Avoiding Kidney Injury Pediatrics

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Pediatric patient population: Postoperative AKI

- Majority of pediatric research focused on acute kidney injury after cardiac surgery & liver transplant

- More pediatric research is required to examine intraoperative management of non-cardiac surgical patients & impact on renal outcomes

- Disclaimer: Evidence provided in this presentation is based on literature from both critical care and perioperative research.

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Objectives

- Discuss incidence and impact of Acute Kidney Injury & Chronic Kidney Disease in pediatric surgical patients
- Review the pathophysiology related to AKI and CKD in children
- Identify definitions & stages of kidney disease for infants and children
- Share registry definitions of kidney injury or failure - review ASPIRE AKI 01 measure
- Provide an overview of the literature studying the prevention and recognition of kidney disease
- Summarize recommendations supported by the literature

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For more information….

- For a more in-depth overview of kidney disease, including staging and definitions, reference
  - Avoiding Kidney Injury - Overview, Pathophysiology, Definitions
- For other specialty specific recommendations, reference the following sections of the toolkit:
  - Avoiding Kidney Injury – Obstetric Patients
  - Avoiding Kidney Injury - Cardiac Surgery
  - Avoiding Kidney Injury - Recommendations for Adult Surgical Patients

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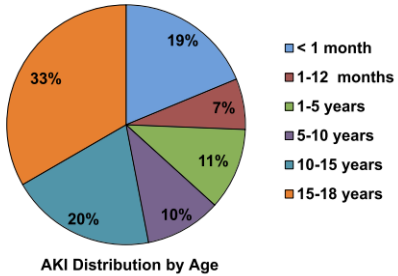
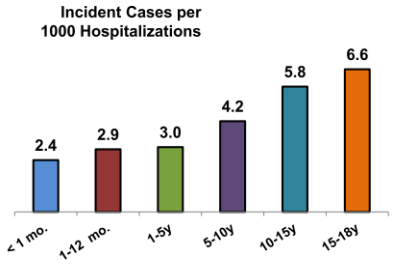
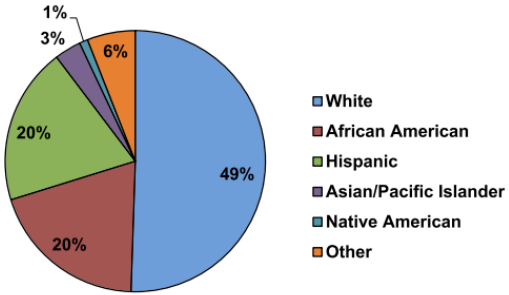
AKI Incidence in Pediatrics [1]

- Largest epidemiologic study of AKI in children using the Kids' Inpatient Database (KID), an all payer inpatient pediatric care database
  - Included 2,644,263 admissions of neonatal (≤ 1 month old) and children (< 18 old) from over 4,000 hospitals in the United States.
- Reported an AKI incidence of 3.9 cases per 1,000 admissions. AKI identified using ICD-9 codes.
- Incidence increased with age: 6.6 events per 1000 admissions in 15-18 year olds
- Mortality was 15.3% for children admitted with AKI compared to non-AKI admissions (0.6%)



AKI Distribution by Age





AKI Distribution by Race

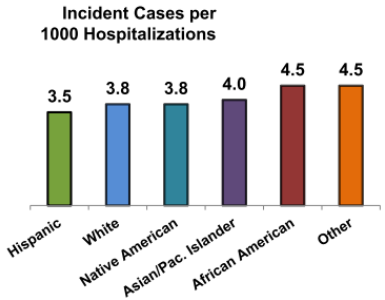


Image Source: Sutherland et al. *J Am Soc Nephrol.* 2013

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Pediatric AKI Multi-national Study [2]

Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study

- Cohort of 4,683 critically ill children and young adults (3 months to 25 years old) admitted to pediatric intensive care unit
  - 30% were post-surgical patients
- 26.9% developed AKI; 3.4% died

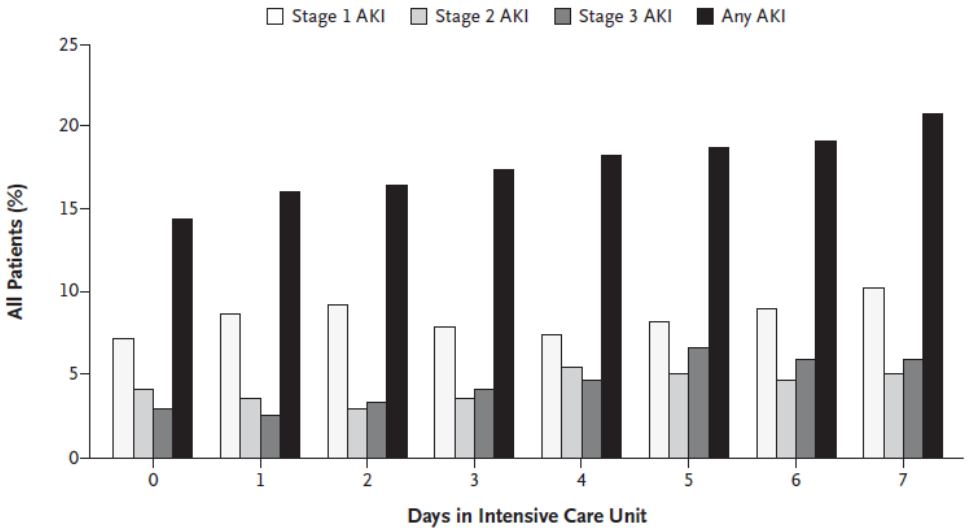

Image Source: Kaddourah et al. *N Engl J Med.* 2017

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Neonatal AKI Multi-national Study [3]

Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Neonates (AWAKEN) study

- 2,022 neonates admitted to NICU
- 29.9% developed AKI - rates varied by gestational age
  - 47.9% (22-29 weeks)
  - 18.3% (29-36 weeks)
  - 36.7% (> 36 weeks)
- Infants with AKI had a higher mortality compared to those without AKI (9.7% vs. 1.4%)
- Highest prevalence in white males with GA < 36 weeks

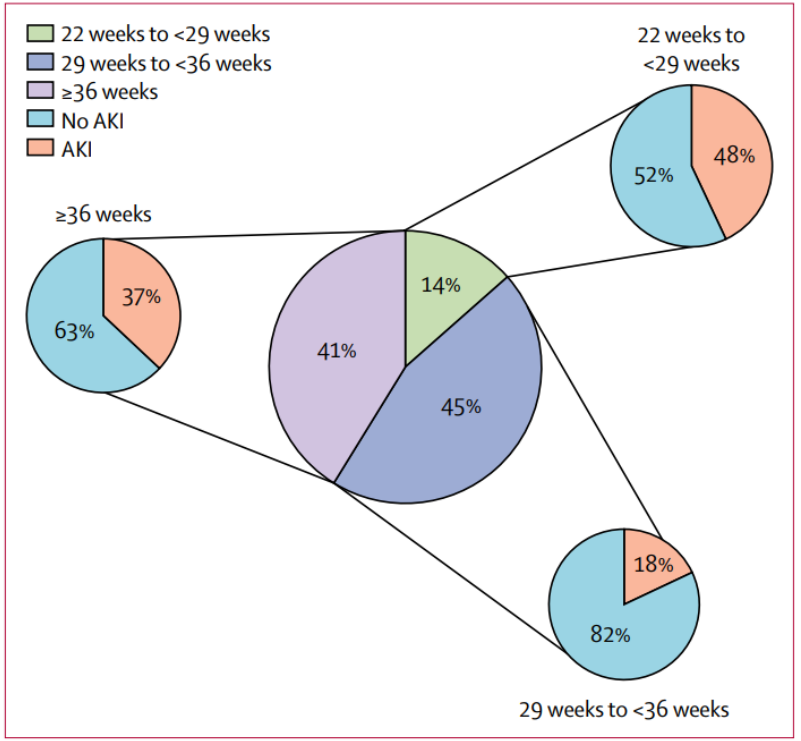

***Figure 2*: Gestational age distribution and AKI incidence**

Image Source: Jetton et al. *Lancet Child Adolesc Health.* 2017

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Chronic Kidney Disease (CKD) Incidence

- ~ 10,000 children in the United States have kidney failure [4]
- 70% of children with CKD from diverse etiologies will progress to ESRD before reaching adulthood [5]
- 30-50% of children and adults with congenital heart disease have CKD [6]
- The ESRD incidence in African American children is twice as that in caucasian children [6]

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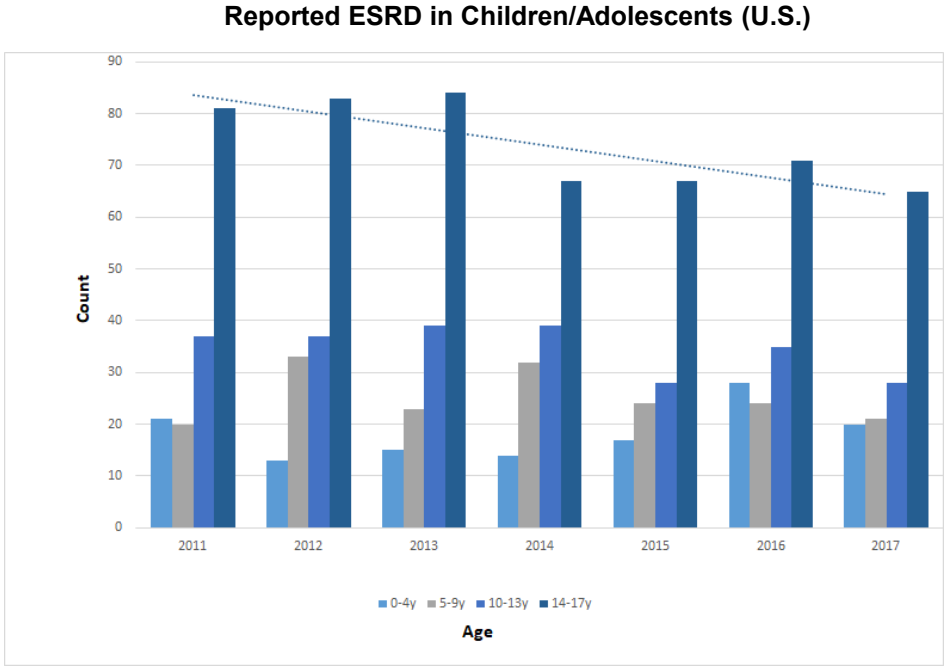
End Stage Renal Disease (ESRD)[7]

- Leading causes of ESRD in children
  - 0 - 4 year olds → Birth defects and hereditary diseases
  - 5 - 14y → Hereditary diseases, nephrotic syndrome and systemic diseases
  - 15 - 19y → Diseases of the glomeruli
- One-Year mortality rate for pediatric patients with ESRD has decreased by 20.4% over the last decade with the most notable improvement in those 0-4 years of age



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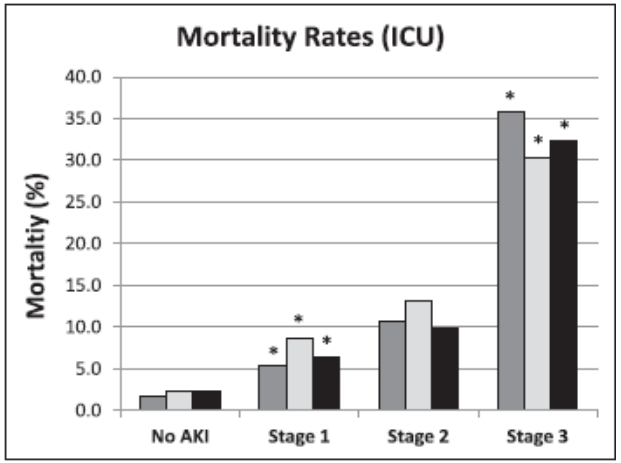
AKI Outcomes

- Mortality increases from 5% to 18% in neonates who develop AKI after non-cardiac surgery [8]
- A prospective national cohort study of 1,343 events of AKI in patients less than 18 years old showed neonatal and pediatric 30 day mortality rates of 4.1%. and 1.2% respectively [9]
- In a retrospective cohort study of 2,041 non-cardiac surgical patients (<18 years old) admitted to the PICU, AKI was independently associated with an increase from 5 to 7 year mortality [10]
- Severe AKI is associated with an increased risk of death (11% vs. 2.5% w/o severe AKI). RRT is the second strongest predictor of death by day 28 after admission [2]
- Length of ICU stay increases in children with AKI from 4 to 10 days [11]



	No AKI	Stage 1	Stage 2	Stage 3
pRIFLE	1.8% (0.9-2.6)	5.5% (3.3-7.5)	10.6% (6.8-14.5)	35.9% (29.2-42.6)
AKIN	2.3% (1.4-3.2)	8.7% (5.5-11.9)	13.2% (8.7-17.8)	30.4% (23.9-36.9)
KDIGO	2.3% (1.3-3.2)	6.4% (3.7-9.2)	10% (5.8-14.1)	32.3% (26.2-38.4)

Image Source: Sutherland et al. *Clin J Am Soc Nephrol*, 2015

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Mortality and Modality – CKD

- The probability of surviving after RRT by age is the lowest for children 0-4 years old (0.83) and young adults 18-21 years old (0.89) [12]
  - Patients who received a kidney transplant have a higher probability of surviving 5 years when compared to those treated with hemodialysis or peritoneal dialysis
- In a study of 1,634 children and adolescents requiring RRT, the long-term survival rate was 79% at 10 years and 66% at 20 years. [13]
- There are a limited number of studies on the risk of CKD in children who experience AKI.

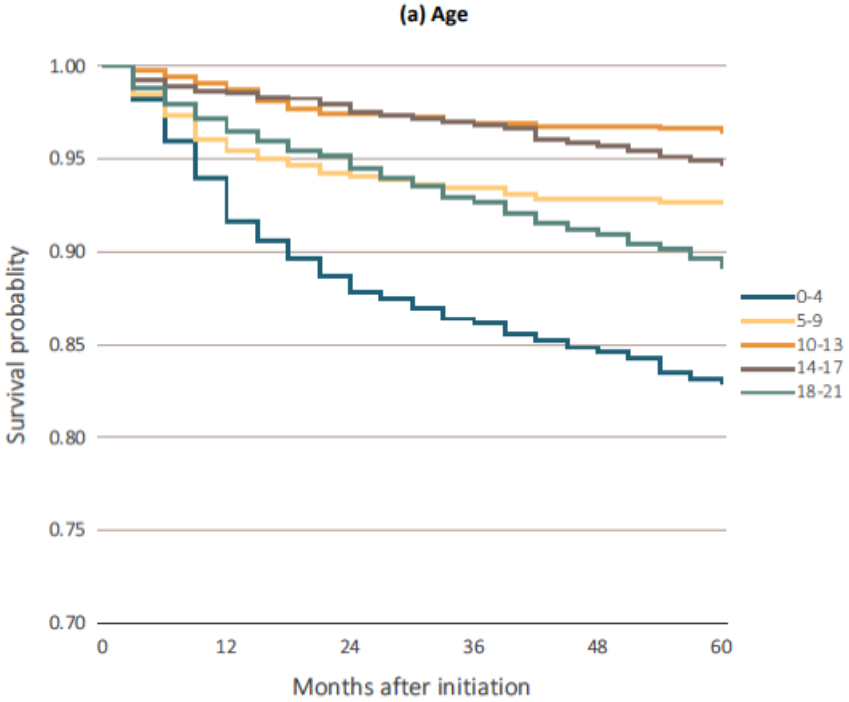

Image Source: *USRDS*, 2019

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Financial Impact of Kidney Disease

- Healthcare expenditures are 7.6x higher for children with CKD and increased by 50% over the last 10 years compared to a 25% increase in spending for children without CKD [14]
- The cost of dialysis for a neonate or infant compared to an adult patient with end stage renal disease is $75,000 to $43,000 respectively [15]

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Acute Kidney Injury Classification Systems

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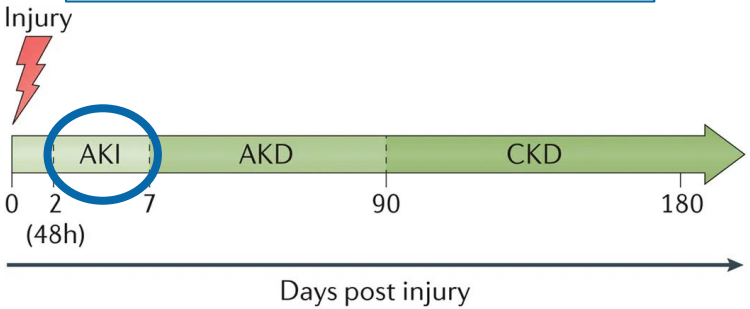
Acute Kidney Injury: General Definition [16-17]

Acute Kidney Injury

An abrupt decline in kidney function occurring over a period of 7 days or less, characterized by:

- Reversible increase in serum blood creatinine and nitrogenous waste products
- Inability of the kidney to appropriately regulate fluid and electrolyte homeostasis.



Nature Reviews | Nephrology

- Several AKI Classification Systems exist:
  - **RIFLE** - Risk, Injury, Failure, Loss, End Stage - 2004
  - **AKIN** - Acute Kidney Injury Network – 2007
  - **pRIFLE/nRIFLE** – Pediatric and neonatal specific RIFLE criteria– 2008
  - **KDIGO** - Kidney Disease Improving Global Outcomes- 2012

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AKI Classification Systems: RIFLE

- First attempt at a unifying definition for AKI (then called acute renal failure) [18]
- Published in 2004, RIFLE graded AKI Stages and provided taxonomies for both severity and recovery [19]
- Proposed 1 week timeframe for AKI Diagnosis [20]
- Published in 2008, modifications for pediatrics (pRIFLE) and neonates (nRIFLE) include wider duration of decreased urine output. [21]

	Serum Creatinine (SCr)	Urinary Output and Duration		
		RIFLE	pRIFLE	nRIFLE
Risk (R)	SCr X 1.5	≤ 0.5 mL/kg/h (6 h)	< 0.5 mL/kg/h for (8 h)	< 1.5 mL/kg/h (24 h)
Injury (I)	SCr X 2.0	≤ 0.5 mL/kg/h (12 h)	< 0.5 mL/kg/h for (16 h)	< 1.0 mL/kg/h (24 h)
Failure (F)	SCr X 3.0 or ≥ 4 or Acute rise > 0.5 mg/dL	≤ 0.3 mL/kg/h (24 h) OR Anuric (12 h)	< 0.3 mL/kg/h (24 h) OR Anuric (12 h)	< 0.7 mL/kg/h (24 h) OR Anuric (12 h)
Limitation (L)	Loss of kidney function for 4 weeks			
End stage (E)	Loss of kidney function > 3 months			

Image Source: Ricci et al. *Kidney Int.* 2008

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AKI Classification Systems: KDIGO Criteria [22]

	GFR Criteria	Urine output criteria
1	Increased creatinine x1.5-1.9 from baseline or ≥ 0.3 mg/dl	UO <0.5ml/kg/hr for 6-12hr
2	Increased creatinine x2.0-2.9 from baseline	UO <0.5ml/kg/hr ≥ 12h
3	Increased creatinine x3 from baseline OR SCr ≥ 4.0mg/dl OR RRT	UO < 0.3 ml/kg/hr for ≥ 24h or anuria ≥ 12h

UO criteria unchanged

SCr criteria mostly unchanged from AKIN

Removed acute rise criteria. Kept RRT criteria from AKIN

Kept SCr increase of ≥ 0.3 mg/dl within 48 hours from AKIN

Used 7 day timeframe for 1.5X increase in SCr from RIFLE

Diagnostic criteria for AKI:

- SCr increase ≥0.3mg/dl within 48h OR
- SCr increase ≥1.5 times baseline, which is known or presumed to have occured within the last 7 days OR
- Urine volume < 0.5 ml/kg for 6h

KDIGO has been validated as a clinically relevant AKI classification system in the pediatric population. There have been calls to utilize the KDIGO AKI definition as the standard for defining AKI in pediatrics [23]

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AKI Classification Systems: KDIGO in neonates

- Serum creatinine is a suboptimal biomarker in the neonatal population due to presence of maternal creatinine, variable degree of creatinine reabsorption, low glomerular filtration rate and maturational differences. [35]
- Modification of KDIGO criteria for neonates (nKDIGO) stages AKI based on an absolute rise in serum creatinine from a previous trough and should be used in children < 120 days of age. [36]
- Severity of AKI based on neonatal KDIGO (nKDIGO) criteria was independently associated with ICU stay, renal replacement therapy and increased in-hospital mortality within 30 days after cardiac surgery.[37]

TABLE 1 Neonatal AKI KDIGO Classification

Stage	SCr	Urine Output
0	No change in SCr or rise <0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 × reference SCr[a] within 7 d	<0.5 mL/kg/h for 6 to 12 h
2	SCr rise ≥2.0–2.9 × reference SCr[a]	<0.5 mL/kg/h for ≥ 12 h
3	SCr rise ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL[b] or Receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

Differences between the proposed neonatal AKI definition and KDIGO include the following:

[a] Reference SCr will be defined as the lowest previous SCr value.

[b] SCr value of 2.5 mg/dL represents <10 mL/min/1.73m^2.

Image Source: Selewski et al. *Pediatrics.* 2015

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Table 1. Staged diagnostic criteria for AKI

Definition and Criteria for AKI Stages	Modifications
pRIFLE	
Stage 1 (Risk): eGFR decreased by 25%	
Stage 2 (Injury): eGFR decreased by 50%	
Stage 3 (Failure): eGFR decrease by 75%	
or	
eGFR <35 ml/min per 1.73 m^2	
AKIN	
Stage 1: Increase in creatinine of ≥50%	0.3-mg/dl increase added to stage 1
or	AKI diagnosed over 48-hr period
Absolute increase in creatinine of 0.3 mg/dl	
Stage 2: Increase in creatinine of ≥100%	
Stage 3: Increase in creatinine of ≥200%	
KDIGO	
Stage 1: Increase in creatinine of ≥50%	eGFR threshold from pRIFLE added to stage 3
or	Creatinine changes (except absolute 0.3-mg/dl increase) required to occur within a 7-d time frame
Absolute increase in creatinine of 0.3 mg/dl	
Stage 2: Increase in creatinine of ≥100%	
Stage 3: Increase in creatinine of ≥200%	
or	
eGFR ≤35 ml/min per 1.73 m^2 (if age <18 yr)	

eGFR was estimated using the Schwartz method. pRIFLE, pediatric RIFLE; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Diseases Improving Global Outcomes.

Image Source: Sutherland et al. *Clin J Am Soc Nephrol.* 2015

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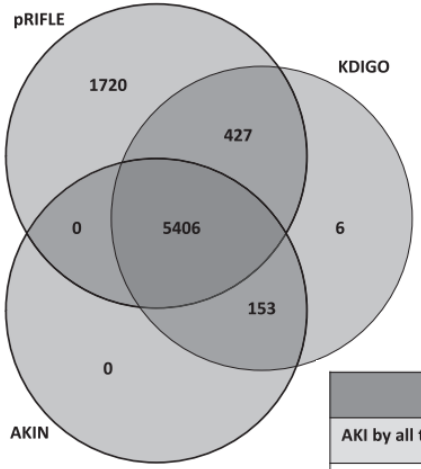
pRIFLE vs. AKIN vs. KDIGO [24]

- pRIFLE provides more sensitivity to identifying a greater number of mild AKI cases children
  - Demonstrated that doubling of SCr in children associated with 27.4% mortality rate
  - 75% of pediatric patients are admitted without a baseline SCr lab value
  - Using 120 mL/min/1.73m^2 in place of an actual baseline can lead to underdiagnosis of AKI using pRIFLE criteria
- AKIN does not require height or baseline creatinine values - may be advantageous as baseline SCr values are rarely available in pediatrics
- KDIGO is applicable to both pediatric and adult patients and has a less restrictive diagnostic timeframe than AKIN. Both pRIFLE and KDIGO determine stages of AKI by changes in serum creatinine (SCr)/estimated creatinine (eCCl) clearance and changes in urine output.



	n	Mortality	LOS
AKI by all three	5406	2.7%	10 (5-21)
No AKI any	6146	0.8%	4 (2-6)
AKI pRIFLE only	1720	1.5%	5 (3-9)
AKI AKIN only	0	n/a	n/a
AKI KDIGO only	6	0%	6 (4-8)
Not diagnosed by pRIFLE	153	0%	5 (3-8)
Not diagnosed by AKIN	427	0.7%	12 (7-18)
Not diagnosed by KDIGO	0	n/a	n/a

Image Source: Sutherland et al. *Clin J Am Soc Nephrol.* 2015

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Estimated Glomerular Filtration Rate (eGFR)

- Calculating an eGFR is necessary for accurate staging of CKD in children. Renal development and function is still maturing in children less than two years old [25]
  - Baseline SCr is often not available in pediatric patients making it difficult to estimate baseline kidney function.
- Chronic Kidney Disease in Children (CKiD) study derived a Schwartz formula for patients 1-16 years of age [26]

eGFR (ml/min/1.73m^2) = [height in cm x 0.413] / SCr in mg/dL

Stages of CKD in children ≥ 2 years of age

Stage	eGFR (ml/min/1.73 m2)
1	≥90
2	60–89
3	30–59
4	15–29
5	≤ 15

Image Source: Sutherland et al. *J Am Soc Nephrol*. 2015

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AKI Pathophysiology and Etiology

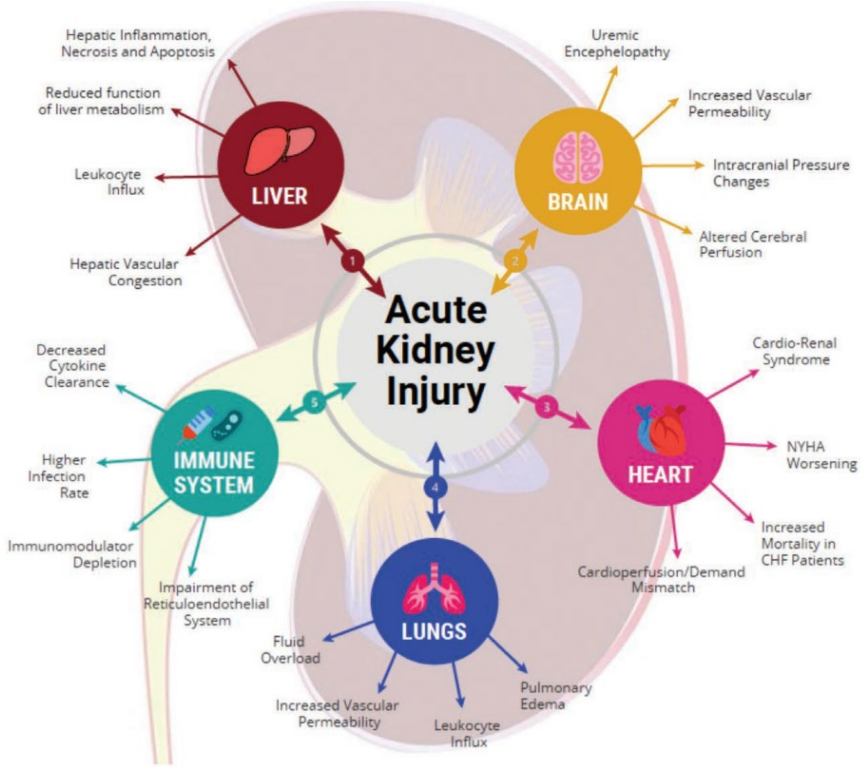

Image Source: Gumbert et al. *Anesthesiology*. 2020

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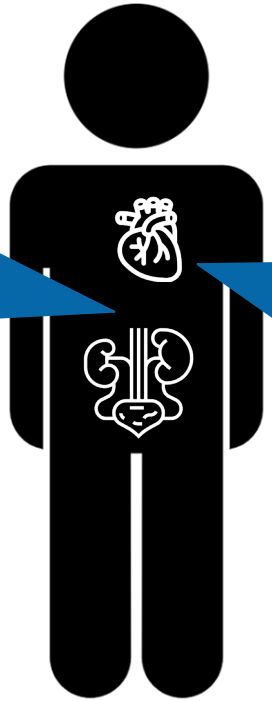
Pathophysiology: Anesthetic Impact on AKI [27-28]

- Hypovolemia and venodilation
- Positive pressure ventilation can impair venous return to the heart
- Anesthetics can reduce arterial tone which decreases perfusion pressure.
- Right sided hemodynamics are critical, as high venous pressure can cause kidney injury through organ congestion.
  - Cardiac surgery: right side of the heart may be compromised from cardioplegia.
  - Thoracic surgery: increased pleural pressure may increase venous “back pressure” on the liver and kidneys
  - Abdominal surgery: High insufflation pressure in the abdomen
- Ischemia-reperfusion causes damage associated molecular pattern (DAMP) molecules to be released into circulation such as myoglobin and uric acid.

Etiology: Pre-renal [16]

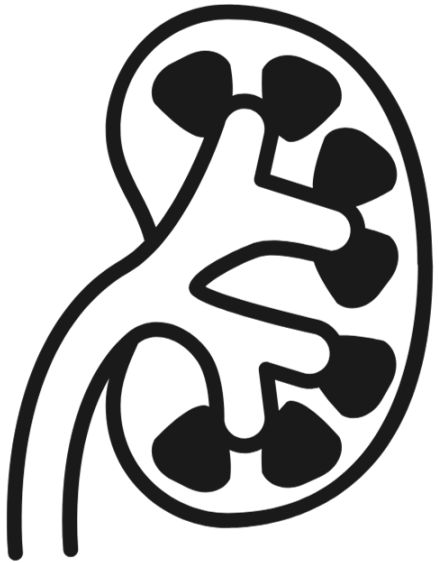
Renal Hypoperfusion due to true volume contraction: Hemorrhage, dehydration, increased insensible losses (burns) and other third space losses such as sepsis, nephrotic syndrome, traumatized tissue and capillary leak syndrome



Decreased effective intravascular volume: Renal perfusion decreased due to low cardiac output states, such as from congenital heart defects

Etiology: Renal (Intrinsic)

- Results of injury to kidney structures: tubules, glomeruli, the interstitium, and intra-renal blood vessels [29]
- Acute Tubulointerstitial nephritis
- 3 Main Causes in Children [30]
  - Acute Glomerulonephritis (stage 1)
  - Septicemia (stage 3)
  - Antibiotic drug-induced AKI (stage 3)



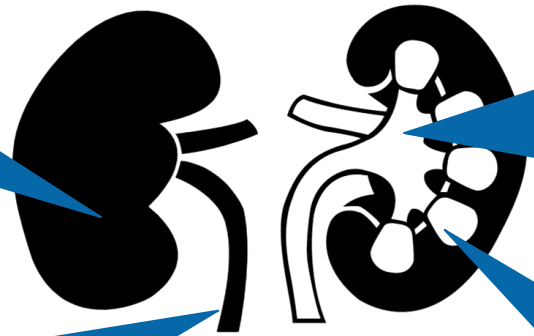
Etiology: Intrinsic Possible Causes [16,29]

Interstitium:

- Infectious (bacterial, viral)
- Medications (antibiotics, diuretics, NSAIDs)
- Acute Interstitial Nephritis (idiopathic or drug induced)

Tubular:

- Renal ischemia (shock, complication of surgery, hemorrhage, trauma, bacteremia),
- Nephrotoxic drugs
- Endogenous toxins such as uric acid excretion caused by tumor lysis syndrome in children with Leukemia



Vascular:

- Cortical necrosis is common in young children, particularly neonates
- Associated with ischemic insults due to perinatal anoxia, placenta abruption and twin-twin or twin-mother transfusions
- Hemolytic uremic syndrome

Glomerular:

- Acute post infectious glomerulonephritis
- Lupus nephritis

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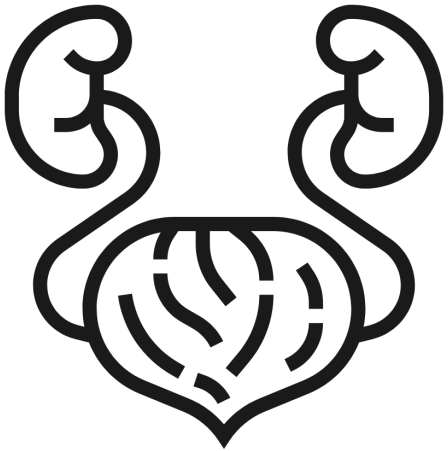
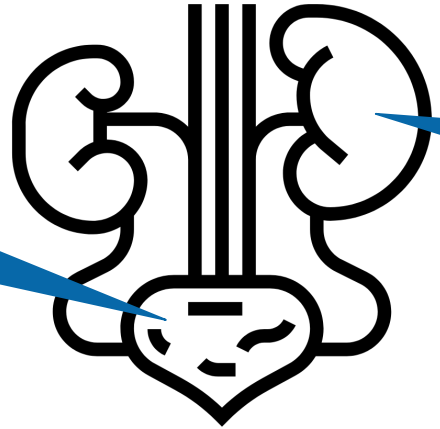
Etiology: Postrenal

- Caused by blockage of urinary flow in the urinary tract [31]
- Obstruction → ↑ intratubular pressure and ↓GFR [32]
  - Leads to build up in the kidney
- Quick resolution = best chance of kidney recovery [29]



Etiology: Post Renal Possible Causes [16,29]

Extrarenal Obstruction:
congenital malformations such as posterior urethral valves, bilateral ureteropelvic junction obstruction or bilateral



Intrarenal Obstruction:
Nephrolithiasis, blood clots

AKI Risk Factors

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Anesthesia-related Risk Factors

Potentially modifiable AKI risk factors in both pediatric cardiac and noncardiac surgery [33-35]

- Hemodilution
- Hemoglobin level
- Intraoperative transfusion
- Hypotension
- Inadequate oxygen delivery
- Use of diuretics
- Use of vasopressors and inotropes
- Selective renal ischemia
- Ischemia reperfusion injury
- Bleeding complications
- Transfusion of allogeneic blood products
- Intraoperative Hypertension
- Nephrotoxic agents (eg abx, contrast agents)

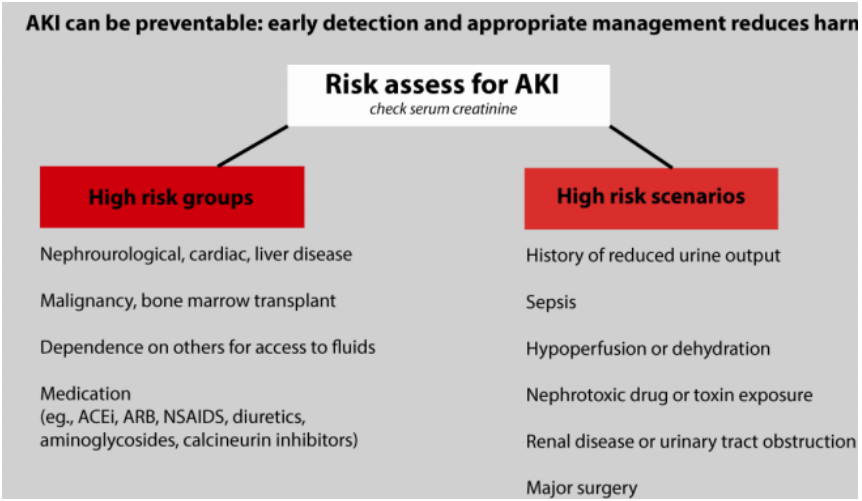

Image Source: Think Kidneys 2019

AKI Risk Factors: Neonatal [8]

- Maternal
  - NSAID use
- Perinatal
  - Gestational age under 32 weeks
  - Congenital heart defect
- Postnatal
  - Low Apgar score (< 7)
  - Low birth weight (< 1500g)
  - Mechanical Ventilation
  - Surgical procedure longer than 120 min
  - Diagnosis of necrotizing enterocolitis
  - Resuscitation with epinephrine [12]
  - Admission diagnosis of hyperbilirubinemia

AKI Risk Factors: Pediatric

- Nephrotoxic Drugs
  - Administration of IV vancomycin with or without IV administration piperacillin/tazobactam [36-38]
  - Aminoglycosides [39-42]
- Comorbidities [39-40, 43-45, 46]
  - Cystic fibrosis
  - Liver transplant recipients
  - Vaso-occlusive crisis
  - Diabetic ketoacidosis
  - Oncologic diagnosis
- Age and sex - no consistent correlations [47]
- Other associated factors [2]
  - Sepsis
  - Heart failure
  - Tumor lysis syndrome

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AKI Risk Factors: Cardiac Surgery

- Independent risk factors for AKI identified in children undergoing cardiac surgery [48]
  - Young age (< 1 year)
  - Risk adjustment in Congenital Heart Surgery category (RACHS-1) ≥ 4
  - Cardiopulmonary Bypass time ≥ 90 minutes
- Children with congenital heart disease have an increased risk of postoperative AKI [4]
  - 86% Incidence using KDIGO → Dependent on age, heart disease, cardiac status, CPB technique, management of anesthesia and postoperative care practices.
  - Other risk factors specific to children with congenital heart disease include previous cardiac surgery, univentricular anatomy, inotrope and captopril use or PICU admission preoperatively with or without mechanical ventilation
- Wide fluctuations in blood glucose intraoperatively increases the risk of AKI (using AKIN criteria). [49]
  - Acute hyperglycemia insults alone does not increase the risk of AKI in this population

Registry Definitions: Kidney Disease

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National Surgical Quality Improvement Program - Pediatrics

Progressive Renal Insufficiency:

- Rise in creatinine of >1 mg/dl from preoperative value, but with no requirement for dialysis within 30 days of the operation.

Acute Renal Failure:

- In a patient who did not require dialysis preoperatively, worsening of renal dysfunction postoperatively requiring hemodialysis, peritoneal dialysis, or ultrafiltration within 30 days of the operation.

Days from Operation until Acute Renal Failure Complication

Source: ACS-NSQIP-Pediatrics User Guide

STS - Congenital Heart Data Registry

The Society of Thoracic Surgeons

Renal Failure requiring Dialysis

- Oliguria with sustained urine output < 0.5 cc/kg/hr for 24 hours and/or a rise in creatinine >1.5x upper limits of normal for age (or 2x the most recent preop values if available), with need for dialysis (including peritoneal dialysis and /or hemodialysis) or hemofiltration
- Requiring dialysis before hospital discharge (even if greater than 30 days after surgery)

OR

- Requiring dialysis after hospital discharge but within 30 days after surgery

Source: STS Congenital Heart Surgery Database Data Specification

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Children's Hospital Solutions for Patient Safety

- Nephrotoxic medication exposure is one of the most common causes of AKI in children
- Defined as a Class 4 (significant temporary harm) Serious Safety Event by the Children's Hospitals' Solutions for Patient Safety
- SPS has partnered with the NINJA program with plans to rollout to all 140 sites by 2020 [42,50]
  - NINJA - Nephrotoxic Injury Negated by Just-in-time Action
  - Uses KDIGO Diagnostic criteria
  - Proactively screens for nephrotoxic drug (NTMx) exposure in EHR
  - High risk patients are monitored via daily SCr lab orders

Source: Solutions for Patient Safety

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ASPIRE Measure Definition: AKI 01

Pediatric Patients ≤ 18 years old

- **KDIGO Criterion used**
- **EGFR Calculation**
  - Bedside Schwartz

EGFR = 0.413 x [(height in cm)/(serum creatinine in mg/dL)]

- **Exclusion criteria:** baseline creatinine <0.2mg/dL
  - Baseline serum creatinine is defined as the most recent serum creatinine resulted in the last 60 days preoperatively
- **Success criteria:**
  - The creatinine level does not go above 1.5x the baseline creatinine within 7 days post-op
  - The creatinine level does not increase by ≥ 0.3 mg/dL obtained within 48 hours after anesthesia end.

Acute Kidney Injury

AKI-01: Acute Kidney Injury

Source: ASPIRE Measures-Acute Kidney Injury

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AKI Pediatric Recommendations

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Pediatric and Neonate Recommendations

01	Identify patients at risk of developing AKI	• Anesthesia related risk factors • Pediatric risk factors (neonates & children) • Risk factors specific to cardiac surgery
02	Prevention of AKI	• Avoid nephrotoxins • Maintain Fluid Balance • Normalize preoperative nutrition status
03	Early recognition of AKI	• Identify precipitating factors of AKI • Early recognition prevents further progression • Renal Angina Index
04	Treatment Considerations	• Correct electrolytes • Avoid fluid overload • Consider Renal Replacement Therapy

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Recommendation #1: Identify patients at risk for AKI

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*See slides 28-32 for pediatric risk factors

Recommendation #2: Prevention of AKI

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Prevention of AKI

TABLE 2.

Acute Kidney Injury Management Guidelines: A Pediatric Modification to KDIGO Criteria

Stage 1	Stage 2	Stage 3
Stop nephrotoxins	Noninvasive diagnostic testing	Renal dose medications
Optimize hemodynamics	Daily weights and strict intakes and outputs	If oliguric, nephrology consultation
Serial serum creatinine measurements		Early renal replacement therapy
Record urine output (Foley catheter)		
Avoid glycemic extremes (<60, >250 mg/dL)		
Weigh risk-benefit of radiocontrast		

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.

Image Source: Basu et al. *Clin J Am Soc Nephrol*, 2018

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Nephrotoxic Medication (NTMx) Exposure Defined [51]

Children's Hospitals' Solutions for Patient Safety
Every patient. Every day.

Nephrotoxic Medication exposure criteria

- ≥ 3 NTMx meds
- ≥ 3 days on any IV aminoglycosides
- ≥ 3 days on Vancomycin

AKI Criteria for NTMX exposed patients

- At least 50% increase in SCr above baseline SCr (lowest SCr in the past 6 months), with the increased value above a threshold of 0.5 mg/dL
- An absolute increase of 0.3 mg/dL in SCr within 48 hours, regardless of the maximum value (minimum threshold value must be 0.5 mg/dL for peak creatinine)

For NTMx-AKI events in NICU:

- Screening begins on day of life 4 (after 72 hours of life)
- Baseline determined by the lowest creatinine on record
- Rationale: up until day ~4, creatinine is reflective of maternal creatinine and is unlikely to be at nadir

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Nephrotoxic Medications for Monitoring

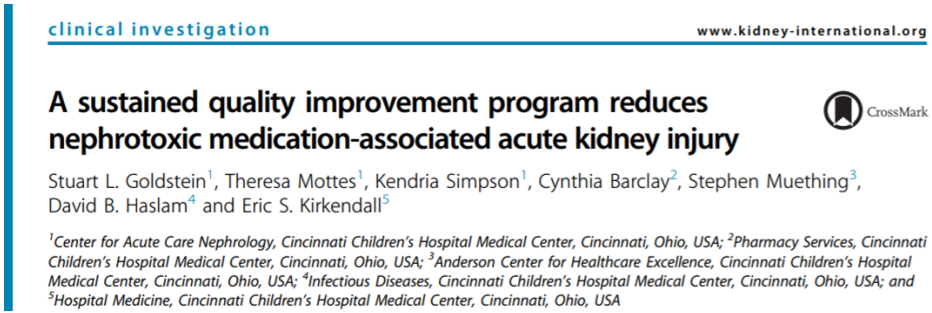
Nephrotoxic Medications for monitoring based on NINJA	Nephrotoxic Medications for monitoring based on NINJA	Medications which can trigger without another medication on day 3 of exposure	Medications which count as an exposure for 7 days
Acyclovir	Mesalamine	Amikacin	Ambisome
Amikacin	Methotrexate	Gentamicin	Cidofovir
Aspirin	Mitomycin	Tobramycin	Diatrizoate meglumine
Captopril	Nafcillin	Vancomycin	Diatrizoate sodium
Carboplatin	Naproxen		Iodixanol (Visipaque) (7days)
Celecoxib	Pamidronate disodium		Iohexol (Omnipaque) (7days)
Cisplatin	Pentamidine		Iopamidol (Isovue)
Colistimethate	Piperacillin		Iopromide
Cyclosporine	Piperacillin/Tazobactam		Ioversol
Deferasirox	Polymixin B		Ioxaglate meglumine and
Enalapril	Sirolimus		Ioxilan
Enalaprilat	Sulfasalazine		
Foscarnet	Tacrolimus		
Ganciclovir	Tenofovir		
Gentamicin	Ticarcillin/Clavulanic Acid		
Ibuprofen	Topiramate		
Ifosfamide	Valacyclovir		
Indomethacin	Valganciclovir		
Ketorolac	Valsartan		
Lisinopril	Zoledronic acid		
Lithium	Zonisamide		
Losartan			

Image Source: Children's Hospitals' Solutions for Patient Safety

Avoid Nephrotoxic Medications

The Nephrotoxic Injury Negated by Just-in-time Action Program (NINJA) [52-53]

- Proactively screens for nephrotoxic drug (NTMx) exposure in EHR and flags patients at high risk for NTMx-AKI
- High risk patients are monitored via daily SCr lab orders
- Single-center implementation reduced exposure of nephrotoxic drugs in children by 38% and AKI rate was reduced by 64%
- Multi-center preliminary data based on a 3 year implementation of NINJA is showing a 23.8% reduction in AKI rates across all nine centers.



clinical investigation www.kidney-international.org

A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

Stuart L. Goldstein[1], Theresa Mottes[1], Kendria Simpson[1], Cynthia Barclay[2], Stephen Muething[3], David B. Haslam[4] and Eric S. Kirkendall[5]

[1]Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [2]Pharmacy Services, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]Anderson Center for Healthcare Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [4]Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; and [5]Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

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Maintain Fluid Balance [54]

Avoid over transfusion during surgery

- A single-center retrospective study (n=220) patients ages 10 days - 19 years who underwent cardiac surgery in 2012
- 41.8% developed AKI (KDIGO) and 8.2% required RRT within the first week after surgery. Majority of patients were AKI stage 1 (25.9%)

Hypovolemia

- “The hypoperfusion due to decreased microvascular flow may contribute to the renal ischemic damage especially during cardiac surgery where low cardiac output and cardiogenic shock may frequently occur”
- Treatment: infuse 10-20 ml/kg of normal saline
  - If urine output does not increase, consider CVP monitoring

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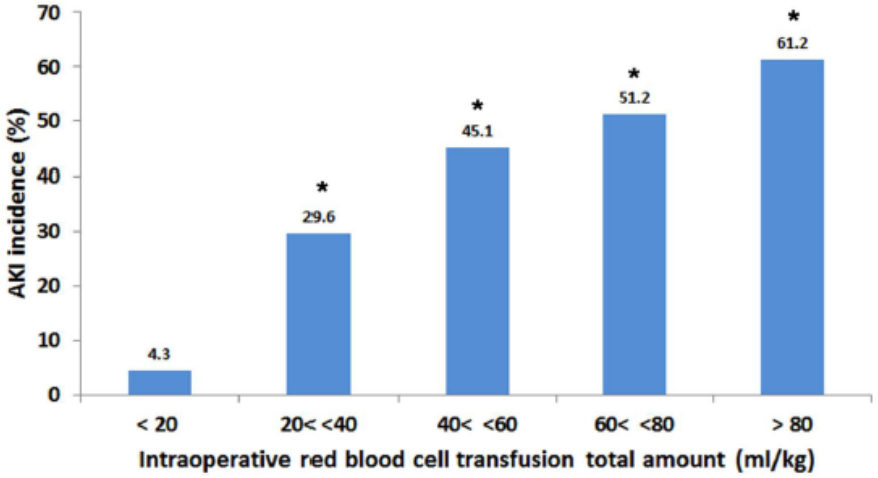
AKI Incidence: Correlation between transfusion volume, hemoglobin level, and AKI



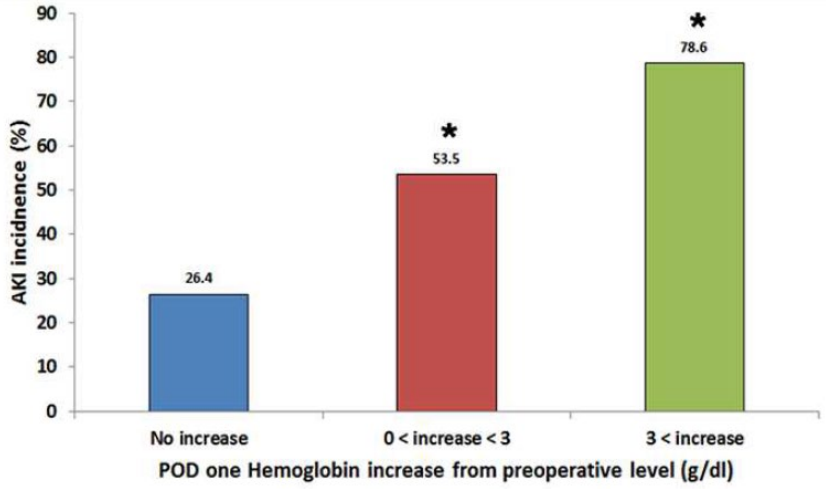


Image Source: Park et al. *PLoS One*. 2016

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Optimize Nutrition Status Preoperatively [55]

In retrospective analysis of 95 neonates who had congenital heart surgery:

- 66 patients (69.5%) did not achieve preoperative caloric goal
- 29 patients (30.5%) did reach caloric goal
- Higher incidence of stage 2 or 3 AKI postoperatively for those who did not reach caloric goal as compared to those who did (P=0.04; odds ratio, 4.48; 95% confidence interval, 1.02-19.63)

Recommendation #3: Early Recognition of AKI

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Early Recognition of AKI

- Identification of patients at risk facilitates early intervention with bundle implementation which has been shown to protect the kidneys and reduce mortality [56-58]
- American Society of Nephrology launched AKI!NOW initiative to promote early recognition and management of AKI which helps optimize treatment and prevent progression.[59]

AKI!NOW Recommendations:

- Provider education at all levels in healthcare regarding AKI, particularly around identifying patients at risk
- Generate specific guidance on AKI evaluation and management
- Develop global toolkit
- Engage hospital administration and make AKI a part of quality initiative
- Raise awareness of AKI as complication of other disease processes

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Emerging Research - Biomarkers

The use of NGAL and Cystatin C to detect AKI in pediatrics after cardiac surgery has been reported as feasible. [4,60]

- **NGAL** - tubular biomarker
  - Most studied in pediatrics, especially cardiac surgery population
  - Can detect changes as early as 2 hours after CPB
  - Associated with AKI severity, length of mechanical ventilation, and length of ICU stay [11, 61-62]
  - Superior to creatinine for detection of aKI [11,64-66]
- **Cystatin C** - functional biomarker
  - Protease inhibitor that is released by nucleated cells at a constant rate → filtered by the glomeruli → reabsorbed in the renal tubules. [19]
  - Reflects a decrease in GFR if found in urine. [4]
  - Superior biomarker to serum creatinine in the assessment of GFR in premature infants [67]
- **Serum phosphorus** - alternative biomarker that can be used for early prediction of AKI in pediatric cardiac surgery as early as 24 hours postoperatively [68]

Emerging AKI Biomarker Research

Biomarker	Source	Function	Clinical utility
NGAL	Distal tubule and collecting duct	Regulates iron trafficking, promotes tubule cell survival	• Confirmed early marker of AKI severity, renal replacement need, mortality, and renal recovery • Three clinical platforms available • Results in 15–30 minutes • Pending FDA approval
KIM-1	Proximal tubule	Promotes epithelial regeneration, regulates apoptosis	• Delayed marker compared with NGAL • Awaits confirmatory studies • No clinical assays available
IL-18	Proximal tubule	Promotes tubule cell apoptosis and necrosis	• Predicts AKI in post-CPB • No clinical assays available
L-FABP	Proximal tubule	Antioxidant, suppresses tubule-interstitial damage	• Awaits confirmatory studies • No clinical assays available
TIMP-2, IGFBP7	Tubule cells	Limits proliferation of damaged tubule cells	• AUC comparable to NGAL for predicting AKI post-CPB • Point-of-care clinical test is FDA approved

Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; FDA, US Food and Drug Administration; KIM-1, kidney injury molecule-1; IL-18, interleukin-18; CPB, cardiopulmonary bypass; L-FABP, liver-type fatty acid-binding protein; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7; AUC, area under the curve.

Image Source: Ciccia & Devarajan. *Int J Nephrol Renovasc Dis*. 2017

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Renal Angina Index: *Proactive* Recognition of AKI [2,69]

- Highly sensitive screening tool for AKI that combines risk factors and early signs of decreased kidney function (increased SCr or degrees of fluid overload) to stratify patients for risk of subsequent severe AKI.
- Predictive efficacy of the RAI for development of severe AKI three days after admission to the ICU was tested in a multinational, multi-center prospective study of 5,237 children
  - AKI Incidence was significantly higher in the group assessed to have renal angina (RAI score of > 8).
- Assessment of AKI according to SCr levels alone failed to identify AKI in 67.2% of patients with low urine output

Renal Angina Index (RAI)

Risk Strata

Risk Criteria	Score
ICU Admission	1
Solid Organ or Stem Cell Transplantation	3
Mechanical Ventilation Vasoactive Support	5

Injury Strata

SCr/Baseline	% FO Accumulation	Score
Decreased or No change	< 5%	1
>1x – 1.49x	5-10%	2
1.5x – 1.99x	10-15%	4
≥ 2x	> 15%	8

Risk x Injury
Scores: 1-40

Renal angina fulfilled with RAI ≥ 8

Image Source: Ciccia & Devarajan. *Int J Nephrol Renovasc Dis*. 2017

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Recommendation #4: Treatment Considerations

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Manage Acidosis & Electrolyte Imbalances [16]

- Kidneys excrete net acids generated by diet & metabolism
- Acidosis is common in AKI and CKD
  - Treat with IV or oral sodium bicarbonate
- Consider serum total and ionized calcium levels before treating acidosis
  - Hypocalcemia is common in AKI & treatment of acidosis can cause tetany or seizures due to drop in ionized calcium
- Hyperphosphatemia is also common
  - Limit dietary phosphorus
  - Treat with oral calcium carbonate (to bind with phosphorus & prevention further absorption)
  - Must take into consideration acid-base balance

Hyperkalemia: Potentially life-threatening [16]

- Kidneys regulate potassium balance
  - 90% of dietary potassium intake is excreted through kidneys
- Hyperkalemia common in AKI and CKD due to:
  - Decreased filtration and tubular secretion
  - Altered distribution of potassium by acidosis → shifts potassium from intracellular to extracellular compartment
- If potassium reaches levels > 6-7 mEq/L or cardiac conduction abnormalities occur, consider treatment:

Agent(s)	Mechanism	Dose	Onset (min)	Complications
Sodium bicarbonate	Shifts K^+ into cells	1 mEq/kg IV over 10–30 min	15–30	Hypernatremia, change in ionized calcium
Albuterol	Shifts K^+ into cells	400 μg by nebulizer	30	Tachycardia, hypertension
Glucose and insulin	Shifts K^+ into cells	Glucose 0.5 g/kg, insulin 0.1 U/kg IV over 30 min	30–120	Hypoglycemia
Calcium gluconate 10%	Stabilizes membrane	0.5–1 mL/kg IV over 5–15 min	Immediate	Bradycardia, arrhythmias, hypercalcemia
Calcium chloride	Stabilizes membrane	10 mg/kg IV over 5–15 min	Immediate	Bradycardia, arrhythmias, hypercalcemia
Sodium polystyrene sulfonate (Kayexalate®)	Exchanges Na^+ for K^+ across the colonic mucosa	1 g/kg orally or PR in sorbitol	30–60	Hypernatremia, constipation, colonic membrane irritation if given PR

K^+ = potassium; **IV** = intravenous; **Na^+** = sodium; **PR** = per rectum.

Image Source: Andreoli. *Pediatric Drugs*. 2008

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Assess for Hyponatremia [16]

- Hyponatremia is common in AKI as kidneys fail to excrete excess fluid leading to dilutional hyponatremia
- Treatment requires fluid restriction or water removal by dialysis or hemofiltration; slow infusion of hypertonic saline solution may be necessary
- If serum sodium level < 120mEq/L due to excess water retention, seizures may result

Table 1: Sodium Concentration

Mild	130-135 mEq/L
Moderate	120-129 mEq/L
Severe	<120 mEq/L

Image Source: Andreoli. *Pediatric Drugs*. 2008

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Renal Replacement Therapy in Children

The most common initial ESRD treatment modality among children is hemodialysis (56 percent) [70]

Factors to consider: [16]

- Age
- Size of child
- Cause of Renal Failure
- Degree of metabolic derangements
- Blood Pressure
- Nutritional Needs
- Peritoneal dialysis vs. intermittent hemodialysis vs. hemofiltration

Table III. Comparison of renal replacement therapies[77]

Parameter	Peritoneal dialysis	Hemodialysis	Continuous venovenous hemofiltration (with a dialysis circuit)
Solute removal	Good	Excellent	Fair (excellent)
Fluid removal	Good	Excellent	Excellent (excellent)
Need for hemodynamic stability	No	Yes	No (no)
Efficiency for treatment of hyperkalemia	Fair	Excellent	Poor-fair (excellent)
Ease of access	Not difficult	Difficult	Difficult (difficult)
Continuous	Yes	No	Yes (yes)
Need for anticoagulation	No	Usually	Variable (variable)
Risk for possible respiratory compromise	Moderate	Low	Low (low)
Risk for peritonitis	High	No	No (no)
Precipitation of hypotension	Low	High	Moderate (moderate)
Disequilibrium	No	High	Low (moderate)
Requirement for specifically trained staff	Moderate	High	High (high)

Image Source: Andreoli. *Pediatric Drugs*. 2008

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Peritoneal and Hemodialysis in Neonates

- Unique challenges with managing AKI in neonates due to developing nephrons, small blood vessels (difficult hemo catheter access) and peritoneal space. [73]
  - Limited evidence that renal replacement therapy (RRT) in patients ≤ 1yo is effective or improves long term outcomes especially patients with:
    - History of abdominal surgeries
    - Surgical site infections
    - Require fluid removal faster than the peritoneal membrane allows
- Peritoneal dialysis (PD) is used more often in children than in adults however, children with CKD are given hemodialysis (HD) more frequently than PD or kidney transplant. [89]
- Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) [55]
  - Five year prospective study designed to develop and implement this machine which has an extracorporeal priming volume of < 30mL and accurate ultrafiltration to within 1g.
  - Used effectively in infants as small as 2.9 kg

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Postoperative AKI
Cardiac, General and Liver

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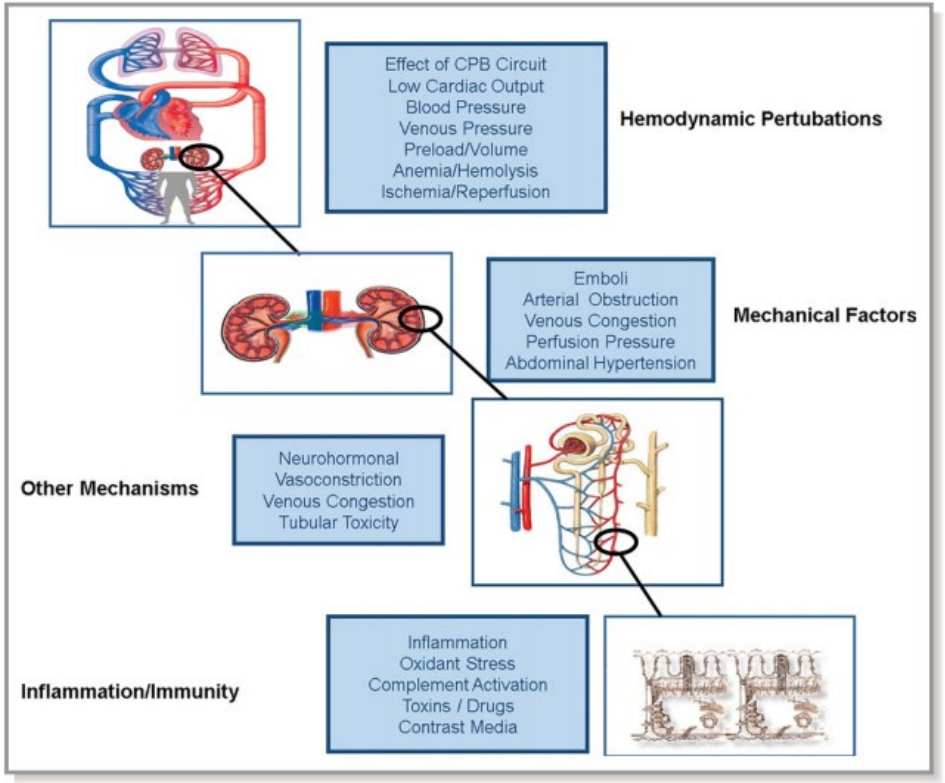
Pathophysiology of AKI related to Cardiopulmonary bypass [71]



Nadim and colleagues depict the many variables associated with cardiac surgery & cardiopulmonary bypass:

- Nonpulsatile blood flow
- Extensive Hemodilution
- Transfusion load
- Release of free hemoglobin & free iron from hemolysis
- Prolonged hypothermia
- Inflammatory response
- Venous congestion

All of these factors can contribute to acute kidney injury.

Image Source: Nadim et al. *J Am Heart Assoc*. 2018

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Peds Cardiac Surgery - AKI

- AKIN definition modified for children 0-36 months old to greater than 0.1 mg/dL increase in SCr was required to assign cardiac surgery-associated acute kidney injury (n=799) [48]
  - 36% of patients had AKI with the majority (76%) having stage II or III AKI.
- A small rise (less than 50%) in SCr on postoperative day 1 predicted AKI within 48 hours after cardiac surgery using pRIFLE criteria [72]
- Mortality rate is higher in patients following recovery from AKI, regardless of staging, compared to those without AKI after cardiac surgery [48]

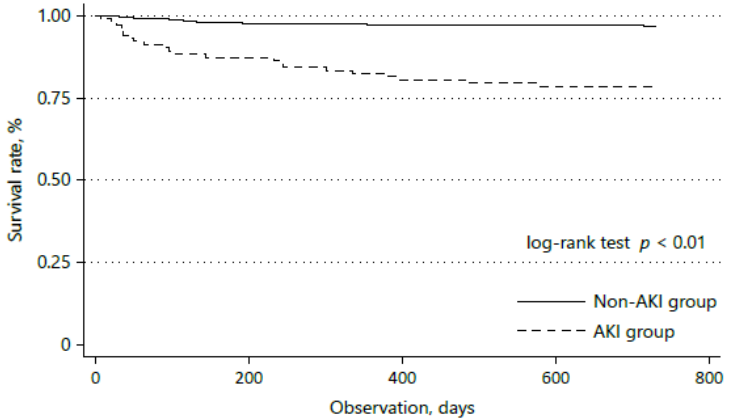

Image Source: Hirano et al. *Am J Nephrol.* 2017

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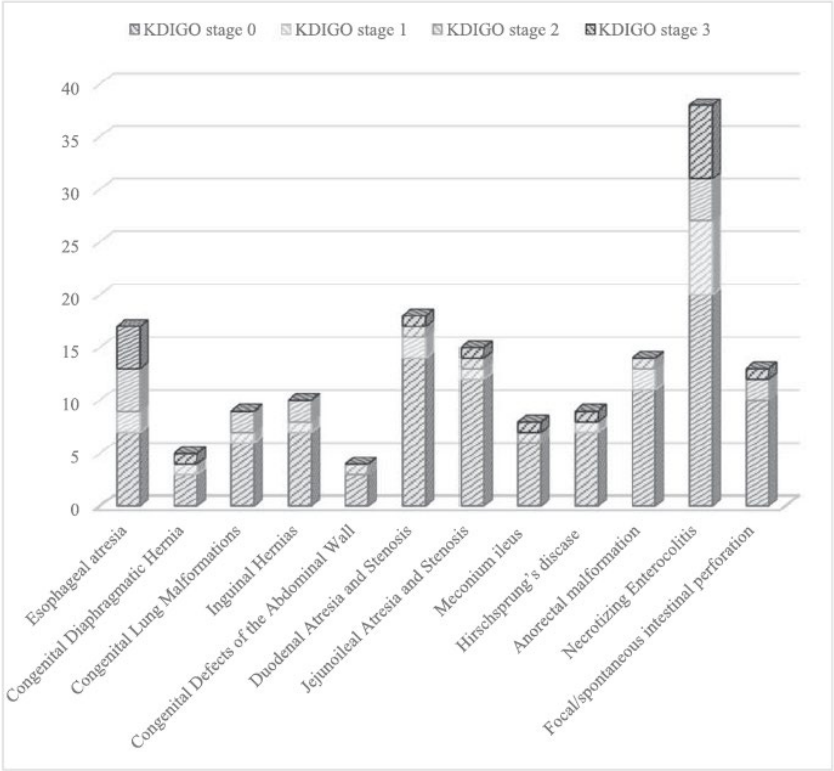
AKI after Pediatric General Surgery [8]

Neonates undergoing non-cardiac surgical procedures with general anesthesia (n=160)

- Using nKIDGO, 33.8% of neonates developed AKI
- Higher mortality rate than those who did not develop AKI



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AKI after Pediatric Liver Transplant

Liver Transplant AKI Risk Factors [73-75]

- Hypoalbuminemia
- High requirement for RBC and 20% human albumin transfusions
- Elevated preop labs: serum sodium, aPTT, bilirubin, end of surgery lactate levels and BUN levels
- High furosemide use and high flow of ascites
- Need for open abdomen

Incidence of AKI after liver transplantation in pediatrics

- pRIFLE is 20% more sensitive than AKIN when determining the severity of AKI (n=57) [75]
- KDIGO staging has shown 35.8% of patients have AKI (n=117) and 15% of those children required RRT postoperatively. [74]
- Another study has demonstrated 46.2% of patients develop AKI using KDIGO (n=156) [73]
  - Assessment of AKI according to SCr levels alone failed to identify AKI in 54.3% of patients with low urine output

Table 6. Comparison of Groups in Terms of Intraoperative Management

	Median (IQR) or No. (%)		
	With AKI (n = 40)	Without AKI (n = 77)	*P* Value
Duration of anesthesia, h	9.0 (IQR, 8.5-10.0)	9.5 (IQR, 8.5-10.5)	.412
Cold ischemia time, h	0 (0)	0 (0)	.609
Incidence of massive hemorrhage	2.0 (5%)	4.0 (5%)	1.000
PRBC per body weight, mL/kg	18.0 (IQR, 9.2-33.2)	16.1 (IQR, 9.5-23.8)	.185
FFP per body weight, mL/kg	11.1 (IQR, 0-25.6)	7.2 (IQR, 0-21.1)	.189
Crystalloids per body weight, mL/kg	114.5 (IQR, 81.1-145.7)	111.5 (IQR, 79.8-154.7)	.891
Use of vasopressors	14.0 (35%)	28 (37%)	1.000
Use of inotropes	11.0 (28%)	14 (18%)	.342
Incidence of acidosis	24.0 (60%)	55.0 (72%)	.210
Lactate levels at end of surgery	7.9 (IQR, 4.3-11.2)	5.3 (IQR, 3.3-8.6)	.044
Highest lactate level, mmol/L	7.4 (IQR, 4.8-10.3)	7.2 (IQR, 4.4-9.0)	.422

Summary

1. Anesthesia providers should focus on reducing the anesthesia-related intraoperative risk factors associated with AKI such as:
    - Avoid nephrotoxins
    - Maintain Fluid Balance
    - Ensure preoperative nutrition status
    - Theophylline administration for neonates
2. Assessing risk factors preoperatively can assist anesthesia providers in identifying patients who may require additional interventions to prevent AKI.
3. Early Recognition of AKI optimizes treatment and reduces risk of progression to later stages of kidney disease.

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