



Acute Kidney Injury and Neonatal Hypertension in Premature Infants

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Conflict of Interest

- ▶ I have a consulting arrangement with Fresenius Medical Care – a dialysis provider in the US.
- ▶ I will only be discussing dialysis equipment to the extent that it is not recommended in Premature Infants for Acute Kidney Injury



Objectives

- ▶ To review typical causes of Neonatal AKI
 - ▶ To discuss potential long-term effects of AKI
 - ▶ To review controversial issues in neonatal AKI
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Definition

- ▶ In 2017 the Kidney Disease: Improving Global Outcomes (KDIGO) provided an updated neonatal definition of AKI
 - ▶ Based on serum creatinine change from baseline and urine output
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KDIGO Criteria for Neonatal AKI

AKI Stage	Serum Creatinine Rise	OR	Urine output (ml/kg/hr)
0	< 0.3 mg/dL		> 0.5 ml/Kg/h
1	>/= 0.3 mg/dL or > 1.5-1.9 x baseline Scr		< 0.5 ml/Kg/h (6-12 hr)
2	> / = 2-2.9 x baseline Scr		< 05 ml/Kg/h (> 12 hrs)
3	>/= 3 x baseline Scr, or use of dialysis		< 0.3 ml/Kg/h > 24 h, or anuria > 12 h

Kidney Int 2012;2:1-138



Problems with Definition of AKI

- ▶ Serum creatinine is not stable in the first week of life (when AKI is common)
 - ▶ Larger children with more muscle mass will have larger fluctuations both in wellness and with renal disease
 - ▶ The rise in serum creatinine with AKI is very dependent on how low the baseline gets.
 - ▶ This definition completely ignores those whose serum creatinine failed to fall in the first week of life
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Modification of KDIGO AKI Definition Proposed by Gupta

- ▶ Gupta recently proposed adding criteria for inadequate initial drop in serum creatinine
 - ▶ Scr should drop by 50% or drop below 0.6 mg/dL within a week of life

In a group of 225 HIE infants treated with hypothermia from 2008-2020,

28% had AKI by KDIGO criteria

31% (additional) infants had AKI by this proposed modification



Risk of AKI based on KDIGO criteria

Overall 30% risk of neonatal AKI

Prematurity:

- ▶ 40% risk in VLBW < 1500g
- ▶ 25% risk in LBW
- ▶ CHD: 52% (range of 27-86%)
- ▶ HIE: 38-72% (variable across institutions)
- ▶ NEC: 32.6%
- ▶ Nephrotoxic meds: depends on exposure (75% exposed to at least one)
- ▶ ECMO: 51-74%
- ▶ Sepsis: about 70% - Carries a high mortality risk



Awaken Trial (reported 2017)

A Multicenter observational cohort study

- ▶ Retrospective study of 2,022 neonates from USA, India, Canada, Australia
 - ▶ AKI= UO < 1 ml/kg/hr and serum cre rise of 0.3 or more
 - ▶ Results showed 30% with at least one episode of AKI
 - ▶ AKI independently predicted LOS (23d vs 19 d) and mortality risk (10% vs 1%)
 - ▶ U shaped curve for LOS and mortality with highest risks for the youngest and oldest
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Biomarkers of AKI

Turn around time negates value

- ▶ Neutrophil gelatinase-associated lipocalin (NGAL): Released by activated neutrophils and some epithelial cells (renal tubular cells)
 - ▶ KIM-1: Proximal tubules release KIM-1 after ischemia/toxicity. Not shown to be independently useful
 - ▶ Cystatin C: This is a more accurate measure of GFR than serum creatinine
 - ▶ Interleukin-18: This is upregulated in AKI and is a marker of proximal tubular injury
 - ▶ Others
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Biomarkers are they worth using?

- ▶ Reasons to consider use:
 - ▶ Serum creatinine lags behind actual GFR
 - ▶ Intervening earlier may be beneficial
- ▶ Reasons to not uses:
 - ▶ Slow turn around time for most markers
 - ▶ Not clear what you would do differently
 - ▶ Not clear which group of AKI would benefit



Conservative Treatment of Neonatal AKI

- ▶ Fluids/diuretics designed to achieve fluid balance
- ▶ Avoid hyponatremia, hyperkalemia, hyperphosphatemia.
- ▶ Treat hypocalcemia, and metabolic acidosis (in that order)
- ▶ Adjust medications for GFR
- ▶ Avoid nephrotoxic drugs as possible
- ▶ Avoid hypotension/hypovolemia
- ▶ Be certain there is no urinary obstruction
- ▶ Consider echocardiogram for LV function



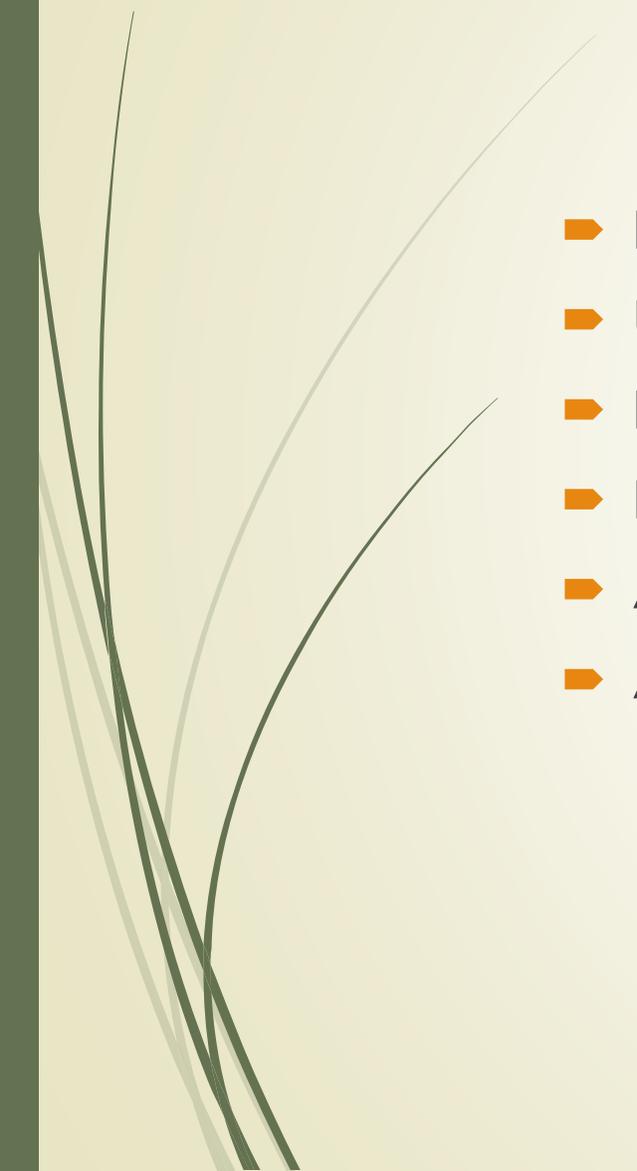
Potential Therapy for neonatal AKI

Methylxanthines

- ▶ Caffeine has been associated with lower incidence of AKI in NEC
- ▶ Theophylline – 8 mg/kg as a single dose has been shown safe and effective in term neonates with severe HIE
 - ▶ KDIGO guidelines suggest a single dose in neonates with severe perinatal asphyxia



Indications for Neonatal Dialysis

- ▶ Hyperkalemia: Can avoid dialysis if urine output can be restored
 - ▶ Uncontrolled Metabolic acidosis: This carries a large mortality risk
 - ▶ Hyperammonemia: Time is important for brain protection
 - ▶ Fluid overload which is causing respiratory failure
 - ▶ Anuria
 - ▶ Azotemia – severe. Bun < 150 and creatinine < 5.0 usually tolerated
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Dialysis Options

Peritoneal Dialysis

- ▶ PD is the lowest risk modality
 - ▶ Risks: leaking PD fluid, peritonitis, omental encasement
 - ▶ Benefits: No special equipment needed.
 - ▶ Limits of use: Leaks are very likely in very small infants.
 - ▶ Weight limit for use in Boise is: 2 kg
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Dialysis Options

Hemodialysis

- Risks:
 - Hypotension/Hypovolemia
 - ischemic leg (from femoral catheter)
 - Need for 8Fr catheter or larger
 - Need for anticoagulation (must be at least 35 weeks gestation)
 - Need for blood prime of dialysis circuit
- Benefits: Rapid correction of life-threatening conditions
- Weight limit is 8 kg in Boise currently

Carpedium neonatal dialysis machine





Neontal Dialysis Options CRRT/Carpedium

- ▶ Benefits:
- ▶ Can be done with citrate or heparin anticoagulation
- ▶ Lower risk of hypotension compared with hemodialysis
- ▶ Larger infants don't need blood prime
- ▶ Risks:
 - ▶ Hypotension/hypovolemia
 - ▶ Need for blood prime if weight < 3-3.5 kg
 - ▶ **Not available in Boise**
 - ▶ Risks of hemorrhage if heparin used for anticoagulation



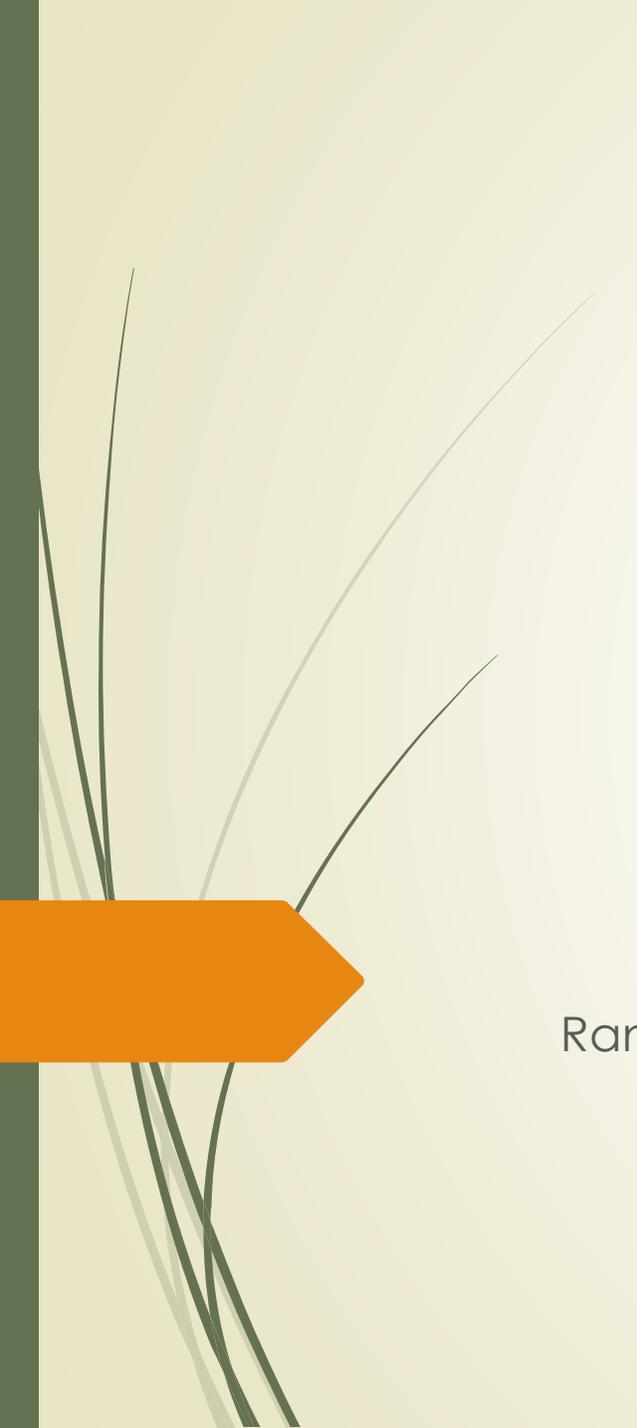
Remaining Uncertainties

- ▶ Which patients would benefit from neonatal or nephrology f/u evaluation after having AKI
 - ▶ Based on severity of AKI? The more severe, the more likely benefit
 - ▶ Based on imaging? Finding suggesting irreversible changes
 - ▶ Based on recovery? Rapid recovery suggest less risk of long-term harm
 - ▶ Base on proteinuria? Persistent proteinuria suggests long-term harm.



Summary

- ▶ AKI is relatively common in premature and sick term infants
 - ▶ Therapy should be directed at avoiding perturbations in volume status and osmolarity
 - ▶ Dialysis is rarely needed
 - ▶ Chronic renal disease can be seen in follow-up
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Neonatal Hypertension 2025

Randall Jenkins MD



Objectives

- ▶ To describe the main etiologies of neonatal hypertension
 - ▶ To review the diagnostic workup of neonatal hypertension
 - ▶ To review treatment of different types of neonatal hypertension
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Neonatal Hypertension First Reports



beve-like thrombus is adherent to an umbilical artery (Goetzman et al, with permission '89).



Background



- ▶ The incidence of neonatal hypertension has been between 1-3%
- ▶ Renal disease remains a common cause of neonatal hypertension
- ▶ In more recent years, high-renin hypertension has all but disappeared, replaced by low-renin hypertension



Things that are not causes of HTN

- ▶ Nephrocalcinosis
- ▶ Caffeine
- ▶ Extreme Prematurity – small size
- ▶ Antenatal Steroids
- ▶ Prolonged length of stay
- ▶ BPD
- ▶ Mild hydronephrosis



Workup of Neonatal Hypertension

- ▶ History and Physical Exam
 - ▶ Timing: Renovascular disease and AKI –related HTN present early. Low-renin HTN presents between 36-44 weeks PMA
 - ▶ Meds: Look for steroids, NaCL, or sympathomimetics
 - ▶ Edema, red face, bp all 4s. Evidence of PDA?
- ▶ Diagnostics:
- ▶ Serum creatinine, plasma renin activity, T4, TSH, UA
 - ▶ Renal ultrasound:
 - ▶ Echo when HTN is severe or ? Of coarctation of the aorta



Term vs Premature Infants

- ▶ HTN in term infants is rare – almost never seen in healthy term newborns. Be skeptical of spurious HTN (normal newborn units don't take bp a lot).
 - ▶ Premature infants are more likely to have acute illness, AKI, fluid overload, medications which can cause hypertension. Most importantly, they are at high risk for toxic exposures which can cause hypertension.
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The Spectrum of Hypertension in Premature Infants (2010-2018)

- ▶ Cardiac 0%
- ▶ Endocrine: 0%
- ▶ Neoplasia: 0%
- ▶ Neurologic: 1% (stroke, IVH)
- ▶ Renovascular: 2%
- ▶ Acute renal disease: 3%
- ▶ Chronic renal parenchymal: 6%
- ▶ Medications: (7%) (largely steroids)
- ▶ Miscellaneous (16%) (**Low-renin hypertension**)
- ▶ BPD: 65% (**Low-renin hypertension**)

Clinical Characteristics of Low-renin Hypertension in Premature Infants.

- ▶ Near universal low plasma renin activity
- ▶ Presentation at 38 +/- 2 weeks gestation
- ▶ Responsive to spironolactone therapy
- ▶ Resolving over 20 weeks time





Looking for the cause of low renin hypertension

- ▶ Low PRA implies sodium retention – but why?
- ▶ Large phthalate exposures have been documented for years
- ▶ DEHP, (the only FDA-approved phthalate in the US) is added to PVC as a flexibility agent)
- ▶ Zhao showed that DEHP metabolites inhibit 11B-HSD2
 - ▶ This is the same enzyme which mediates AME or licorice-induced HTN (It inhibits conversion of cortisol to cortisone).
- ▶ Zhao B, Lian Q, Chu Y, Hardy DO, Li XK, Ge RS, The inhibition of human and rat 11B-HSD2 by perfluoroalkylated substances, J Steroid Biochem. Mol. Biol. 125 (1-2):143-147.



Prospective mechanistic trial 2014-2017

- ▶ Looking to link phthalates to low-renin hypertension, a prospective study was launched at St. Luke's and OHSU in 2014
- ▶ we hypothesized that phthalates (specifically DEHP) exposure was causing low-renin hypertension in premature infants
- ▶ We examined plasma renin, urine cortisol to cortisone ratio, phthalate exposure and blood pressure
- ▶ 20 neonates enrolled at two sites

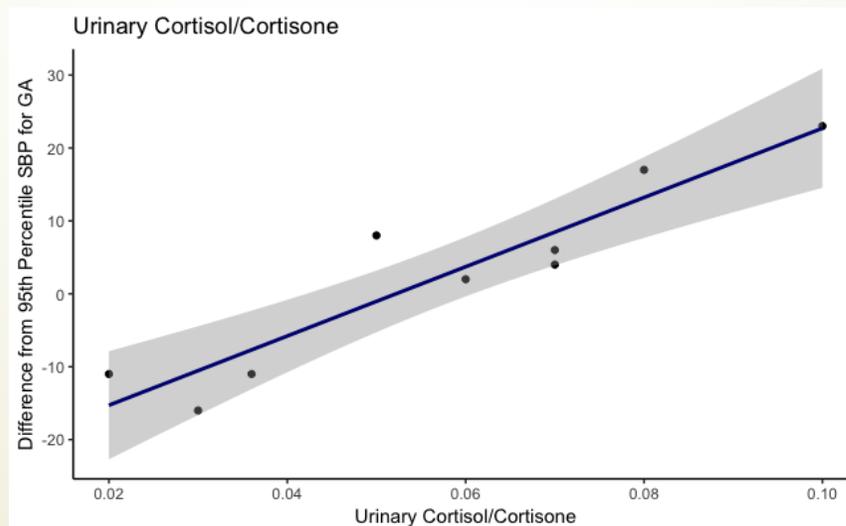


Trial Findings

- ▶ Phthalate exposure was associated with increased blood pressure in 9 premature infants.
 - ▶ Hypertension appeared near 38 weeks – plasma renin activity was low in all cases of hypertension.
 - ▶ Patients responded to spironolactone and HTN resolved within several months after NICU discharge.
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Key Evidence Implicating Phthalates (DEHP)

- ▶ Urinary cortisol/cortisone mediates the effect of IV DEHP exposure on systolic blood pressure difference
- ▶ MEHP inhibition of 11 β -HSD2 is the likely mechanism of action to explain the effect of DEHP on blood pressure in unexplained hypertension in premature infants.





Treatment of Neonatal Hypertension

- ▶ low-renin phthalate HTN: Spironolactone works best, chlorothiazide is second best. A combo reduces K worry
- ▶ Early and life-threatening HTN should be treated as renovascular even if unclear
- ▶ Moderate HTN associated with mild AKI can often be from a PDA.
- ▶ Steroid related HTN is best treated with diuretics – but may occasionally need two drugs



Summary

- ▶ Phthalate exposures are the likely cause for 80% of today's neonatal hypertension
 - ▶ Incidence is dropping as DEHP exposures are reduced
 - ▶ Most neonatal hypertension resolves within a few months after discharge from NICU
 - ▶ When HTN persists, it is usually related to chronic renal disease or significant renal injury
 - ▶ Renovascular HTN is now rare
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Drugs for Hypertension

Captopril 0.05 mg/kg PO q 6-8 hrs. Consider test dose of 0.01 mg/kg. **BEWARE if on diuretics or volume depleted**

- ▶ **Can increase K⁺**
- ▶ **Can induce AKI**
- ▶ Enalapril or Lisinopril: same concerns as captopril: Reonvascular htn only.
- ▶ Spironolactone: 2-3 mg/kg/day in 2 split doses. - Can increase K⁺
- ▶ Chlorothiazide: 5-10 mg/kg/day in 2 split doses. Can deplete K⁺
- ▶ Beta blocker: propranolol or atenolol.
- ▶ Calcium channel blocker: isradipine or amlodipine: few side effects
- ▶ Hydralazine: vasodilator. Can cause tachycardia. Not very potent.
- ▶ Clonidine: central acting. Mostly used as a PRN med.



Current Hypothesis for How DEHP Causes Neonatal Hypertension

- ▶ DEHP exposures early in gestation (not sure when) cause an epigenetic change to the gene for 11-B HSD-2, making those infants exquisitely sensitive to subsequent DEHP exposures.
- ▶ Unknowns:
 - ▶ What is the window of vulnerability?
 - ▶ What is the duration of epigenetic change?
 - ▶ Are exposures early in life more or less significant than later exposures?