CKD: An update on recent developments

Robert Lewis
Wessex Kidney Centre
Anatomy and functions of the kidney

Key functions of the kidney

• Waste excretion
• Acid-base balance
• Salt/water homeostasis
• Blood pressure control
• Glycaemic control
  – Gluconeogenesis
  – Glucose absorption
  – Insulin metabolism & excretion
• Secretion of hormones including erythropoietin (EPO) and calcitriol

T2DM: Type 2 diabetes mellitus

Financial impact of CKD

• The annual cost of CKD to the NHS in England was estimated at £1.45 billion in 2009–10
  – Represents 1.3% of all NHS spending that year
  – Equivalent to £1 in every £77 spent
• There are thought to be around 1 million people in England who have undiagnosed CKD

Care for a patient on dialysis costs the NHS around £27,000 a year, while the cost of slowing down kidney deterioration is around £235 a year

CKD=chronic kidney disease.
Targeted screening for CKD:

- diabetes
- hypertension
- acute kidney injury in last 2-3 years
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement - for example, systemic lupus erythematosus
- family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease
- opportunistic detection of haematuria.
NICE 2014: Diagnosis of CKD

Two eGFR estimations <60 mL/min/1.73 m² over a period not less than 90 days

OR

ACR >3 mg/mmol

ACR=albumin:creatinine ratio; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate.
NICE (2014) Available at: https://www.nice.org.uk/cg182 (accessed 22.10.2014)
## Classification of CKD: NICE guidelines 2014

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²), description and range</th>
<th>ACR categories (mg/mmol), description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (≥90) Normal and high</td>
<td>A1 (&lt;3) Normal to mildly increased</td>
</tr>
<tr>
<td>G2 (60–89) Mild reduction related to normal range for a young adult</td>
<td>A2 (3–30) Moderately increased</td>
</tr>
<tr>
<td>G3a (45–59) Mild–moderate reduction</td>
<td>A3 (&gt;30) Severely increased</td>
</tr>
<tr>
<td>G3b (30–44) Moderate–severe reduction</td>
<td></td>
</tr>
<tr>
<td>G4 (15–29) Severe reduction</td>
<td></td>
</tr>
<tr>
<td>G5 (&lt;15) Kidney failure</td>
<td></td>
</tr>
</tbody>
</table>

• NB: ACR is an important indicator of cardiovascular risk and progression.
• ACR=albumin:creatinine ratio; CKD=chronic kidney disease; GFR=glomerular filtration rate.
• NICE (2014) Available at: [https://www.nice.org.uk/cg182](https://www.nice.org.uk/cg182) (accessed 22.10.2014)
Percentage of subjects with CKD stage 3-5 (eGFR<60mls/mm) by age and gender

de Lusignan et al 2005
eGFR<60mls/min in people over 75 years old

Stage 4-5
Stage 3a
Stage 3b
When CKD category G3a A1 is open to question

- Poor validation of the eGFR formula
  - Very elderly
  - Children
- Erroneously low eGFR (i.e. function looks worse than it is)
  - People with high BMI or muscle bulk
  - Dehydration
  - High protein intake
  - Trimethoprim

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate.
MDRD: A mathematical confection

eGFR* = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \\
\times 1.210 \ (\text{if black}) \times 0.742 \ (\text{if female})

*\text{mL/min/1.73 m}^2\\
eGFR=\text{estimated glomerular filtration rate}; \ MDRD=\text{Modification of Diet in Renal Disease}.\\
Sample: people under the age of 75 with known renal impairment
Evidence of poorer outcomes in people over 75 years with CKD only evident after eGFR < 45 mls/min

“In older people, identification and management of CKD should prioritize the smaller numbers with more severe CKD”.
BTS/Renal Association UK Guidelines for LRD Transplantation

<table>
<thead>
<tr>
<th>Age</th>
<th>Acceptable GFR ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40y</td>
<td>86</td>
</tr>
<tr>
<td>50y</td>
<td>77</td>
</tr>
<tr>
<td>60y</td>
<td>68</td>
</tr>
<tr>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>80</td>
<td>50</td>
</tr>
</tbody>
</table>
Cardiovascular risk of CKD stratified by age

Adapted from Raymond et al NDT (2007) 22:3214-3220
Can we improve the accuracy of eGFR as a measure of risk?

- New formula: $\text{CKD}_{EPI}^1$
- New assay: cystatin C$^2$

CKD$_{EPI}$=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate.
Cystatin C may be a useful alternative to creatinine for estimation of GFR when early CKD is suspected.

<table>
<thead>
<tr>
<th>Cystatin C to estimate GFR</th>
<th>Creatinine to estimate GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced by all nucleated cells $^{1,2}$</td>
<td>Produced by muscle cells $^{1,2}$</td>
</tr>
<tr>
<td>100% filtered at the glomerulus with no tubular secretion $^2$</td>
<td>100% filtered at the glomerulus with some tubular secretion $^2$</td>
</tr>
<tr>
<td>Blood level independent of muscle mass or diet. Therefore unaffected by age, gender or race $^2$</td>
<td>Blood level dependent on muscle mass. Therefore affected by age, gender and race. Also affected by meat content of diet $^2$</td>
</tr>
<tr>
<td>Blood level is falsely raised in hypothyroidism and lowered in hyperthyroidism $^3$</td>
<td>Unaffected by thyroid activity $^3$</td>
</tr>
<tr>
<td>Assay costs approximately £2.50 $^4$</td>
<td>Assay costs approximately £0.25 $^4$</td>
</tr>
</tbody>
</table>

CKD=chronic kidney disease; GFR=glomerular filtration rate.
Cystatin C based eGFR in the diagnosis of CKD

At initial diagnosis to confirm or rule out CKD in people with:
- An eGFR (estimated using serum creatinine) of 45–59 mL/min/1.73 m², sustained for at least 90 days and:
  - No albuminuria (ACR less than 3 mg/mmol) or other marker of kidney disease

Do not diagnose CKD in people with:
- An eGFR (estimated using serum creatinine) of 45–59 mL/m
- An eGFR (estimated using cystatin C) of more than 60 mL/min
- No other marker of kidney disease

• ACR=albumin:creatinine ratio; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate.
• NICE (2014) Available at: https://www.nice.org.uk/cg182 (accessed 22.10.2014)
Proteinuria

- **Dipstick**
  - Detects (predominately) albumin
  - Becomes positive when protein >30 mg/dL
  - Affected by urinary concentration/dilution

- **ACR**
  - Measures albumin
  - Detects “microalbuminuria” (ACR between 3–30 mg/mmol)

- **PCR**
  - Measures total protein
  - Correlates with 24 hour urinary protein
  - Only correlates with risk above 45 mg/mmol

ACR=albumin:creatinine ratio; PCR=protein:creatinine ratio.

Preferred test: ACR

When:
- Recommended for initial detection of albuminuria and subsequent monitoring
  - ACR >3 mg/mmol is abnormal in men and women

How:
- Preferably early morning urine (not dipstick or 24 hour urine collection)
- If early morning sample not practical, send spot urine
  - If ACR <3 mg/mmol, no need to obtain early morning sample.
  - If ACR 3-70 mg/mmol, send MSU to exclude infection and repeat ACR using a subsequent early morning sample
  - If the ACR is >70 mg/mmol, a repeat sample needed: unequivocally abnormal and significant
- 3 samples required for diagnosis of nephropathy (within 3 months)
  - Effect of exercise, hypertension

ACR=albumin:creatinine ratio; MSU=mid-stream urine.
1. NICE (2014) Available at: https://www.nice.org.uk/cg182 (accessed 22.10.2014); 2. Based on speaker’s experience
Urine testing: summary

- Do not use reagent strips to identify proteinuria (but required to detect haematuria).
- Significant proteinuria is present when ACR >3 mg/mmol in men and women.
- The term microalbuminuria is obsolete.
- EMU only necessary if ACR 3-70mg/mmol.

ACR=albumin:creatinine ratio.
NICE (2014) Available at: https://www.nice.org.uk/cg182 (accessed 22.10.2014)
Define accelerated progression of CKD as:

• a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months or

• a sustained decrease in GFR of 15 ml/min/1.73 m² 6 per year.
**NICE 2014: Blood pressure control in CKD**

<table>
<thead>
<tr>
<th>No diabetes or proteinuria</th>
<th>&lt;140/90 mmHg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes or ACR &gt;70 mg/mmol</td>
<td>&lt;130/80 mmHg</td>
</tr>
</tbody>
</table>

* Note: less stringent than QOF indicator of 140/85 mmHg.

ACR=albumin:creatinine ratio; CKD=chronic kidney disease; QOF=quality and outcomes framework.

Mode of action of ACE inhibitors and ARBs

ACE inhibitors and ARBs → Glomerulosclerosis → RENAL FUNCTION → Reduction in number of functioning glomeruli

Intraglomerular hypertension → Increased blood flow to remaining nephrons

ACE=angiotensin-converting-enzyme; ARB=angiotensin receptor blocker.
Irbesartan diabetic nephropathy trial

Time to doubling of serum creatinine

Irbesartan

RRR=37%
P<0.001

Amlodipine

RRR=33%
P=0.003

Control

NS=non-significant; RRR=unadjusted relative risk reduction.
Indications for ACE inhibitors in CKD: Determined by level of proteinuria

- Diabetes and an ACR >3 mg/mmol
- Hypertension and an ACR >30 mg/mmol
- ACR >70 mg/mmol (irrespective of hypertension or cardiovascular disease)

- Check eGFR 7–10 days after starting*
  - <10% fall: safe to continue
  - 10–25% fall: repeat 10 days later
  - >25% fall: stop

*Advice based upon speaker’s experience and adapted from NICE (2014).
ACE=angiotensin-converting-enzyme; ACR=albumin:creatinine ratio; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate.
ACE inhibitors and ARBs: Effect on GFR

ACE inhibitors and ARBs: Effect on GFR

- Slowly deteriorating CKD
- Acute reduction eGFR – expected and OK – up to 25%
- Long-term stabilisation in GFR
  (most likely in proteinuric patients)
- Progressive fall in GFR, caused by renal artery stenosis or other cause of global reduction in renal perfusion

ACE=angiotensin-converting-enzyme; ACEi=ACE inhibitor; ARB=angiotensin receptor blocker; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate.

Adapted from: NICE (2014) Available at: https://www.nice.org.uk/cg182 (accessed 22.10.2014)
ACE inhibitors: Cautions

• Care with those at increased risk of pre-renal acute kidney injury
  – Especially if:
    • Elderly
    • Pre-existing cardiac, renal disease
    • Suspected renal vascular disease (PVD ± IHD, CVA)

• Check U+E and stop ACE inhibitor when acutely unwell

ACE=angiotensin-converting enzyme; CVA=cerebrovascular accident; IHD=ischaemic heart disease; PVD=peripheral vascular disease; U+E=urea + electrolytes.
The causes of hypertension may be different in old people

• Reduced large arterial compliance (ISH) ↑
  – Atheroma
  – Medial calcification
  – Endothelial dysfunction (↓NO)

• High incidence of CKD
  – Decline in Na/K ATPase (↑intracellular Ca, vasoconstriction)
  – Reduced sodium excretion

• High coincidence of secondary HT
  – Renovascular disease
  – NSAIDs
Diagnosing hypertension in older people has pitfalls

• Pseudohypertension
  – prevalence unknown (7-70%?)

• White coat hypertension
  – More common in the elderly (prevalence 25%?)
  – The risk-predictive value of ambulatory BP compared to office BP increases with age \(^1\)

• Out-of-office BP monitoring
  – Difference between office/home readings greater in the elderly than middle-aged \(^2\)

1. Staessen 1999
2. Brobie 2004
Hypertension looks different at different ages

Aronow et al NEJN 2007
Old people handle medication differently

- Pharmacokinetics
  - Lower liver volume and blood flow
- Body composition
  - $T_{\frac{1}{2}}$ of lipophilic drugs increased
- Reduced renal clearance
- Changes in receptors at target organs
Older people are more susceptible to side effects of antihypertensive medication

- Renovascular disease: ACEi and ARBs
- Impaired tubular function: thiazides
  - Hypokalaemia
  - Hyponatraemia
- Cardiac conduction defects: β-blockers, CCBs
- Dysregulation of baroreflex-mediated reflexes (orthostatic hypotension)
The elderly are sailing close to the wind

- Absence of reserve capacity
  - Dehydration falls, AKI
  - Sepsis falls, CCF, AKI
  - NSAIDs AKI, CCF

- Antihypertensive medication (diuretics, ACE-i) may inhibit corrective responses
What defines “elderly”

- Biological age?
- Comorbidities?
- How can management guidelines be tailored to the individual?
NICE: Acute Kidney Injury

Flavour of the month
Only 50% of AKI care was rated good by the panel

A fifth of post admission AKI was both predictable and avoidable
AKI is associated with poor outcomes

• Adjusted mortality increased 4 fold in hospital and extends beyond discharge
• Increased hospital length of stay
  – Portsmouth: AKI/CKD v Controls
  – LOS 12 days v 7 days (p=.002)
• Progression of CKD and increased incidence of ESRD.
Patient Safety Alert

Stage Three: Directive
Standardising the early identification of Acute Kidney Injury

9 June 2014

Alert reference number: NHSPSAD2014/010
Alert stage: Three - Directive

National patient safety data tells us that patients are dying and suffering severe harm due to a delay in detecting Acute Kidney Injury (AKI). AKI often occurs without causing any symptoms or signs and its presence frequently goes unrecognized by patients and doctors alike.

“A patient with a complex physical and mental health background became unwell over the weekend. Despite persistent hypertension there was no record of fluid balance. Bloods were delayed until late Sunday night, indicating acute kidney injury. Acute kidney injury not recognised or commented on until mid way through the following day. Medications given to the patient over the weekend included drugs contraindicated in renal failure. The patient was admitted to ICU and on admission was unconscious/hoarse. There were multiple systemic failures in the management of this patient including a life threatening delay in critical care of ±12 hours and systems failure in the recognition of deteriorating patient.”

Acute Kidney Injury (AKI) is a sudden reduction in kidney function. Complex long term medical conditions, medication and intercurrent illness are often complicated by AKI. It is estimated that 1 in 5 emergency admissions into hospital are associated with AKI, prolonging inpatient care and resulting in 100,000 deaths in secondary care. National Confidential Enquiry into Patient Outcome and Death (NCEPOD) estimated that one quarter to one third of cases have the potential to be prevented.

A national algorithm, standardising the definition of AKI has now been agreed. This provides the ability to ensure that a timely and consistent approach to the detection and diagnosis of patients with AKI is taken across the NHS.

This algorithm has been endorsed by NHS England and it is recommended that the algorithm is implemented across the NHS. When integrated into a Laboratory Information Management System (LIMS) the algorithm will identify potential cases of AKI from laboratory data in real time and produce a test result. The laboratory system will then send the test result using existing IT connections to patient management systems.

NHS England in partnership with the UK Renal Registry has launched a National AKI Prevention Programme which will include the development of tools and interventions. A priority for the Programme is the development and adoption of elet algorithms based on the test result, which will proactively notify clinicians when a patient has AKI, supporting implementation of AKI NICE guidance (CG169).

Although primary care is an important focus for detection and prevention of AKI, it is anticipated that AKI results will be sent to primary care in a second phase of the programme. Meanwhile trusts are expected to discuss with primary care representatives the management of AKI test results, particularly at times when deputising AKI is providing medical cover.

Further support will be provided by the National Programme as exemplar elet algorithms are developed: www.england.nhs.uk/AKIProgramme

The AKI detection algorithm can be found at the following link: www.england.nhs.uk/AKI-algorithm

Actions

Who: NHS acute trusts and foundation trusts providing pathology services

When: By 9 March 2015

1. Bring this alert to the Director of Pathology/T with responsibility for the upgrading of LIMS systems

2. Work with local LIMS supplier to integrate AKI algorithm into LIMS system

3. Work with local LIMS supplier to ensure the test result goes to local patient management systems and into a data message sent to a central point for national monitoring purposes

4. Communicate with appropriate primary care providers to ensure they seek advice if test results are received

5. Regularly access NHS England AKI website where additional resources and information will be provided as developed

Supporting information
For further information to support the implementation of this alert go to www.england.nhs.uk/AKI-algorithm

Contact us: patientsafety.enquiries@nhs.net
Sign up for regular updates: www.england.nhs.uk/patientsafety

Patience Safety | Domain 5
www.england.nhs.uk/patientsafety

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<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI Stage 1</td>
<td>1.5 – 1.9 times baseline or ≥ 26.5 µmol/l increase</td>
</tr>
<tr>
<td>AKI Stage 2</td>
<td>2.0 – 2.9 times baseline</td>
</tr>
<tr>
<td>AKI stage 3</td>
<td>3.0 times baseline or Increase to ≥ 354 µmol/l or need for dialysis</td>
</tr>
</tbody>
</table>
Pathogenesis

Risk Factors
- Old age
- CKD
- Diabetes
- Pre-existing cardiac and hepatic failure
- Vascular disease
- Chronic diarrhoeal diseases
- Usual medication
  - ACE/ARB
  - Diuretics
  - NSAIDS

Insults
- Acute sepsis (cytokine storm)
- Intravascular volume depletion (D&V, diuretics)
- Toxins
  - Radiocontrast
  - Gentamicin
  - NSAIDS
  - myoglobin
Objective Assessment

• Volume status
  – Physical signs
  – Serum albumin

• Fluid balance
  – Urine output/fluid intake
  – Weight?
  – JVP

• Drug review
  – Stop renovasoactive agents
Investigation

• Cause?
  – Pre-renal
  – Renal
  – Post-renal

• Ultrasound

• Urine analysis
Management

- Fluid replacement (goal directed)
- Correction of acidosis
- Management of hyperkalaemia
- Dopamine? Furosemide?
- Referral if unresponsive to medical therapy
Learning points: AKI

• AKI is common and has serious implications for the patient
• AKI is preventable – (forethought)
• Early management prevents morbidity
• Alert system in place throughout UK March 2015