Guidance for clinicians managing children at risk of, or with, acute kidney injury

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This guidance is intended for doctors, nurses and allied healthcare professionals looking after children. It is therefore written in a manner to be accessible to all groups. It is intended to improve the care of children at risk of, or with, Acute Kidney Injury (AKI).

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Disclaimer
To the best of our knowledge, the contents of this publication are in line with National Institute for Health and Care Excellence guidance relating to the management and treatment of acute kidney injury. Professional advice should be sought before taking, or refraining from taking, any action on the basis of the content of this publication. We cannot be held responsible for any errors or omissions therein, nor for the consequences of these or for any loss or damage suffered by readers or any third party informed of its contents. The UK Renal Registry disclaims all liability and responsibility arising from any reliance placed on the information contained in this publication by you or any third party who may be informed of its contents.
1. Background
The National Institute for Health and Care Excellence (NICE) Acute Kidney Injury (AKI) clinical practice guideline CG169 identified a number of key priorities for implementation, which included recognising patients at risk of AKI in different settings. NHS England in partnership with the UK Renal Registry has established the ‘Think Kidneys’ national programme with the main aim of ensuring that avoidable harm related to AKI is prevented in all care settings. The AKI workstream of the British Association for Paediatric Nephrology developed this guidance, which provides support to health and care professionals who are managing patients at risk of, or with AKI. Further information can be found on the Think Kidneys website: www.thinkkidneys.nhs.uk

2. Introduction
AKI, previously known as acute renal failure, is a global healthcare challenge (Lewington et al 2013, Mehta et al 2015). It is characterised by a sudden decline in kidney function and is rarely caused by trauma to the kidneys. AKI can occur without symptoms and is detected through a routine blood test (serum creatinine) and/or a decrease in urine output (KDIGO 2012). It has many different causes but most commonly occurs secondary to other serious illnesses such as sepsis or conditions associated with hypovolaemia and a drop in blood pressure e.g. vomiting, diarrhoea or blood loss. In some cases, certain medications can also affect the kidneys adversely and this can cause AKI or increase its severity. AKI is associated with an increased risk of death, length of hospital stay, risk of chronic kidney disease (CKD) and cost to the NHS.

It is estimated that one in five of all adult emergency admissions to hospital have AKI (Wang et al, 2012). Up to 100,000 deaths in hospitals are associated with AKI, of which a quarter to a third could potentially be prevented, as reported by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2009) Adding Insult to Injury 2009. The financial burden of AKI on the NHS is significant with estimates indicating the cost is £1.02bn in England for the acute care and £179mn following the episode related to an increase in patients with CKD and end stage kidney disease, as calculated for adults with AKI (Kerr et al, 2014).

3. What do blood test results mean?

Children’s creatinine changes with age, and depends on how big they are and how much muscle mass they have. So, the interpretation of a creatinine value must bear this in mind.

The table below is a recommended set of age related reference ranges for creatinine. These ranges were proposed at the Paediatric Laboratory Medicine Network (PaLMnet) meeting in 2014. PaLMnet is a subgroup of the Association of Clinical Biochemists Scientific Committee.

Of note:
- These recommended ranges apply to results obtained by enzymatic methods for creatinine estimation only.
- These are the preferred reference ranges for paediatrics.
- Abbreviations: Lower limit reference interval (LLRI), upper limit reference interval (ULRI).
4. How to recognise AKI and interpret AKI warning scores

Children with a creatinine above the acceptable range may have Chronic Kidney Disease (CKD) or may have AKI.

The hallmark of AKI is a recent increase in creatinine from a previous baseline (if a previous result is available) or a value greater than 1.5x upper limit of the reference interval for age. AKI is usually associated with a fall in urine output.

Following the National Patient Safety Alert for AKI, hospitals are required to issue electronic AKI warning scores. These are based on measurements of serum creatinine (as indicated below). However, these alerts need to be coupled together with appropriate assessment and institution of clinical management plan.

Recognise AKI:

Serum creatinine:
- > 1.5x reference creatinine (=previous baseline if known)
- >1.5x age specific upper limit of reference interval (ULRI)
  (if creatinine between ULRI and 1.5x ULRI, repeat measurement)

Urine output:
- <0.5mls/kg/hr for 8 hours

Interpretation of AKI warning score:

AKI 1: Measured creatinine >1.5-2x reference creatinine/ULRI

AKI 2: Measured creatinine 2-3x reference creatinine/ULRI

AKI 3: Serum creatinine >3x reference creatinine/ULRI
AKI 1 is often unrecognised. It may represent a physiological response to dehydration, which resolves with appropriate fluid management or may herald more significant intrinsic renal disease, which may progress to AKI 2, and 3. It is important to recognise all stages of AKI and take appropriate action to manage and investigate the cause of AKI.

See Section 7 and APPENDIX 1 (page 10) for further management details.

5. Paediatric risk groups
Certain children are at greater risk of AKI either because of pre-existing disease / risk factors or because they fall into an acute high-risk scenario (see below). Children at high risk of AKI or in a high-risk scenario should have their serum creatinine measured.

Steps should be taken to prevent AKI by adequately monitoring kidney function, maintaining adequate hydration and by minimising harm.

Minimisation of harm includes reviewing medication (see section 8 Medicines Optimisation below) and avoiding nephrotoxic agents such as intravenous contrast if possible.

Children at high risk of AKI include those with:
- Nephro-urological, cardiac or liver disease
- Malignancy and/or a bone marrow transplant
- Dependence on others for access to fluids
- History of taking medication that may adversely affect renal function (ACEI/ARB, NSAIDs, aminoglycosides, calcineurin inhibitors)

Scenarios in which children can be at high risk of AKI include:
- History of reduced urine output
- Sepsis
- Hypoperfusion or dehydration
- History of exposure to drugs or toxin that may adversely affect renal function
- Renal disease or urinary tract obstruction
- Major surgery

6. What steps should be taken to prevent AKI?
The following steps should be undertaken to prevent AKI in high risk groups / scenarios:

3Ms - Monitor, Maintain and Minimise

1. **Monitor** - Children should have their creatinine checked and repeated if there are any concerns. Their fluid balance including urine output, weight, urinalysis and Paediatric Early Warning Score (PEWS) should also be recorded and reviewed on a daily basis. Any signs of sepsis should be urgently investigated and treated.
2. **Maintain** - Attention should be paid to a child’s circulatory volume to ensure they have an adequate circulatory volume and perfusion pressure. Hypo-perfusion should be addressed urgently with fluid boluses and inotropic support once the child is volume replete. *For further detailed guidance on fluid therapy please refer to the NICE guidance: Intravenous fluid therapy in children and young people in hospital (NG29).*

3. **Minimise** - Further harm should be reduced by reviewing, adjusting and monitoring medication that may adversely affect renal function e.g. NSAIDs, ACEI, ARB, aminoglycosides and calcineurin inhibitors. Intravenous contrast should also be avoided if possible.

*See appendix 1 (page 10) for full details.*

7. **How should AKI be managed to prevent permanent damage?**

Once AKI has developed the **3Ms** - **Monitor, Maintain and Minimise**, should be undertaken to prevent further harm.

To establish the cause of AKI, a consultant should assess the child urgently. In the majority of cases AKI will be pre-renal due to hypovolaemia and will be corrected with adequate fluid repletion. Further investigations allow identification of established intra-renal disease and obstruction. Early detection and referral of children with intra-renal disease such as nephritis, vasculitis and haemolytic uraemic syndrome may help ameliorate the course of the child’s disease and reduce the risk of progression to CKD.

The following investigations are recommended for all children with AKI:
- Full blood count, creatinine, electrolytes, bone profile, bicarbonate
- Urinalysis, urine microscopy
- Urinary tract Ultrasound

Further Management (including referral guidance):

**AKI 1:** If clinically relevant - C3/C4, ASOT, immunoglobulins, ANA, ANCA, anti-GBM antibodies, CK, LDH, blood film. **Consider discussion with:** a paediatrician with a specialist interest in nephrology (SPIN) or tertiary nephrologist particularly if known CKD/ patient with kidney transplant or if there are features of intrinsic renal disease e.g. nephritis or haemolytic uraemic syndrome

**AKI 2:** Investigations as for AKI 1. **Discuss with SPIN or tertiary nephrologist**

**AKI 3:** Investigations as for AKI 1. **Discuss with tertiary nephrologist**

*See appendix 1 (page 10) for list of indications for urgent referral to Paediatric Nephrologist and suggested Follow-up.*
8. Medicines optimisation in children with AKI
AKI can be prevented or reduced in severity by early detection and appropriate management.

When a patient is either admitted with AKI, or develops AKI during an admission episode, a thorough review of medication is required:

- To eliminate potential cause / risk / contributory factor for AKI
- To avoid inappropriate combinations of medications in the context of AKI
- To reduce adverse events
- To ensure that doses are appropriate for the patient’s level of renal function
- To ensure all medicines prescribed are clinically appropriate.

Summary of drugs to be stopped, avoided, reduced or monitored in AKI

See Appendix 2 (page 12) for list of high-risk medication and actions required in context of AKI.
9. Conclusion

There are no good data for the incidence of AKI in children. It is likely that early AKI currently goes unrecognised and a number of AKI cases in at risk groups/ high-risk scenarios are preventable. For this reason, it is important to have a high index of suspicion when reviewing a child who is in the high-risk group for AKI. Early steps to address physiological disturbances and to reduce exposure to drugs that may adversely affect renal function will prevent progression to more severe renal dysfunction and so reduce morbidity and mortality.

10. References

11. Acknowledgements

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APPENDIX 1

BAPN AKI MANAGEMENT RECOMMENDATIONS

AKI can be preventable: early detection and appropriate management reduces harm

Risk assess for AKI
check serum creatinine

High risk groups
- Nephrourological, cardiac, liver disease
- Malignancy, bone marrow transplant
- Dependence on others for access to fluids
- Medication (eg., ACEI, ARB, NSAIDS, diuretics, aminoglycosides, calcineurin inhibitors)

High risk scenarios
- History of reduced urine output
- Sepsis
- Hypoperfusion or dehydration
- Nephrotoxic drug or toxin exposure
- Renal disease or urinary tract obstruction
- Major surgery

Prevention: 3Ms

- MONITOR (Early Warning Score, fluid balance, daily weight, urinalysis, serum creatinine and electrolytes)
- MAINTAIN circulation (treat hypoperfusion adequately)
- MINIMISE kidney insults (review, monitor and adjust medication)

Recognise AKI

<table>
<thead>
<tr>
<th>Serum creatinine:</th>
<th>Urine output:</th>
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<tbody>
<tr>
<td>&gt; 1.5x reference creatinine (=previous baseline if known)</td>
<td>&lt;0.5mls/kg/hr for 8 hours</td>
</tr>
<tr>
<td>&gt;1.5x age specific upper limit reference interval (ULRI) (if creatinine between ULRI and 1.5x ULRI, repeat measurement)</td>
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</table>

AKI stage

AKI 1: Measured creatinine >1.5-2x reference creatinine/ULRI

AKI 2: Measured creatinine >2-3x reference creatinine/ULRI

AKI 3: Measured creatinine >3x reference creatinine/ULRI
Management of confirmed AKI: 4Ms

1. Recognise and treat the underlying cause
2. Evaluate and review according to the following cycle:
   - **Management**
     - Urgent consultant review
     - Initial investigations: FBC, creatinine, electrolytes, bone profile, bicarbonate, urine microscopy, urinary tract ultrasound scan (within 24 hours)
   - **Monitor**
     - EWS, fluid balance, daily weight, urinalysis, serum creatinine and electrolytes
   - **Minimise kidney injury**
     - Review, monitor and adjust medication especially aminoglycosides, calcineurin inhibitors, ACEI, ARB, NSAIDS, diuretics
   - **Maintain circulation**
     - Treat hypoperfusion adequately

Further management

**AKI 1:** If clinically relevant: C3/C4, ASOT, ANA, ANCA, anti-GBM antibodies, immunoglobulins, blood film, LDH, CK. **Consider discussion** with a specialist paediatrician with an interest in nephrology (SPIN) or tertiary nephrology

**AKI 2:** Investigations as for AKI 1. **Discuss** with SPIN or tertiary nephrology

**AKI 3:** Investigations as for AKI 1. **Discuss** with tertiary nephrology

**PAEDIATRIC NEPHROLOGY REFERRAL**

1. AKI in a patient with CKD4 or 5 or a renal transplant
2. Early referral if AKI is associated with multisystem disease or suspected intrinsic renal disease eg. haemolytic uraemic syndrome

**Immediate referral** in any stage of AKI with the following:
- Potassium >6.5mmol/l (non-haemolysed sample)
- Oligoanuria and plasma sodium <125mmol/l
- Pulmonary oedema or hypertension unresponsive to diuretics
- Plasma urea >40mmol/l unresponsive to fluid challenge

**Follow-up**

All patients who required dialysis or who have persisting proteinuria or reduced renal function at 3 months should be followed up by SPIN or tertiary nephrology

*the 4Ms were adapted with kind permission of London AKI Network*
APPENDIX 2

High Risk Medicines: *actions required in context of AKI*

The following list is not exhaustive. Refer to the BNF/BNFc for more information. Consider ALL medications including any “usual” long term medication. Check medication history thoroughly and ask about “Over the Counter” preparations and alternative therapies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Problem</th>
<th>Action in presence of AKI</th>
<th>Education Points</th>
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<tr>
<td><strong>Analgesics</strong></td>
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<tr>
<td>NSAIDs</td>
<td>Acute interstitial nephritis Altered intraglomerular hemodynamics</td>
<td>Avoid</td>
<td>Avoid taking whilst at risk of hypovolemia.</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Accumulation of active metabolites – increased CNS side effects.</td>
<td>Reduce dose of short acting preparation</td>
<td>May accumulate in acute kidney injury. Seek advice if at risk of dehydration. If needed, use opiates with minimal renal excretion e.g. fentanyl, oxycodone, hydromorphone.</td>
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<tr>
<td><strong>Antibiotics / Antifungals / Antivirals (See In house guidelines where available)</strong></td>
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<tr>
<td>Aciclovir</td>
<td>Crystal nephropathy. Accumulates in reduced renal function leading to mental confusion, seizures. Avoid rapid infusions. Infuse IV over one hour</td>
<td>Reduce dose</td>
<td>Ensure high fluid intake – enteral or IV Seek medical advice if at risk of dehydration.</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Tubular cell toxicity, ototoxicity</td>
<td>Avoid if possible</td>
<td>Monitor drug levels and renal function regularly.</td>
</tr>
<tr>
<td>Amphotericin IV – Fungizone®</td>
<td>Tubular cell toxicity, Hypokalemia Avoid rapid infusion</td>
<td>Avoid. Consider Ambisome® preparation</td>
<td>Interactions, (e.g. monitor tacrolimus levels and reduce dose as appropriate; withhold statins as risk of rhabdomyolysis).</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Accumulation leading to acute mental confusion, coma, seizures.</td>
<td>Reduce dose and check drug interactions</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Side Effect/Adverse Effect</td>
<td>Management</td>
<td>Notes</td>
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<tr>
<td>Ganciclovir</td>
<td>Crystal nephropathy&lt;br&gt;Accumulates in reduced renal function leading to neutropenia, anemia and thrombocytopenia. Avoid rapid infusions.</td>
<td>Reduce dose</td>
<td></td>
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<tr>
<td>Penicillins</td>
<td>Acute interstitial nephritis &lt;br&gt;Glomerulonephritis&lt;br&gt;Accumulation leading CNS side effects including seizures.</td>
<td>Reduce dose</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Accumulation leading to CNS excitation, seizures, &amp; blood dyscrasias.</td>
<td>Reduce dose</td>
<td>Monitor levels</td>
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<tr>
<td>Trimethoprim OR Co-trimoxazole</td>
<td>Acute interstitial nephritis (rare) &lt;br&gt;Interferes with tubular secretion of creatinine (without affecting actual GFR), so can cause apparent AKI particularly amongst patients with CKD &lt;br&gt;Accumulation leading to Hyperkalemia (particularly with high doses), nausea &amp; vomiting.</td>
<td>Avoid or reduce dose</td>
<td>Encourage good fluid intake (oral or IV). Seek medical advice if at risk of dehydration.</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Acute interstitial nephritis&lt;br&gt;Accumulation leading to renal toxicity, ototoxicity.</td>
<td>Reduce dose / increase dose interval &lt;br&gt;Monitor levels</td>
<td></td>
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<tr>
<td><strong>Antiepileptics (including drugs used for neuropathic pain)</strong></td>
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<tr>
<td>Gabapentin / Pregabalin</td>
<td>Accumulation in kidney impairment – increase in CNS side effects</td>
<td>Reduce dose</td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>Acute interstitial nephritis &lt;br&gt;Risk of phenytoin toxicity if patient has low serum albumen levels</td>
<td>Monitor levels</td>
<td></td>
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<tr>
<td><strong>Anti-hypertensives</strong></td>
<td>Hypotension &lt;br&gt;May exacerbate renal hypoperfusion &lt;br&gt;Longer acting, renal cleared drugs may accumulate in renal impairment</td>
<td>Consider withholding / reduce dose depending on clinical signs</td>
<td></td>
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<tr>
<td>ACEI / ARBs</td>
<td>Altered hemodynamics &lt;br&gt;Hyperkalemia</td>
<td>These drugs can impair the kidneys’ ability to maintain GFR when perfusion is compromised. In some situations, e.g. heart failure with a decent blood pressure, continuing them might actually be helpful</td>
<td>Avoid taking whilst at risk of hypovolemia. Seek medical advice if at risk. Monitor BP. If patient is hypertensive, consider alternative antihypertensive</td>
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<tr>
<td><strong>Diuretics</strong></td>
<td><strong>Hypo perfusion</strong></td>
<td><strong>Monitor and adjust dose as necessary.</strong></td>
<td><strong>Dose reduction may be required. Seek medical advice if at risk of hypovolemia.</strong></td>
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<tr>
<td><strong>Diuretics – potassium sparing</strong></td>
<td>Hyperkalemia</td>
<td>Avoid</td>
<td>Dose reduction may be required. Seek medical advice if at risk of hypovolemia.</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td>Accumulation with risk of nephrotoxicity, neurotoxicity and hyperkalaemia</td>
<td>Seek advice of transplant centre regarding monitoring levels and dose adjustment.</td>
<td>May accumulate in reduced renal function. Seek medical advice/advice from transplant team if at risk of hypovolemia.</td>
</tr>
<tr>
<td><strong>Calcineurin inhibitors e.g. ciclosporin, tacrolimus</strong></td>
<td>Crystal nephropathy</td>
<td>Dose modification as required Monitor levels and consider folinic acid rescue Correct fluid balance</td>
<td>May accumulate in reduced renal function. Seek medical advice if at risk of hypovolemia.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Accumulation leading to bradycardia, visual disturbances, mental confusion. Aggravates hyperkalemia</td>
<td>Reduce dose</td>
<td>May accumulate in acute kidney injury. Seek medical advice if at risk from hypovolaemia.</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Nephrotoxic – tubular and glomerular damage.</td>
<td>Avoid</td>
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<td><strong>5 –amino salicylates</strong></td>
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<tr>
<td><strong>Digoxin</strong></td>
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