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

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Think Kidneys is a national programme led by
NHS England in partnership with UK Renal Registry

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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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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).

Age Group	Male (Creatinine µmol/l)		Female (Creatinine µmol/l)	
	Lower (LLRI)	Upper (ULRI)	Lower (LLRI)	Upper (ULRI)
0 - <14days	27	81	27	81
14d - <1yr	14	34	14	34
1 - <3yr	15	31	15	31
3 - <5yr	23	37	23	37
5 - <7yr	25	42	25	42
7 - <9yr	30	48	30	48
9 - <11yr	28	57	28	57
11yr	36	64	36	64
12yr	36	67	36	67
13yr	38	76	38	74
14yr	40	83	43	75
15yr	47	98	44	79
16yr	54	99	48	81
>16yr	Adult Range		Adult Range	
	59	104	45	84

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.

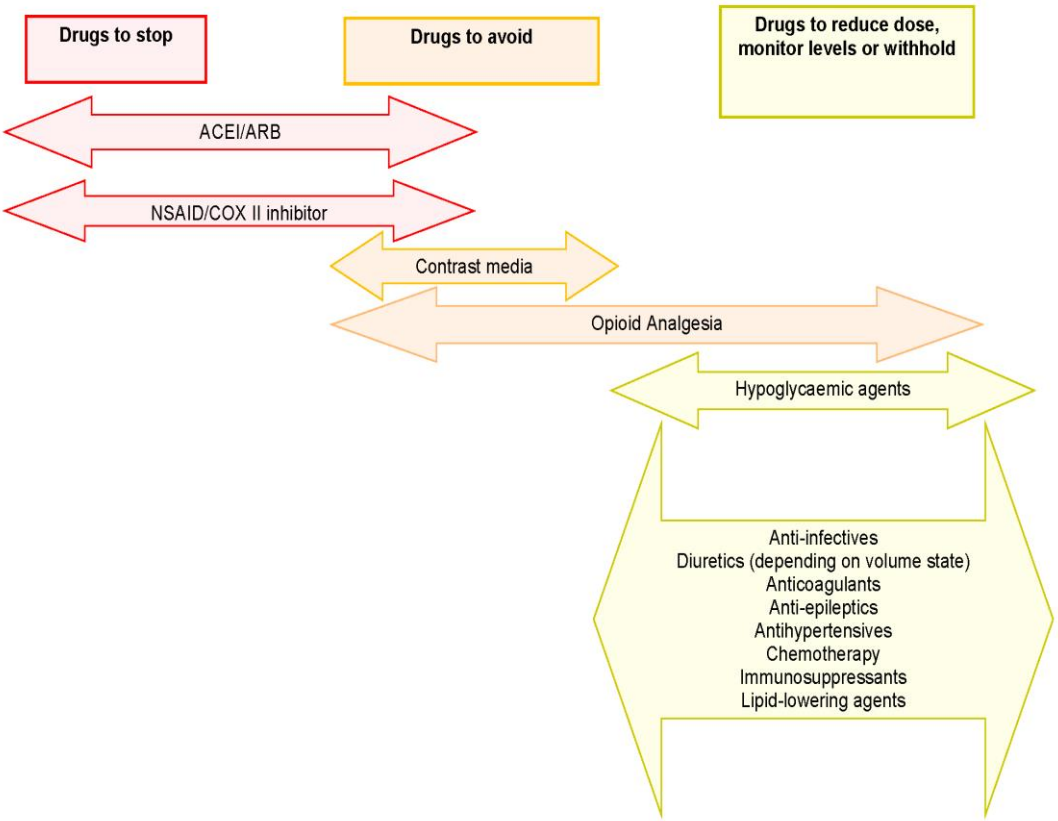
8. Medicines optimisation in children with AKI

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

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11. Acknowledgements

BAPN AKI Working Group:

Martin Christian
Consultant Paediatric Nephrologist
Nottingham Children's Hospital

David Hughes
Consultant Paediatric Nephrologist
Royal Hospital for Children, Glasgow

Carol Inward
Consultant Paediatric Nephrologist
Bristol Royal Hospital for Children

Rachel Lennon
Consultant Paediatric Nephrologist
Royal Manchester Children's Hospital

Andy Lunn
Consultant Paediatric Nephrologist
Nottingham Children's Hospital

David Milford
Consultant Paediatric Nephrologist
Birmingham Children's Hospital

Manish Sinha
Consultant Paediatric Nephrologist
Guys & St Thomas NHS Foundation Trust

Rukshana Shroff
Consultant Paediatric Nephrologist
Great Ormond Street Hospital for Children NHS Foundation Trust

Kay Tyerman
Consultant Paediatric Nephrologist
Leeds Children's Hospital

Additional expert contributors:
Caroline Ashley
Renal Pharmacist, Royal Free London NHS Foundation Trust

Julie Baker
Paediatric Pharmacist, Birmingham Children's Hospital

Hong Thoong
Paediatric Pharmacist, Royal Manchester Children's Hospital

Marlies Ostermann
Consultant in Nephrology and Critical Care, Guys and St Thomas' NHS Foundation Trust

Sue Shaw
Renal Pharmacist, Derby Teaching Hospitals NHS Foundation Trust

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 **W**arning **S**core, fluid balance, daily weight, urinalysis, serum creatinine and electrolytes)

MAINTAIN circulation (treat hypoperfusion adequately)

MINIMISE kidney insults (review, monitor and adjust medication)

Recognise AKI

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

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

AKI stage

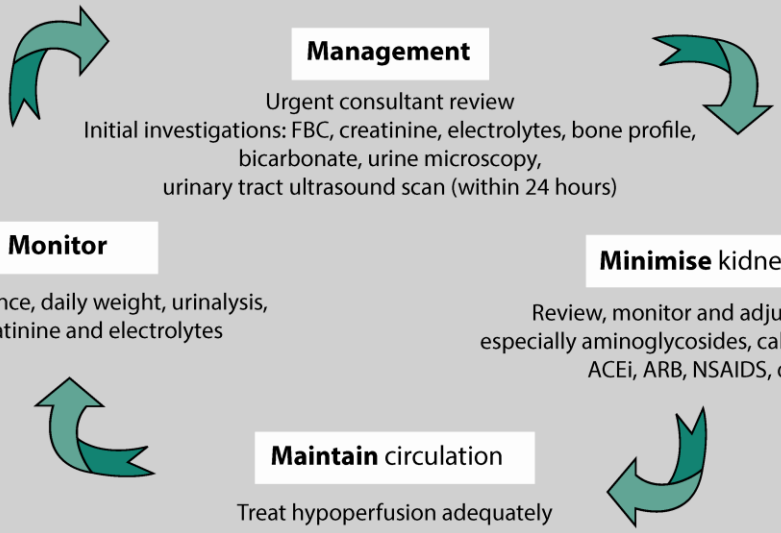
AKI 1: Measured creatinine >1.5-2x *reference* creatinine/ULRI

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:



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

British Association for Paediatric Nephrology

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.

Drug	Problem	Action in presence of AKI	Education Points
Analgesics			
NSAIDs	Acute interstitial nephritis Altered intraglomerular hemodynamics	Avoid	Avoid taking whilst at risk of hypovolemia.
Opioid analgesics	Accumulation of active metabolites – increased CNS side effects.	Reduce dose of short acting preparation	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.
Antibiotics / Antifungals / Antivirals (See In house guidelines where available)			
Aciclovir	Crystal nephropathy. Accumulates in reduced renal function leading to mental confusion, seizures. Avoid rapid infusions. Infuse IV over one hour	Reduce dose	Ensure high fluid intake – enteral or IV Seek medical advice if at risk of dehydration.
Aminoglycosides	Tubular cell toxicity, ototoxicity	Avoid if possible Monitor drug levels and renal function regularly.	
Amphotericin IV – Fungizone®	Tubular cell toxicity, Hypokalemia Avoid rapid infusion	Avoid. Consider Ambisome® preparation	
Fluconazole	Accumulation leading to acute mental confusion, coma, seizures.	Reduce dose and check drug interactions	Interactions, (e.g. monitor tacrolimus levels and reduce dose as appropriate; withhold statins as risk of rhabdomyolysis).

Ganciclovir	Crystal nephropathy Accumulates in reduced renal function leading to neutropenia, anemia and thrombocytopenia. Avoid rapid infusions.	Reduce dose	
Penicillins	Acute interstitial nephritis Glomerulonephritis Accumulation leading CNS side effects including seizures.	Reduce dose	
Teicoplanin	Accumulation leading to CNS excitation, seizures, & blood dyscrasias.	Reduce dose Monitor levels	
Trimethoprim OR Co-trimoxazole	Acute interstitial nephritis (rare) Interferes with tubular secretion of creatinine (without affecting actual GFR), so can cause apparent AKI particularly amongst patients with CKD Accumulation leading to Hyperkalemia (particularly with high doses), nausea & vomiting.	Avoid or reduce dose	Encourage good fluid intake (oral or IV). Seek medical advice if at risk of dehydration.
Vancomycin	Acute interstitial nephritis Accumulation leading to renal toxicity, ototoxicity.	Reduce dose / increase dose interval Monitor levels	
Antiepileptics (including drugs used for neuropathic pain)			
Gabapentin / Pregabalin	Accumulation in kidney impairment – increase in CNS side effects	Reduce dose	
Phenytoin	Acute interstitial nephritis Risk of phenytoin toxicity if patient has low serum albumen levels	Monitor levels	
Anti-hypertensives	Hypotension May exacerbate renal hypo-perfusion Longer acting, renal cleared drugs may accumulate in renal impairment	Consider withholding / reduce dose depending on clinical signs	
ACEI / ARBs	Altered hemodynamics Hyperkalemia	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	Avoid taking whilst at risk of hypovolemia. Seek medical advice if at risk. Monitor BP. If patient is hypertensive, consider alternative antihypertensive

		Seek nephrologist advice if undergoing contrast procedure or at risk of AKI.	agents, e.g., calcium channel blockers, alpha-blockers, beta-blockers if appropriate.
Diuretics	Hypo perfusion Loop diuretics preferred as thiazides less effective if GFR very low. However they can potentiate the effects of loop diuretics.	Monitor and adjust dose as necessary.	Dose reduction may be required. Seek medical advice if at risk of hypovolemia
Diuretics – potassium sparing	Hyperkalemia Hypo perfusion	Avoid	Dose reduction may be required. Seek medical advice if at risk of hypovolemia
Immunosuppressants			
Calcineurin inhibitors e.g. ciclosporin, tacrolimus	Accumulation with risk of nephrotoxicity, neurotoxicity and hyperkalaemia	Seek advice of transplant centre regarding monitoring levels and dose adjustment.	May accumulate in reduced renal function. Seek medical advice / advice from transplant team if at risk of hypovolemia.
Methotrexate	Crystal nephropathy Accumulation increases side effects, eg. Excessive bone marrow depression, mucositis, acute hepatic toxicity, acute interstitial pneumonitis.	Dose modification as required Monitor levels and consider folinic acid rescue Correct fluid balance	May accumulate in reduced renal function. Seek medical advice if at risk of hypovolemia.
Others			
5 –amino salicylates	Nephrotoxic – tubular and glomerular damage.	Avoid	
Digoxin	Accumulation leading to bradycardia, visual disturbances, mental confusion. Aggravates hyperkalemia	Reduce dose Monitor drug level	May accumulate in acute kidney injury. Seek medical advice if at risk from hypovolaemia