Early Detection of Renal Failure

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Summary

• Early detection
  ▫ Essentially to avoid progression
  ▫ “cost effective”

• Screening for renal involvement/disease
  ▫ History, medications (illicit, OTCs), BP
  ▫ Renal function: electrolytes; urea; creatinine; eGFR
  ▫ MSU: proteinuria; WBC, RBC
    • Casts, specific gravity
  ▫ Quantify proteinuria
    • ACR or PCR
Summary

• Goal BP
  ▫ <160/90mmHg in non-renal disease
  ▫ 130/80 in CKD and proteinuria
  ▫ ?140/80 in CKD
  ▫ 125/75 in DM with DN (CKD and proteinuria)

• Minimise proteinuria
  ▫ ACEi; ARB
  ▫ non-dihydropyridine CCB
  ▫ spironolactone

• Avoid nephrotoxins
CKD categories

- CKD1 – eGFR > 90ml/min/1.73m² BSA
- CKD2 – eGFR 60-89ml/min/1.73m² BSA
- CKD3 – eGFR 30-59ml/min/1.73m² BSA
  - CKD3A = 45-59
  - CKD3B = 30-45
- CKD4 – eGFR 15-29ml/min/1.73m² BSA
- CKD5 – eGFR <15ml/min/1.73m² BSA

NOT ALONE:
  - Presence of other potential renal issues
Heart Disease in Haemodialysis Patients

Log Annual Mortality (%)

500

40

25-34 35-44 45-54 55-64 65-74 75-84 >85

Age (years)
Heart Disease in Haemodialysis Patients

Log Annual Mortality (%)

Age (years)

30 year old risk = 80 year old
Protective Potential

• Decline in GFR
  ▫ Hypertension control
  ▫ Minimisation of proteinuria
  ▫ Avoidance of nephrotoxins
  ▫ Other renal damage – trauma, stones, pyelonephritis

• Monitor for renal dysfunction
  ▫ depends upon expected rate of progression
Prevalent Dialysis and Transplant New Zealand (at 31 December)

Number of patients over the years 2005 to 2009, showing the distribution between Dialysis (D), Transplant (Tx), Prevalent Dialysis (PD), and Functioning Transplant (Functioning Tx). The chart illustrates a trend in the number of patients across different treatments over the specified period.
Prevent what?

- Renal failure - ESRF
- Partial renal damage - CKD
  - How bad is temporary damage?
- Avoid complications of renal failure
  - Pharmaceuticals dose adjustments
  - Acid-base; anaemia; cardiovascular; endocrine; nutrition; neurological; musculoskeletal...
Cardiovascular risk
CKD / CAD and death rates

- Medicare (US) – 2 year follow-up ($n=1,000,000$)
  - 22,000 CKD without DM
    - 1.6% required RRT
    - 17.7% died
    - 30.7% had heart failure
  - 16,000 CKD + DM
    - 3.4% required RRT
    - 19.9% died
    - 52.5% had heart failure
CKD / CAD and death rates

- Longitudinal follow-up of 30,000 patients with eGFR < 90ml/min/1.73m² BSA (= CKD2-5); followed for 5 years....risk of RRT and death:
  - CKD 2: 1.1% 19.5%
  - CKD 3: 1.3% 24.3%
  - CKD 4: 19.9% 45.7%
- Those who died had more of:
  - Coronary artery disease; heart failure; diabetes mellitus; anaemia
CKD / CAD and death rates

- 12,000 older patients with DM:
  - 48% had DN (defined as CKD 3-5; or proteinuria)
  - @ 3 years mortality rates:
    - Normal RF 5%
    - CKD 2 6%
    - CKD 3 10%
    - CKD 4 20%
    - CKD5 30%
  - Cf. need for RRT <1% (CKD2); 14% (CKD4)
CKD / CAD and death rates

- Nat Health and Nutrition Examination Survey cardiovascular death rate:
  - eGFR > 90 (CKD1) 4.1 deaths per 1000 person-year
  - eGFR 70-89 8.6 deaths per 1000 person-year
  - eGFR <70 (CKD2) 20.5 deaths per 1000 person-year
CKD / CAD and death rates

- CKD is a risk factor for IHD
  - Risk of cardiac death > 10 fold
  - Risk of heart failure > 20 fold
  - Death rate increases with severity of CKD
    - 2-18 fold (mortality at better renal function)
      - CKD 2 (1:7-17.7); CKD4 (1:2.1-2.3)

- More likely to die from CVD than end up with RRT
- Risk of IHD is higher in CKD
Overall cardiac risk - summary

- Absolute risk of CV events in CKD alone is about half that of patients with pre-existing heart disease and **without** CKD
- Risk increases with progressive CKD and/or proteinuria
  - Pragmatically CKD is eGFR < 60ml/min/1.73m²
  - And proteinuria >1g/24 hours
    - ~PCR 80-100 or ACR 50-60mg/mmol (g/mol)
Hypertension
Risk of ESRD and hypertension
Hypertension in CKD

- Causes/factors
  - Reduced sodium clearance
  - Increased renin-angiotensin system activity
  - 2° hyperparathyroidism -> hypercalcaemia -> vasoconstriction
  - Increased sympathetic activity
  - Low erythropoietin levels
  - Higher central pulse pressure, “stiff vessels”; and isolated systolic hypertension
Hypertension in CKD

• Goal of 130/80mmHg or below
  ▫ Requires 3 or more drugs
  ▫ Include:
    • ACE and/or ARB
      • In combination hyperkalaemia is limiting factor
    • Diuretic – loop +/- chlorthalidone
      • In combination with Na⁺ restriction diet (<100mmol)
    • CCB – diltiazem or verapamil
      • Not dihydropyridines by choice - but are OK to use
    • 4th agent...spironolactone (K⁺)
Hypertension

• Non-diabetics with CKD with proteinuria (>500mg/24 hrs; ~ PCR 30-50)
  ▫ Goal BP is < 130/80mmHg reduces progression of CKD and maybe mortality

• Non-proteinuric patients
  ▫ JURY STILL OUT (no evidence yet)
    • ?<140/90; or ?130/80 (maybe the later since CKD is a CVD risk factor)
Hypertension in CKD

- Diabetes mellitus
  - With proteinuria (and therefore assume DN)
  - Goal BP <125/75mmHg
Proteinuria

- Meta-analysis of general population cohort: 
  $n=105,872$ (ACR), plus $n=1,128,310$ (dipstick proteinuria); mean follow-up of 7.9 years (cf. a group with mean eGFR of 95)
  - Hazard ratios for all cause mortality
    - eGFR 60: 1.18 (CI 1.05-1.32)
    - eGFR 45: 1.57 (CI 1.39-1.78)
    - eGFR 15: 3.14 (CI 2.30-4.13)
Other proteinuria evidence

- Presence of proteinuria alone -> RR of cardiovascular event = 1.3
- Nat Health and Nutrition Examination Survey cardiovascular death rate (unadjusted):
  - Proteinuria <30: 6.2 deaths / 1000 person-yr
  - Proteinuria 30-299: 17.9 deaths / 1000 person-yr
  - Proteinuria >300: 37.2 deaths / 1000 person-yr
- When adjusted:
  - Relative hazard 1.57 (30-299 cf. <30 cohort)
  - Relative hazard 1.8 (>300 cf. <30 cohort)
Microalbuminuria

- Associated with LV dysfunction; stroke; MI
  - Especially in type I DM
- Indicator of inflammation
  - Within renal tissue
  - Endothelium
Dietary salt and proteinuria?

• Anti-proteinuria effects of ACE reduced with high salt diet in NON-DIABETICS
• Therefore in the non-diabetic with proteinuria
  ▫ With good BP (systolic < 130mmHg)
  ▫ Should have sodium restricted diet
    • 24 hour urine Na < 100mmol.
So what do we do in clinical practice?
Osler Principles to Renal Medicine

- **Look**
  - Skin
    - Rashes
    - Vasculitis
    - CT diseases
  - Anaemia
  - Fundi
  - Oedema
Osler Principles to Renal Medicine

• Feel
  ▫ Pulses
    • asymmetry
  ▫ Cardiac
    • Apex
    • Thrust/heave
  ▫ Oedema; ascites
  ▫ Bladder
  ▫ Prostate
Osler Principles to Renal Medicine

- **Listen**
  - **BP**
    - Lying and standing
    - Both arms
  - **Murmurs**
  - **Bruit**
Osler Principles to Renal Medicine

• Smell
  ▫ Foetor breath
    • Ammonia
  ▫ Acidosis
  ▫ Urine (incontinence)

• Taste
Investigation internal medicine

• Asymptomatic
  ▫ Down to your last 10% of renal function before symptoms
  ▫ Renal disease symptoms are NON specific

• Laboratory testing
  ▫ Blood
  ▫ MSU
  ▫ Proteinuria - PCR vs ACR

• Radiology testing
  ▫ USS
Kidney Disease - AKI model

- **Pre-renal**
  - BP, vascular/PVD, vasculitis

- **Post-renal**
  - Obstruction
  - USS
  - Rarely functional – DTPA

- **Renal**
  - Everything else
  - Laboratory and radiology investigation
Monitoring

- How often?
  - Depends upon progression rates (annual)
    - DM2 – 10-12ml/min/1.73m² BSA
    - 3 monthly diabetes care programme
    - Gn – 1-2ml/min/1.73m² BSA
    - Body rot – 0.5-1ml/min/1.73m² BSA
Nephrotoxins

- PPI
  - Class effect
- NSAIDs
  - COX-2 is no different
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• Avoid nephrotoxins
Nephrotoxins
Nephrotoxins

- Present as...
  - Interstitial nephritis picture
    - Sterile pyuria
  - May have proteinuria
  - May have impaired renal function
    - Acutely or chronically
Avoiding Nephrotoxins

- Common toxins
  - Lithium.
  - Some chemotherapeutic agents.
  - NSAIDs; COX-2 inhibitors
  - Allopurinol.
  - H₂ / proton pump blockers – omeprazole, pantoprazole, lansoprazole, etc.
  - OTC/herbals.
  - Fibrates.
  - Quinolone antibiotics (uncommon)
Nephrotoxins

- Chinese herbals:
  - Aristolochic acid (Guan Xin Su He)
  - NSAID (Sang Ju Gan Mao Pian)
  - NSAID (Yen Qiao Jie Du Pian)
  - NSAID (tung Shueh pills)
  - Others: Guan Mu Tong; Dahuong Qingwei, Daochi, Fenqing Wulin, Longdon Xiegan pills; Xiaoer Jindan tablets.
Nephrotoxins

- Glycyrrhiza
  - Fanconi syndrome

- Noni juice
  - Hyperkalaemia and diuretic

- Cat’ claw (*Uncaria tomentosa*)
  - AKI

- *Taxus celebica*
  - AKI, haemolysis
Nephrotoxins

- **Salicin**
  - Willow bark
- **Sorrel** (*Rumex acetosa*)
  - Oxalosis, kidney stones
- **Essiac** (*Ulvis spp*)
  - Oxalosis, kidney stones
- **Peppermint oil**
  - Interstitial nephritis
- **St John’s wort**
  - Interstitial nephritis
# Nephrotoxins

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<td>Yohimbine</td>
<td>Progressive CKD</td>
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Evaluation for proteinuria

- Not at ↑ risk
  - Standard dipstick
    - ≥1+
      - Recheck at periodic health evaluation
    - Negative/trace
      - Total protein/creatinine ratio
        - >200 mg/g
          - Diagnostic evaluation
            - Treatment
        - ≤200 mg/g
          - Recheck at periodic health evaluation

- At ↑ risk
  - Albumin-specific dipstick
    - Negative
    - Positive
      - Albumin/creatinine ratio
        - ≤30 mg/g
          - Consultation
        - >30 mg/g
          - Treatment
Proteinuria measurement
## Proteinuria measurement

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<th>ACR (mg/L)</th>
<th>24 hour proteinuria</th>
<th>PCR (mg/L)</th>
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<tr>
<td>30</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>225</td>
<td>6</td>
<td>400</td>
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<tr>
<td>350</td>
<td>10</td>
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Proteinuria reduction

• Most of the evidence is in ACEs (type 1 DM) and in ARBs (type 2 DM)
DN2 - Irbesartan (and RENAAL)
What about ACEi AND ARB?

• Together in BOTH type 1 and 2 DN
• ACE + ARB reduces proteinuria
• BUT
  ▫ No evidence that combination is better than monotherapy in progression of CKD
• AND adverse events (ONTARGET trial)
  ▫ Hyperkalaemia
  ▫ Decline in eGFR/renal function
    • Accept rise up to 30% from baseline serum creatinine
More on proteinuria

- **Aldosterone antagonists**
  - 34% reduction cf. placebo in proteinuria
  - (cf. losartan – 17% reduction)
  - BUT Ace + ARB + aldo antag -> +++[K⁺]s

- **Diltiazem and verapamil (in diabetics only)**
  - Verapamil + ACE at non-max doses had similar effect, with less side effects (hyperkalaemia) in DN of DM-2.
Lipids and kidneys
Lipids and kidney disease

• Reduce cardiac disease in *absence* of CKD
  
  SHARP
  ▫ Lipid lowering in CKD (not on RRT) reduced CV events, BUT NOT overall mortality

• Statins have a pleiotropic effect
  ▫ May reduce progression of CKD

• No trials that tell us the goal cholesterol
  ▫ Trials that look at statin dose
    ▪ CV risk falls with LDL reduction
  ▫ Trials that document dyslipidaemia lowering
Aspirin in CKD

• HOT trial
  ▫ Reduction in CV events in CKD3A
  ▫ Increased risk of bleeding in some CKD groups
    • CV benefit out-weighed this bleeding risk
    • Overall risk ~ 2.5% per person-year ($n=255$ HD*)

• DOPPS
  ▫ Reduced stroke
  ▫ Increased risk of CV events (MI)
    • But wise variety of use:
    • Japan (8%) cf. 41% (ANZ)

*HD = haemodialysis
Other factors in delaying CKD progression

- Smoking cessation
- Maintenance of IBW
- Active lifestyle
- Other possibilities:
  - Correction of anaemia
  - Reduction of oxidative stress
  - Ca-P product
  - Systemic inflammation reduction
Diabetes control and progression of renal disease
Glycaemic control

- Type 1 DM
  - Good control of blood glucose levels...
    - Partly reverses the hyperfiltration and glomerular hypertrophy
    - Delays development of albuminuria
    - Regress/completely reverse albuminuria
      - May take 2 years of normal glucose levels
    - Following pancreas transplant (PAK)
      - Prevents recurrent DN in renal allograft
Glycaemic control

- Type 2 DM
  - Good control of blood glucose levels...
    - Delays development of albuminuria
Salt and hypertension
Case 1

- 58 male
  - BP sub-optimal control
    - 130/85 – 160/110; ?recurrence of RAS
  - eGFR 58ml/min/1.73m² (creat 118 μmol/L)
- Kidney stones (2x in 10 years)
- R renal a stenosis
  - 5 years prior, check 12/12 later – OK
- Gout
- Accountant; rarely etOH; non-smoker
Case 1

**Medications:**
- Allopurinol 100mg
- Colchicine prn (rarely)
- Accupril 10mg bd
- Hyzaar 50/12.5 mane
- Atenolol 50mg daily
- Cartia 1 daily
Case 1

- Examination
  - Thin, well-looking
  - 146/76 lying; 140/74 standing
  - PR 60/min
  - Good peripheral pulses
  - No abdominal bruit
  - Feel L kidney, not right
  - No other abnormality
Case 1

Plan:

- **Hypertension**
  - 24 hour BP monitor
  - Goal <130/80
  - Home monitoring

- **Gout**
  - Stop thiazide of Hyzaar – Cozaar
  - Aim for uric acid <0.36mmol/L

- **eGFR**
  - Renal tract USS; myeloma screen
Case 1

- **Progress:**
  - USS normal
  - BP 150-159/96-97; 146/93 average at home
  - 361mmol Na+/24 hours
    - Dietitian
    - Breakfast cereal, breads, Vegemite®,

- **Review**
  - 5 months: 62mmol Na+/24 hours
Dietary salt and proteinuria?

- Anti-proteinuria effects of ACE reduced with high salt diet in NON-DIABETICS
- Therefore in the non-diabetic with proteinuria
  - With good BP (systolic < 130mmHg)
  - Should have sodium restricted diet
    - 24 hour urine Na < 100mmol.
Protein restriction
Dietary protein restriction

• DM – type 1
  ▫ 2 small trials ($n=54$ in total)
  ▫ Diet protein and phosphate restriction
    • Decline in GFR from 12ml/min pa to 3ml/min pa
Dietary protein restriction

• BUT larger studies have shown no benefit on progression of CKD (in DM)
  ▫ Better BP and proteinuria control

• NON-DM dietary restriction
  ▫ Low protein diet results in more CHO and fat
  ▫ Malnutrition
    • Especially PEM
    • Results in greater mortality
Uric acid
Hyperuricaemia

- Association of hyperuricaemia and:
  - CHD and mortality
- Cause, association, surrogate or effect?
  - Increased risk of hypertension
  - ?oxidative stress
  - Marker for hypertension; abnormal lipids; DM

- Or is hyperuricaemia a marker of CKD?
Calcification of arterial tree
Arterial calcification

- In meta-analysis of 17 studies ($n>15,000$)
- “Arterial stiffness” (aortic pulse wave)
  - pulse wave velocity between carotid and femoral
- When comparing APW (aortic pulse wave)
  - RR of any coronary event: 2.26
  - RR of CV mortality: 2.02
  - RR of all-cause mortality: 1.90

- CKD
  - Calcium phosphate abnormalities
  - Hyperparathyroidism
  - Calcium phosphate binders
Arterial calcification

• HMO study (n=139,849)
  ▫ Follow-up mean of 28 years
  ▫ Aortic calcification on CXR
  ▫ RR of CAD (men) 1.27
  ▫ RR of CAD (women) 1.22
  ▫ RR of stroke (women) 1.46

• Framingham study (n=2,515)
  ▫ Follow-up 22 years
  ▫ Increased risk of aortic calcification -> death
Arterial calcification

• Large long-duration observational studies have shown calcification of aorta is associated with increased risk of CVD death.
Arterial calcification

- CKD
  - Calcium - phosphate abnormalities
  - Hyperparathyroidism
  - Calcium-based phosphate binders
- More recent techniques of CT of coronary vessel calcification in CKD patients similarly associated with increased death rate
  - Is *only* an association
  - What will happen with intervention and calcium load reduction?
Hyperphosphataemia
Hyperphosphataemia of CKD

- Framingham Study subgroup ($n=3,368$), mean age 44 years.
  - Hyperphosphataemia associated with increased risk of CAD
    - RR 1.55 (high vs. low serum phosphate)
Nephrotoxins
Nephrotoxins

- Present as...

- Interstitial nephritis picture
  - Sterile pyuria

- May have proteinuria

- May have impaired renal function
  - Acutely or chronically
Avoiding Nephrotoxins

• Common toxins
  ▫ Lithium.
  ▫ Some chemotherapeutic agents.
  ▫ NSAIDs; COX-2 inhibitors
  ▫ Allopurinol.
  ▫ \( H_2 / \) proton pump blockers – omeprazole, pantoprazole, lansoprazole, etc.
  ▫ OTC/herbals.
  ▫ Fibrates.
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