whether C_2, C_3, C_4 and C_5 monitoring can provide a better correlation. In practice, 12-hour trough levels are routinely measured for tacrolimus, with most units aiming for whole blood levels of 10–15 nanograms/mL for the first 2 months post transplant, reducing over the following year so that by 12 months post transplant levels of 5–10 nanograms/mL are achieved. The half-life of tacrolimus has been reported to be 12–16 hours, so

again 2–3 days is the time usually required to achieve steady-state concentrations, both on initiating therapy and after each dose change.

(b) **Liver function tests.** Reversible dose-related hepatotoxicity may be seen with both drugs, resulting in increases in serum bilirubin and liver enzymes.

(c) **Serum glucose levels.** Hyperglycaemia may develop as a result of ciclosporin, tacrolimus or concomitant corticosteroid therapy.

(d) **Serum potassium levels.** Toxic levels of ciclosporin or tacrolimus are often associated with hyperkalaemia.

(e) Blood pressure monitoring. Hypertension is frequently observed and has been associated with seizures. It is not generally dose related, but may result from the vasoconstrictive effects of these drugs.

(f) **Plasma lipid levels.** As ciclosporin and tacrolimus can both cause reversible increases in plasma lipids, serum cholesterol and triglycerides should be regularly monitored.

Are there any parameters that should be monitored when mycophenolate mofetil (MMF) is prescribed?

MMF therapy is associated mainly with dose-dependent reversible bone marrow suppression, and with disturbances of the gastrointestinal tract.

Because of the risk of developing neutropenia, the patient should have a full blood count taken once a week for the first month of therapy, then every 2 weeks for months 2 and 3 of therapy, then monthly for the rest of the first year. If the patient develops neutropenia (defined as a neutrophil count $<1.3 \times 10^3$/microL), it may be appropriate to interrupt or discontinue MMF therapy. Patients should also be monitored for signs of infection, unexpected bruising, bleeding, or any other manifestations of bone marrow suppression.

MMF therapy is also associated with an increased risk of bacterial and fungal infection, especially viral infections. In addition, the patient will be more susceptible to opportunistic infections such as cytomegalovirus (CMV), and so should be appropriately monitored for signs of infection, e.g. by measuring CMV viral load by the quantitative Polymerase Chain Reaction (PCR) method.

Mycophenolate is well known to cause adverse effects such as nausea, vomiting and diarrhoea. There is also an increased risk of further gastrointestinal tract adverse events such as ulceration, haemorrhage and perforation.

Blood levels of the metabolite mycophenolic acid may be measured, although this is not routine practice in all transplant units. Typically a 12-hour trough level is measured, the therapeutic range being 2–4 micrograms/mL.

What other medications should be prescribed for Mr JO, and why?

As well as the immunosuppression therapy to prevent graft rejection, Mr JO will also require prophylactic therapy.

Most transplant units have their own standard prophylaxis regimen, although they are all variations on an original theme. Typically, patients will be prescribed aspirin 75 mg daily, as there is evidence that the antiplatelet effect of low-dose aspirin helps to prevent thrombosis of the transplanted renal artery, thereby maintaining good perfusion of the transplanted kidney. Most units will also prescribe some form of gastric mucosal protection, either as ranitidine or as a proton pump inhibitor, as patients are initially on a relatively high dose of steroids and are

also at increased risk of developing stress ulceration.

Other therapies that are frequently used include antifungal prophylaxis with either nystatin or amphotericin mouthwash, and co-trimoxazole 480 mg daily for the prevention of *Pneumocystis carinii* (*Pneumocystis jirovici*) infection.Since most renal transplant units use the powerful combination of tacrolimus and mycophenolate as their standard immunosuppression regimen, patients are now at increased risk of contracting or re-activating cytomegalovirus (CMV) disease. To try and prevent this, the majority of transplant units now prescribe prophylactic valganciclovir for up to 6 months post-transplantation.

Some units maintain patients on vitamin D (alfacalcidol) therapy and erythropoietin injections for a month or so post transplant, as the synthetic functions of the kidney may take a while to work at full capacity and the patient may be at risk of exacerbating their renal bone disease or their renal anaemia. However, this practice is not universal, and other units stop these drugs immediately after transplantation. Many transplant patients will require statin therapy to reduce cholesterol levels. Concomitant therapy with a calcineurin inhibitor and a statin carries an increased risk of myositis or rhabdomyolysis, so the lowest possible dose of statin should be used and the patient carefully monitored for adverse effects.

Would you have recommended amlodipine as an antihypertensive for Mr JO?

Yes.

Renal patients often have high renin profiles, resulting in systemic vasoconstriction and hypertension. Vasoconstriction may also be catecholamine mediated, and this may also partly explain the hypertension associated with ciclosporin therapy. Vasodilators are probably the most appropriate method of reducing the blood pressure acutely.

Amlodipine is a vasodilator and does not require dosage adjustment in renal failure. It has a longer duration of action than nifedipine, and tends not to be associated with some of the undesirable effects that nifedipine can cause, such as severe headache.

Research has indicated that calcium-channel blockers may cause increases in glomerular filtration rate (GFR) and renal blood flow, despite a substantial reduction in blood pressure. As vasoconstriction appears to play a role in acute as well as chronic ciclosporin or tacrolimus-induced renal dysfunction, amlodipine may counteract these effects on renal vasculature. However, some patients on calcium-channel blockers develop marked vasodilation-dependent oedema, which may cause alarm by suggesting renal impairment.

IV antihypertensives such as glyceryl trinitrate, hydralazine and labetalol are usually reserved for more severe hypertension. Overzealous treatment of hypertension could compromise the function of the transplanted kidney by reducing renal perfusion.

How should Mr JO's acute rejection episode be managed?

Methylprednisolone 500 mg to 1 g IV in 100 mL of either glucose 5% or sodium chloride 0.9%, administered over 60 minutes once daily for 3 days.

Acute rejection is most commonly seen 5–10 days post transplant. The three agents most frequently used to treat acute rejection are methylprednisolone and both monoclonal and polyclonal antibodies.

(a) **Methylprednisolone.** This is the cheapest alternative and has been demonstrated to reverse 72–83% of first allograft rejections. Up to two consecutive rejection episodes may be treated with this drug. Thereafter, concern for the cumulative corticosteroid dose given

increases and other strategies need to be considered, depending on the degree of severity of the rejection as determined by transplant renal biopsy.

(b) **Monoclonal (OKT3) and polyclonal (ATG) antibodies**. These are very expensive and their use tends to be reserved either for third or subsequent rejection episodes, or for severe acute rejection not responsive to IV methylprednisolone. It should be noted that the chimeric/humanised monoclonal antibodies basiliximab and daclizumab are ineffective in the treatment of an established severe rejection episode.

Methylprednisolone 750 mg/day for 3 days is thus the preferred option for Mr JO's first rejection episode.

What precautions should be taken when starting ATG?

(a) A test dose of ATG (5 mg diluted in 100 mL 0.9% sodium chloride administered over 1 hour) is often given first. This is to check Mr JO's tolerance, as ATG has been associated with anaphylaxis, due to allergy to rabbit protein.

(b) Ensure that IV epinephrine (adrenaline), hydrocortisone and chlorphenamine are available and ready for use during administration of the first dose, in case they are required urgently.

(c) Administer ATG via a large vein, preferably a central line, to avoid thrombophlebitis and localised pain.

How should the dose be calculated?

The initial dose is 1.5–2.5 mg/kg ATG (Genzyme brand) per day until the biological signs and symptoms improve. A typical course would be 5–10 days in duration. Each subsequent day's dosage is determined by monitoring the patient's full blood count, including WBC and lymphocytes. The aim is to maintain a WBC count of 2–4 3 10^9/L and a total lymphocyte count of 0.1–0.4 3 10^9/L. ATG dosing schedules vary with local protocols.

Some centres administer ATG using alternate-day regimens to minimise the risk of neutropenia. If the total WBC is <3 x 10^9/L but >2x10^9/L , the next dose of ATG should be halved, but if the total WBC is <2x10^9/L, the next dose of ATG should be omitted.

Platelets should be similarily monitored during treatment and any thrombocytopenia <100□000/mm^3 necessitates halving the dose; a count <50 000/mm^3 will require interruption of treatment.

How should ATG be administered?

Each 25 mg vial should be diluted in 50 mL 0.9% sodium chloride, but in practice, on the prescriber's responsibility, a higher concentration (e.g. 1 mg/mL) may be administered, so that the sodium and fluid load is not too great for the patient.

Alternatively, glucose 5% may be used as the diluent. The infusion should be administered over not less than 6 hours (usually 8–12 hours) via a large vein (preferably via a central line). A 0.22 micrometre inline filter should be used to avoid the inadvertent administration of particulate matter following reconstitution. Any associated fever or shivering may be relieved by administering chlorphenamine or hydrocortisone IV 1 hour prior to the infusion.

Should the doses of his other immunosuppressants be adjusted during ATG therapy?

Mr JO's MMF therapy should be reduced or stopped while the ATG course is in progress. Both drugs are myelosuppressive, and concurrent use may cause a marked leukopenia, necessitating the withdrawal of the ATG. The prednisolone and tacrolimus doses should initially be unchanged; however, 2 days before the end of the ATG course the prednisolone dose should be doubled, as practice has shown that episodes of acute rejection may occur shortly after stopping ATG.

Immediately the ATG course finishes the MMF should be restarted at a reduced dose, which should be gradually increased (e.g. weekly) if the WBC count remains stable. The prednisolone therapy is then reduced back to the maintenance dose of 20 mg each morning. The tacrolimus should remain at the current dose, provided blood level monitoring indicates that this is still appropriate.

How long should Mr JO remain on immunosuppressants?

Immunosuppressive therapy can rarely be stopped completely after transplant. Even the briefest cessation may precipitate an acute rejection episode; however, intensive immunosuppression is usually only required for the first few weeks post transplant or during a rejection crisis. Subsequently the graft may often be maintained on much lower doses of immunosuppressive drugs, and hence fewer adverse drug effects are experienced by the patient.

In addition, the aim of immunosuppressive therapy nowadays is to tailor the drug regimen to the needs of the individual patient, in order to maximise efficacy and at the same time minimise side-effects. Although acute rejection episodes are not as common and are easily treated, even modern immunosuppressive agents appear to have little effect on chronic rejection – or, as it is now known, chronic allograft nephropathy (CAN). The precise mechanism of this process is not fully understood, but there is some evidence that long-term use of some immunosuppressive drugs such as ciclosporin or tacrolimus may contribute to the process. Long-term use of these agents is also known to be nephrotoxic, so there is now a move to switch patients to agents with an antiproliferative effect, such as sirolimus or mycophenolate, which theoretically will prevent the histological changes seen in CAN and so prolong the life of a transplanted kidney.

How long is Mr JO likely to require concomitant prophylactic therapy?

Omeprazole therapy is likely to continue while Mr JO remains on high-dose prednisolone. Some units discontinue such therapy once the patient is down to a maintenance dose of 5 mg daily, whereas others continue with therapy indefinitely. Other prophylactic agents such as amphotericin and co-trimoxazole are likely to be stopped 3–6 months post transplant, once the patient is on lower doses of maintenance immunosuppression. Prophylactic oral amphotericin may be needed if Mr JO requires any further courses of antibiotics.

What has predisposed Mr JO to infection?

Corticosteroids, MMF and tacrolimus all increase Mr JO's susceptibility to infection. In addition, Mr JO had recently undergone a course of ATG, which would impair his lymphocyte function and hence his resistance to infection for several months afterwards.

What types of infection is Mr JO susceptible to?

During the first 1 or 2 months post transplantation patients are susceptible to most opportunistic infections.

Mr JO could develop fungal infections (e.g. Candida, Aspergillus), protozoal infection (e.g. Pneumocystis carinii (*Pneumocystis jiroveci*) pneumonia (PCP)), viral infection (e.g. CMV, herpes, Epstein-Barr (EBV) and BK virus) or common or uncommon bacterial infections (including reactivation of past tuberculosis). He could also contract common illnesses such as flu more easily than usual, and find it harder to recover from such infections.
CMV disease is very common in renal transplant patients, especially in the first few months. It is characterised by a swinging fever and can manifest as pneumonitis, accompanied by breathlessness and blood oxygen desaturation, interstitial shadowing on the chest X-ray, and a reduced platelet and WBC count. Other organs that can be affected are the liver (causing CMV hepatitis, with raised liver enzymes), the gastro-intestinal tract (causing acute diarrhoea) and the bone marrow (resulting in severe bone marrow depression).
Influenza A and its sub-types are very easily contracted by patients on immunosuppresant therapy, and generally result in a more severe illness than that experienced by the general population. Often necessitating admission to hospital.

What course of treatment would you recommend?

Estimating Mr JO's creatinine clearance does not pose quite the same problems as in the immediate post-transplant period, as his serum creatinine results now appear more stable. The Cockcroft and Gault formula is not always accurate in transplant patients, because they have only one functioning kidney, and Mr JO's estimated creatinine clearance is 70mL/min. The hospital lab reports his eGFR to be 58 ml/min/1.73m^2.

Oseltamivir is a pro-drug that is extensively metabolised in the liver to the active carboxylate metabolite which in turn is entirely excreted in the urine. Hence one would need to adjust the dose of oseltamivir according to the patient's level of renal function.For Mr JO's level of renal function the Summary of Product Characteristics recommended that the appropriate dose of oseltamivir was 30mg twice daily. However, in immunocompromised patients there have been instances of undertreatment with the SPC doses. The UK Renal Association guidelines recommend a dose of 75mg twice daily for 5 days. During treatment, Mr JO's renal and liver function and full blood count should be closely monitored to detect signs of oseltamivir toxicity. It would also be wise to reduce temporarily the dose of MMF, as its use can hinder the immune response to viruses, making it much harder to eradicate them effectively.

What could have caused tacrolimus toxicity?

Co-administration of clarithromycin and tacrolimus.

Acute reversible nephrotoxicity has been associated with tacrolimus levels >20 nanograms/mL, although it can occur at levels much lower than this. Mr JO's tacrolimus levels may have been increased by concomitant clarithromycin therapy. Studies in healthy adults suggest that clarithromycin can substantially reduce the plasma clearance of tacrolimus, by inhibition of the cytochrome P450 3A4 system. Patients who experience tacrolimus toxicity often exhibit a fine tremor and are found to be hypertensive, owing to vasoconstriction within the kidney. It is also worth noting that it is most unlikely that the administration of IV furosemide 40mg worsened

Mr JO's established tacrolimus nephrotoxicity. Only diuretic doses large enough to cause a marked hypovolaemia would be likely to have such an adverse effect.

Which drugs interact with tacrolimus?

(a) Drugs reported to increase the nephrotoxicity of tacrolimus include aciclovir, ganciclovir, aminoglycosides, amphotericin B, co-trimoxazole, ciprofloxacin, furosemide (and other potent diuretics), cephalosporins, vancomycin, gyrase inhibitors and non-steroidal anti-inflammatory drugs.

(b) Drugs reported to increase tacrolimus levels, by inhibition of metabolism, include clarithromycin, erythromycin, ketoconazole, fluconazole, itraconazole, methylprednisolone, protease inhibitors, tamoxifen, omeprazole, danazol, -diltiazem and verapamil.

(c) Drugs reported to reduce tacrolimus levels, by induction of metabolism, include phenytoin, phenobarbital, carbamazepine, rifampicin, metamizole and isoniazid.

(d) Tacrolimus is extensively bound to plasma proteins, so there is the possibility of interactions with other drugs known to have high affinity for plasma proteins, e.g. oral anticoagulants and oral antidiabetic agents.

How can tacrolimus nephrotoxicity be differentiated from rejection?

Tacrolimus nephrotoxicity is difficult to differentiate from organ rejection.

Differentiation is necessary to determine whether an increased or reduced dose of immunosuppressants is required.

Rejection is usually associated with fever, low urine output, a rapidly rising serum creatinine level, graft tenderness or enlargement and MAG3 scans that show reduced renal perfusion. Tacrolimus levels are usually low or within the trough reference range, and on further reduction of the dose there is either no change or a worsening of renal function.

Tacrolimus toxicity is usually associated with an afebrile patient, low urine output, slowly or rapidly increasing creatinine levels, non-tender grafts and MAG3 scans that show reduced renal perfusion. Serum potassium levels may be high and the patient may be hypertensive. Tacrolimus levels are usually high (>15–20 nanograms/mL) and reduction of the tacrolimus dose improves renal function.

The differentiation of the two is, however, often unclear and histological examination is frequently required. This may reveal renal tubular atrophy and interstitial scarring in the case of tacrolimus toxicity. Small blood vessels (arterioles) may show nodular thickening. The mechanism for tacrolimus nephrotoxicity is unclear, but one proposal is that the drug reduces renal perfusion by interfering with renal prostaglandin release, which may explain any accompanying hyperkalaemia. Tacrolimus toxicity usually responds to a reduction in dose; however, if it appears that the patient is exhibiting signs of toxicity even though the blood levels are not particularly high, then the intolerant patient may be switched to an alternative agent, e.g. sirolimus.

Why is sirolimus an appropriate immunosuppressive agent to use now?

Sirolimus is a second-generation immunosuppressant. It is an mTOR (mammalian Target of Rapamycin) inhibitor which is also known as rapamycin. Despite its similar name, it is not a calcineurin inhibitor (CNI) like tacrolimus or ciclosporin. However, it has a similar

suppressive effect on the immune system. Sirolimus inhibits the response to interleukin-2 (IL-2) and thereby blocks the activation of T and B cells. In contrast, tacrolimus and ciclosporin inhibit the production of IL-2.

As CAN evolves there are two distinct phases. The initial phase shows early tubulointerstitial damage from ischaemic injury, evidence of prior severe rejection and subclinical rejection; the later phase is characterised by microvascular and glomerular injury. Progressive luminal narrowing, increasing glomerulosclerosis and additional tubulointerstitial damage are associated with the use of CNIs. Once this damage is established it is irreversible, resulting in declining renal function and ultimately graft failure.

The chief advantage of sirolimus over the calcineurin inhibitors is that it is not toxic to kidneys. Because of its antiproliferative effects it can impair wound healing and cause wound dehiscence, so it tends not to be used in the immediate post-transplant period; however, there is now a large body of evidence which demonstrates that switching from a CNI-based to a sirolimus-based immunosuppression regimen can impede the progression of CAN, and in some cases even reverse some of the damage to the graft. NICE guidance stipulates that these are exactly the circumstances under which sirolimus is to be prescribed. As Mr JO is exhibiting signs of CAN, switching him from tacrolimus to sirolimus would be a logical decision in an attempt to preserve the function of his graft.

When should blood levels of sirolimus be measured?

Sirolimus has a long half-life (53–63 hours), so it will take approximately 1 week to reach steady state. Hence the tacrolimus was continued at half-dose for a week after initiation of the sirolimus therapy to ensure the patient maintains therapeutic levels of immunosuppressive therapy during the switch-over period.

It is recommended that when initiating therapy, and after each dose change, a minimum of 7 days elapse before blood levels are checked. Levels should then be checked at weekly intervals until the patient is in the desired therapeutic range. Once the patient has been stabilised on this therapy, levels need only be checked at each clinic visit. As with other immunosuppressive agents, trough levels are measured: in this case 24-hour trough levels, as sirolimus is taken once daily. Again, Mr JO should be advised not to take his sirolimus on the days he is coming to clinic until he has had his blood tests taken.

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Acute kidney injury

Case study and questions

Day 1 Mrs NC, a 69-year-old woman, was admitted urgently at the request of her general practitioner (GP). His letter detailed the following history: Mrs NC had collapsed at home, where she had been complaining of nausea and loss of appetite for 2 or 3 days (her current weight was 61 kg) and had vomited two or three times in the previous 24 hours. She had fallen 2 days ago but had recovered quickly.

She had a long history of biventricular cardiac failure which had been controlled for some time with:-

Furosemide 80 mg in the morning,
Isosorbide mononitrate MR 60mg once daily,
Ramipril 5 mg once daily,

although a degree of ankle oedema had recently required an increase in the dose of furosemide to 120 mg in the morning. However, this increase had precipitated gout, for which the pain had been treated with diclofenac 50 mg three times daily for the previous 21 days.

The patient herself was a poor historian. On examination she was pale and tired looking, with sunken eyes. Her pulse rate was 120 beats per minute (bpm) and her blood pressure was 105/70 mmHg lying and 85/60 mmHg standing. She had no ankle oedema and there was no evidence of pulmonary oedema. Her extremities were cold and there was a marked reduction in skin turgor.

Mrs NC's serum biochemistry results were:

- Sodium 131 mmol/L (reference range 135–150)
- Potassium 5.5 mmol/L (3.5–5.0)
- Bicarbonate 17 mmol/L (22–31)
- Creatinine 312 micromol/L (60–110)
- Urea 27.2 mmol/L (3.2–6.6)
- Glucose 4.8 mmol/L (3.5–6.0)
- Mean cell volume 71 fL (77–91)
- Osmolarity 306 mmol/kg (275–295)

A diagnosis of pre-renal Acute Kidney Injury (AKI) was made.

She was prescribed an infusion of 1 L sodium chloride 0.9% every 4–6 hours.

The following investigations were requested: full blood count; culture and sensitivity of blood and urine; 24-hour urine collection for determination of creatinine clearance; urinary sodium, urea and osmolarity; chest and abdominal X-ray.

Q1 Could Mrs NC's drug therapy have contributed to her renal problems?
Q2 What is the aim of intravenous (IV) sodium chloride 0.9% therapy?
Q3 What would you include in a pharmaceutical care plan for Mrs NC?
Q4 Which methods of assessing and monitoring Mrs NC's status would you recommend?

Day 2 The 24-hour urine collection yielded a volume of only 290 mL.

The low urine volume obtained despite the concurrent volume expansion indicated that further measures were required to try to establish a urine output, and so furosemide 250 mg was administered by slow IV infusion. A further dose of 500 mg was administered after 6 hours, but neither produced an increase in urine production. A diagnosis of established acute kidney injury (AKI) was made. The following recommendations were proposed: daily fluid charts; daily weights; daily serum urea and electrolyte estimations.

Q5 Would mannitol have been an appropriate alternative to high-dose furosemide therapy?
Q6 Would you have recommended the use of high-dose IV furosemide at this point?
Q7 Would you have used dopamine in this patient?

Day 4 Mrs NC complained of having diarrhoea, which was described by the nursing staff as black and tarry in appearance. A full blood count revealed a normochromic and normocytic anaemia with a haemoglobin of 81 g/L (120–160 g/L). Omeprazole 20 mg at night was prescribed.

Serum biochemistry results revealed the following:

- Sodium 137 mmol/L (135–150)
- Potassium 7.1 mmol/L (3.5–5.0)
- Calcium 2.04 mmol/L (2.25–2.6)
- Bicarbonate 19 mmol/L (22–31)
- Phosphate 1.8 mmol/L (0.9–1.5)
- Albumin 34 g/L (33–55)
- Urea 31.7 mmol/L (3.2–6.6)
- Creatinine 567 micromol/L (60–110)
- pH 7.28 (7.36–7.44)

A 10mL bolus dose of calcium gluconate 10% was administered IV, followed immediately by an IV injection of 10 units of soluble insulin with 50 mL of 50% glucose solution; the latter was written up for three further administrations over the next 12 hours. Therapy with Calcium Resonium 15 g orally four times daily was also initiated. A monitor was ordered to observe for cardiac toxicity, but no electrocardiogram (ECG) changes were apparent.

Q8 What factors may have contributed to Mrs NC's low haemoglobin? Is omeprazole therapy appropriate?
Q9 Is Mrs NC's hyperkalaemia being treated appropriately? Should her hypocalcaemia, hyperphosphataemia and acidosis be treated at this point?
Q10 What factors should be considered when initiating drug therapy for a patient with AKI?

Day 5 Mrs NC complained of breathlessness which was increased on lying flat, and examination revealed crepitations in both lung bases. She complained of nausea and was noted to be drowsy and to have developed a flapping tremor.

Her serum biochemistry results included:

- Potassium 6.6 mmol/L (3.5–5.0)
- Bicarbonate 17 mmol/L (22–31)
- Urea 40.5 mmol/L (3.2–6.6)
- Creatinine 588 micromol/L (60–110)
- pH 7.24 (7.36–7.44)

It was decided to treat Mrs NC by haemodialysis, and arrangements were made for the insertion of a temporary central dialysis catheter.

Q11 What were the indications for dialysis in Mrs NC?
Q12 What forms of dialysis therapy are available, and what are their advantages and disadvantages?

Q13 What factors affect drug therapy during dialysis?

Day 10 Mrs NC developed a temperature of 39.6°C and a tachycardia of 120 bpm. Subjectively she complained of headache and feeling 'awful'. A full blood count revealed a neutrophil count of 10.5×10^9/L ($2.2–7.0 \times 10^9$). A diagnosis of septicaemia was made, and blood samples were sent for culture and sensitivity. All indwelling catheters were removed and the following therapy was written up:

- Cefotaxime 1 g IV every 12 hours
- Gentamicin 80 mg IV every 24 hours
- Metronidazole 500 mg IV every 8 hours

Q14 Is this therapy appropriate for Mrs NC's septicaemia?

Q15 What are the dangers associated with prescribing gentamicin for Mrs NC? How should her gentamicin therapy be monitored?

Day 11 Mrs NC complained of acute abdominal pain, with non-specific findings on physical examination. The decision was made to send her for a computed tomography (CT) scan of her abdomen with contrast enhancement, so she was prescribed sodium bicarbonate 1.26% IV, 500mL prior to the scan and another 500 mL afterwards.

Q16 Why was Mrs NC prescribed the sodium bicarbonate? What else can be used for the same indication?

Day 12 Microbiological assays revealed the infective organism to be *Staphylococcus aureus*. Gentamicin and metronidazole therapy was discontinued and, as Mrs NC was clinically much improved, cefotaxime was continued as sole antibiotic therapy.

Day 17 Mrs NC reported that she was starting to pass increasing volumes of urine again.

Day 19 Mrs NC, now free of infection, passed over 4 L of urine. It was felt that she was over the worst and that she would continue to improve.

Q17 Did Mrs NC follow the normal course of AKI? What is her prognosis?

AKI Case Study Answers

Could Mrs NC's drug therapy have contributed to her renal problems?

Yes. Mrs NC's furosemide, ramipril and/or diclofenac therapy may have contributed to her admission.

Mrs NC demonstrates many of the traditional signs of sodium and water depletion, including tachycardia, hypotension, postural hypotension, reduced skin turgor, reduced ocular tension, collapsed peripheral veins and cold extremities. Evidence that Mrs NC had suffered from AKI can be seen by the elevation in her serum urea and creatinine levels, together with the other biochemical abnormalities. The symptoms Mrs NC suffers which cannot be explained by the sodium and water depletion (nausea, loss of appetite and vomiting) can be attributed to her high blood urea level (uraemia). Acute kidney injury (AKI) is defined as a rapid deterioration (several hours to several days) of renal function secondary to a physiological or toxicological insult to the kidneys, and associated with the accumulation of nitrogenous waste in the body.

One of the physiological responses to sodium and water depletion is a reduction in renal perfusion, which may in turn lead to intrinsic renal damage with a consequent acute deterioration in renal function. The condition may be caused by any significant haemorrhage, or by septicaemia, in which the vascular bed is dilated, thereby reducing the circulating volume. It may also be caused by excessive sodium and water loss from the skin, urinary tract or gastrointestinal tract. Excessive loss through the skin by sweating occurs in hot climates and is rare in the UK, but it also occurs after extensive burns. Gastrointestinal losses are associated with vomiting or diarrhoea. Urinary tract losses often result from excessive diuretic therapy but may also occur with the osmotic diuresis caused by hyperglycaemia and glycosuria in a diabetic patient (for this reason a random blood glucose level was measured for Mrs NC).

Mrs NC had vomited two or three times, but at a late stage in her illness. Although it was more likely to be a symptom of her condition rather than the cause, it was probably the final insult that led to her collapse. The most likely explanation is that her plight has been brought about by the diuresis induced by her recently increased furosemide therapy, plus the co-prescribing of diclofenac in someone already taken ramipril.

Despite a large blood supply, the kidneys are always in a state of incipient hypoxia because of their high metabolic activity, and any condition that causes the kidney to be underperfused may be associated with an acute deterioration in renal function. However, such a deterioration may also be produced by nephrotoxic agents, including drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) in particular are associated with renal damage, and even a short course of an NSAID (such as diclofenac) has been associated with AKI, especially in older patients. The main cause of NSAID-induced renal damage is inhibition of prostaglandin synthesis in the kidney, particularly prostaglandins E_2, D_2 and I_2 (prostacyclin). These are all potent vasodilators, and consequently produce an increase in blood flow to the glomerulus and the medulla. In normal circumstances they do not play a large part in the maintenance of the renal circulation; however, in patients with increased amounts of vasoconstrictor substances (such as angiotensin II) in the blood, vasodilatory prostaglandins become important in maintaining renal blood flow. The maintenance of blood pressure in a variety of clinical conditions, such as volume depletion (which Mrs NC has), biventricular cardiac failure (which she had also had) or hepatic cirrhosis

with ascites, may rely on the release of vasoconstrictor substances. In these circumstances, inhibition of prostaglandin synthesis may cause unopposed renal arteriolar vasoconstriction, which again leads to renal hypoperfusion. NSAIDs thus impair the ability of the renovasculature to adapt to a fall in perfusion pressure or to an increase in vasoconstrictor balance.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may also produce a reduction in renal function by preventing the angiotensin II-mediated vasoconstriction of the efferent glomerular arteriole, which contributes to the high-pressure gradient across the glomerulus. This problem is important only in patients with renal vascular disease, particularly those with bilateral stenoses, and is consequently rare. Its aetiology is as follows: when there is a significant degree of renal artery stenosis, renal perfusion falls. To maintain the pressure gradient across the glomerulus, efferent arteriolar resistance must rise. This is predominantly accomplished by angiotensin-induced efferent vasoconstriction. If ACEIs are administered this system is rendered inoperable, and there is no longer any way of maintaining effective filtration pressure. This leads to a fall in glomerular filtration rate (GFR) and AKI. In these circumstances deterioration in renal function is seen shortly after ACEI initiation. Although Mrs NC has been taking her ramipril therapy for a while, the effects of ACEIs on renal haemodynamics, coupled with the effects of the NSAID will have contributed to her developing AKI.

Factors such as fluid and electrolyte imbalance and drug nephrotoxicity can be identified in over 50% of cases of hospital-acquired AKI and also play a large role in many cases of -community-acquired AKI. It has been estimated that up to 20% of individuals over the age of 65 are prescribed diuretics, with a lesser number receiving NSAIDs. AKI that requires dialysis is fortunately rare, with only 50–70 patients per million of the population affected annually, but less severe degrees of impairment may occur in up to 5% of hospital inpatients.

What is the aim of intravenous (IV) sodium chloride 0.9% therapy?

The aim of therapy is to restore her extracellular fluid volume.

The initial therapeutic aim in the management of AKI is immediate correction of reversible causes. Support of renal perfusion, with either volume infusion or therapeutics that improve renal oxygen delivery, should be considered before any attempt to improve urinary flow. The fluid infused should mimic the nature of the fluid lost as closely as possible, and should therefore be blood, colloid or saline. Patients should be observed continuously and the infusion stopped when features of volume depletion have been resolved, but before volume overload has been induced.

A diagnosis of AKI due to renal underperfusion implies that restoration of renal perfusion will reverse the renal impairment. Mrs NC is depleted of both water and sodium ions. Sodium chloride 0.9% is therefore an appropriate choice of IV fluid, as it replaces both water and sodium ions in a concentration approximately equal to that of plasma.

Situations occasionally arise where a patient is hyponatraemic but not water depleted, as a result of either sodium depletion or water retention; such a condition may be treated with an infusion containing sodium chloride in excess of its physiological concentration, e.g. sodium chloride 1.8% or higher. Similarly, should water depletion with hypernatraemia occur, isotonic solutions that are either free of, or low in, sodium are available, e.g. glucose 5%, or sodium chloride 0.18% with glucose 4%.

Possibly the most common cause of AKI is the peripheral vasodilation that occurs in septic shock. In such cases it would be appropriate to infuse a colloid as well as sodium chloride, as

this would help restore the circulating volume. It is important to remember, however, that not all shocked patients are hypovolaemic and some, notably those in cardiogenic shock, could be adversely affected by a fluid challenge by developing pulmonary oedema.

The effect of fluid replacement therapy on urine flow and central venous pressure (CVP) should be carefully monitored. CVP provides a guide to the degree of fluid deficit and reduces the risk of pulmonary oedema resulting from over-rapid transfusion. If the kidneys do not respond to replacement treatment, the probable diagnosis is acute tubular necrosis, but it is still common (incorrect) practice to try other measures, such as treatment with mannitol and loop diuretics, to try to recover some degree of kidney function.

What would you include in a pharmaceutical care plan for Mrs NC?

The pharmaceutical care plan for Mrs NC should include the following:

(a) Her drug therapy must be reviewed to ensure that any agents that might be contributing to her condition are discontinued, in particular, ACEIs, ARBs, diuretics, NSAIDs.
(b) Avoid all nephrotoxic drugs if possible, eg. Contrast media, aminoglycosides.
(c) All drug therapy should be monitored for efficacy and safety.
(d) Adjust the doses of any medications according to the degree of renal impairment, if appropriate, and monitor plasma drug levels if necessary.
(g) Steps must be taken to ensure that prescribed therapy is re-started after discharge, including any drugs which may have been witheld during the episode of AKI, eg. ACEIs, ARBs.

Which methods of assessing and monitoring Mrs NC's status would you recommend?

(a) Creatinine clearance (CrCl).

Creatinine is a byproduct of normal muscle metabolism and is formed at a rate proportional to the mass of muscle. It is freely filtered by the glomerulus, with little secretion or reabsorption by the tubule. When muscle mass is stable, any change in plasma creatinine reflects a change in its clearance by glomerular filtration. Consequently, measurement of CrCl gives an estimate of the GFR.

The easiest method is to measure the plasma creatinine concentration and collect those patient factors that affect the mass of muscle, i.e. age, sex and weight (preferably ideal body weight). This allows an estimation of CrCl to be made from average population data. The equation of **Cockcroft and Gault** is a useful way of making such an estimation:

$$\text{CrCl} = \frac{F \times (140 - \text{age}) \times \text{weight (kg)}}{\text{plasma creatinine (micromol/L)}}$$

where F = 1.04 (females) or 1.23 (males).

Assuming the normal CrCl to be 120 mL/min, this enables classification of renal impairment as follows: mild, GFR 20–50 mL/min; moderate, GFR 10–20 mL/min; severe, GFR <10mL/min. Using the method of Cockroft and Gault, Mrs NC's CrCl can be estimated as 12 mL/min and her renal impairment could thus be classified as moderate verging on severe.

There are, however, limitations to using this equation, and in the following situations caution needs to be exercised when interpreting the assessment:

ii(i) Obesity: use ideal body weight (IBW).
i(ii) Muscle wasting: CrCl will be overestimated.

(iii) Oedematous patients: use IBW.
(iv) Ascites: use IBW and consider the dilutional effect on serum creatinine.
i(v) ARF: when two serum creatinine levels measured in 24 hours differ by >40micromol/L this may represent non-steady-state serum creatinine levels, therefore the degree of renal impairment may be underestimated.

The latest means of estimating a patient's renal function is to calculate the eGFR (estimated GFR) from the **MDRD** (Modified Diet in Renal Disease) equation.

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 [Serum Albumen] $^{+0.318}$

This is now quoted by most clinical chemistry laboratories, and can be easily calculated via the internet, using the patient's age, serum creatinine, gender and race. It should be noted that the eGFR is a normalised value, in that it reports renal function in units of mL/min/1.73 m^2. Hence, for greater accuracy it needs to be corrected for an individual patient's actual body surface area. Mrs NC is calculated to have an eGFR of 14 mL/min/1.73 m^2.

(b) Serum urea levels.

These are commonly used to assess renal function; however, the rate of production of urea is considerably more variable than that of creatinine, and it fluctuates throughout the day in response to the protein content of the diet. It may also be elevated by dehydration or an increase in protein catabolism, such as occurs with haemorrhage into the gastrointestinal tract or body tissues, severe infections, trauma (including surgery) and high-dose steroid therapy. The serum urea level is therefore an unreliable measure of renal function, but it is often used as a crude test because it does give information on the patient's general condition and state of hydration.

(c) Fluid charts and weight.

Fluid charts are frequently used in patients with sodium and water depletion, but they are often inaccurate and should not be relied upon exclusively. Records of daily weight are more reliable but are rarely available before renal failure is diagnosed.

(d) Central venous pressure.

This is of value in assessing circulating volume. The normal range is 10–15 cmH_2O.

(e) Serum electrolyte levels.

Plasma potassium should be measured regularly because hyperkalaemia, which occurs in AKI, may be fatal.

Would mannitol have been an appropriate alternative to high-dose furosemide therapy?

No. Mannitol is inappropriate because it can be nephrotoxic.

The rationale for using mannitol arises from the theory that tubular debris may contribute to

the oliguria of AKI by causing mechanical obstruction, and that the use of an osmotic diuretic may wash out the debris. However, before producing a diuresis, IV mannitol will cause a considerable increase in the extracellular fluid volume by attracting water from the intracellular compartment. This expansion of the extracellular volume is potentially dangerous for patients with cardiac failure, especially if a diuresis is not produced. In addition, mannitol has no renoprotective effects and can cause significant renal impairment by triggering osmotic nephrosis. Hence its use has now been discredited.

Would you have recommended the use of high-dose IV furosemide at this point?

Yes, provided Mrs NC was euvolaemic before it was started.

As well as producing substantial diureses, all loop diuretics have been shown to increase renal blood flow, probably by stimulating the release of renal prostaglandins. This haemodynamic effect can be inhibited by diclofenac and other NSAIDs. It has been argued that furosemide, - especially at high doses, may convert oliguric AKI to non-oliguric AKI and thus reduce the requirement for dialysis. However, meta-analysis has shown that furosemide is not effective in the prevention and treatment of AKI in adults. It does not reduce mortality, the requirement for dialysis, the proportion of patients remaining oliguric (urine output <500mL/day) or the length of hospital stay.

As furosemide is excreted largely unchanged in the urine and influences tubular reabsorption from the luminal side, it is the urinary excretion of the drug and not its plasma concentration that determines the efficacy of its diuretic action. Non-oliguric AKI is generally associated with a better prognosis than oliguric AKI, and studies have shown that patients who have a diuretic response to furosemide have less severe AKI and so are more likely to recover anyway. However, it is undeniable that any increase in urine volume produced will simplify the future management of Mrs NC by reducing the risk of fluid overload and hyperkalaemia.

The patient must be euvolaemic before furosemide is considered, or diuresis could lead to severe cardiovascular volume depletion. Doses of up to 1 g may be given IV at a rate of not more than 4 mg/min, as higher infusion rates may cause transient deafness. The addition of metolazone orally may also be considered. Metolazone, which is by itself a weak diuretic, has been shown to act synergistically with loop diuretics to produce a more effective diuresis. If fluid repletion followed by furosemide challenge fails to achieve a diuresis this therapy should be discontinued, as the kidneys are evidently incapable of mounting any response, and further doses of furosemide could cause increased nephrotoxicity and ototoxicity.

Would you have used dopamine in this patient?

No.

Dopamine was used for many years as a renoprotective agent, but numerous clinical trials have now shown that the use of a low-dose dopamine infusion is of no benefit in patients with acute renal dysfunction and systemic inflammatory response syndrome. The theory behind its use was that dopamine at low doses (e.g. 1–5 micrograms/kg/min) has a vasodilator effect on the kidney. At slightly higher doses (e.g. 5–20 micrograms/kg/min) inotropic effects on the heart produce an increase in cardiac output. This dual effect increases renal perfusion. However, at even higher doses (e.g. 20 micrograms/kg/min and above) dopamine also acts on □ receptors, causing peripheral and renal vasoconstriction which results in impairment of renal perfusion. As with furosemide, dopamine may produce increases in urine volume even in those patients who

progress to AKI; however, dopamine also has a number of potential disadvantages. Even at low doses it may increase cardiac contractility and systemic resistance, and it has been reported to cause tissue necrosis. It has also been suggested that desensitisation of renal dopaminergic receptors occurs with prolonged administration.

What factors may have contributed to Mrs NC's low haemoglobin? Is omeprazole therapy appropriate?

Mrs NC's low haemoglobin may be a result of reduced erythropoietin secretion, but it is more likely to be the result of gastrointestinal bleeding, and so omeprazole therapy is appropriate.

Erythropoietin, the hormone that stimulates production of red blood cells, is produced almost exclusively by the kidney and a normochromic normocytic anaemia due to reduced erythropoietin secretion is a very common symptom of chronic kidney disease. However, the time course of AKI is often too short for this type of anaemia to become a problem, and although it may be present in a patient on the verge of chronic kidney disease who has an acute crisis, this does not appear to be the case with Mrs NC.

Anaemia may also arise if there is a haemolytic element to the condition (e.g. severe septicaemia) or if a haemorrhage occurs, either as the cause of the AKI or as a result of it. Although stress ulcers are not uncommon in acutely ill patients, uraemic gastrointestinal haemorrhage is a recognised consequence of AKI. It probably occurs as a result of reduced mucosal cell turnover owing to high circulating levels of uraemic toxins. Gastrointestinal haemorrhage is also a well-recognised consequence of treatment with NSAIDs such as diclofenac, which Mrs NC had been taking prior to admission.

Mrs NC has passed melaena (black, tarry stools) and has been diagnosed as having had a gastrointestinal bleed. This is therefore the most likely cause of her low haemoglobin. Proton pump inhibitors or H_2-receptor antagonists are effective in this situation, and it is unlikely that any one would be more advantageous than another. Omeprazole was thus an appropriate choice of treatment, and because it is metabolised in the liver to inactive metabolites it was appropriate to prescribe it at the normal therapeutic dose, even though Mrs NC's estimated GFR was <10mL/min at this stage in her illness.

Is Mrs NC's hyperkalaemia being treated appropriately? Should her hypocalcaemia, hyperphosphataemia and acidosis be treated at this point?

A11 Yes. The methods used to treat Mrs NC's hyperkalaemia are appropriate. However, Mrs NC's calcium and phosphate levels and serum pH, although abnormal, are not sufficiently deranged to warrant treatment yet.

(a) **Hyperkalaemia.** Hyperkalaemia is a particular problem in AKI, not only because of reduced urinary potassium excretion, but also because of potassium release from cells. Particularly rapid rises are to be expected when there is tissue damage, as in burns, crush injuries and sepsis, although this is not the case for Mrs NC. She is, however, acidotic, and this aggravates the situation by provoking potassium leakage from healthy cells. It is worth noting that ACEIs and ARBs can increase serum potassium levels, and in this case although Mrs NC has been on ramipril for some time without ill effects, the sudden decrease in GFR will potentiate the adverse effects of the ACEI, thus contributing to the development of hyperkalaemia.

Hyperkalaemia may be life-threatening as a result of causing cardiac arrhythmias and, if untreated, may result in asystolic cardiac arrest. Emergency treatment is necessary if the serum potassium is >7.0 mmol/L (as in Mrs NC's case) or if there are ECG changes. Emergency treatment consists of:

ii(i) 10–20 mL of calcium gluconate 10% IV. This has a stabilising effect on the myocardium but no effect on the serum potassium concentration.

i(ii) 10 units of soluble insulin plus 50 mL of 50% glucose. The insulin stimulates potassium uptake into cells, thereby removing it from the plasma. The glucose counteracts the hypoglycaemic effects of the insulin.

(iii) Calcium Resonium 15 g three or four times a day, orally or by enema. This ion-exchange resin binds potassium in the gastrointestinal tract, releasing calcium in exchange. It is used to lower serum potassium over a period of hours or days, and is required because the effect of insulin and glucose therapy is only temporary. Both the oral and the rectal routes of administration have disadvantages. Administration of large doses by mouth may result in faecal impaction, which is why it is recommended that lactulose should be co-prescribed. The manufacturer recommends that the enema be retained for 9 hours: retaining it is not usually the problem, rather the reverse. Oral therapy is not contraindicated after a - gastrointestinal bleed, so this is probably more appropriate for Mrs NC. Using a calcium-exchange resin is also appropriate as she is hypocalcaemic.

(iv) 250–500 mL of sodium bicarbonate 1.26% or 1.4% IV may be used in addition to insulin and glucose therapy. As well as stimulating potassium reuptake by cells, this helps to correct the acidosis of AKI. However, its use can be limited in AKI as there are potential problems with volume overload.

(b) **Hyperphosphataemia.** Phosphate is normally excreted by the kidney. Phosphate retention and hyperphosphataemia may also occur in AKI, but usually only to a slight extent, and the condition rarely requires treatment. Should it become necessary, phosphate-binding agents may be used to retain phosphate ions in the gut. The most common agents are calcium-containing agents, e.g. Calcichew (calcium carbonate) or Phosex (calcium acetate).

(c) **Acidosis.** Metabolic acidosis in AKI results from increased acid production, reduced renal reabsorption of bicarbonate, and an inability of the kidney to excrete hydrogen ions. In itself this is generally not a serious problem, although it may contribute to hyperkalaemia. It may be treated orally with sodium bicarbonate 1–6 g/day in divided doses, although if elevations in plasma sodium preclude the use of sodium bicarbonate, extreme acidosis (plasma bicarbonate <10 mmol/L) is best treated by dialysis.

Although Mrs NC does not currently require treatment for her electrolyte abnormalities, it is essential that she is carefully monitored for any further derangement.

What factors should be considered when initiating drug therapy for a patient with AKI?

A12 Whether the drug to be prescribed is intrinsically nephrotoxic; is the drug excreted via the kidneys, or is it metabolised by the liver, but the metabolites are pharmacologically active and excreted renally? Both these situation would imply a dose amendment will be required.

An alteration in total daily dose can be achieved by altering either the dose itself, the dosage interval, or a combination of both as appropriate. Unfortunately, for this method it is not always possible readily to obtain the fraction of drug excreted unchanged in the urine. In practice it is therefore often simpler to use the guidelines to prescribing in renal impairment found in standard references such as the *Renal Drug Handbook* or *Drug Prescribing in Renal Failure*.

Some drugs are known to be capable of damaging the kidney by a variety of mechanisms. The commonest forms of damage are interstitial nephritis (hypersensitivity reaction with inflammation affecting those cells lying between the nephrons) and glomerulonephritis (thought to be caused by the passive trapping of immune complexes in the glomerular tuft eliciting an inflammatory response). The list of potentially nephrotoxic drugs is long, but the majority cause damage by producing idiosyncratic hypersensitivity reactions and are quite safe in most patients. Some drugs, however, are directly nephrotoxic and their effects on the kidney are consequently more predictable. Such drugs include the aminoglycosides, amphotericin, colistin, the polymyxins and ciclosporin/tacrolimus. The use of any drug with recognised nephrotoxic potential should be avoided in any patient if at all possible. This is particularly true in patients with pre--existing renal impairment or renal failure, such as Mrs NC. Inevitably, occasions will arise when the use of potentially nephrotoxic drugs becomes necessary, and on these occasions constant monitoring of renal function is essential.

In conclusion, the simplest solution to prescribing in renal failure is to choose a drug that:

(a) Is <25% excreted unchanged in the urine.
(b) Is unaffected by fluid balance changes.
(c) Is unaffected by protein-binding changes.
(d) Has a wide therapeutic margin.
(e) Is not nephrotoxic.

What were the indications for dialysis in Mrs NC?

A13 Her severe uraemic symptoms (nausea, reduced consciousness, flapping tremor) and evidence of pulmonary oedema indicate that dialysis would be of value for Mrs NC.

Dialysis should be started in a patient with AKI when there is: hyperkalaemia >7 mmol/L; increasing acidosis (pH <7.1 or plasma bicarbonate of <10 mmol/L); severe uraemic symptoms such as impaired consciousness; fluid overload with pulmonary oedema; or any combination of the above that may threaten life.

What forms of dialysis therapy are available, and what are their advantages and disadvantages?

A14 There are traditionally two types of dialysis patients with chronic kidney disease: haemodialysis and peritoneal dialysis. Both put the patient's blood on one side of a semipermeable membrane and a dialysate solution on the other. Exchange of metabolites occurs across the membrane. In haemodialysis, blood is diverted out of the body, passed through an artificial kidney (dialyser) and returned to the patient, whereas in peritoneal dialysis the fluid is run in and out of the patient's abdominal cavity, and the peritoneum itself acts as the semipermeable membrane. Other options for Mrs NC are

continuous haemofiltration and haemodiafiltration.

In haemodialysis, blood is taken from an arterial line, heparinised, actively pumped through a dialyser where diffusion and ultrafiltration occur, and returned to the patient via the venous line. The dialyser contains synthetic semipermeable membranes which allow the blood to come into close proximity with the dialysate. Metabolites and excess electrolytes pass from the blood to the dialysate, and by increasing the pressure of the blood, water can also be removed from the patient. Haemodialysis is performed three times a week and the duration of a single dialysis is usually about 4 hours. One disadvantage of haemodialysis is its dependence on expensive technology which requires specially trained staff, so it is seldom undertaken outside a renal unit. Haemodialysis also produces rapid fluid and electrolyte shifts, which may be dangerous in an unstable patient. However, it does treat renal failure and reverse metabolic abnormalities much more rapidly than peritoneal dialysis, and is therefore essential in hypercatabolic renal failure, where urea is produced faster than peritoneal dialysis can remove it.

Peritoneal dialysis is a technique whereby dialysate is run into the peritoneal cavity via an indwelling catheter, where it dwells for a variable length of time before being drained out and fresh fluid run in. Both haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) have been used for acute renal replacement therapy (RRT), although haemodialysis or a continuous RRT modality such as haemofiltration or haemodiafiltration are now the mainstays of treatment for AKI, and are usually used in an intensive care setting.

Haemofiltration is the process of convection and ultrafiltration by which water and solutes (including drugs) are removed from the blood through a highly permeable membrane when pressure is applied.

The rate of blood flow past the membrane generates hydrostatic pressure, which forces plasma water across the membrane dragging various solutes with it. The solution produced containing this solute is called ultrafiltrate or haemofiltrate. Excess fluid is best removed by haemofiltration, but large volumes of fluid need to be removed if solutes are to be cleared effectively from the plasma.

Haemodiafiltration is a process that combines dialysis with large-volume ultrafiltration and diffusion to remove water and solutes. Dialysis fluid is introduced through the filter in a counter current direction to the blood flow in order to create a concentration gradient (between the blood compartment and the dialysis fluid compartment) across the semipermeable membrane. Dialysis fluid is usually introduced at a rate of 1–2 L/h, depending on the efficiency of the system

Both haemofiltration and haemodiafiltration are continuous, well tolerated haemodynamically, and avoid the ‘peaks and troughs’ in metabolic, electrolyte, acid–base and volume control which are a feature of intermittent dialysis treatments. Hence it is these types of renal replacement therapy that are most often used in patients with AKI as they are available in any intensive care unit, whereas intermittent haemodialysis requires the facilities of a specialist renal unit.

What factors affect drug therapy during dialysis?

A15 Whether or not the drug is significantly removed by dialysis.

Drugs that are not removed will require dose reductions in order to avoid accumulation and possible toxic effects. In general, because haemodialysis, haemofiltration and haemodiafiltration depend on filtration, the processes can be considered analogous to glomerular filtration. Thus, drug characteristics that favour clearance by the glomerulus are

similar to those that favour clearance by dialysis or haemofiltration. They include low molecular weight, high water solubility, low protein binding, small volume of distribution and low metabolic clearance. With continuous haemofiltration the situation is more manageable than in intermittent processes, as there are fewer oscillations in drug elimination.

A number of other factors that depend on the dialysis process itself also affect clearance by dialysis. These include the duration of the dialysis procedure, the rate of blood flow to the dialyser, the surface area and porosity of the dialyser, and the composition and flow rate of dialysate.

Is this therapy appropriate for Mrs NC's septicaemia?

A16 No. Cefotaxime should be replaced by an agent with broader activity against Gram-positive organisms, such as a penicillin (e.g. ampicillin, amoxicillin or co-amoxiclav).

Patients with AKI are prone to infection and septicaemia and this is a common cause of death in this population. Between 50% and 80% of all dialysis patients are carriers of *Staphylococcus aureus* and/or *Staphylococcus epidermidis*. Bladder catheters and IV lines should therefore be used with care in order to reduce the chance of bacteria gaining access to the patient. Leukocytosis is sometimes seen in AKI and does not necessarily imply infection, but when seen in conjunction with pyrexia, as in Mrs NC, aggressive treatment is suggested. Samples of blood, urine, sputum and any other material should be sent for culture before antibiotic therapy is started. Therapy should be prescribed to cover as wide a spectrum as possible until a causative organism is identified.

Aminoglycoside therapy is appropriate for Mrs NC as this class of compounds is highly active against most Gram-negative organisms as well as having useful activity against *S. aureus*. Gentamicin is also inexpensive. Metronidazole is highly active against anaerobic organisms. Cefotaxime is a 'third-generation' cephalosporin with increased sensitivity against Gram-negative organisms, although this is balanced by reduced activity against some Gram-positive organisms, notably *S. aureus*. It can be useful when given in combination with an aminoglycoside, but it would be more advantageous to Mrs NC to use an agent with greater activity against Gram-positive organisms, e.g. ampicillin or one of its analogues such as amoxicillin or co-amoxiclav. An alternative agent with good Gram-positive and Gram-negative cover and less nephrotoxicity than gentamicine would be piperacillin/tazobactam. All penicillins may cause renal damage, most commonly acute interstitial nephritis, but the damage is a hypersensitivity reaction and therefore unpredictable, and it is not an absolute contraindication to penicillin use.

What are the dangers associated with prescribing gentamicin for Mrs NC? How should her gentamicin therapy be monitored?

A17 Gentamicin can cause nephrotoxicity and toxicity to the eighth cranial nerve. Regular monitoring for these side-effects, and of Mrs NC's gentamicin serum levels, is essential.

Treatment with an aminoglycoside is justified for the reasons given in **A16**; however, all aminoglycosides are potentially nephrotoxic, being associated with damage to the proximal tubule. Aminoglycosides can also precipitate AKI. Because of this, they should generally be avoided in renal impairment; however, their bactericidal activity against an extremely broad spectrum of Gram-negative organisms means that they are often prescribed for seriously ill patients with systemic infections. They are excreted solely by the kidney, so accumulation may

lead to a vicious circle of increasing drug levels causing further renal deterioration and hence further accumulation. The risk of nephrotoxicity is increased when their use is combined with other nephrotoxic drugs, notably the loop diuretics. Mrs NC was prescribed the loop diuretic furosemide at an early stage of this admission, but her diuretic therapy has now been discontinued; however, if it is required again, the doses of aminoglycoside and loop diuretic must be staggered as much as possible.

In addition to being nephrotoxic, aminoglycosides are toxic to the eighth cranial nerve and may produce vestibular symptoms (i.e. loss of sense of balance) or adversely affect hearing. Such symptoms should therefore be checked for on a regular basis.

Traditionally aminoglycosides were given in two to three divided doses over 24 hours; however, there is now a large body of evidence that administration once a day reduces the risk of toxicity while maintaining superior efficacy. Also, owing to its prolonged half-life, and risk of accumulation in severe renal impairment, gentamicin may only need to be administered every 24 hours, or even less frequently. In practice, many renal units give 'stat' doses of gentamicin, e.g. 2 mg/kg to patients with severe renal impairment. The levels are monitored, and when the level is <2mg/L the dose is re-administered. Alternatively, the *Renal Drug Handbook* gives recommendations for once-daily gentamicin dosing according to GFR.

In general, it is thought that the risk of nephrotoxicity and eighth cranial nerve toxicity is associated with peak serum concentrations persistently >10 mg/L and, perhaps more importantly, troughs persistently >2 mg/L, although persistently low levels do not guarantee freedom from nephrotoxicity.

Why was Mrs NC prescribed the sodium bicarbonate? What else can be used for the same indication?

A18 She was prescribed sodium bicarbonate to prevent contrast-induced nephropathy. Alternatives would be sodium chloride 0.9% or *N*-acetylcysteine infusions.

Contrast-induced nephropathy (CIN) is defined as a creatinine level increased by at least 40 micromol/L, or more than 25%, above baseline. Renal impairment usually peaks within 3–5 days after completion of the diagnostic procedure and is usually self-limiting. Contrast agents, in particular non-ionic (iodine-based) contrast media, cause nephropathy primarily through renal ischaemia and, possibly, through direct toxicity to tubular epithelial cells. After contrast is injected, renal blood flow transiently increases. There is then a prolonged decrease caused by renal vasoconstriction, suggesting that renal ischaemia is a major factor in the pathogenesis of CIN. Pre-existing renal insufficiency is the single greatest risk factor for CIN, occurring in an estimated 60% of patients with CIN. The more severe the baseline renal insufficiency, the greater the risk that a patient will develop CIN, but anyone with a GFR <60 mL/min is considered to be at risk.

The best strategy to avoid the development of CIN is for patients to receive hydration therapy, starting 2–4 hours before the administration of contrast, during the radiographic procedure and continuing for 4–6 hours afterwards. Various solutions have been used, including IV sodium chloride 0.9% or sodium bicarbonate 1.26% or 1.4%. A typical regimen for sodium chloride 0.9% would be 1–2 L beginning at least 3 hours before the procedure at a rate of 100–150 mL/h, and continuing at least 6–8 hours post procedure at a slower rate depending on the patient's clinical status.

Sodium bicarbonate is believed to work by alkalising the tubular environment, thereby reducing the formation of free radicals, and it has been shown to be more effective than

sodium chloride in this respect. A typical hydration regimen is 3 mL/kg/h for 1 hour prior to the procedure, followed by 1 mL/kg/h for 6 hours afterwards.

An alternative to sodium bicarbonate is the administration of *N*-acetylcysteine solution, where the mechanism of action is considered to be the trapping and destruction of free radicals. Despite several single studies and several meta-analyses, the true benefit of *N*-acetylcysteine is still unclear; however, it is used in some centres, with typical doses being either 600-1200 mg orally every 12 hours the day before and repeated the day after the procedure, or 1 g IV given both before and after the procedure.

Did Mrs NC follow the normal course of AKI? What is her prognosis?

A19 Yes. Mrs NC's illness followed the typical course of AKI and her survival to this stage is a good prognostic sign.

Acute tubular necrosis, the commonest form of AKI, involves the death of renal tubular cells and usually occurs as a consequence of severe shock or as a result of sodium and water depletion giving rise to hypotension and generalised vasoconstriction, which in turn give rise to renal ischaemia. This was the sequence that resulted in Mrs NC's AKI. Since renal tubular cells are constantly being shed and replaced, if the cause of the ATN is removed, the tubules can be repaired and hence recovery of renal function is likely.

The course of AKI may be divided into two phases. The first is the oliguric phase, where both the glomerulus and the renal tubule are no longer able to function properly. It is characterised by a urine volume of only 200–400 mL in 24 hours, a volume at which the kidney is unable adequately to excrete the products of metabolism. This inevitably leads to uraemia and hyperkalaemia unless adequate management is provided. This phase usually lasts no longer than 7–14 days, but may last for up to 6 weeks. If the patient does not die in this period, he or she will enter the second phase, where the glomerulus recovers and is now able to filter, but the tubule has not recovered sufficient function to properly reabsorb solutes and concentrate the urine. This phase is characterised by a urine volume that rises over a few days to several litres in a 24-hour period. This, the diuretic phase, lasts for up to 7 days, and patients who survive into this phase, as Mrs NC has, have a relatively good prognosis. Recovery of renal function takes place slowly over the following months, although the GFR rarely returns to its initial level. The elderly recover function more slowly and less completely.

The mortality for AKI varies according to the cause, but overall is about 50%. Death due to uraemia and hyperkalaemia is rare nowadays. The major causes of death are septicaemia and, to a lesser extent, gastrointestinal haemorrhage. Death is more common in patients aged over 60.

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Useful websites

http://www.globalrph.com/renaldosing2.htm

http://www.kdp-baptist.louisville.edu/renalbook/adult/1/