Interpretation Of Renal Function Tests and The Renal Effects of Lithium

John Collins (April 2014)
Causes of Kidney disease

• Diabetes

• Glomerulonephritis

• Genetic disorders-
  Polycystic kidney disease
Causes of Kidney disease

- Reflux Nephropathy
- Vascular Disease/Hypertension
- Others processes that lead to chronic kidney damage
Natural History of Kidney Disease

• **Initial Injury** which may lead to chronic progressive loss of kidney function or directly to End Stage Renal Failure (rare),

• **After acute renal insults** recovery may occur, possibly back to normal renal function, or persistent renal abnormalities (haematuria, proteinuria) but often reduced kidney function (Glomerular Filtration Rate=GFR)

• **Adaptation of the kidney to injury**
  Hyperfiltration of remaining functioning glomeruli
  Preserved fluid/electrolyte homeostatic balance

• **Long term secondary glomerular damage and Interstitial Scarring**
  Progressive loss of renal function
  Eventually loss of homeostatic maintenance of ECF (as GFR trends below 30 mls/min)
  Some progress to End Stage Renal Failure
Current Definition of Chronic Kidney Disease (CKD)

- Evidence of Kidney Damage
  - Albuminuria
  - Urine sediment-casts, red cells
  - Histology (renal biopsy)
  - Imaging (structural kidney disease)
  - Evidence of tubular disorders
- And/or decreased GFR (GFR<60 mls/min)
- And Duration >3 months

CKD Guidelines. KDIGO. Kidney International.2012.3 (1)
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>GFR</th>
<th>Treatment Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage, normal or increased GFR</td>
<td>&gt;90 mls/min</td>
<td>T if kidney transplant</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage, mild decrease in GFR</td>
<td>60-90 mls/min</td>
<td>T if kidney transplant</td>
</tr>
<tr>
<td>3a</td>
<td>Mild to moderate decrease in GFR</td>
<td>45-60 mls/min</td>
<td>T if kidney transplant</td>
</tr>
<tr>
<td>3b</td>
<td>Moderate to severely decreased GFR</td>
<td>30-45 mls/min</td>
<td>T if kidney transplant</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-30 mls/min</td>
<td>T if kidney transplant</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 mls/min</td>
<td>D if dialysis</td>
</tr>
</tbody>
</table>
Problems with Serum Creatinine: Individual Variability

Each patient has their own ‘set point’ (a 20% change is significant)

Population ref. range

S.Creatinine (µmol/L)
Up to 50% loss of GFR can occur with serum creatinine remaining within population reference range.
Glomerular Filtration Rate

- Rate at which fluid passes into nephrons after filtration
- Normal > 90ml/min
- 150 – 200 L per day
- Creatinine reflects GFR but doesn’t account for body size and muscle mass
Ways of Determining of Glomerular Filtration rate (GFR)

- Isotope or Inulin Clearance = **Gold Standard**
- Creatinine Clearance-traditional approach
- Estimation of GFR with a validated formula

Examples
1. Cockgroft-Gault Equation
2. Abreviated MDRD Equation
3. CKD EPI equation
Advantages of CKD-EPI GFR

- Doesn’t require patient weight or height
- Already adjusted for body surface area
- More reliable than C-G in elderly
- More accurate than C-G in chronic kidney disease
- Less underestimation of GFR around 60 mls/min than MDRD
- It is a very useful tool and combined with staging, estimation equations have radically changed our approach to CKD
Disadvantages of estimates of GFR

• Still Imprecise in relationship to true GFR
• Tends to underestimate GFR at and above 60 mls/minute and probably should not be applied in isolation
• Cannot be applied where serum creatinine rising or falling significantly (eg acute kidney injury)
• Not validated for children or extremes of body composition (eg very obese people)
• Not validated for exceptional diets-very high protein, creatine, or vegetarian
• Not validated in pregnancy
• Validation issues in different racial groups
Classification of CKD as designed by KDOQI and modified by KDIGO

Prognosis of CKD by GFR and albuminuria category

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>30-300 mg/g 3-30 mg/mmol</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>Severely increased</td>
</tr>
<tr>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
<td></td>
</tr>
</tbody>
</table>

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
</tr>
<tr>
<td>≥90</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>60-89</td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>45-59</td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>30-44</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>15-29</td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>&lt;15</td>
<td></td>
</tr>
</tbody>
</table>

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
Glomerulus

Free filtration of Sodium and Water at Glomerulus
FIGURE 5-1 Percentage reabsorption of filtered Na⁺-Cl⁻ along the euvolemic nephron. ALH, Thin ascending limb of the loop of Henle; CCD, cortical collecting duct; DCT, distal convoluted tubule; DLH, thin descending limb of the loop of Henle; IMCD, inner medullary collecting duct; OMCD, outer medullary collecting duct; PCT, proximal convoluted tubule; PST, proximal straight tubule; TAL, thick ascending limb.

Osmolality

• An osmole is a unit of measurement that describes the number of moles of a compound that contribute to the osmotic pressure of a solution
• Osmolality = concentration of osmoles of solute/litre of solvent
• In circulation and urine, osmolality related primarily to: Sodium chloride, potassium, (glucose) (bicarbonate) urea
Renal water and sodium handling

- Bulk sodium and water reabsorption in similar proportions to filtered fluid occurs in the proximal tubule.
- Desalination occurs in loop and distal tubule.
- Water excretion determined in collecting duct dependant on ADH and intact tubular cell mechanism of action.
Anti Diuretic Hormone (ADH)

- Vasopressin
- Produced in Hypothalamus
- Increases absorption of water by collecting ducts
- Increased ADH = more concentrated urine
Drivers of ADH Release

- Osmolality, S.Na > 135 mmol/L
- Reduced Blood Pressure
MECHANISM OF ACTION OF ADH

- ADH attaches to a V2 receptor and activates a cascade through a Gs protein, adenylyl cyclase, cAMP and protein kinase A to cause the insertion of aquaporin 2 into the apical membrane.
- H₂O moves through aquaporin 2 in response to an osmotic gradient and thence through aquaporins 3 and 4 in the basolateral membrane.
Interpretation of electrolytes in blood and urine

- There are no normal values for the urinary excretion of water and electrolytes
- Data should be interpreted by consideration of the prevailing stimulus and the “expected” renal response

Kamel et al. 897-929. The Kidney. 2012
Hyponatremia

- **Water Disorder**
- **Salt depletion only present in some circumstances**
- **Requires clinical assessment of patient’s fluid status**
  - BP lying and standing
  - JVP (elevated OR depressed)
  - Tissue Turgor
  - Presence of oedema
- **Key lab tests are:**
  - serum and urine:-
    - osmolality, sodium, creatinine, potassium
Polyuria definitions

- Conventional - 24 hour urine volume >2.5 litres

- Physiology-based – 24 hour urine volume is higher than expected in a specific setting
Case

- 22 year old woman living in a hot climate
- Concerned about fitness and body image
- To avoid “dehydration” she drinks 5L of water a day
- She is health conscious and consumes a low salt/low protein diet
- Seeks advice because she wakes up 2-3 times at night to pass large volumes of urine
Case

- Serum sodium 130 mmol/L
- 24 hour urine volume 5 litres
- Urine osmolality 80 mOsm/Kg water

So

- A water diuresis is present (high urine flow rate and low urine osmolality)
- However as Serum sodium is < 135 mmol/l you would expect a maximal urine flow rate (10 mls/min->10 Litres/day) as no ADH present
- So in this context, the urine flow rate is lower than anticipated
Case

- Increased salt wasting (sweat) and low salt intake (which can be deduced from her daily osmole excretion of 80 mmosmx5=400. Usual 600-900 on Western diet) leads to a lower effective arterial blood flow
- Relatively lower GFR and increased proximal sodium reabsorption.
- Lower delivery of solute to collecting duct results in diminished ability to excrete free water (even despite Urine osmolality of 80 mosm/L)
Case-possible consequences

• **Risk of more severe hyponatremia** (if she has a sudden increase in water intake, or marked drop off in sweat, or non-osmotic secretion of ADH e.g. nausea, Extasy drugs etc) and its consequences (increased intracranial pressure)

• **Risk of sudden hypernatremia** (if given large salt load) and possible demyelination
Case-management

• Reduce water intake to reduce requirement to excrete free water load
• Increase urinary solute load- liberalize sodium intake +/- protein intake (urea) would facilitate ability to excrete a free water load in context of no ADH
The Renal effects of Lithium
Lithium and the Kidney

- Lithium(Li) has a MW of 7 (sodium is 23). It is filtered freely at the glomerulus
- 75% of lithium is reabsorbed before the distal convoluted tubule by mechanisms similar to those for sodium
- Dietary sodium restriction leads to increased lithium re-absorption in the collecting duct
- This process is mediated by the amiloride-sensitive sodium channel. ENaC.
Sodium Transporters in Nephron

ENaC in Collecting Tubule

Na/H exchanger PCT

NKCC2 in Loop
Sites of Sodium Reabsorption

- PCT
- PST
- DLH
- ALH
- DCT
- TALH
- OMCD
- IMCD
- CCD

Reabsorption percentages:
- PCT: 60%
- PST: <1%
- DCT: 7%
- TALH: 30%
- OMCD: 2-3%
- IMCD: <1%
Lithium and the Kidney

- Lithium results in decreased AQP2 expression and luminal membrane localisation
- Mechanism was thought to be due to Li reducing cAMP response to vasopressin
- Likely related to multiple effects
Lithium Cellular effects are broad and complex

• In a rat model of lithium administration, proteomic analysis revealed 77 different proteins affected either directly or indirectly by Li treatment.

• Functions of these proteins include signal transduction, regulation of gene expression, cytoskeletal organisation, cellular reorganisation, apoptosis and cell proliferation.

Li Renal Toxicity

- Nephrogenic Diabetes Insipidus
- Nephrotic Syndrome
- Chronic Interstitial nephritis
- Renal Tubular Acidosis (mild)
- Hyperparathyroidism
- Oedema during episodes of mania
Lithium and Nephrogenic Diabetes Insipidus (NDI)

• Approximately 50% of patients on Li have a concentrating defect and about 20% had clinical features of NDI (Am J Kidney Dis. 1987.10). Others suggest incidence up to 40%

• Discontinuation early, results in improvement but with chronic Li use NDI becomes irreversible

• Water deprivation test to exclude primary polydipsia and central DI
Amiloride, lithium and Nephrogenic Diabetes Insipidus (NDI)

- Amiloride prevents uptake of Li into the collecting duct by blocking ENaC
- Li induced down-regulation of AQP2 is thus diminished
- Amiloride thus ameliorates or reverses polyuria associated with Li
Figure 1. Twenty-Four-Hour Urine Volume (Left Panel) and Urine Osmolality (Right Panel) before (Open Circles) and during (Closed Circles) Amiloride (A) Treatment. These findings were obtained before and after 24±6 days of amiloride treatment while patients had an unrestricted fluid intake. Li denotes lithium.
Managing Polyuria in Lithium Treated patients

Lithium-induced Nephrogenic Diabetes Insipidus: Renal Effects of Amiloride


Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus

Crossover RCT of Amiloride in Li treated patients (all had at least partial NDI)

Table 3. Demographic data of participants in the placebo/amiloride study

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Age (yr) [mean ± SD (range)]</th>
<th>Time on lithium (yr) [mean ± SD (range)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9</td>
<td>2</td>
<td>58 ± 4 (37-71)</td>
<td>20 ± 3 (8-34)</td>
</tr>
</tbody>
</table>

Values are Other medications include the following: doxazosin, clozapine, carbamazepine (3), doxepin, risperidone (3), dothiepin, paroxetine, quetiapine, fluoxetine (2), citalopram, zopiclone.

Table 4. Baseline plasma physiologic parameters of participants on lithium therapy in the amiloride/placebo crossover study

<table>
<thead>
<tr>
<th></th>
<th>Osmolality (mOsm kg⁻¹)</th>
<th>Na⁺ (mmol l⁻¹)</th>
<th>Li⁺ (umol l⁻¹)</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline placebo</td>
<td>298 ± 3</td>
<td>142 ± 1</td>
<td>0.73 ± 0.09</td>
<td>95 ± 12</td>
</tr>
<tr>
<td>Baseline amiloride</td>
<td>296 ± 1</td>
<td>141 ± 1</td>
<td>0.70 ± 0.08</td>
<td>90 ± 6</td>
</tr>
</tbody>
</table>

Values (mean ± SEM) are after 6 wk of amiloride or placebo therapy. Samples were taken after a 12-h overnight fluid deprivation, before dDAVP administration.
Effect of amiloride on patients managed with lithium

CJASN.2008.Bedford et al
Amiloride and lithium

- Amiloride effective when mild to moderate concentrating defect present
- Need to monitor Li levels more closely
- Often ineffective when maximum concentrating ability <200 mosm/L
- In these patients tubular damage often permanent even when LI discontinued
NDI and treatment options

- Amiloride
- Thiazides +/- sodium restriction (decrease distal water delivery, upregulate AQP2 receptors)
- NSAIDs (decrease prostaglandin synthesis. Prostaglandins antagonise the action of ADH)
Li Renal Toxicity

- Nephrogenic Diabetes Insipidus
- **Nephrotic Syndrome**
- Chronic Interstitial nephritis
- Renal Tubular Acidosis (mild)
- Hyperparathyroidism
- Oedema during episodes of mania
Nephrotic Syndrome

- Uncommon
- Minimal change Disease or Focal Segmental Glomerulosclerosis (FSGS)
- Probably related to glomerular epithelial toxicity
- Minimal Change onset usually in first year after 1-2 months-responds to Li withdrawal
- FSGS occurs later often associated with interstitial nephritis and doesn’t improve on Li withdrawal (suggesting it is not directly caused by Li but is secondary to tubular injury)
Li Renal Toxicity

- Nephrogenic Diabetes Insipidus
- Nephrotic Syndrome
- **Chronic Interstitial nephritis**
- Hyperparathyroidism
- Renal Tubular Acidosis (mild)
- Oedema during episodes of mania
Chronic Interstitial Nephritis

- Major risk-duration of Li exposure and cumulative dose
- Other risk factors
  - Episodes of acute intoxication
  - Increasing age
  - Other co-morbid disease (DM, Hypertension)
Chronic Interstitial Nephritis

- Insidious onset
- Mild proteinuria
- 15-20% of patients develop a moderate decline in GFR to 40-60 mls/min
- Progressive renal failure due solely to Li leading to ESRD is uncommon
- Rate of loss of GFR 2-3 mls/min so on average
- Latent period from onset of therapy to ESRD- 20 years in small numbers who do progress
Lithium Nephrotoxicity: A Progressive Combined Glomerular and Tubulointerstitial Nephropathy

- 24 patients with biopsy proven Li toxicity
- Li therapy duration 13.6 (2-25) years
- Bx because of CKD, 47% proteinuria
- CTIN-100%
- FSGS-50%
- 7/9 with serum creatinine > 200umol/L progressed to ESRD despite stopping Li

Renal failure occurs in chronic lithium treatment but is uncommon

Bendz et al. Kidney International 2010.77.219-224

Table 4 | Absolute numbers of individuals; observed and expected cases of ESRD in the lithium population; by sex and age

<table>
<thead>
<tr>
<th>Age strata</th>
<th>General population</th>
<th>Lithium population</th>
<th>Females</th>
<th>Lithium population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All males</td>
<td>ESRD cases</td>
<td>All males</td>
<td>ESRD observed cases</td>
</tr>
<tr>
<td>0-19</td>
<td>320,233</td>
<td>20</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>80,509</td>
<td>18</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>25-34</td>
<td>179,605</td>
<td>74</td>
<td>119</td>
<td>0</td>
</tr>
<tr>
<td>35-44</td>
<td>191,956</td>
<td>176</td>
<td>216</td>
<td>0</td>
</tr>
<tr>
<td>45-54</td>
<td>173,672</td>
<td>251</td>
<td>293</td>
<td>2</td>
</tr>
<tr>
<td>55-64</td>
<td>172,598</td>
<td>356</td>
<td>380</td>
<td>3</td>
</tr>
<tr>
<td>65-74</td>
<td>107,585</td>
<td>266</td>
<td>216</td>
<td>2</td>
</tr>
<tr>
<td>75-84</td>
<td>74,729</td>
<td>202</td>
<td>94</td>
<td>0</td>
</tr>
<tr>
<td>85-99</td>
<td>22,650</td>
<td>23</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0</td>
<td>Unknown</td>
<td>0</td>
</tr>
</tbody>
</table>

Total       | 1,323,537 | 1386     | 1370      | 7                  | 2.2669               | 1,351,816   | 816      | 1999      | 11                 | 1.8897               |

Abbreviation: ESRD, end-stage renal disease.

Six-fold higher Incidence of ESRD in lithium using population compared to general population
Renal failure occurs in chronic lithium treatment but is uncommon

Bendz et al. Kidney International 2010.77.219-224

- 18 patients on Li developed ESRD
- All Li treated patients were aged >46 years at time of commencement of Renal replacement therapy
- Mean treatment time for Li was 23 years in RRT group
- 10 patients had been off Li for >10 years at time of commencement of RRT
- Prevalence of CKD (serum creatinine > 150umol/L) was 1.2% in 3369 patients on Li (excluding those on RRT)
CKD and Li

- ESRD uncommon but not rare
- Characterised by chronic tubulo-interstitial nephritis and secondary FSGS
- A number of risk factors identified
- Regular GFR monitoring mandatory in patients on Li
- Early discontinuation of Li (if possible) when CKD develops is likely to be beneficial
Li Renal Toxicity

- Nephrogenic Diabetes Insipidus
- Nephrotic Syndrome
- Chronic Interstitial nephritis
- Hyperparathyroidism
- Renal Tubular Acidosis (mild)
- Oedema during episodes of mania
The End