Update on Renal Therapeutics

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Kongress für Arzneimittelinformation
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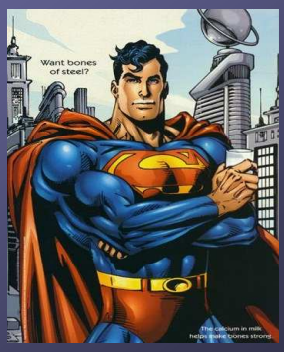
What are we going to discuss?

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

Creatinine 120 µmol/l, eGFR 34 ml/min



Creatinine 120 µmol/l, eGFR 130 ml/min

Staging of CKD *(K-DOQI)*

Stage	Description	GFR (ml/min)
1	Normal GFR with another abnormality	> 90
2	Mild reduction in GFR with another abnormality	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	End-stage renal disease	<15 or dialysis

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

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

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

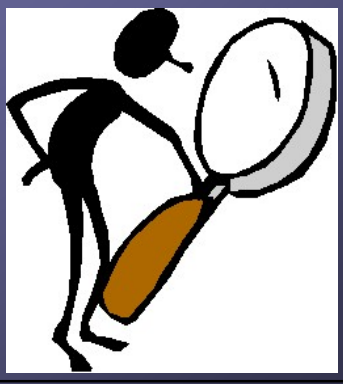
GFR (ml/min/1.73m^2) =

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

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

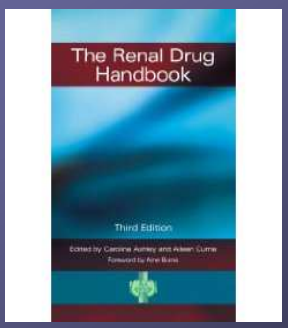
If in doubt, and for narrow therapeutic index drugs,

- Use Cockcroft and Gault

Bennett

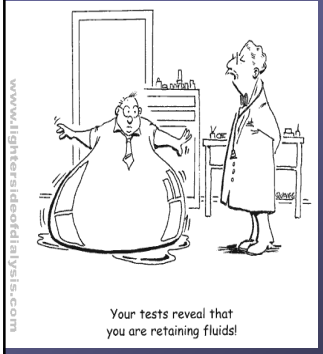
- Also available on-line http://www.kdp-baptist.louisville.edu/renalbook/
- Fully referenced
- Does not use K-DOQI classification
- Normal, >50ml/min, 10-50ml/min, <10ml/min

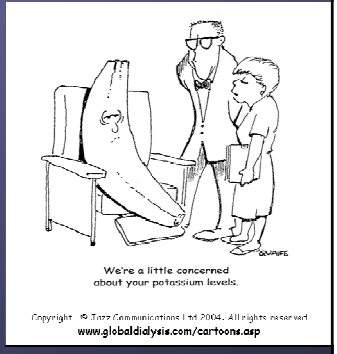
Renal Drug Handbook



- 3rd edition published January 2009
- > 760 drug monographs

When do we start dialysis?

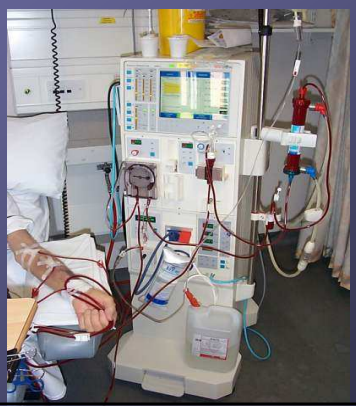




Nomenclature

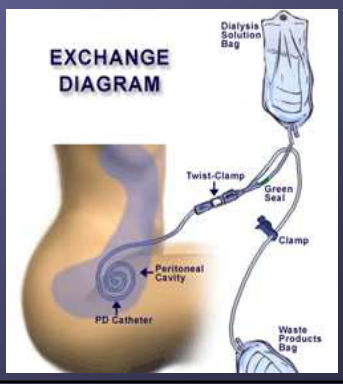
- Continuous Renal Replacement Therapy (CRRT)
- Continuous Arterio-Venous Haemofiltration (CAVH)
- Continuous Veno-Venous Haemofiltration (CVVH)
- Continuous Arterio-Venous Haemodiafiltration (CAVHD)
- Continuous Veno-Venous Haemodiafiltration (CVVHD)
- Intermittent Haemodialysis (IHD)
- Dialysate
-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

Intermittent Haemodialysis



Peritoneal Dialysis

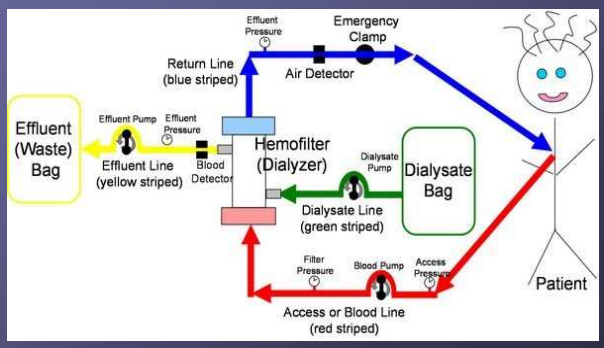
- CAPD
- APD



Indications for CRRT

- Metabolic acidosis (pH>7.3 & falling)
- Hyperkalaemia (K+ >6.0mmol/L & ↑)
- Fluid overload that compromises gas Xchange
- 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

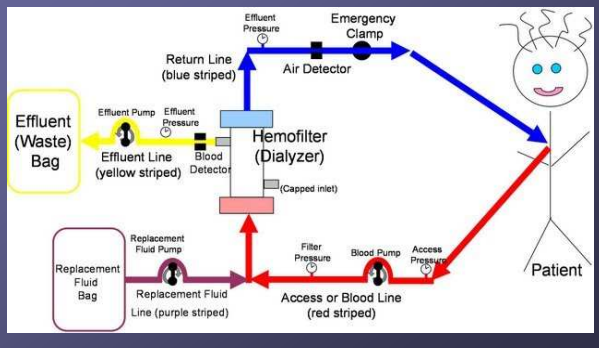
CVVHD



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



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

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.

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.

Any Questions???