Ten tips on how to reduce Iatrogenic AKI

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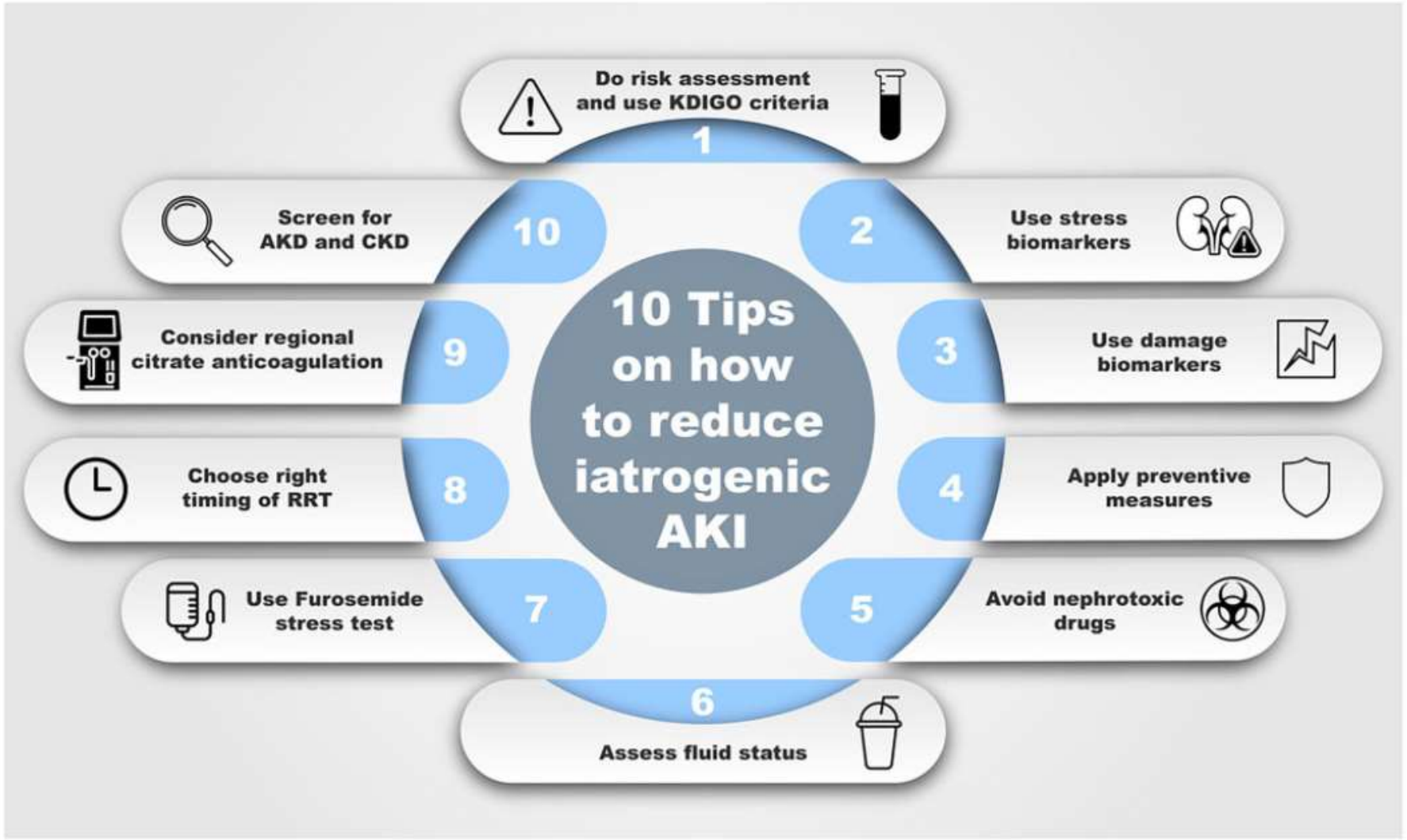
Introduction

- Acute kidney injury (AKI) is common in critically ill affecting almost 1 in 4 critically ill children
- Timely identification & appropriate measures to prevent and manage AKI has better outcome
- Given the significant risk of CKD , patients with AKI require long-term follow up



https:/doi.org/10.1093/ckj/sfae412

What is AKI?

- Abrupt loss in kidney function leading to decline in GFR
- Hours to days
- Leading to reduced urine termed as oliguria/anuria
- Retention of metabolic waste products
- Dysregulation of fluid, electrolyte & acid-base homeostasis

KDOQI Commentary. Am J Kidney Dis. 2013;61:649-72

AKI staging

- AKI describes a sudden loss of kidney function determined by increased S Cr & reduced UOP limited to 7 days
- KDIGO classification is preferred as it applies to children (>1yr) & adults

Stage	SCr	UO
1	Increase in SCr ≥ 0.3 mg/dL (≥26.5 μmol/L) or increase in SCr ≥ 150% to 200% (1.5 to 1.9X)	<0.5 mL/kg/h (>6 h)
2	Increase in SCr > 200% to 300% (>2 to 2.9X)	<0.5 mL/kg/h (>12 h)
3	Increase in SCr > 300% (≥3X) or Increase in SCr to ≥4 mg/dL (≥353.6 μmol/L) or initiation of renal replacement therapy	<0.3 mL/kg/h (24 h) or anuria (12 h)

SCr: serum creatinine; UO: urine output.

Nephron 2012, 120, c179–c184.

When to anticipate AKI?

- Children in critical care unit
- Child with edema & reduced UOP
- Child with abnormal loss of fluids or dehydrated
  - AGE
  - Blood loss
  - Renal loss – DI & other tubular disorder
  - Burns

When to anticipate AKI?

- Child brought for envenomation, insect bite or indigenous drugs
- Child being managed for fulminant infections
- Child with a background of compromised cardiac, pulmonary, glomerular diseases or rapidly developing anemia (hemolysis, hemorrhagic diseases or visceral blood loss)
- CAKUT with obstruction
- Children receiving nephrotoxic medication

Case Scenario 1

- 5 yrs old boy weighing 20kg (previous 21 kg), Ht 110cm admitted with AGE & dehydration. He is a known case of SRNS under remission. He is on Enalapril and Tacrolimus.
- O/E - Pulses well felt, HR 109/min, BP 100/70 mmHg, No edema
- His creatinine at admission was 1.0 mg/dl, BUN 30 mg/dL and had reduced UOP past 6 hours (passed small quantity 4 hrs ago). His S Cr a month back was 0.5 mg/dL
- Is this AKI? If yes, then what is the stage of AKI? How will you manage?

Case Scenario 1

1	Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
2	Increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
3	Urine volume <0.5 mL/kg/h for 6 hours.

AKI is *staged for severity* according to the following criteria

Stage 1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 µmol/L) absolute increase in sCr	Urine volume <0.5 mL/kg/h for 6–12 hours
Stage 2	sCr ≥2.0–2.9 times baseline	Urine volume <0.5 mL/kg/h for ≥12 hours
Stage 3	sCr ≥3.0 times from baseline OR Increase in sCr to ≥4.0 mg/dL(≥353.6 µmol/L) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	Urine volume <0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

sCr=serum creatinine, eGFR= estimated glomerular filtration rate

Case Scenario 1

To which stage of KDIGO does this child belong to?

2 x 0.5 = 1 (2 times the baseline) = stage 2

How to manage?

Stop Enalapril & Tacrolimus

Manage the underlying problem

Is this pre-renal or renal AKI?

Indices to differentiate Pre-Renal & Renal AKI

Lab findings	Pre-Renal	Intrinsic
Urinalysis		Dysmorphic RBCs, casts
Urine Specific Gravity	**>1.020**	**<1.010**
Urine Osmolality	>500 mOsm	<350 mOsm
Urine Na	<20 mEq/L	>40 mEq/L
FENa	**<1%**	**>2%**
FEUrea	<35%	>35%
Serum BUN:Cr	**>20:1**	**10-20:1**

Case Scenario 1

Is this child pre-renal or renal AKI?

BUN:S Cr >20:1

H/O vomiting & diarrhoea – Give importance to the cause

Clinical features of dehydration

S/O Pre Renal AKI

Correct dehydration with IV fluids

Stop nephrotoxic medications

Case Scenario 2

5 year old child weighing 20 kg and height 110cm is admitted in PICU for Sepsis

On Examination:

No edema, pulses just felt, HR 124/min, BP 70/40

Given fluid bolus followed by inotropic support

Started on IV antibiotics

Investigations at admission :

BUN 15 mg/dL

Cr 0.6 mg/dL (eGFR – 75)

Na 145 mEq/L

K 5.2 mEq/L

HCO3 18 mEq/L

Which IV fluid is preferred?

Crystalloid Vs Colloid

The use of Hydroxylethyl starch or IV albumin is not recommended [1]

Initial Fluid Reusciation

Isotonic crystalloids preferred solution

Repeated boluses of NS may lead to hyperchloremia, renal vasoconstriction & renal injury[2]

Avoid in fluid overload states

Balanced Solutions

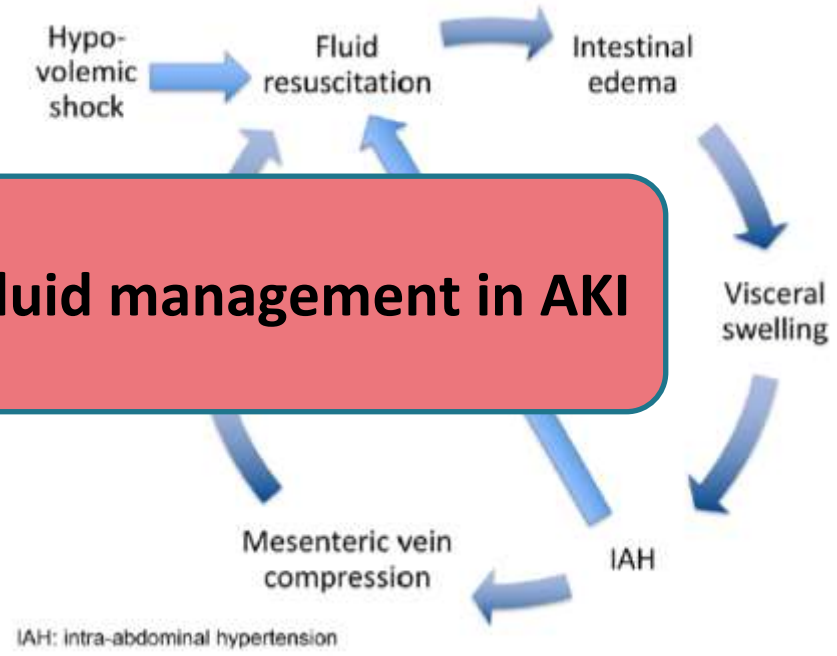
1. *Weiss L et al. Pediatr Crit Care Med. 2020;21:e52-106.*
2. *Umal A .Journal of Pediatric Critical Care 5(2):p 60-63, Apr–Jun 2018.*

Principles of Fluid Management in septic shock

- The quantity, rate & type of fluids in critically ill patients is debated
- The f
  is sug
- Fluid
  optimization, stabilization & evaluation / deresuscitation) for fluid therapy in septic shock should be considered

There is no "One Size Fits All" strategy for fluid management in AKI

Vicious cycle of septic shock resuscitation



Malbrain et al.Ann. Intensive Care 8, 66 (2018). https://doi.org/10.1186/s13613-018-0402-x

Case Scenario 2

- Fluid status is reviewed at 10 hrs
- Child received fluid bolus for hypotension & continued on maintenance IVF
- Input - 1200 ml, Output 200 ml
- FO = [(Total Fluid In - Total fluid out) in Litres/ Admission Weight in Kg] * 100

  (1.2 – 0.2/ 20) x 100 = 5%

Will this child renal status further deteriorate and require KST?

Renal Anginal Index

- In 2012, Basu et al proposed RAI as a predictor of AKI in critically ill children
- It is a bedside tool to predict the occurrence of severe AKI in PICU patients
- RAI is a product of risk & injury scores assessed 8–12 h after ICU admission

Pediatric Nephrol. (2012) 27:1067–78. doi: 10.1007/s00467-011-2024-5

Renal Anginal Index

Risk strata

Risk criteria	Score
Admission to intensive care unit	1
Solid organ or stem-cell transplantation	3
Mechanical ventilation or vasoactive support, or both	5

Injury strata

Serum creatinine relative to baseline	FO accumulation (%)	Score
Decreased or no change	<5	1
>1×–1·49×	5–10	2
1·5×–1·99×	11–15	4
≥2×	>15	8

Risk × injury
Scores: 1–40

Renal angina fulfilled with renal angina index score ≥8

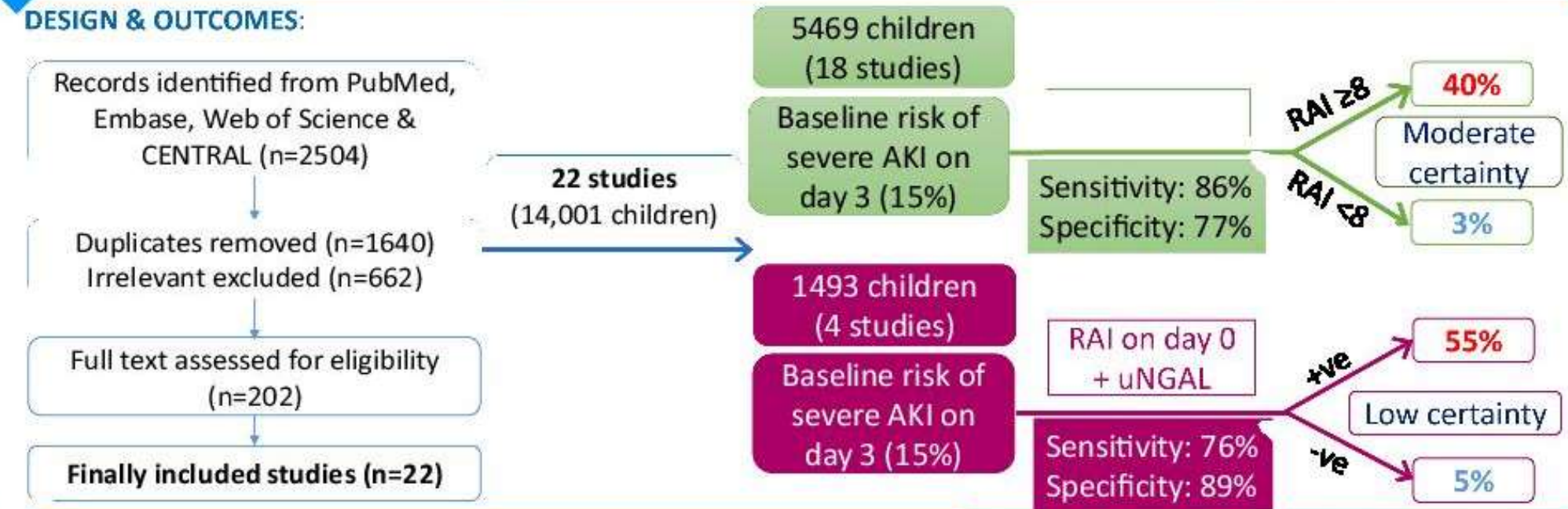
Kidney International 2014;85: 659-667

Diagnostic accuracy of renal angina index alone or in combination with biomarkers for predicting acute kidney injury in children

Graphical Abstract

HYPOTHESIS: RAI ± novel biomarkers may help in improving the risk prediction of AKI in critically sick children

DESIGN & OUTCOMES:



CONCLUSION: RAI score ≥8 has good predicting ability in recognizing the children at risk of development of severe AKI. Combination of RAI+uNGAL further improves the prediction accuracy.

Meena et al. 2021

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association

RAI in our child

Risk strata

Risk criteria	Score
Admission to intensive care unit	1
Solid organ or stem-cell transplantation	3
Mechanical ventilation or vasoactive support, or both	5

Injury strata

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Risk × injury
Scores: 1–40

Renal angina fulfilled with renal angina index score ≥8

Risk criteria = 5
Injury strata = 2
5 x 2 =10

Kidney International 2014;85: 659-667

Furosemide Stress Test (FST)

- In early AKI, the response to furosemide might indicate tubular integrity
- It was first described in critically ill adults, in whom UOP < 200 mL over 2 h following 1 mg/kg IV furosemide satisfactorily predicted stage-3 AKI (1)
- But it is not validated in children

1. *Chawla LS et al . Crit Care. 2013;17:R207*

Furosemide stress test to predict acute kidney injury progression in critically ill children

Graphical Abstract

HYPOTHESIS: Furosemide stress test (FST) may predict stage 3 acute kidney injury (AKI) in critically ill children

DESIGN & OUTCOMES

Prospective cohort

Critically ill children admitted to ICU having AKI stage 1 or 2

IV Furosemide 1 mg/kg after catheterization (FST)

Hourly urine output x 6h; Urine volume < 2 mL/kg at 2h deemed FST non-responsive

480 children screened over 2 years

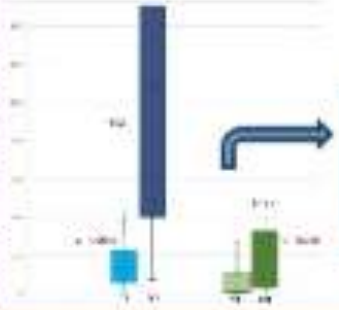
51 developed AKI stage 1-2, underwent FST

FST non-responsive (NR) n = 9

AKI 3: n = 8 (89%)
KST: n = 7 (78%)
Death: n = 5 (56%)

FST responsive (FR) n = 42

AKI 3: n = 5 (12%)
KST: n = 2 (5%)
Death: n = 3 (7%)



NGAL and PENK biomarkers higher in FST non-responsive group

AUC of FST for predicting
AKI stage 3: 0.93
KST need: 0.96
Mortality: 0.93

KST: Kidney support therapy

CONCLUSION: Furosemide stress test is a simple, inexpensive and robust biomarker for predicting stage 3 AKI and KST need in critically ill children. FST outperformed the other blood biomarkers NGAL and PENK; addition of biomarkers to FST did not improve the diagnostic accuracy.

Krishnasamy et al. 2024

Pediatric Nephrology
Journal of the International Pediatric Nephrology Association
IPNA

Biomarkers in AKI

- Detection of biomarkers provides the window of opportunity for therapeutic interventions to be effective
- Despite decades of research, a troponin-like biomarker for pediatric AKI remains elusive
- NGAL remains the most widely tested biomarker in children
- In a meta-analysis of 56 studies investigating 49 biomarkers in 8617 children post-cardiac surgery, the urine NGAL to creatinine ratio had the highest diagnostic odds ratio (91%) with 91.3% sensitivity and 89.7% specificity

Van den Eynde J et al. Eur J Pediatr. 2022 May;181(5):1909-1921. doi: 10.1007/s00431-022-04380-4

Case 2 cont.....

- **On day 3,**
  - BUN 77 mg/dL
  - Cr 3.5 mg/dL
  - K 5.5 mEq/L
  - HCO3 15 mEq/L
- D1 I/O = 1900 ml/300 ml, D2 I/O = 1000/400 ml, D3 I/O = 800 ml/ 300 ml
  - FO = [(3.7 – 1.0)/ 20] x 100 = 13.5%
- A threshold of > 10 -15% defines 'clinically significant' FO that merits KST, lower values may also impact outcomes

JAMA Pediatr. 2018 Jan 22;172(3):257–268. doi: 10.1001/jamapediatrics.2017.4540

Association Between Fluid Balance and Outcomes in Critically Ill Children

A Systematic Review and Meta-analysis

Rashid Alobaidi [1], Catherine Morgan [2], Rajit K Basu [3], Erin Stenson [4], Robin Featherstone [5], Sumit R Majumda
Sean M Bagshaw [7,✉]

- This systematic review & meta-analysis included 44 studies (7507 children)
- FO was associated with increased in-hospital mortality (17 studies [n = 2853]; odds ratio [OR], 4.34 [95% CI, 3.01-6.26]; I^2 = 61%)
- There was a 6% increase in odds of mortality for every 1% increase in FO (11 studies [n = 3200]; adjusted OR, 1.06 [95% CI, 1.03-1.10]; I^2 = 66%)
- FO was associated with increased risk for prolonged mechanical ventilation (>48 hours) (3 studies [n = 631]; OR, 2.14 [95% CI, 1.25-3.66]; I^2 = 0%) & AKI (7 studies [n = 1833]; OR, 2.36 [95% CI, 1.27-4.38]; I^2 = 78%)

Diuretics in fluid overload state

- A trial of furosemide may be attempted to induce diuresis
- Helps to convert AKI from oliguric to non-oliguric form
- Loop diuretic therapy does not significantly alter the natural course of AKI
- It obviates the need for KST in some situations
- *Probably due to improvement in fluid overload!!!*

  (KDIGO recommends in fluid overload states)

- In our child there was no improvement after diuretics

Is KST indicated in this child? Which modality to choose?

Indications for KST in AKI

- Metabolic or Electrolyte imbalance
  - Hyperkalemia (>6 with ECG change)
  - Metabolic acidosis pH<7.15
  - Urea > 200 mg/dL (symptomatic)
  - Refractory or symptomatic hyponatremia
  - Severe hyperuricemia or hyperphosphatemia associated with TLS
  - Hypermagnesemia (>8 with absent DTR)

Gibney N. Clin J Am Soc Nephrol 2008; 3: 876-880
KDIGO AKI guidelines 2012

Indications for KST in AKI

- Fluid overload
- Space for nutrition, drugs & blood products
- Toxin removal
- Hyperammonemia secondary to IEM & liver failure

Decision to start KST

Consider conditions that can be modified

Trends of laboratory test, rather than single values

Consider KST if oliguria & azotemia persist beyond 48 hrs

Gibney N. Clin J Am Soc Nephrol 2008; 3: 876-880. KDIGO AKI guidelines 2012

Modalities of KST for AKI

Parameter	Peritoneal dialysis (PD)	Intermittent hemodialysis (IHD)	Sustained low-efficiency dialysis (SLED)	Continuous kidney replacement therapy (CKRT)
Duration	Continuous	2–4 h/d	6–12 h/d	Continuous
Technicality	Simple	Complex	Complex	More complex
Hemodynamic alterations	Minimal	Large	Mild	Minimal
Control of fluid removal	Least	Modest	Better	Very accurate
Anticoagulation	Not required	Generally required	Necessary	Necessary
Mechanism of solute clearance	Diffusion	Diffusion	Diffusion ± convection (SLED-F)	Convection (SCUF, CVVH) ± diffusion (CVVHD, CVVHDF)
Risk of cerebral edema	-	+++	++	-
Rapidity of toxin removal	+	+++	++	+
Middle molecule clearance	Poor	+	+	+++
Patient mobility	+	+++	++	-
Cost of therapy	-	+	+	+++

CVVH Continuous venovenous hemofiltration, *CVVHD* Continuous venovenous hemodialysis, *CVVHDF* Continuous venovenous hemodiafiltration, *SCUF* Slow continuous ultrafiltration, *SLED-F* Sustained low-efficiency daily diafiltration

Which modality to choose in this child?

CRRT

Hemodynamically unstable, Fluid overload,
Dyselectrolytemia & increasing creatinine trend

When to stop KST?

- Patient characteristics
  - Hemodynamic status
  - Urine output
  - Volume status
  - Respiratory status
  - Overall prognosis
- Logistic characteristics
  - Staff availability
  - Cost
  - Circuit clotting

Gibney N. Clin J Am Soc Nephrol 3: 876-880, 200
Mallappallil MC. Nephron 2015;130(1):41-7.

Drug dosing & Nephrotoxic medication

- Drug dosing is difficult in critically ill patients with AKI due to altered pharmacokinetics, reduced clearances, extracorporeal removal during KST & dynamic organ functions
- Antibiotic dosing while on KST follows recommendations for adults
- Where feasible, therapeutic drug monitoring should be done
- Electronic alerts (‘NINJA’, ‘Baby NINJA’) following use of nephrotoxic medications reduce the incidence of drug-induced AKI

A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children.

Single center application

Spread

Exposure Criteria:

- >=3 NTMx medications on same day

OR

- IV Aminoglycoside for >=3 consecutive days

AKI Criteria:

Serum Creatinine increase of 50% and/or 0.3mg/dL over baseline

NINJA

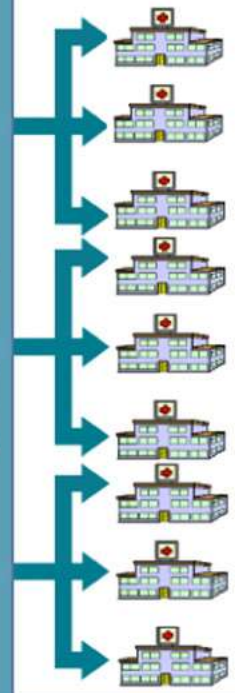
Single Center Results:

NTMx AKI rate reduction of 62%

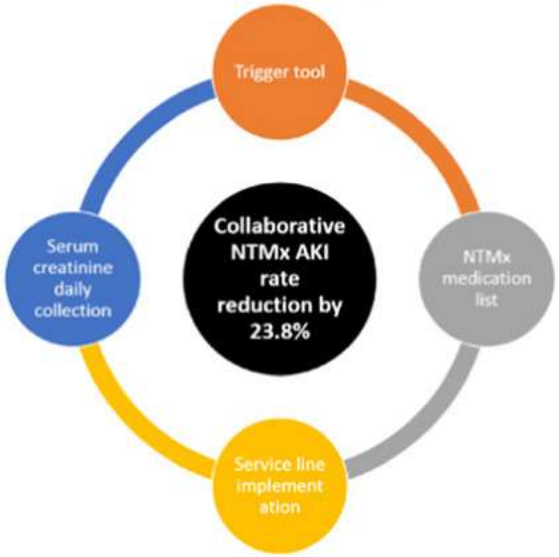
Core Measures:

- NTMx exposure rate per 1000 patient days
- NTMx AKI rate per 1000 patient days
- Percent of NTMx exposures that develop into AKI
- AKI days per 100 NTMx exposure days

NINJA



Improvement in core elements of NINJA deployment



CONCLUSION:

NINJA was successfully disseminated across 9 centers with sustainable decreased harm rates

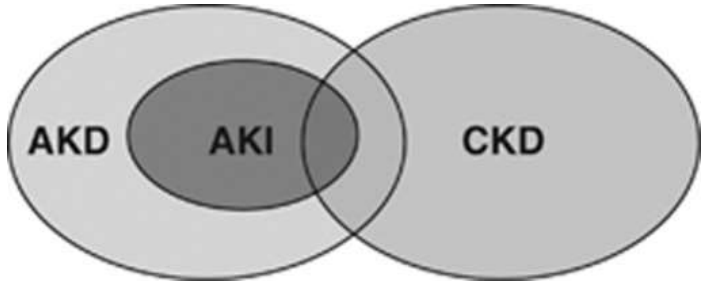
ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Goldstein, et al, 2019

Contrast Induced - AKI

- AKI defined as per KDIGO staging
- Risk factors - CKD, hypotension, DM, recent previous exposure to contrast
- Nephrotoxic drugs should be withdrawn before contrast administration
- Use the lowest possible dose of contrast medium in patients at risk for CI-AKI
- Use either iso or low osmolar iodinated contrast media
- Volume expansion with either NS or sodium bicarbonate in patients at increased risk for CI-AKI is recommended
- NAC role is not well established
- High risk Children need follow up creatinine to ensure kidney functions remain stable

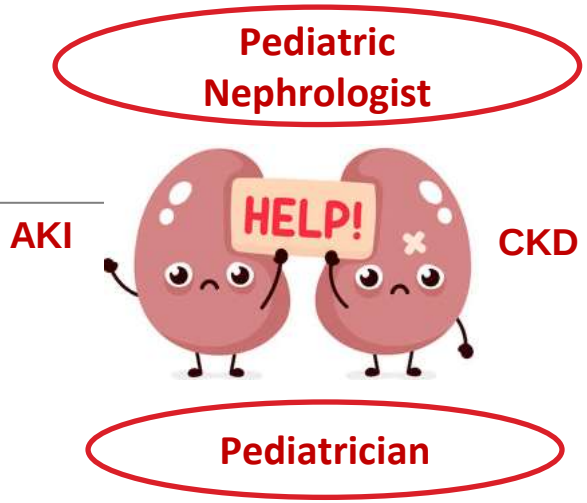
Long Term Outcomes in Pediatric AKI



- Data from critically ill children with AKI suggest survivors are at risk of CKD
- AKD – reduced kidney function < 3months (above 3 months its CKD)
- At 3 - 5 yrs follow-up in 29 critically ill children with AKI
  - 14% developed decreased eGFR
  - 21% developed HTN
- At 1-3 yrs follow-up in 126 critically ill children with AKI & no pre-existing CKD
  - 10% developed CKD
  - 47% were considered at risk of CKD
- Long term & serial assessment of renal functions needs to be done in neonates & children following recovery from AKI

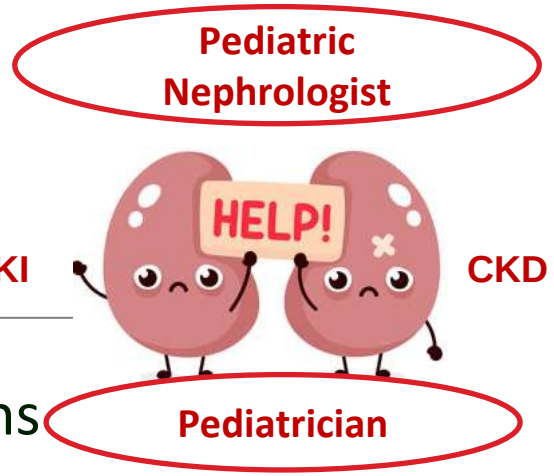
Askenazi DJ. Kidney Int 2006; 69: 184-189
Mammen C. Am J Kidney Dis 2012; 59: 523–530

Key Messages



- Step 1: Identify at risk population
- Step 2: Use KDIGO criteria to classify AKI
- Step 3: Identify cause and remove triggering factor
- Step 4: Appropriate fluid resuscitation (Pre renal is most common)
- Step 5: Do risk assessment in critically ill children
- Step 6: Assess fluid status
- Serial assessment of daily weights and fluid balance is essential, especially for critically ill children

Key Messages



- Step 7: Avoid NTX medications. If needed monitor renal functions
- Step 8: Initiate KST at the appropriate time
- Step 9: Consider condition that can be modified & trends of lab test rather than single test for KST initiation
- Step 10: Monitoring at risk children is the key to minimize risk of progression to CKD
- Outcome depends on early diagnosis and timely intervention
- Soon we might include biomarkers to help in early identification

All for this one moment

Question 1

Choose the correct option to define the time period for AKI, AKD and CKD respectively

a. Reduced renal function < 3 -5 days, < 1 month and >1 month
b. Reduced renal function <7 days, < 1 month and >1 month
c. Reduced renal function <7 days, < 3 months and >3 months
d. Reduced renal function <1 month, < 3 months and > 3months

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d. Reduced renal function <1 month, < 3 months and > 3months

Question 2

What percentage of fluid threshold best defines initiation of KST in children with AKI

a. <5%
b. 5-10%
c. 10-15%
d. >20%

Answer 2

What percentage of fluid threshold best defines initiation of KST in children with AKI

a. <5%
b. 5-10%
c. 10-15%
d. >20%

Question 3

- Which trial showed that Electronic alerts following use of nephrotoxic medications reduce the incidence of drug-induced AKI
- NAJA trial
- NOAJA trial
- NINJA trial
- NITA trial

Answer 3

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