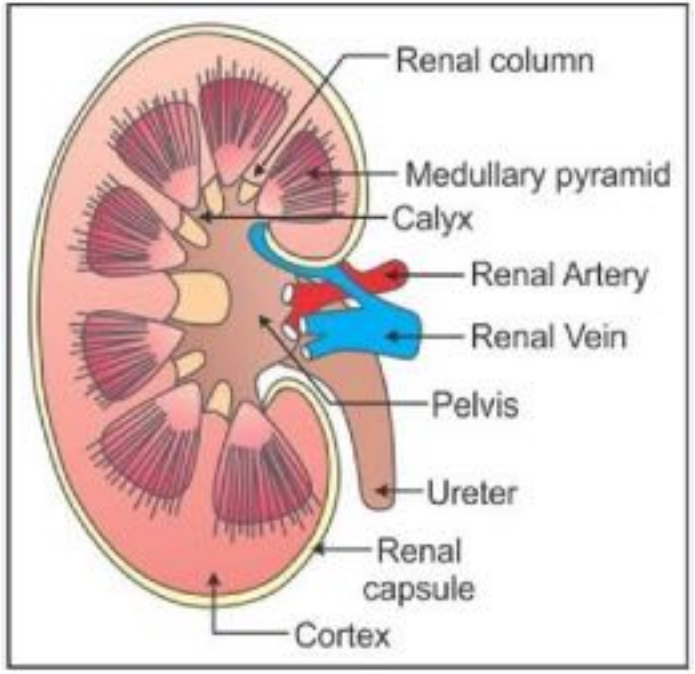
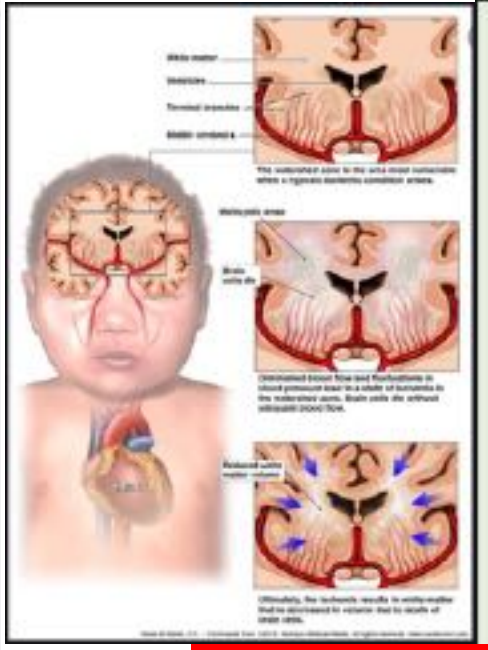
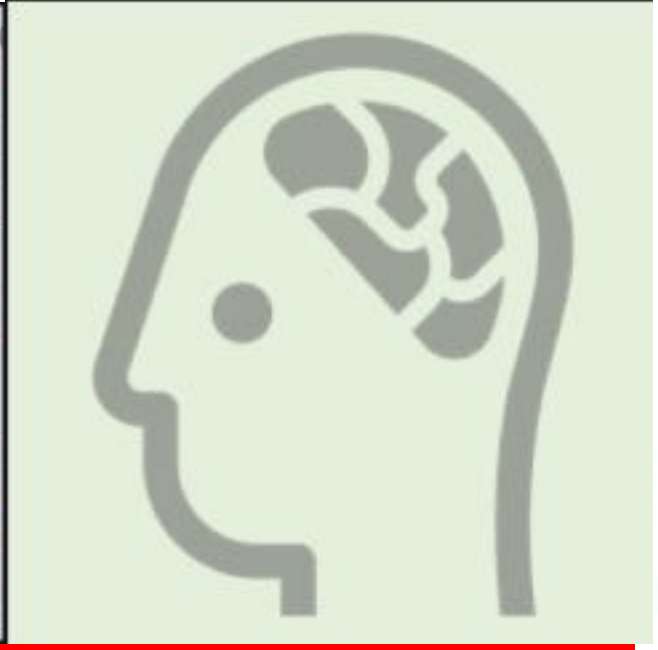
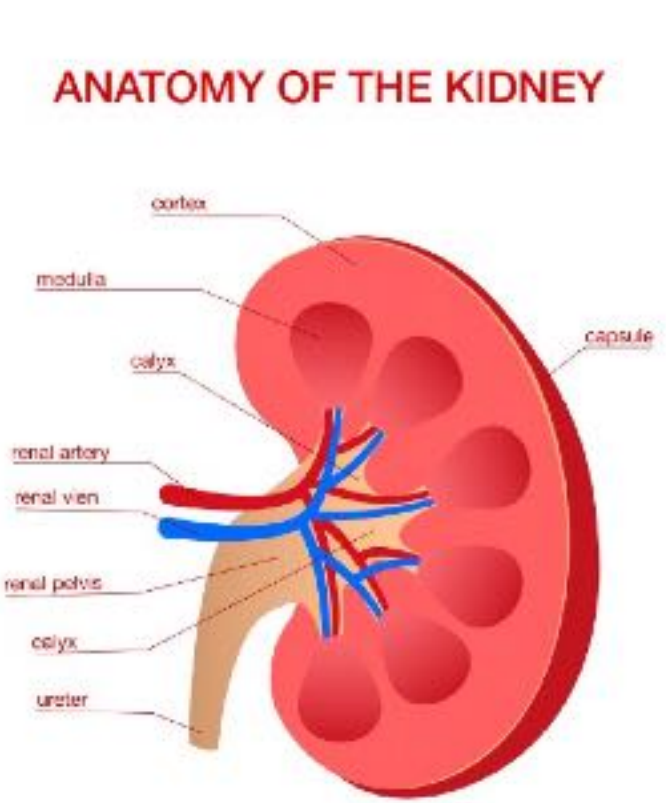




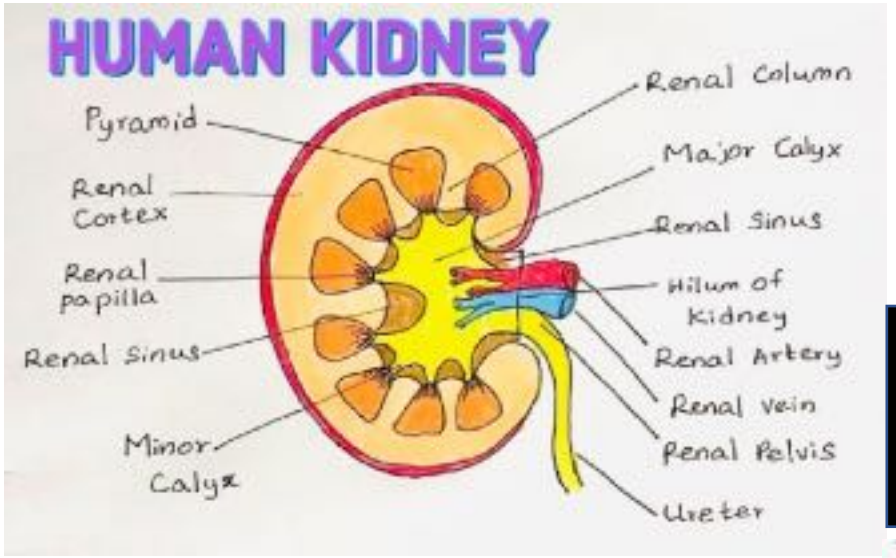


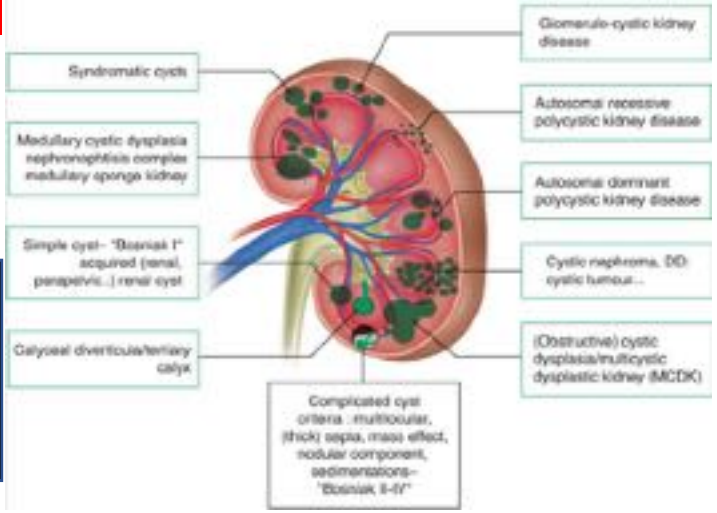


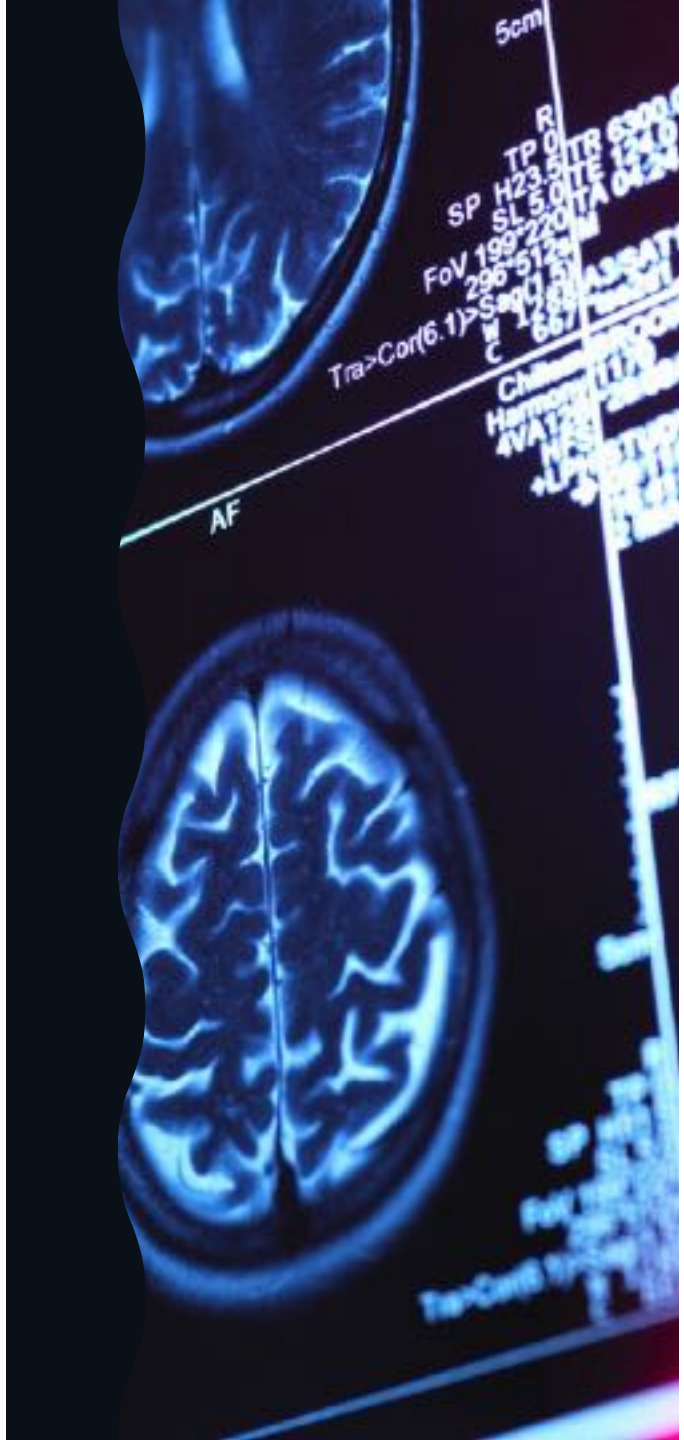
AKI in HIE

Dr Hisham Awad

Ain Shams University







Definition

- Neonatal encephalopathy (NE) is a complex disease of the newborn characterized by:
  - an altered level of consciousness,
  - seizures,
  - poor tone,
  - an inability to initiate or maintain respiration
  - and is associated with multi organ dysfunction .

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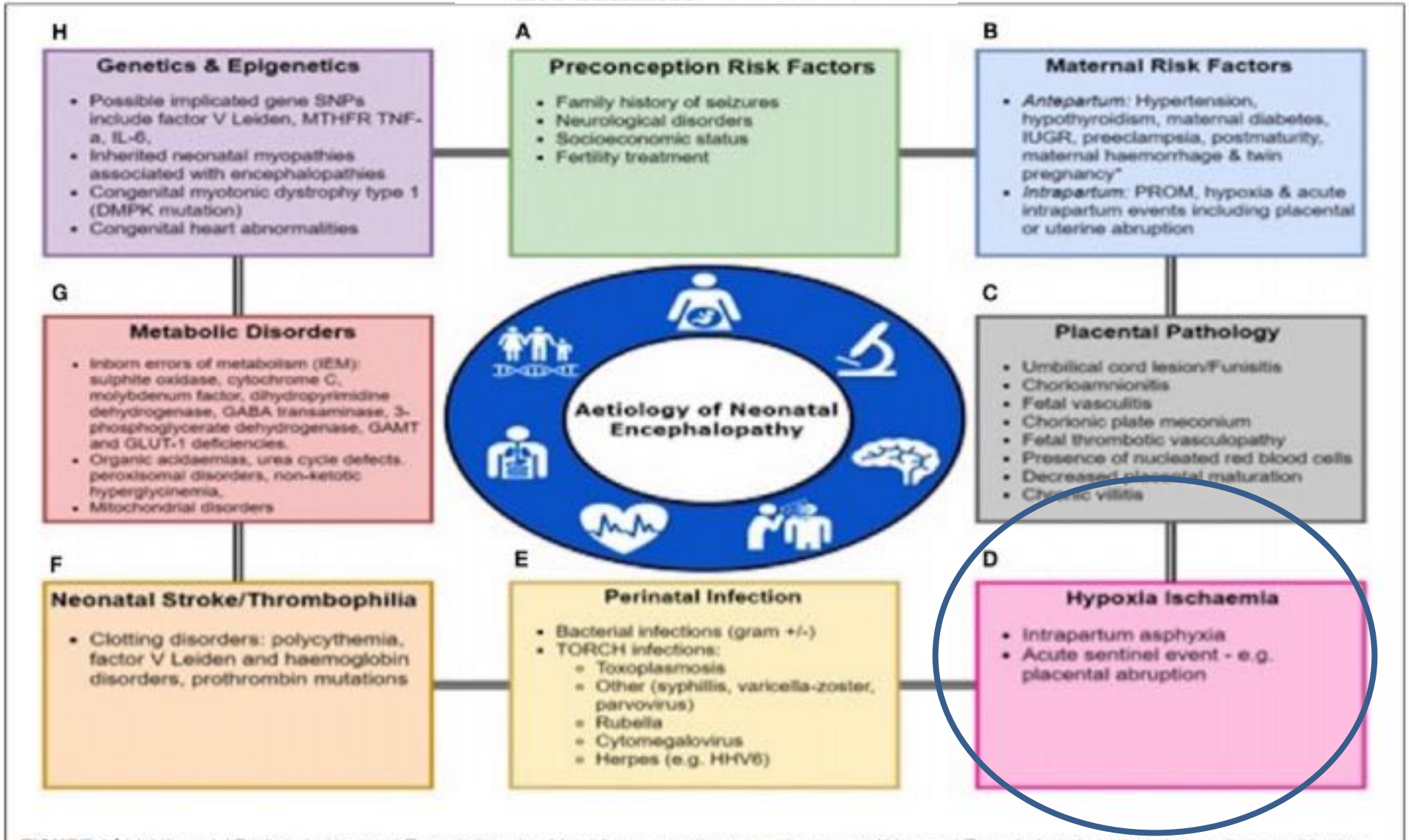


FIGURE 1 | Multifactorial Etiology In Neonatal Encephalopathy. Many factors predispose to the onset of Neonatal Encephalopathy either alone or in a combination including **(A)** Preconception Risk Factors, **(B)** Maternal Antepartum/Intrapartum comorbidities or events, **(C)** Placental pathology, **(D)** Hypoxia-ischaemia, **(E)** Perinatal infection, **(F)** Neonatal stroke or thrombophilia, **(G)** Metabolic disorders, and **(H)** Genetic and epigenetic abnormalities. PROM, prolonged rupture of membranes; IUGR, intrauterine growth restriction.

- The use of the term NE vs. HIE is controversial. It has been proposed that in term and late preterm infants with no identifiable **sentinel events** the term NE should be used.

Type and Timing of Contributing Factors That Are Consistent With an Acute Peripartum or Intrapartum Event-I-

- A **sentinel** hypoxic or ischemic event occurring immediately before or during labor and delivery:
  - Ruptured uterus
  - Severe abruptio placentae
  - Umbilical cord prolapse
  - Amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia
  - Maternal cardiovascular collapse
  - Fetal exsanguination from either vasa previa or massive fetomaternal hemorrhage

Type and Timing of Contributing Factors That Are Consistent With an Acute Peripartum or Intrapartum Event-II-

- Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event, particularly a category I fetal heart rate pattern on presentation that converts to one of the following patterns:
  - Category III pattern
    - **sinusoidal pattern or absent baseline variability plus recurrent late decelerations, recurrent variable decelerations, or bradycardia**.
  - Tachycardia with recurrent decelerations
  - Persistent minimal variability with recurrent decelerations

Markers of an Acute Peripartum or Intrapartum Hypoxic-ischemic Event

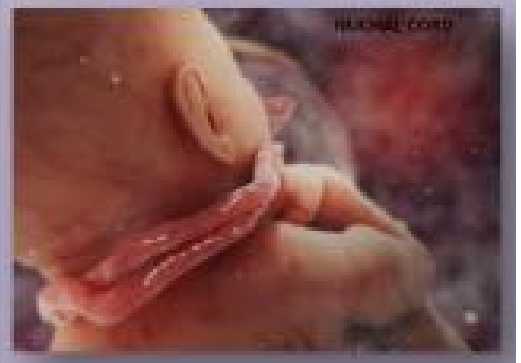
- **Neonatal signs consistent with an acute peripartum or intrapartum event:**
  - Apgar score of less than 5 at 5 minutes and 10 minutes
  - Fetal umbilical artery acidemia: fetal umbilical artery pH less than 7.0, or base deficit ≥12 mmol/L, or both
  - Neuroimaging evidence of acute brain injury seen on brain MRI or MRS consistent with hypoxia-ischemia
  - Presence of multisystem organ failure consistent with hypoxic-ischemic encephalopathy

CAUSES OF HIE

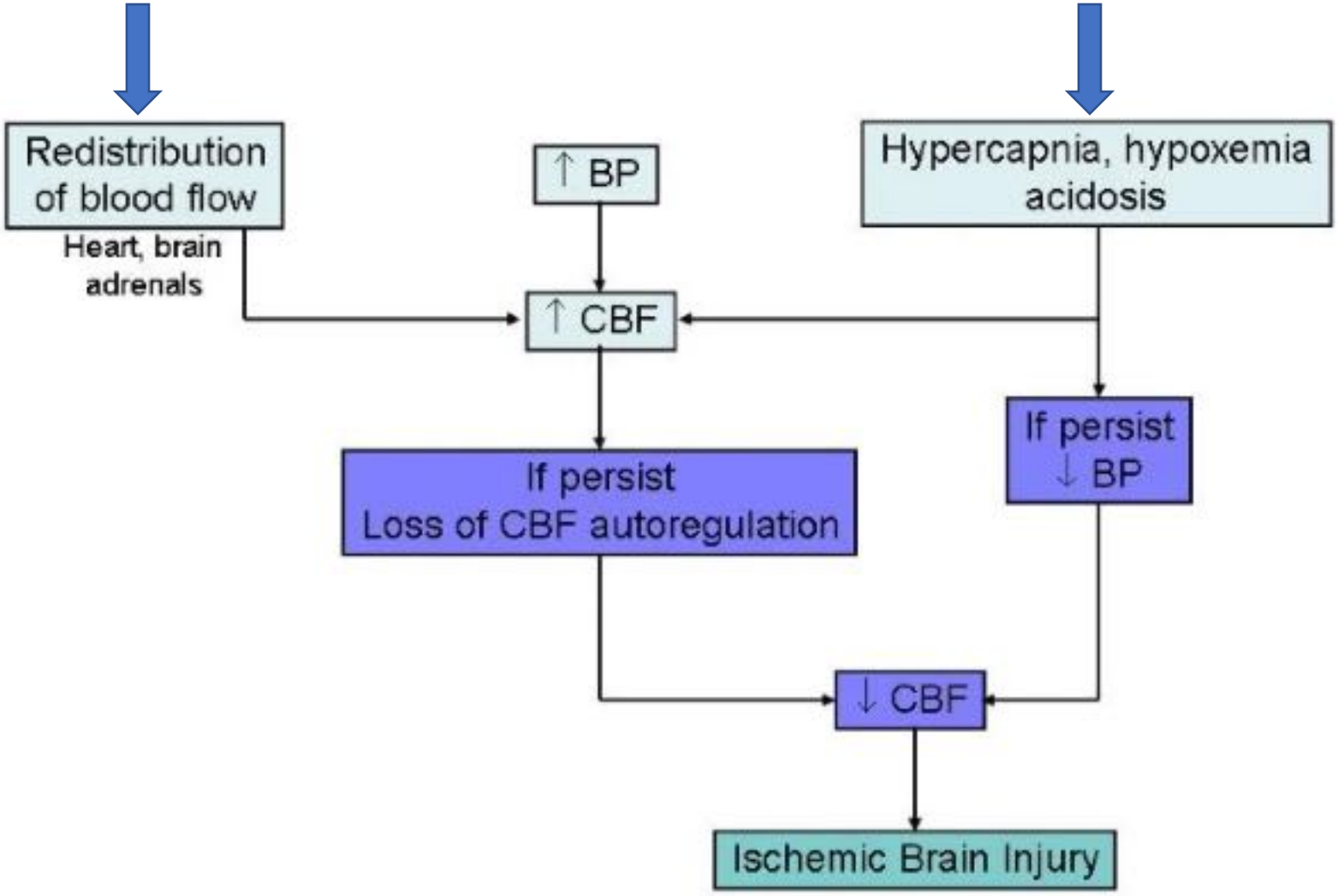
MATERNAL
Cardiac arrest
Asphyxiation
Severe anaphylactoid reaction
Status epilepticus
Hypovolemic shock

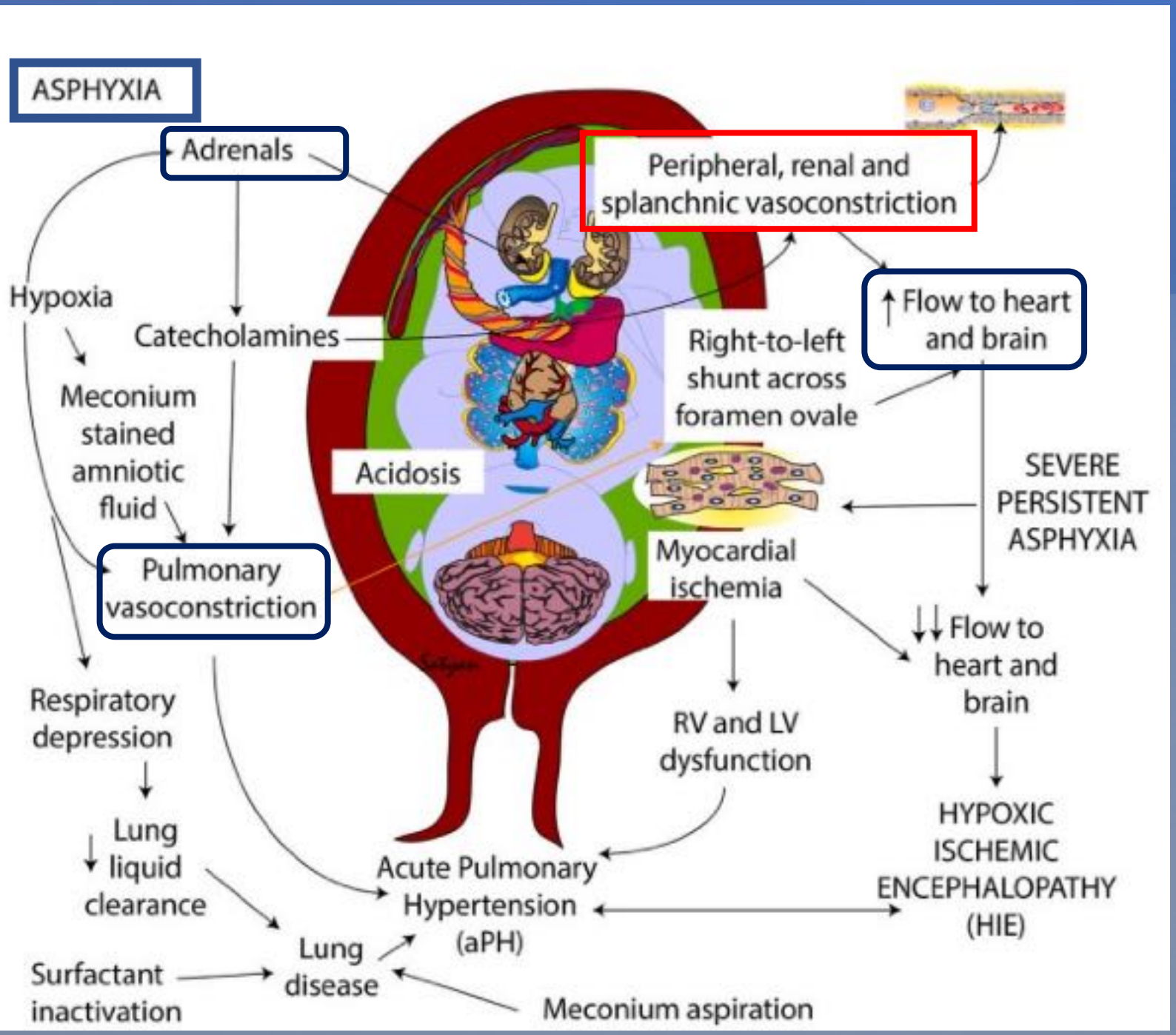
UTEROPLACENTAL
Placental abruption
Cord prolapse
Uterine rupture
Hyperstimulation with oxytocic agents

FETAL
Fetomaternal hemorrhage
Twin-to-twin transfusion syndrome
Severe isoimmune hemolytic disease
Cardiac arrhythmia



HYPOXIA/ISCHEMIA

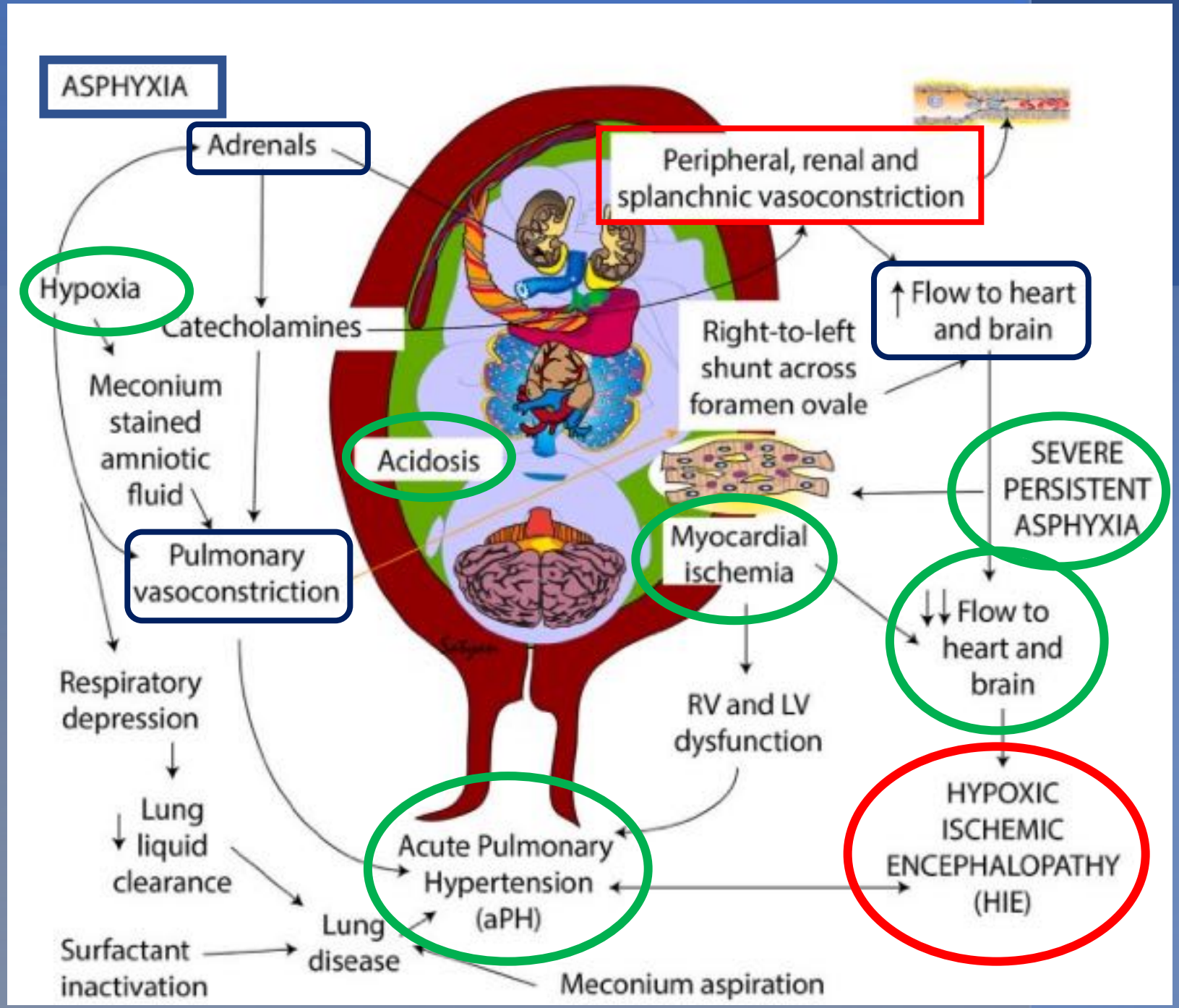


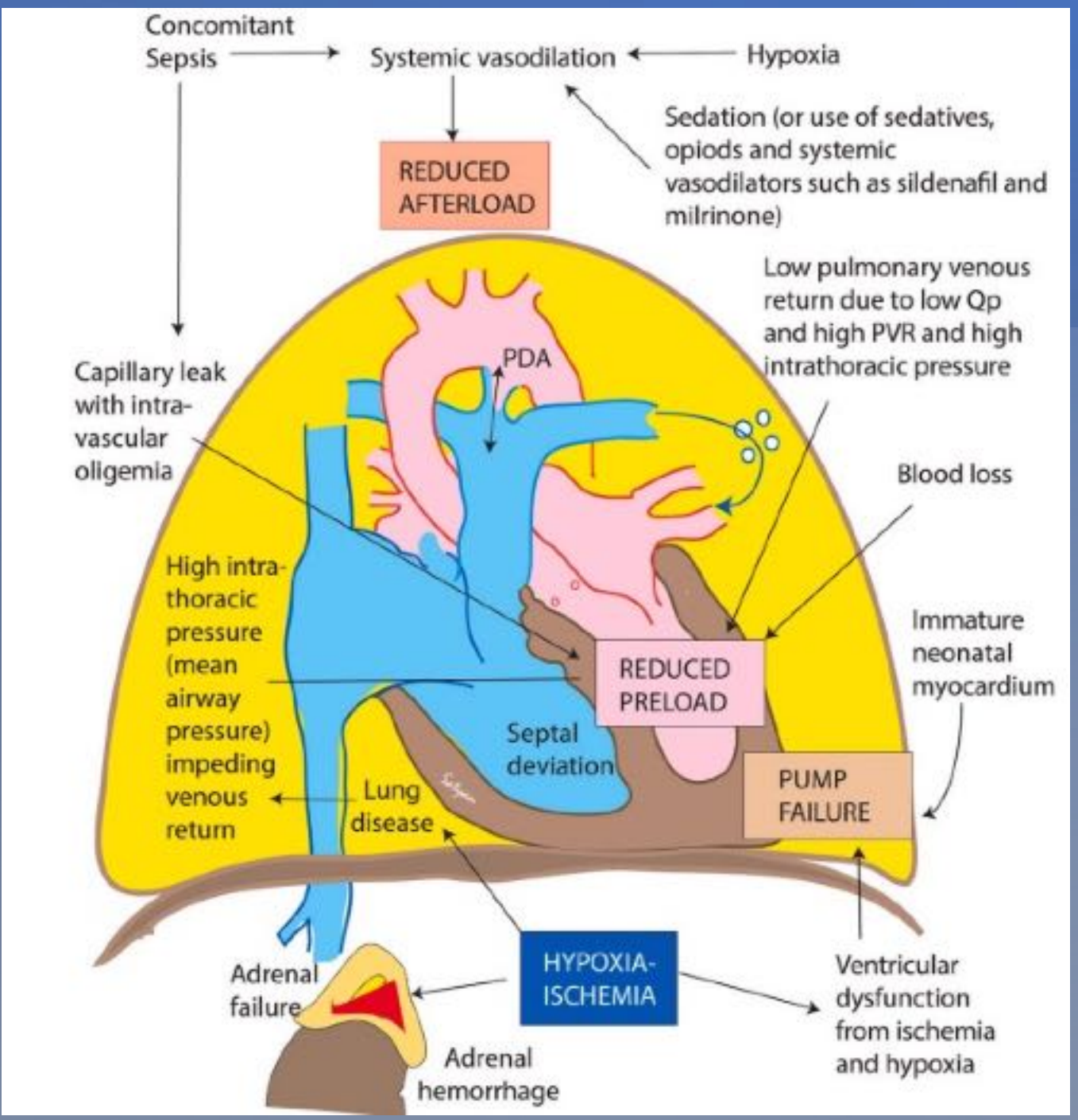


Fetal asphyxia, neonatal encephalopathy (NE) and acute pulmonary hypertension.

Mild to moderate fetal hypoxia leads to peripheral, renal, splanchnic, and pulmonary vasoconstriction diverting blood to the brain, heart, and adrenals. Increased pulmonary arterial pressure leads to increased right-to left shunt at the foramen ovale and increases blood flow in the ascending aorta thereby enhancing cerebral and coronary perfusion.

However, severe hypoxia leads to reduced blood flow to brain and heart causing NE, myocardial ischemia, right and left ventricular dysfunction, and pulmonary hypertension.


ASPHYXIA
Adrenals
Peripheral, renal and splanchnic vasoconstriction
Hypoxia
Catecholamines
↑ Flow to heart and brain
Right-to-left shunt across foramen ovale
Meconium stained amniotic fluid
Acidosis
SEVERE PERSISTENT ASPHYXIA
Pulmonary vasoconstriction
Myocardial ischemia
↓↓ Flow to heart and brain
Respiratory depression
RV and LV dysfunction
Lung liquid clearance
Acute Pulmonary Hypertension (aPH)
HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)
Surfactant inactivation
Lung disease
Meconium aspiration



Causes of systemic hypotension in pulmonary hypertension associated with neonatal encephalopathy (NE).

- Pump failure (often due to ventricular dysfunction from ischemia),
- Reduced preload (from reduced pulmonary venous return exacerbated by high intrathoracic pressure from the ventilator)
- Reduced afterload due to adrenal failure and effect of medications.
- Adrenal failure can be secondary to bilateral adrenal hemorrhage.

Management of systemic hypotension is crucial to optimize blood flow and oxygen delivery to the brain and heart

System	Effect
Central Nervous System	Hypoxic Ischemic Encephalopathy, Infarction, Intra Cranial Hemorrhage, Seizures, Cerebral Edema, Hypotonia and Hypertonia
Cardiovascular System	Cardiogenic Shock, Myocardial Ischemia, Poor Contractility, Tricuspid Insufficiency, Hypotension
Pulmonary	Pulmonary Hypertension, Pulmonary Hemorrhage, Respiratory Distress Syndrome
Renal	Acute Tubular Or Cortical Necrosis
Adrenal	Adrenal Hemorrhage
Gastrointestinal	Perforation, Ulceration With Hemorrhage And Necrosis
Metabolic	Inappropriate Secretion Of Anti - Diuretic Hormone. Hyponatremia, Hypoglycemia, Hypocalcemia, Myoglobinuria

Various effects of Perinatal asphyxia on different organ systems.

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Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- Neonates with perinatal asphyxia, often develop multiorgan failure, which impacts virtually every organ system.
- AKI has been shown to occur commonly in infants with HIE with an incidence ranging from 38 to 72%.
- In a single center study of 96 neonates with HIE undergoing therapeutic hypothermia, AKI occurred in 38% of neonates.
- It independently predicted prolonged duration of mechanical ventilation and NICU stay.

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- In a follow-up study, AKI during therapeutic hypothermia was found to be associated with the development of abnormal magnetic resonance imaging (MRI) findings at 7–10 postnatal days.
- The impact of therapeutic hypothermia on the incidence of AKI in HIE remains unclear, with trials and retrospective studies demonstrating conflicting results.

Therapeutic Hypothermia and Temperature Management > Ahead of Print | normal

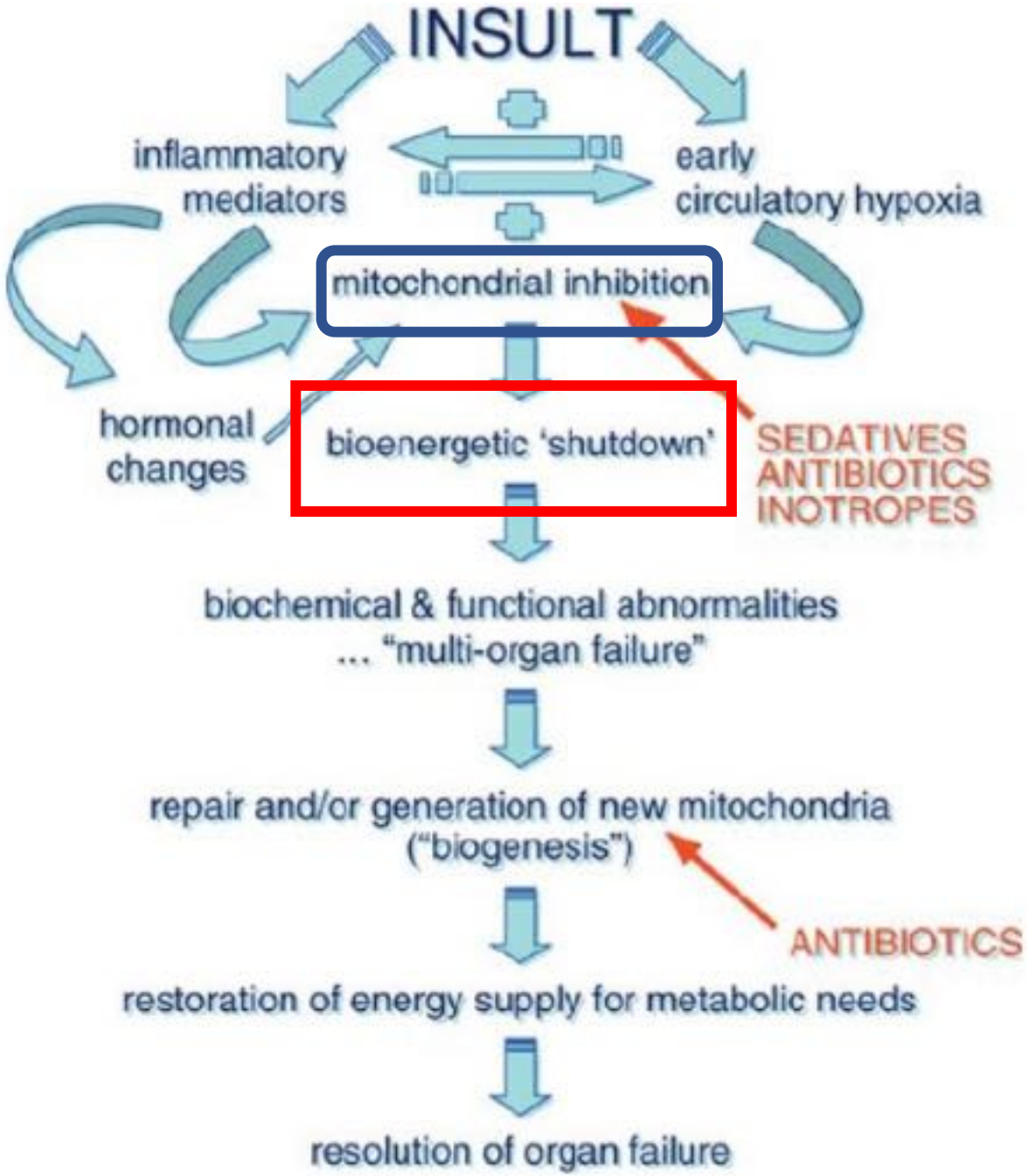
Acute Kidney Injury in Neonatal Hypoxic-Ischemic Encephalopathy Patients Treated with Therapeutic Hypothermia: Incidence and Risk Factors

Emre Dincer, Sevilay Topçuoğlu, Elif Betül Keskin Çetinkaya, Özge Yatır Alkan, Elif Özalkaya, Selim Sancak, and Güner Karatekin

Published Online: 21 Jun 2023 | https://doi.org/10.1089/ther.2023.0009

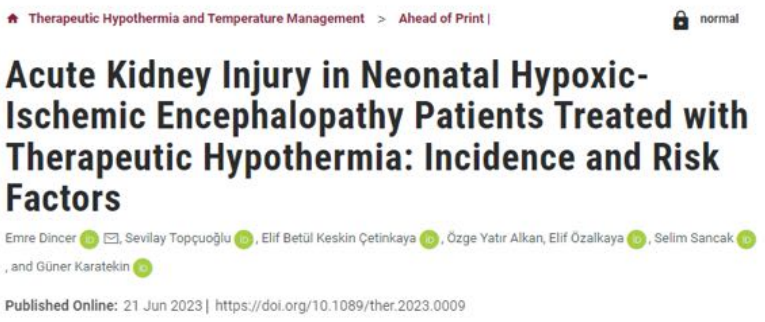
- Studies in infants with hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia have generally focused on neurological outcomes.
- Although acute kidney injury (AKI) rate decreased in advent of therapeutic hypothermia (TH), it is still a common and important entity..

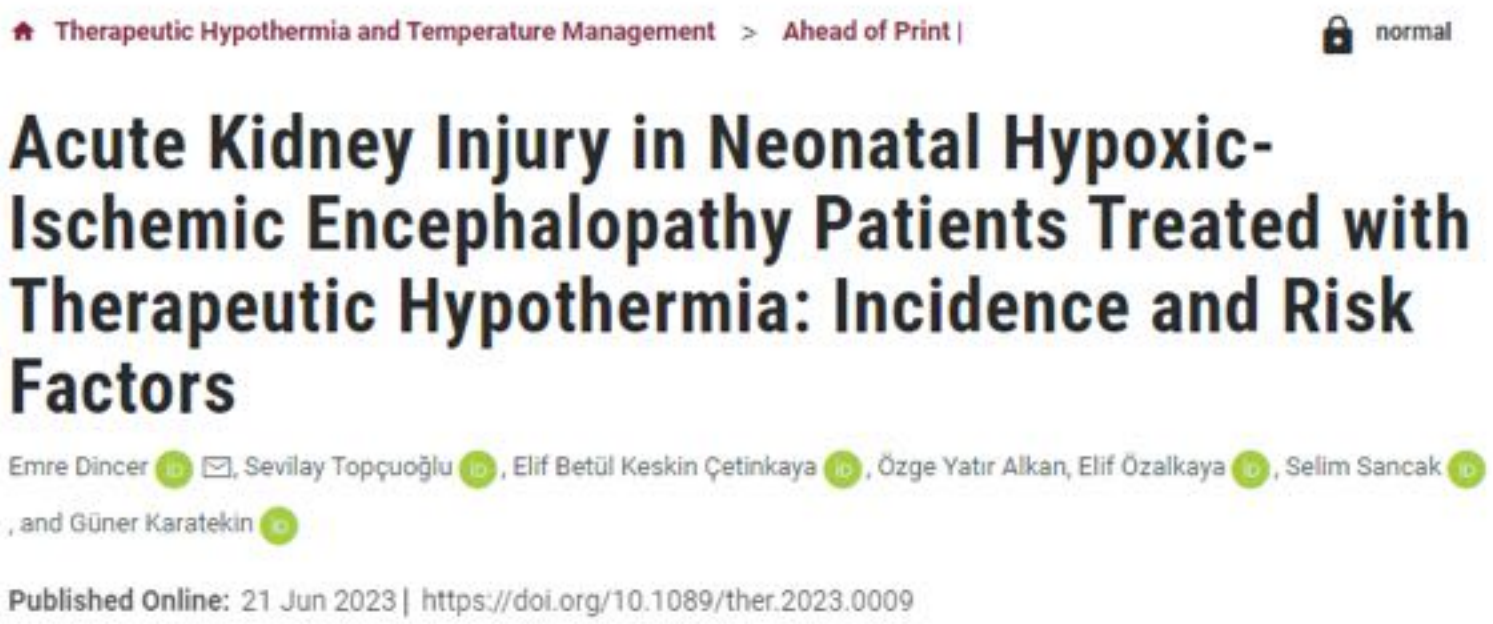
- In this retrospective study, the risk factors for AKI in HIE patients treated with hypothermia were investigated.
- Infants treated with TH due to HIE were reviewed retrospectively and infants who developed AKI and not were compared.


INSULT
inflammatory mediators
early circulatory hypoxia
mitochondrial inhibition
hormonal changes
bioenergetic 'shutdown'
SEDATIVES
ANTIBIOTICS
INOTROPES
biochemical & functional abnormalities
... "multi-organ failure"
repair and/or generation of new mitochondria
("biogenesis")
ANTIBIOTICS
restoration of energy supply for metabolic needs
resolution of organ failure

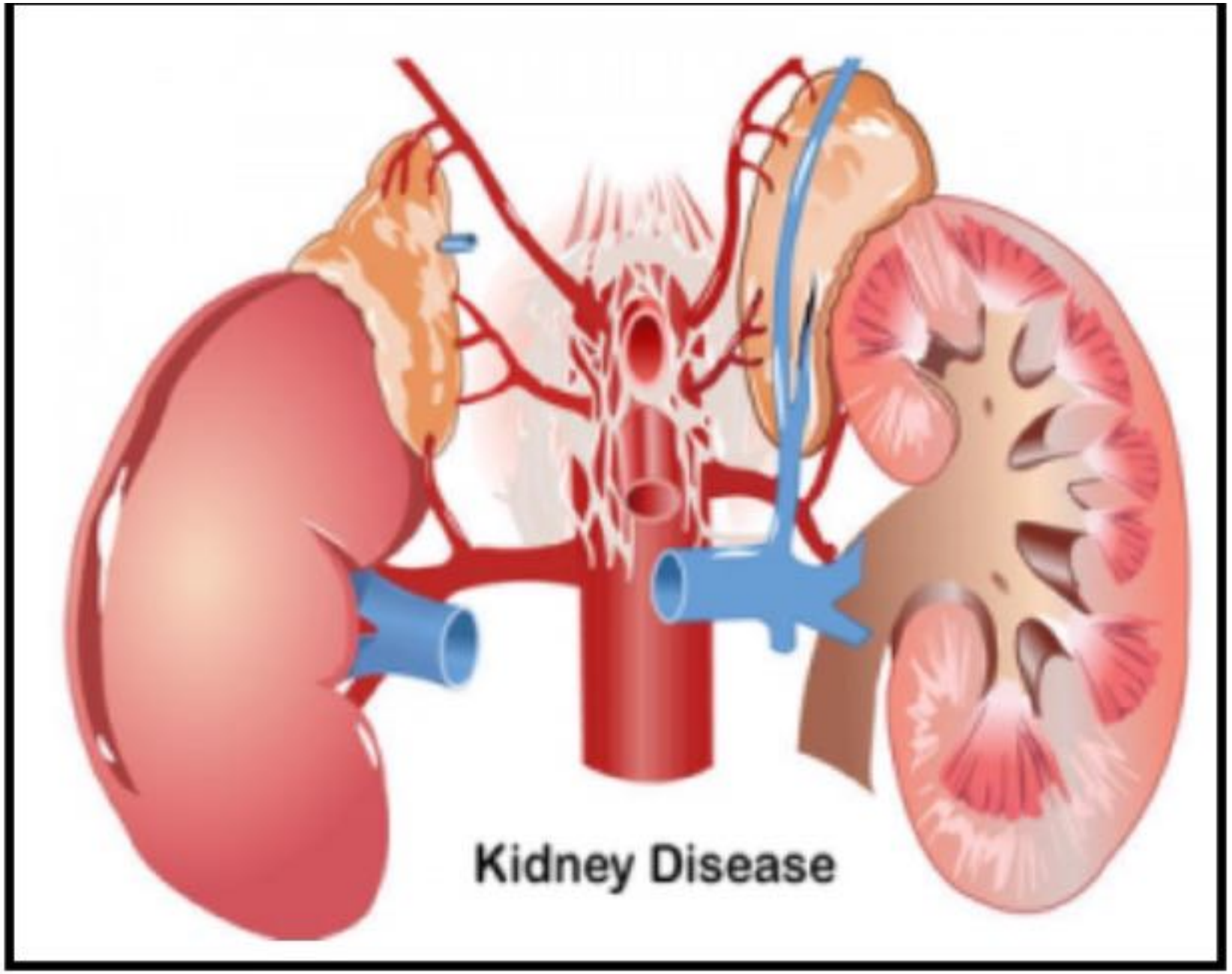
- Ninety-six patients were enrolled in the study.
  - AKI developed in 27 (28%) patients
  - 4 (14.8%) of them were stage III AKI.

- In the AKI group, risk factors for AKI were:
  - gestational age of the patients was significantly higher ($p = 0.035$),
  - the 1st minute Apgar score was significantly lower ($p = 0.042$),
  - convulsions ($p = 0.002$),
  - amplitude-integrated electroencephalography disorders ($p = 0.025$),
  - sepsis ($p = 0.017$),
  - need for inotropic therapy ($p = 0.001$),
  - need of invasive mechanical ventilation ($p = 0.03$),
  - systolic dysfunction in echocardiography ($p = 0.022$) were significantly higher..





- In logistic regression tests, Apgar score at the 1st minute was found to be independent risk factor for developing AKI.
- AKI has the potential to worsen the neurological damage and correlates with morbidities of perinatal asphyxia.



DIAGNOSTICS

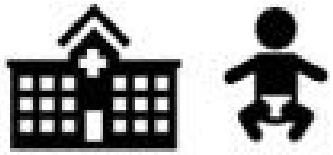
Definitions of KDIGO and Gupta AKI Criteria

Neonatal AKI-KDIGO Criteria		
Stage	Serum Creatinine	Urine Output
	or	
	≤46% on day of life 7	

KDIGO is the process of developing the Clinical Practice Guideline for Acute Kidney Injury and Acute Kidney Disease

A new approach to recognize neonatal impaired kidney function (IKF)

DESIGN



- Retrospective study.
- 329 critically ill newborns
- 40-27 weeks of GA

Reviewed for:

- Serum Creatinine (SCr)
- SCr decline 1st week of life

CONTROLS (n = 255)
Normal SCr at day of life 7 ± 1 + normal SCr decline 1st week of life.

IKF (n = 53)
Abnormal SCr at day of life 7 ± 1 + abnormal SCr decline 1st week of life.

AKI-KDIGO (n = 21)
Increase SCr ≥ 0.3 mg/dl within 48 hours, during 1st week life.

OUTCOMES

IKF vs. Controls

Increased length of stay.
Required more days of mechanical ventilation, more diuretics and vasopressor drugs.
Higher mortality and BUN levels.
No significant differences in urine output.

AKI-KDIGO vs. IKF

Higher mortality during the 1st two weeks of life.
Higher BUN levels, lower urine output, required more diuretics. No significant differences in other clinical parameters described above.

CONCLUSION: The SCr decline during the 1st week of life, combined with SCr thresholds, identifies a distinctive group of newborns with IKF that is missed by the neonatal AKI-KDIGO definition and warrants close monitoring.

KI REPORTS
KIReports.org
Perazzo et al., 2020

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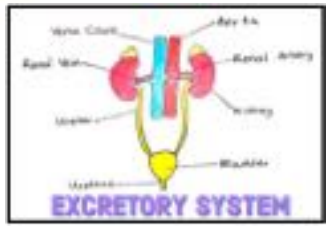


Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **Diagnostics**
- SCr is currently the "gold-standard" of biomarkers to identify AKI.
- However SCr serves as a measure of kidney function, rather than injury.
- Furthermore, SCr is a delayed (up to 48–72 h) marker of kidney function, which may not change until 25–50% of the kidney function has been lost.
- These impediments taken together may explain the challenges faced with the development of successful clinical trials and interventions in AKI.
- Efforts to detect AKI earlier have led to the development of novel biomarkers that lead to the timely diagnosis of AKI, improved clinical trials, and improved outcomes.

Biomarker	Properties and production	Findings
Cystatin C (CysC)	Cysteine protease produced at a constant rate by all nucleated cells	Urine CysC cut-off > 204.4 ng/mL: ◦ AUC 0.937, p < 0.001 ◦ ----- --Sensitivity 100% ◦ ----- --Specificity 91.7%

Biomarker	Properties and production	Findings
Neutrophil gelatinase-associated lipocalin (NGAL)	**Protein expressed by multiple tissues including kidney**	**Serum NGAL** cut-off > 89.6 ng/mL: ◦ AUC: 0.942, p < 0.001 ◦ Sensitivity 100% ◦ Specificity 92.3% **uNGAL** cut-off > 18.61 ng/mL: ◦ AUC 0.865, p < 0.001 ◦ Sensitivity 100% ◦ Specificity 83.3%

Biomarker	Properties and production	Findings
Interleukin-18 (IL-18)	**Pro-inflammatory cytokine induced in proximal tubule after AKI and renal tubular injury**	• uIL-18 independently associated with AKI in non-septic critically ill neonates ◦ OR 2.27, AUC 0.72

Biomarker	Properties and production	Findings
Kidney injury molecule-1 (KIM-1)	type 1 transmembrane protein that has been found to be highly upregulated in the proximal tubule epithelial cells; secreted in urine after AKI	• **Compared to survivors, non-survivors had higher KIM-1** ◦ **Non-survivors: 385 pg/mL (95% CI 231, 1,028)** ◦ **Survivors: 264 (95% CI 147, 549)** ◦ **For every 100 pg/mL rise in KIM-1, there was a 10% higher odds of death (OR 1.1 (1.0–1.2), p < 0.02; AUC 0.64)**

Biomarker	Properties and production	Findings
Osteopontin (OPN)	Cytokine expressed and upregulated during inflammation and AKI	• Compared to subjects without AKI, those with AKI had higher OPN ◦ AKI: 468 ng/mL (95% CI 247, 655) ◦ No AKI: 217 ng/mL (95% CI 115, 280) ◦ For every 100 ng/mL rise in OPN, the odds of AKI increased by 220% (OR 3.2 (1.5–9.9), $p < 0.01$; AUC 0.83) ◦ Combining NGAL and OPN improved ability to detect AKI (AUC 0.90)

Biomarker	Properties and production	Findings
Beta-2 microglobulin (B2mG)	Peptide produce from cellular membrane turnover, particularly elevated with tubular dysfunction or injury	• In term asphyxiated neonates, uB2mG levels were significantly higher in infants with AKI compared to those without AKI and were found to be predictive of **AKI within the first 24 h** after asphyxiation ◦ AKI: 6.8 mg/L vs. ◦ no AKI: 2.6 mg/L, $p < 0.001$ ◦ AUC: 0.944 ◦ Ideal cut off: 3.8 mg/L 81% sensitive 81.6% specific

Renal oximetry for early acute kidney injury detection in neonates with hypoxic ischemic encephalopathy receiving therapeutic hypothermia

HYPOTHESIS: Renal NIRS is a useful clinical tool to evaluate for ongoing kidney injury in neonates with hypoxic ischemic encephalopathy.

DESIGN & OUTCOMES:

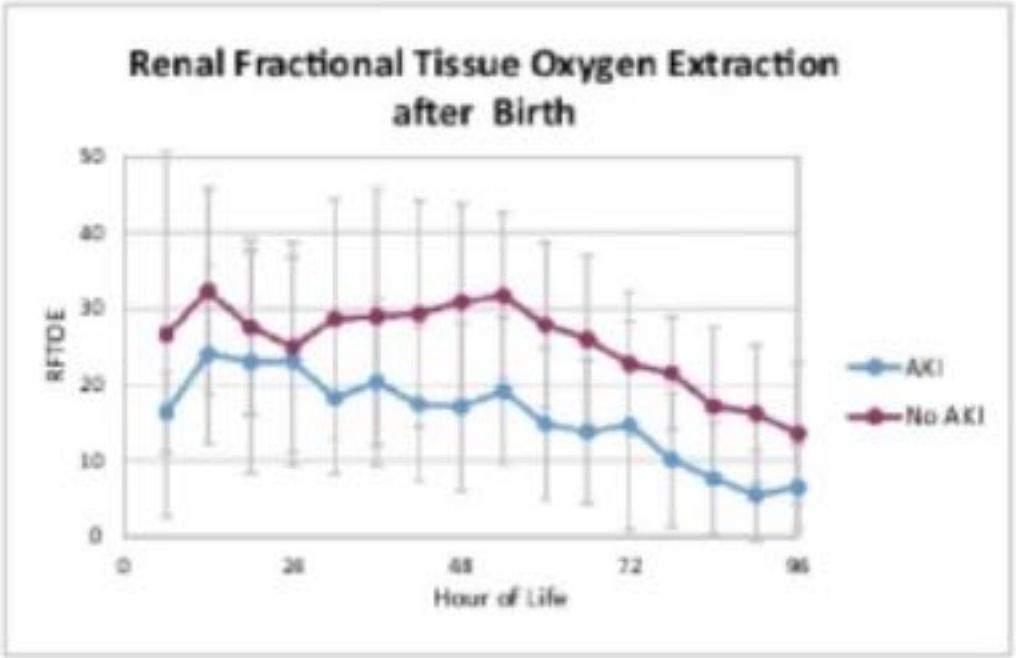
38 Neonates

On therapeutic hypothermia for hypoxic ischemic encephalopathy

2 sites

AKI
In 53% of neonates based on a delayed rate of serum creatinine decline

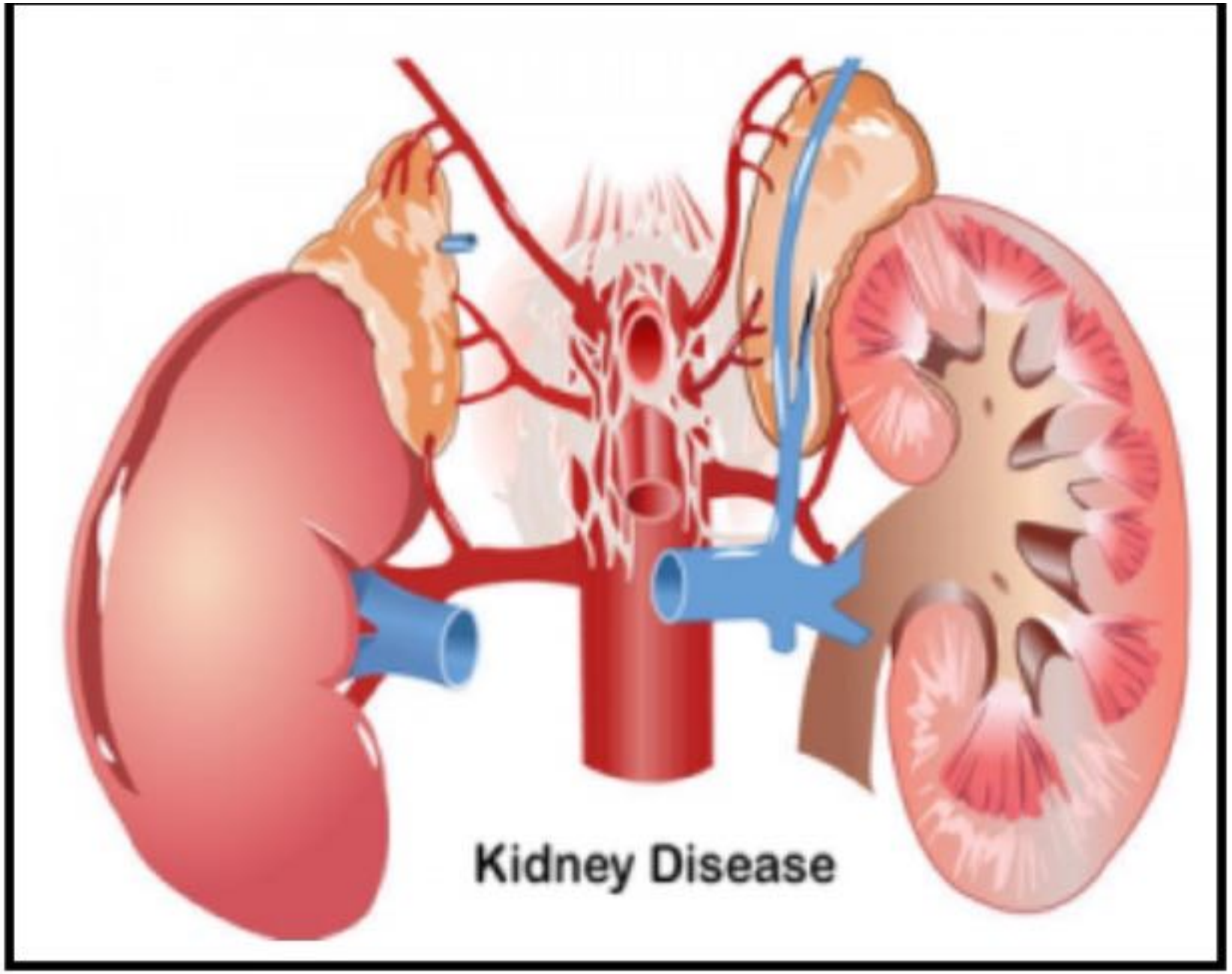
- ▲ **Renal saturations**
- ▼ **Renal fractional tissue oxygen extraction**
- ▼ **pH on first blood gas**



CONCLUSION: Renal NIRS, specifically lower renal fractional tissue oxygen extraction, and a greater level of acidosis on infant first blood gas were early predictors of kidney injury in neonates with hypoxic ischemic encephalopathy receiving therapeutic hypothermia.

Rumpel et al. 2022

Pediatric Nephrology
Journal of the
International Pediatric Nephrology Association
IPNA



PROGNOSIS

Kidney outcomes in early adolescence following perinatal asphyxia and hypothermia-treated hypoxic-ischaemic encephalopathy

HYPOTHESIS: Survivors of perinatal asphyxia and hypothermia-treated HIE may have signs of CKD in early adolescence

DESIGN & OUTCOMES:

Perinatal asphyxia and hypothermia-treated HIE

- No neonatal AKI (n=27)
- Neonatal AKI (n=20)

→ **10 – 12 years**

- GFR
- Albuminuria
- Blood pressure
- Kidney volume
- Plasma FGF 23

→

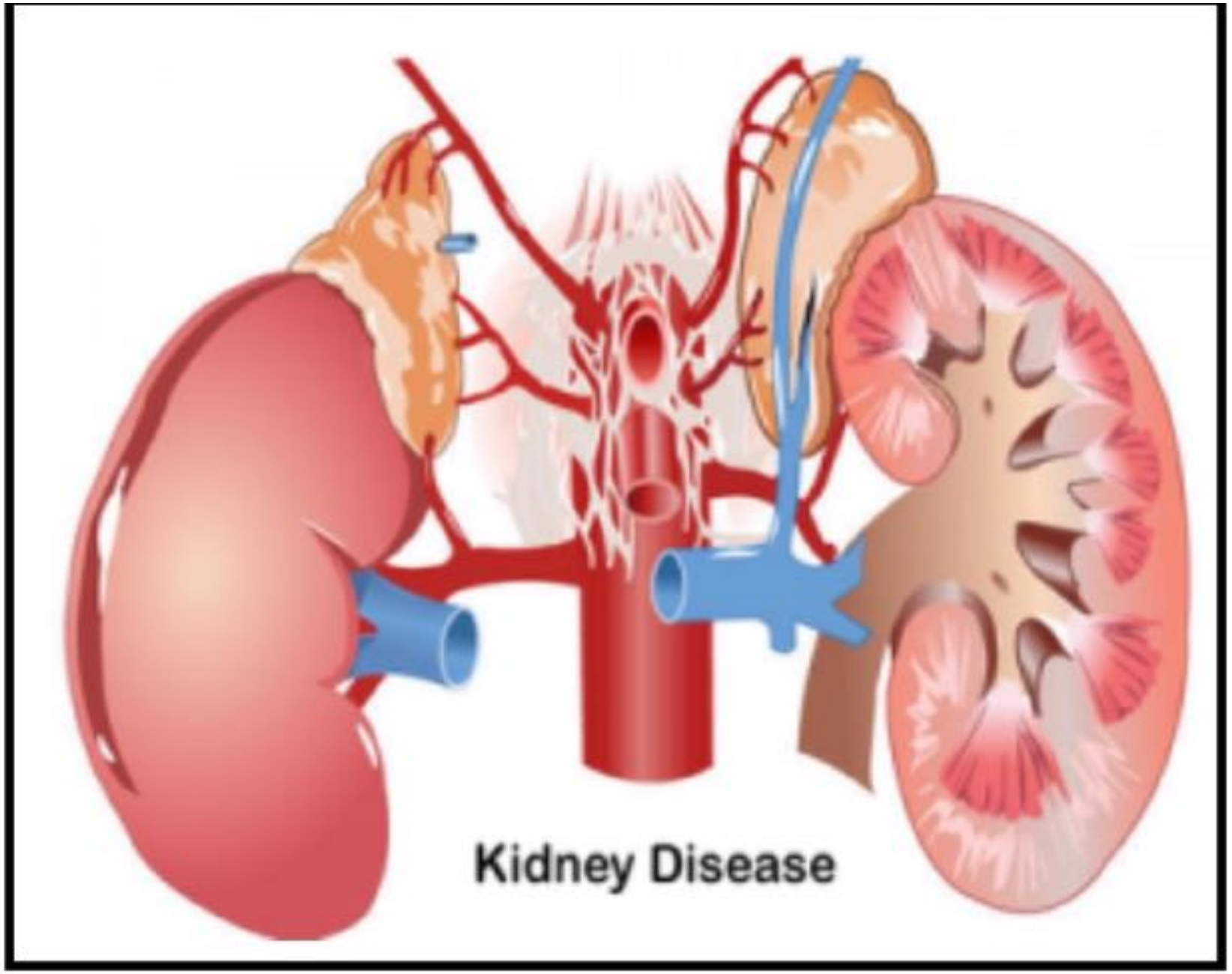
- 1 child with high normal blood pressure
- 1 child with mildly decreased GFR
- 1 child with KDIGO category A2 albuminuria

Prospective population-based study

CONCLUSION: Kidney abnormalities were rare in early adolescence following hypothermia-treated HIE, regardless of presence or absence of a history of neonatal AKI. More studies are needed to elucidate long-term kidney consequences in this patient population.

Robertsson Grossmann et al. 2022

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association



PREVENTION and MITIGATION

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Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **<u>Prevention and Mitigation</u>**

  Risk Stratification

  “renal angina.”

Variables	β coefficient	β coefficient × 10	Score to the nearest integer/100	Assigned score
Age at entry in NICU[a] (h)				
<25.5	1.29	12.9	6	6
≥25.5				0
PPV in the delivery room				
Yes	1.66	16.6	7	7
No				0
Gestational age (weeks)				
<28	1.51	15.1	7	7
≥28				0
Sepsis (during the NICU stay)				
Yes	1.46	14.6	6	6
No				0
Significant cardiac disease				
Yes	2.16	21.6	10	10
No				0
Urine output[a] (ml/kg/h)				
<1.32	1.59	15.9	7	7
≥1.32				0
Serum creatinine[a] (mg/dl)				
≥0.98	4.60	46.0	20	20
<0.98				0
Use of nephrotoxic drugs				
Yes	2.46	24.6	11	11
No				0
Use of furosemide				
Yes	1.96	19.6	9	9
No				0
Use of inotropes				
Yes	3.78	37.8	17	17
No				0

Nephrotoxic drugs included vancomycin or colistin or amphotericin B.
PPV positive pressure ventilation, *NICU* neonatal intensive care unit.
[a]First 12 h post admission in NICU.

STARZ
Neonatal Acute Kidney Injury Stratification Score

Score Assigned To Each Significant Variable Of The Best Fit Model

Validation of the STARZ neonatal acute kidney injury risk stratification score

Graphical Abstract

HYPOTHESIS: STARZ neonatal AKI Risk Prediction Score reliably predicts AKI in admitted neonates

DESIGN & OUTCOMES:

Multicenter, National, Prospective Cohort study
11 centers across India

N = 744 admitted neonates < 28 days [iv fluids x 48 hours]
September 2019-August 2020

- Clinical & demographic variables recorded
- Daily serum creatinine

Validation of STARZ scoring [10 variables; (9 clinical & 1 lab)]

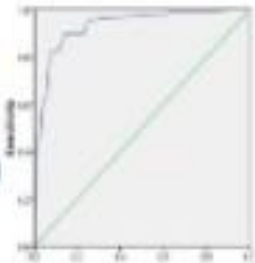
STARZ performance

STARZ cut-off score ≥ 31.5

Prediction of Neonatal AKI

- **Sensitivity 82.1%**
- **Specificity 91.7% p**
- **Positive Predictive Value 81.2%**
- **Negative Predictive Value 92.2%**
- **Accuracy 88.8%**

Area under ROC curve
0.932
(95% CI: 0.910 - 0.954)
[p < 0.001]



CONCLUSION: STARZ neonatal score serves to rapidly and quantitatively determine the risk of AKI in neonates admitted to the neonatal intensive care unit.

Sethi SK, Raina R et al. 2021

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association

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REVIEW
published: 07 April 2022
doi: 10.3389/fped.2022.842544

Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **<u>Prevention and Mitigation</u>**

Nephrotoxic Medications

Acyclovir	Indomethacin
Amikacin	Piperacillin/Tazobactam
Amphotericin B	Vancomycin
Gentamicin	

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- **Prevention and Mitigation**

Nephroprotection : **Methylxanthine Therapy: Theophylline and Caffeine**

Methylxanthines are adenosine-receptor antagonists.

In high risk populations methylxanthines have been shown to prevent the development of AKI by :

preventing adenosine driven pre-glomerular vasoconstriction

preventing post-glomerular vasodilation

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- **Prevention and Mitigation**

Nephroprotection : **Methylxanthine Therapy: Theophylline and Caffeine**

Theophylline has been extensively studied in neonates with HIE.

9 RCT in term neonates with HIE: a single dose of theophylline (5– 8 mg/kg) vs. placebo.

These studies show that theophylline is safe and reduces AKI rates, protects the renal tubule, and improves fluid balance, GFR and urine output.

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Neonatal Acute Kidney Injury

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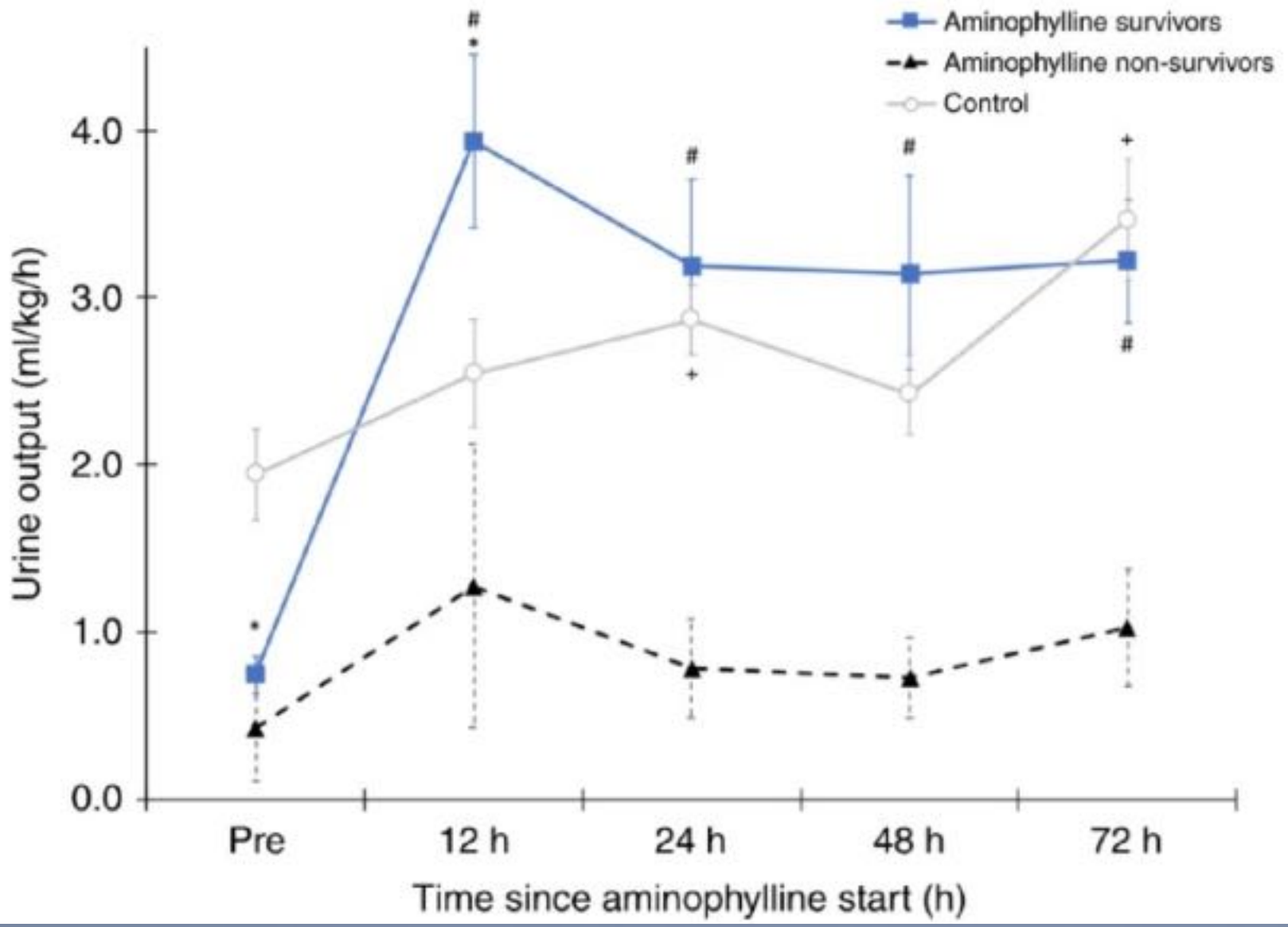
- **Prevention and Mitigation**

Nephroprotection : **Methylxanthine Therapy: Theophylline and Caffeine**

The current KDIGO clinical practice guidelines “suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia who are at high risk for AKI”

Fig. 1: Changes in urine output.



Neonates receiving aminophylline (n = 12 survivors and n = 4 non-survivors) had lower urine output (UOP) during the 12-h period prior to the start of aminophylline compared to an age-matched time period in control patients (n = 16) ($^{*}p < 0.05$ vs. control at time point). A significant increase in UOP from baseline was seen after aminophylline treatment in survivors at all time points ($^{\#}p < 0.001$ vs. "pre" time point) and in control patients at 24 and 72 h ($^{+}p < 0.05$ vs. "pre" time point). UOP was significantly higher during the first 12 h after aminophylline start in survivors compared to control patients ($^{*}p < 0.05$ vs. control at time point), but no differences in UOP between these two groups were seen at later time points. UOP in non-survivors who received aminophylline did not increase significantly over the study period.

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Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **<u>Treatment of Sequelae: Kidney Support Therapy</u>**

The indications for KST in neonates are similar to those in older children and include :

uremia,

electrolyte abnormalities,

metabolic syndromes,

inability to provide adequate nutrition,

the pathologic state of FO.

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Neonatal Acute Kidney Injury

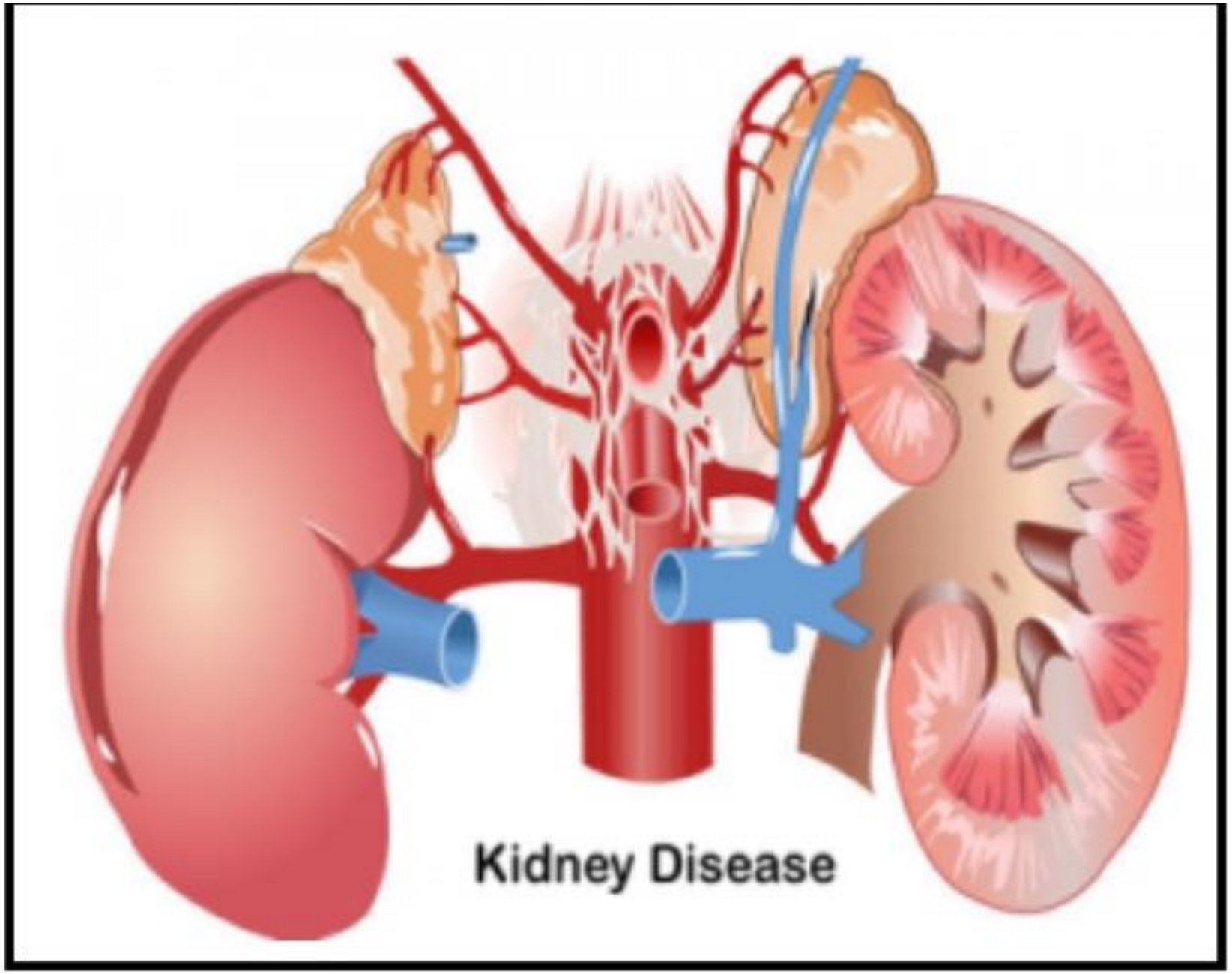
*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **<u>Treatment of Sequelae: Kidney Support Therapy</u>**

The two modalities of KST commonly utilized in neonates are:

peritoneal dialysis (PD)

continuous kidney support therapy (CKST).



NUTRITION

- Nutrition The goal is to provide 100 kcal/kg/day.
- Proteins or amino acids can be provided in a dose of 1-2 g/kg/day.
- Total parenteral nutrition can be provided if baby enteral nutrition cannot be established.
- Full enteral feeding is possible, breast milk can be used.
- Caloric density can be increased by adding corn oil, medium chain triglycerides or maltodextrins.
- If breast milk cannot be given low phosphate formula milk with low renal load can be given.

Hypoglycemia

- A study of 185 term infants with severe fetal acidemia (umbilical arterial pH < 7.00) suggested an important role for postasphyxial postnatal hypoglycemia in the genesis of brain injury.
- Thus 27 (14.5%) of the 185 infants had an initial blood glucose level of 40 mg/dL or lower. Of these 27 infants, 56% (15) had an abnormal neurological outcome, whereas only 16% (26) of the 158 infants with a blood glucose level higher than 40 mg/dL had an abnormal outcome.
- Consistent with these observations, recent MRI studies of infants with postasphyxial hypoxic-ischemic encephalopathy show more frequent and more severe brain injury in infants who had complicating hypoglycemia postnatally than in those who did not.

Terrie E. Inder , Joseph J. Volpe Hypoxic-ischemic and related disorders :Pathophysiology: General Principles VOLPE'S NEUROLOGY OF THE NEWBORN, SIXTH EDITION

- Almost one in three babies who receive therapeutic hypothermia in NHS neonatal units are fed during hypothermia, predominantly with maternal breastmilk.
- Necrotising enterocolitis is rare in these babies, and after matching for an extensive list of background characteristics, pragmatically defined necrotising enterocolitis was diagnosed less frequently in babies fed during therapeutic hypothermia than in babies who were unfed.
- Milk feeding during therapeutic hypothermia was also associated with other beneficial outcomes, including shorter length of neonatal unit stay, higher incidence of breastfeeding, and a lower incidence of suspected infection, all after matching for multiple potential confounding factors

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy Chang L.L et al 2018

Outcomes for babies fed enterally versus not fed enterally during therapeutic hypothermia

	No enteral feeds (n=1618)	Enterally fed (n=1618)	Difference between groups	Estimated odds ratio	p value
Necrotising enterocolitis (pragmatic definition)	1·1% (0·7–1·4)	0·5% (0·2–0·9)	−0·5% (−1·0 to −0·1)	0·50 (0·22–1·12)	0·028
Late-onset infection (National Neonatal Audit Programme definition)	0·5% (0·2–0·7)	0·3% (0·04–0·4)	−0·2% (−0·5 to 0·1)	0·55 (0·17–1·80)	0·19
Late-onset infection (pragmatic definition)	28·4% (26·7–30·0)	16·7% (15·0–18·4)	−11·6% (−14·0 to −9·3)	0·51 (0·43–0·60)	<0·0001*
Hypoglycaemia	18·1% (16·7–19·5)	16·6% (15·0–18·3)	−1·5% (−3·7 to 0·6)	0·90 (0·75–1·08)	0·17
Survival at discharge	90·8% (89·7–91·8)	96·0% (95·0–96·8)	5·2% (3·9–6·6)	2·42 (1·80–3·26)	<0·0001*
Breastfeeding at discharge	46·7% (44·8–48·5)	54·6% (52·4–56·8)	8·0% (5·1–10·8)	1·38 (1·20–1·58)	<0·0001*
Length of stay, days	14·8 (14·2–15·5)	12·7 (12·0–13·3)	−2·2 (−3·0 to −1·2)	NA	<0·0001*
Onset of breastfeeding, days†	8·7 (8·4–9·0)	7·3 (6·9–7·7)	−1·4 (−1·9 to −0·9)	NA	<0·0001*
First maternal milk, days‡	5·4 (5·4–5·5)	3·3 (3·2–3·4)	−2·1 (−2·2 to −2·0)	NA	<0·0001*
Duration of parenteral nutrition, days	3·7 (3·5–3·8)	3·0 (2·7–3·4)	−0·7 (−1·1 to −0·2)	NA	0·0018*
Duration of central venous line, days	5·5 (5·3–5·7)	4·3 (4·1–4·5)	−1·2 (−1·5 to −0·9)	NA	<0·0001*
Weight-for-gestational-age SD score at discharge from neonatal unit	−0·60 (−0·65 to −0·55)	−0·54 (−0·59 to −0·48)	0·06 (−0·01 to −0·13)	NA	0·11

Data are estimated odds ratio (95% CI). Results were averaged over the 25 replications of the matching procedure. NA=odds ratio could not be estimated for continuous data. *Outcome measure remains statistically significant after accounting for multiple testing using the Bonferroni correction. †Breastfeeding refers to suckling at the breast and does not include babies that received expressed breastmilk by bottle. ‡First maternal milk includes receipt of maternal breastmilk by bottle.

Gale C .et al, Feeding during neonatal therapeutic hypothermia, assessed using routinely collected National Neonatal Research Database data: a retrospective, UK population-based cohort study Lancet Child Adolesc Health 2021; 5: 408–16

- Kidney injury is a very common complication of HIE.
- Avoidance of hypotension during HIE is extremely important in mitigating kidney injury in HIE .
- Kidney in injury in HIE do have long term consequences.
- Therapeutic hypothermia has got a beneficial effects not only on the brain but also on the kidneys.
- New markers of renal injury are available and need further evaluation

- Methyl xanthines have got a definit role in attenuating kidney injury.
- Renal replacement therapy could be life saving.
- Kidney injury in HIE is an important independent risk factor for worse prognosis.
- Proper nutrition is essential during therapeutic hypothermia.

THANK YOU

MERCI

GRAZIE

- Energy requirements are a function of the sum of the oxygen consumption rates of all of the organs in the body.
- Each organ has different energy requirements.
- The brain of nn consumes an astounding 60% of total body metabolism, far out of proportion to other mammals.
- Heart has high metabolic rate, whereas lungs and kidneys do not.
- Ds of organs with high BMR disproportionately increase the total body oxygen consumption and thus total energy demand.
- Thus, heart failure and recurrent or ongoing seizures increase energy requirements by approximately 30%.

The Impact of Neonatal Illness on Nutritional Requirements— One Size Does Not Fit All Ramel S., Brown L. and Georgieff M.2014

Feeding during therapeutic hypothermia

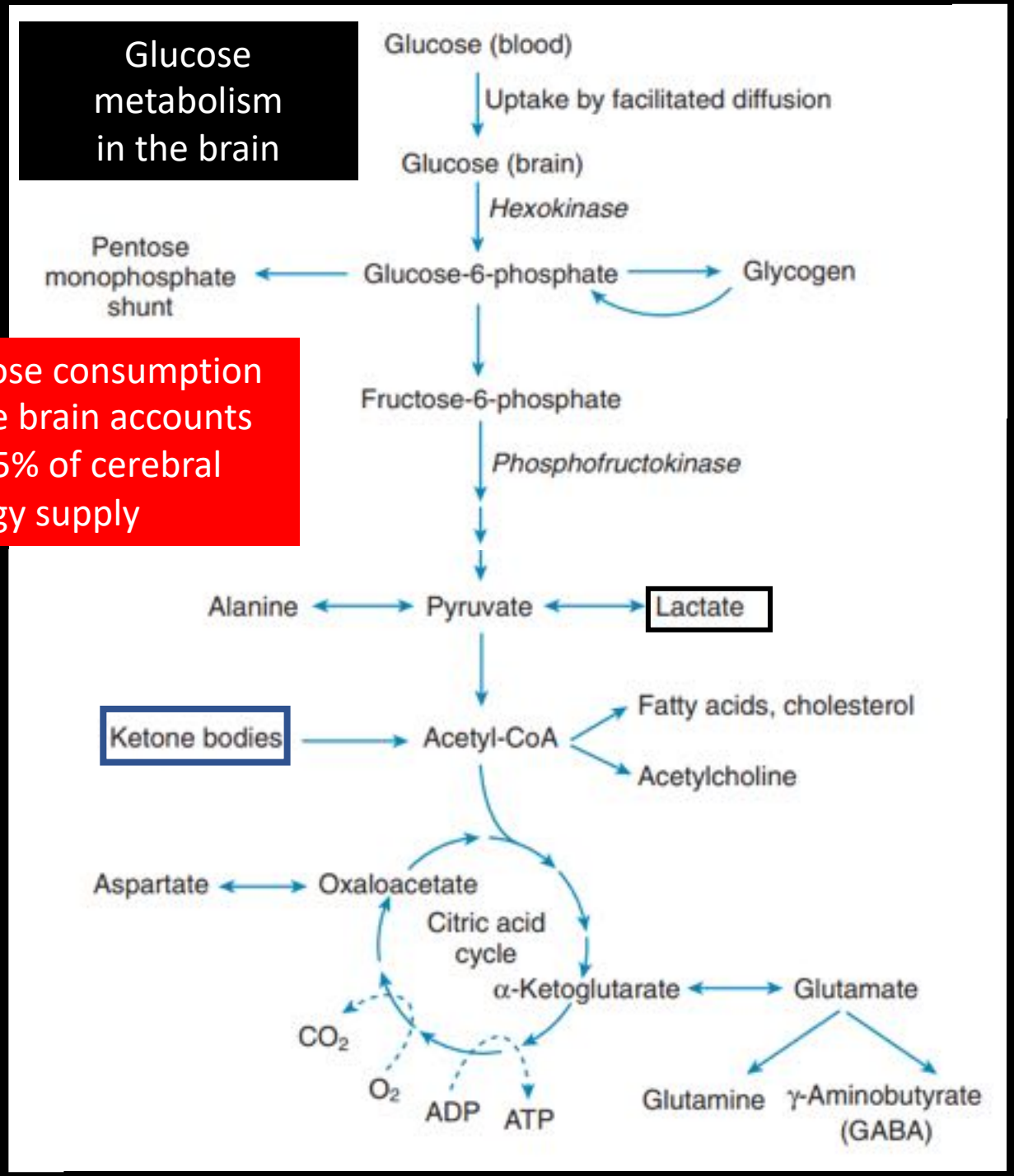
Dr Hisham Awad

Ain Shams University

Principles Of Nutritional Requirements

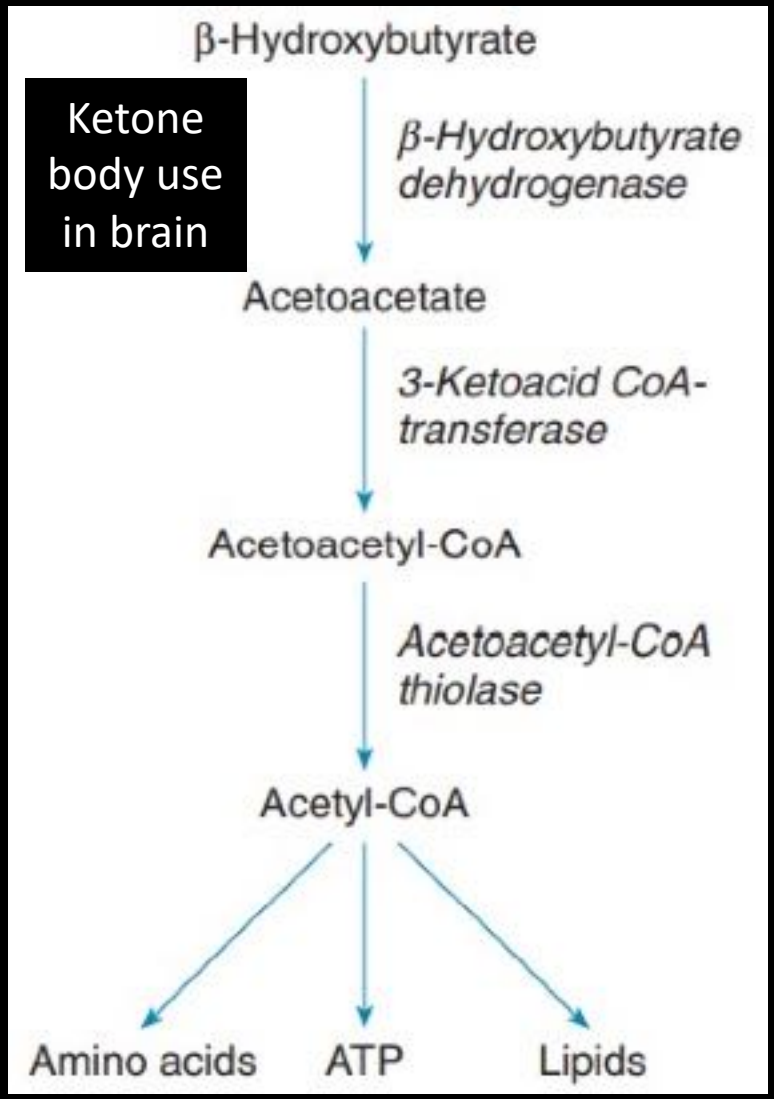
Nutrition of the Brain

Glucose metabolism in the brain



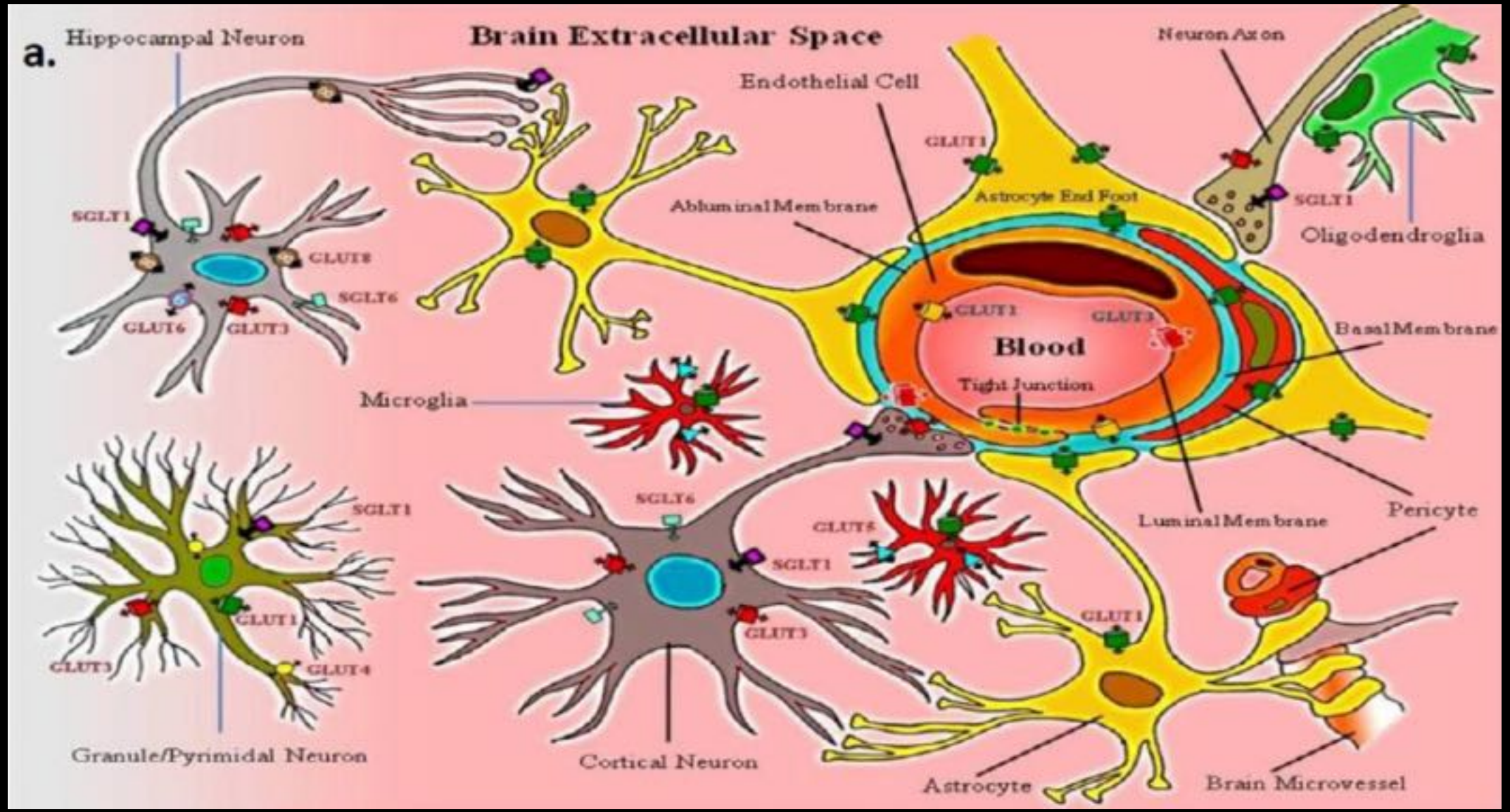
Glucose consumption in the brain accounts for 95% of cerebral energy supply

Ketone body use in brain



Nutrition of the Brain: Glucose

- Glucose Uptake Glucose from blood is taken up by the brain through a process of carrier-mediated, facilitated diffusion
- Specific glucose transporter proteins are involved.
- The transport process is not energy-dependent.
- Glucose transport across the blood-brain barrier uses the heavily glycosylated form of the facilitative glucose transporter protein, GLUT1 (55 kDa).
- Transport across glial membranes is facilitated by the lower molecular form of GLUT1 (45 kDa)
- Transport across the neuronal membrane is facilitated by GLUT3.
- The levels of these proteins are relatively low in the immature brain and are limiting to glucose transport and utilization.


a.
Hippocampal Neuron
Brain Extracellular Space
Endothelial Cell
Neuron Axon
GLUT1
Astrocyte End Foot
SGLT1
Abluminal Membrane
Oligodendroglia
SGLT1
GLUT8
SGLT6
GLUT6
GLUT3
GLUT1
GLUT3
Blood
Basal Membrane
Tight Junction
Microglia
Luminal Membrane
Pericyte
SGLT1
SGLT6
GLUT5
SGLT1
GLUT1
GLUT3
GLUT3
GLUT4
GLUT1
Granule/Pyrimidal Neuron
Cortical Neuron
Astrocyte
Brain Microvessel

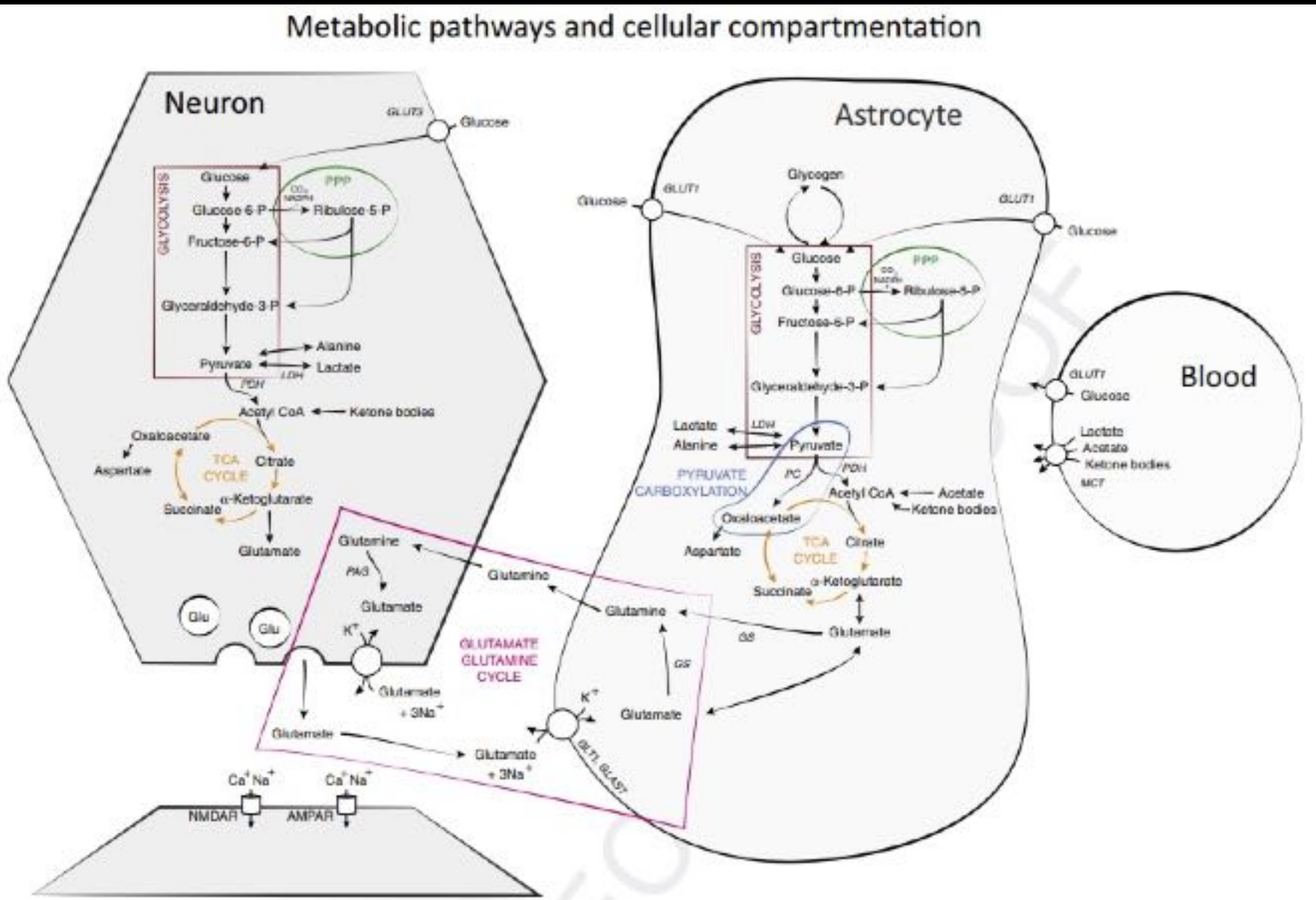


Fig. 1. Illustration of the pathways studied and compartmentation of metabolism in neurons and astrocytes. Associated pathways, metabolites, enzyme activities and pathway activities are marked with corresponding colors in Figs. 1–4. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GLAST, glutamate aspartate transporter; Glu, glutamate; GLT1, glutamate transporter 1; GLUT, glucose transporter; GS, glutamine synthetase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NMDAR, *N*-methyl-D-aspartate receptor; PAG, phosphate activated glutaminase; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PPP, pentose phosphate pathway.

- ATP generated is transported from the mitochondrion by a specific carrier.
- It is used in the brain for two major purposes:
  - **transport**
  - **synthetic processes**.
- Quantitatively, the most important **transport** processes involve ions in neurons for impulse transmission(Sodium and potassium) and maintenance of Ca2+ homeostasis.
- Aproximately 60% to 75% of ATP is used for maintenance of membrane gradients of these three ions, especially Na+ and K+
- **Synthetic processes** are important in the developing brain and involve neurotransmitters, structural and functional proteins, and membrane lipids

Nutrition of the Brain: Glycogen

- Glycogen is found in relatively small concentrations in the brain but represents an important storage form of carbohydrate.
- Glycogen synthesis and degradation occur primarily in astrocytes.
- Glycogen in astrocytes provides fuel to neurons first by conversion to lactate and then transport of lactate to neurons.
- By a similar mechanism, astrocytes degrade glycogen to lactate that is provided to developing oligodendrocytes, primarily for lipid biosynthesis.

Hypoxic Ischemic Encephalopathy

Definition

- Hypoxic-ischemic encephalopathy (**HIE**) is a type of newborn brain damage caused by oxygen deprivation and limited blood flow.

- Hypoxic-ischemic encephalopathy (HIE) is a significant cause of morbidity and mortality in neonates.

- The incidence of HIE ranges from 1 to 8 per 1,000 live births in developed countries to as high as 26/1,000 live births in underdeveloped countries

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy Chang L.L et al 2018

- The pathophysiology of hypoxic-ischemic brain injury is multifactorial.
- An inflammatory response may be generated in the brain locally or because of systemic inflammation.
- While the exact source of inflammation is unknown, patients who have had major surgery, trauma, or burns show a significant systemic inflammatory response due to **intestine-derived inflammation secondary to ischemic injury.**

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy Chang L.L et al 2018

Major Mechanisms for Biochemical Effects of Hypoxemia on Carbohydrate and Energy Metabolism

↑ **Glucose influx to brain**
Link to accelerated glucose utilization
↑ **Glycogenolysis**
Phosphorylase activation (↑ cAMP)
↑ **Glycolysis**
Phosphofructokinase activation (↑ cAMP, ↑ ADP, ↑ P_i, ↓ ATP, ↓ phosphocreatine)
Hexokinase activation (↑ cAMP)
↓ **Brain glucose**
Glucose utilization > glucose influx
↑ **Lactate (and hydrogen ion)**
Anaerobic glycolysis
Impaired utilization of pyruvate (through mitochondrial citric acid cycle–electron transport system)
↓ **Phosphocreatine**
↑ Hydrogen ion production through anaerobic glycolysis
↓ ATP, ↑ ADP
↓ **ATP**
↓ Oxidative phosphorylation

ADP, Adenosine diphosphate; *ATP*, adenosine triphosphate; *cAMP*, cyclic adenosine monophosphate; P_i, inorganic phosphate.

The limited availability of energy for neuronal functions is not the same in all brain regions

Propensity Of Neonatal Cerebral White Matter To Hypoxic Injury

- It appears that anaerobic glycolysis with its accelerated glucose utilization was capable of preserving the energy state in gray matter but not in white matter.
- Glucose levels declined more drastically in white matter than in gray matter.
- Glucose influx could not meet the increased demands for glucose in white matter.
- The local CBF increased insignificantly in relation to **white matter** but dramatically in relation to **gray matter.**
- This is due to apparently limited vasodilatory capacity in white matter.
- This imbalance between glucose needs and glucose delivery may contribute to the propensity of neonatal cerebral white matter to hypoxic injury.

Hypoglycemia: Hypoglycemia and Ischemia Enhanced Vulnerability of the Hypoglycemic Brain to Ischemic Insult in Animals

- The vulnerability of the brains of mature animals to ischemic insult is enhanced by concomitant hypoglycemia.
- Increases of mortality, acute neurological phenomena (e.g., seizures), and neurological deficits in survivors were apparent in the hypoglycemic versus normoglycemic animals.
- The diminished glucose reserves in the hypoglycemic brain were unable to maintain the accelerated glycolytic flux necessary to maintain cerebral energy reserves under anaerobic (ischemic) conditions. (Recall the 19-fold difference in ATP production from glucose metabolism under anaerobic versus aerobic conditions.

Terrie E. Inder , Joseph J. Volpe Hypoxic-ischemic and related disorders :Pathophysiology: General Principles VOLPE'S NEUROLOGY OF THE NEWBORN, SIXTH EDITION

Hypoglycemia

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- Thus 27 (14.5%) of the 185 infants had an initial blood glucose level of 40 mg/dL or lower. Of these 27 infants, 56% (15) had an abnormal neurological outcome, whereas only 16% (26) of the 158 infants with a blood glucose level higher than 40 mg/dL had an abnormal outcome.
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Hypoglycemia

- Forty-one (22%) infants developed an abnormal neurologic outcome:
  - 14 (34%) with severe hypoxic ischemic encephalopathy (HIE) died
  - 24(59%) with moderate to severe HIE
  - three (7%) with seizures.
- By multivariate logistic analysis, four variables were significantly associated with abnormal outcome:
  - initial blood glucose 40 versus > 40 mg/dL [p Z 0.001, odds ratio (OR) 18.5 being the most significant
  - cord arterial pH 6.90 versus > 6.90, OR 9.8 (p Z 0.003)
  - a 5-minute Apgar score 5 versus > 5 (p Z 0.006, OR 6.4)
  - the requirement for intubation cardiopulmonary resuscitation (CPR) versus neither (p Z 0.02, OR 4. 7) 1.2e17.9) being less so.
- These data suggest that hypoglycemia is an important risk factor for perinatal brain injury, particularly in depressed term infants with severe fetal academia who require resuscitation. Thus, in the ongoing management of hypoxiae-ischemia, a glucose level should be screened shortly after birth and monitored closely. If the blood glucose is low it should be corrected promptly.

Terrie E. Inder , Joseph J. Volpe Hypoxic-ischemic and related disorders :Pathophysiology: General Principles VOLPE'S NEUROLOGY OF THE NEWBORN, SIXTH EDITION

Prognosis and Management

- Among survivors, ≥25% show permanent neuropsychological handicaps, in the form of cerebral palsy with or without associated mental retardation, learning disabilities, or epilepsy.
- Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe HIE.
- However, a majority of babies treated with hypothermia will have neurodevelopmental impairments

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy Chang L.L et al 2018

A key factor in improving the prognosis is by avoiding fluctuations in blood sugar

This can be achieved by proper nutrition especially during therapeutic hypothermia which should be initiated as early as possible

- Which dietary modifications are included in the treatment of hypoxic-ischemic encephalopathy (HIE)?
- Updated: Jul 18, 2018
- Author: Santina A Zanelli, MD; Chief Editor: Dharmendra J Nimavat, MD, FAAP more...

- As such, in the USA, it is common practice to withhold enteral feeding during hypothermia based on concerns of developing necrotizing enterocolitis or feeding intolerance.

- Strong evidence for this clinical practice does not exist.

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy Chang L.L et al 2018

- In most cases (particularly in severe hypoxic-ischemic encephalopathy [HIE]), the infant is restricted to nothing by mouth (NPO) until the general level of alertness and consciousness improves and the hemodynamic status stabilizes.
- In addition, most infants undergoing therapeutic hypothermia should remain NPO until rewarmed.
- A study of 51 neonates with HIE indicated that minimal enteral nutrition (1-2 mL/kg boluses every 3h) may be safe in hemodynamically stable infants undergoing therapeutic hypothermia.

- Enteral feeds should be carefully initiated, and the use of trophic feeds is recommended for 24-48 hours (2 mL/kg every 3 h). Infants should be monitored carefully for signs and symptoms of necrotizing enterocolitis, for which infants with perinatal asphyxia are at high risk. Individualize increments in feeding volume and composition.

Parenteral nutrition-I-

- In high-income settings, infants who receive therapeutic hypothermia receive some form of intravenous fluid support: commonly intravenous dextrose with electrolytes as required, or parenteral nutrition.
- Hazeldine et al found that 29% (14/49) of responding UK neonatal units report routine use of parenteral nutrition.
- While dextrose provides sufficient carbohydrate energy to prevent hypoglycaemia, it does not limit catabolism as effectively as parenteral nutrition.
- This is the rationale for giving parenteral nutrition to infants receiving therapeutic hypothermia: to improve overall growth, brain growth and potentially neurodevelopment—although we note that this conjecture is not backed up by any human studies.

Optimising nutrition during therapeutic hypothermia Shalini Ojha, Jon Dorling, Cheryl Battersby, Nicholas Longford, Chris Gale Arch Dis Child Fetal Neonatal Ed May 2019 Vol 104 No 3

Parenteral nutrition-II-

- Studies in adults.
- The Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial reached a conclusion that early provision of parenteral nutrition may be harmful. This trial randomised 1440 critically ill children (including 209 term neonates) to receive parenteral nutrition within 24hours of admission, or for parenteral nutrition to be delayed for 7days.
- While mortality rates were similar in the two groups, children who had parenteral nutrition withheld for 7days had a significantly lower rate of new infection (10.7% vs 18.5%).
- A preplanned secondary analysis of the 209 term neonates included in the PEPaNIC trial confirmed lower likelihood of infection and higher rate of survival to discharge in infants for whom parenteral nutrition was withheld, but at the cost of an increased risk of hypoglycaemia.

Optimising nutrition during therapeutic hypothermia Shalini Ojha, Jon Dorling, Cheryl Battersby, Nicholas Longford, Chris Gale Arch Dis Child Fetal Neonatal Ed May 2019 Vol 104 No 3

Parenteral nutrition

Early Versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC)

- Secondary observational analyses of the PEPaNIC trial indicate that early provision of parenteral amino acids could explain the worse clinical outcomes in the intervention group
- The risk of all studied outcomes gradually increased up to a median daily amino acid dose of 1.15 g/kg (IQR 1.10-1.22), representing 40-50% of reference doses for age and weight. However, higher doses did not further increase the risk of harm.
- The authors discuss whether this negative effect of parenteral amino acids is caused by the suppression of autophagy, an amino acid load above the metabolic capacity of the liver and kidneys or a suboptimal composition of the amino acid formulations used.
- Interestingly, higher average doses of lipids were associated with a greater likelihood of earlier live discharge and with a greater likelihood of earlier live weaning from mechanical ventilation in the neonates.
- These findings support the notion that lipids play an important role during critical illness. Higher plasma 3- hydroxybutyrate (3HB) and lower blood glucose concentrations were also associated with earlier weaning from mechanical ventilator support and live discharge.
- The ketogenic fasting response in the late PN group was however not associated with new infections.

Nutritional Management of the Critically Ill Neonate: A Position Paper of the ESPGHAN Committee on Nutrition Moltu et al .JPGN Volume 73, Number 2, August 2021

What about enteral nutrition?

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Necrotising enterocolitis (pragmatic definition)	1·1% (0·7–1·4)	0·5% (0·2–0·9)	−0·5% (−1·0 to −0·1)	0·50 (0·22–1·12)	0·028
Late-onset infection (National Neonatal Audit Programme definition)	0·5% (0·2–0·7)	0·3% (0·04–0·4)	−0·2% (−0·5 to 0·1)	0·55 (0·17–1·80)	0·19
Late-onset infection (pragmatic definition)	28·4% (26·7–30·0)	16·7% (15·0–18·4)	−11·6% (−14·0 to −9·3)	0·51 (0·43–0·60)	<0·0001*
Hypoglycaemia	18·1% (16·7–19·5)	16·6% (15·0–18·3)	−1·5% (−3·7 to 0·6)	0·90 (0·75–1·08)	0·17
Survival at discharge	90·8% (89·7–91·8)	96·0% (95·0–96·8)	5·2% (3·9–6·6)	2·42 (1·80–3·26)	<0·0001*
Breastfeeding at discharge	46·7% (44·8–48·5)	54·6% (52·4–56·8)	8·0% (5·1–10·8)	1·38 (1·20–1·58)	<0·0001*
Length of stay, days	14·8 (14·2–15·5)	12·7 (12·0–13·3)	−2·2 (−3·0 to −1·2)	NA	<0·0001*
Onset of breastfeeding, days†	8·7 (8·4–9·0)	7·3 (6·9–7·7)	−1·4 (−1·9 to −0·9)	NA	<0·0001*
First maternal milk, days‡	5·4 (5·4–5·5)	3·3 (3·2–3·4)	−2·1 (−2·2 to −2·0)	NA	<0·0001*
Duration of parenteral nutrition, days	3·7 (3·5–3·8)	3·0 (2·7–3·4)	−0·7 (−1·1 to −0·2)	NA	0·0018*
Duration of central venous line, days	5·5 (5·3–5·7)	4·3 (4·1–4·5)	−1·2 (−1·5 to −0·9)	NA	<0·0001*
Weight-for-gestational-age SD score at discharge from neonatal unit	−0·60 (−0·65 to −0·55)	−0·54 (−0·59 to −0·48)	0·06 (−0·01 to −0·13)	NA	0·11

Data are estimated odds ratio (95% CI). Results were averaged over the 25 replications of the matching procedure. NA=odds ratio could not be estimated for continuous data. *Outcome measure remains statistically significant after accounting for multiple testing using the Bonferroni correction. †Breastfeeding refers to suckling at the breast and does not include babies that received expressed breastmilk by bottle. ‡First maternal milk includes receipt of maternal breastmilk by bottle.

Gale C .et al, Feeding during neonatal therapeutic hypothermia, assessed using routinely collected National Neonatal Research Database data: a retrospective, UK population-based cohort study Lancet Child Adolesc Health 2021; 5: 408–16

- In adults, a delay in enteral nutrition both after trauma and surgery increases mortality, presumed secondary to bacterial translocation from the gut, sepsis, and an increased likelihood of systemic inflammatory response.
- This finding supports the concept that the inflammatory response in the gut can be a “motor” for systemic inflammation.
- Neonatal brain injury from HIE may occur in the setting of pathologic cytokine and chemokine production via neuroinflammatory pathways

Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy. Chang L.L.et al Neonatology 2018;113:347–352

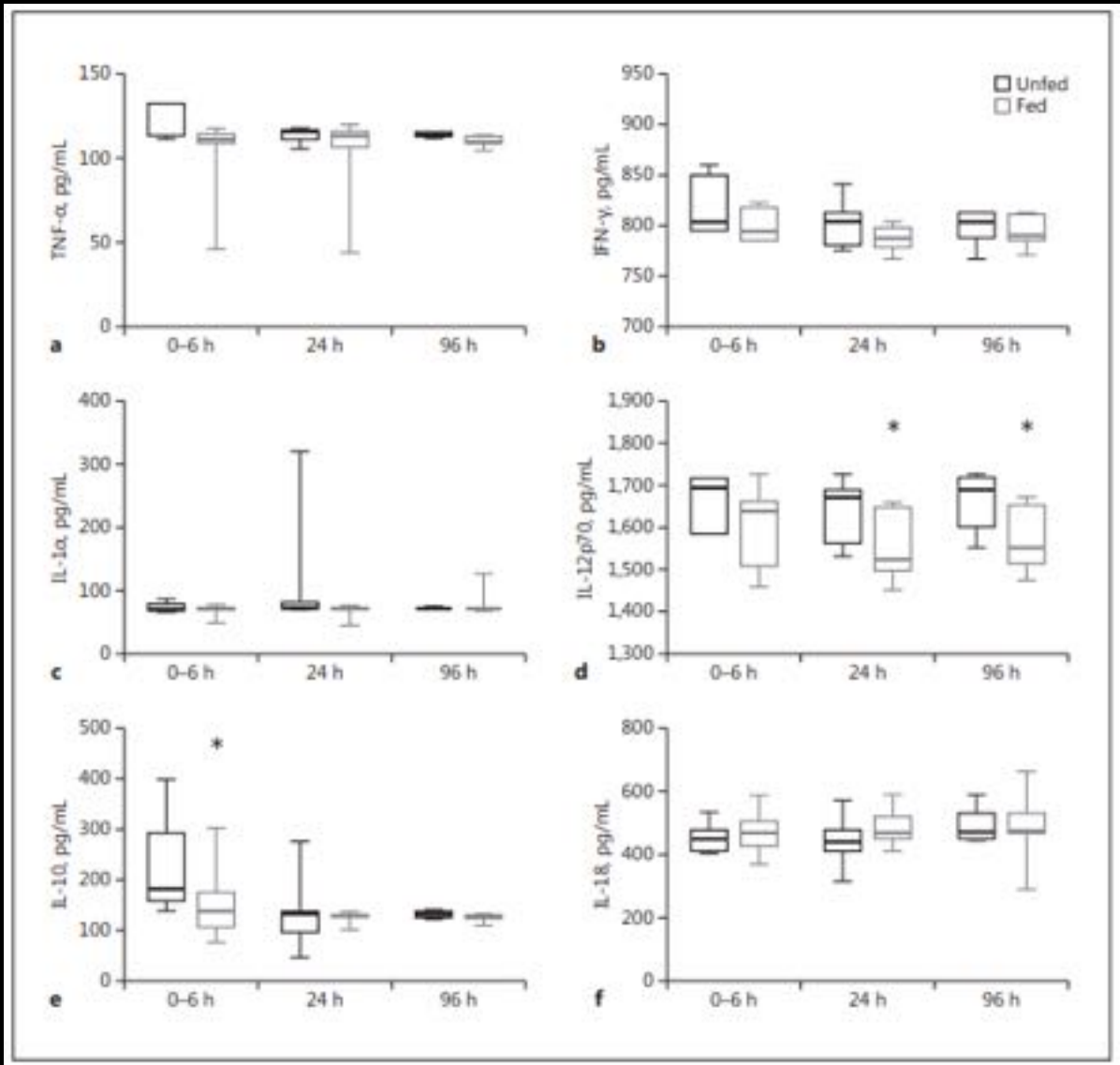


Fig. 1. Box-whisker plots for the inflammatory cytokines in the MEN group versus the unfed group are shown for TNF-α (**a**), INF-γ (**b**), IL-1α (**c**), IL-12p70 (**d**), IL-10 (**e**) and IL-18 (**f**) at 0–6, 24, and 96 h. The concentration of IL-10 was lower in the MEN group at 0–6 h (* $p = 0.02$). IL-12p70 concentrations were lower in HIE neonates fed during hypothermia than in those that were not fed, at 24 and 96 h of life (* $p < 0.05$).

No differences between the 2 groups at any time point for IL-1β, IL-2, IL-6, IL-8, IL-13, TNF-α, MCP-1, MIP-1α, and IP-10. Serum **IL-12p70 concentrations were reduced** in neonates with HIE that received MEN during hypothermia compared to those who were unfed.

IL-12 is a proinflammatory and prostimulatory cytokine with a key role in the development of Th1 cells .

Take Home Message

- Nutrition during therapeutic hypothermia is important.
- Maintenance o normal glycemia is of primordial importance.
- Parenteral nutrition should be used judiciously with minimal I.V. protein and emphasis on intravenous lipids.
- Enteral nutrition is not only without harm but may be of great importance in mitigating the intestinal induced systemic inflammatory response.
- Do every effort to resort to freshly expressed maternal milk


THANK

- Overall, necrotising enterocolitis is rare in term and near-term babies receiving therapeutic hypothermia and might be less common in babies who were fed during therapeutic hypothermia. The introduction of enteral feeds in term and near-term babies during therapeutic hypothermia appears to be safe and might be associated with benefits, including a higher proportion of babies breastfeeding at discharge, and shorter length of neonatal unit stay

-).Mild to moderate hypothermia is known to be protective against intestinal ischaemia reperfusion injury(17). There is strong experimental evidence that HT ameliorates liver energy failure(18), attenuates lung neutrophil infiltration(19), preserves cardiac metabolism(20) and prolongs survival(18) when moderate HT is applied after intestinal ischemia reperfusion. Therapeutic hypothermia is, in fact, now being explored as a treatment option following NEC(21). However, NEC is a main concern following HIE. In our study, no cases of NEC were observed.

Glucose as the Primary Metabolic Fuel for Brain

- The role of glucose as the primary fuel for the production of chemical energy and the maintenance of normal function in the mature brain are supported by three main facts.26,28,37,38 First, the respiratory quotient (i.e., carbon dioxide output/oxygen uptake) of the brain is approximately 1, a finding indicating that carbohydrate is the major substrate oxidized by neural tissue. Glucose is the only carbohydrate extracted by the brain in any significant quantity. Second, cerebral glucose uptake is almost completely accounted for by cerebral oxygen uptake. Third, central nervous system function is rapidly and seriously disturbed by hypoglycemia

Terrie E. Inder , Joseph J. Volpe Hypoxic-ischemic and related disorders :Pathophysiology: General Principles VOLPE'S NEUROLOGY OF THE NEWBORN, SIXTH EDITION

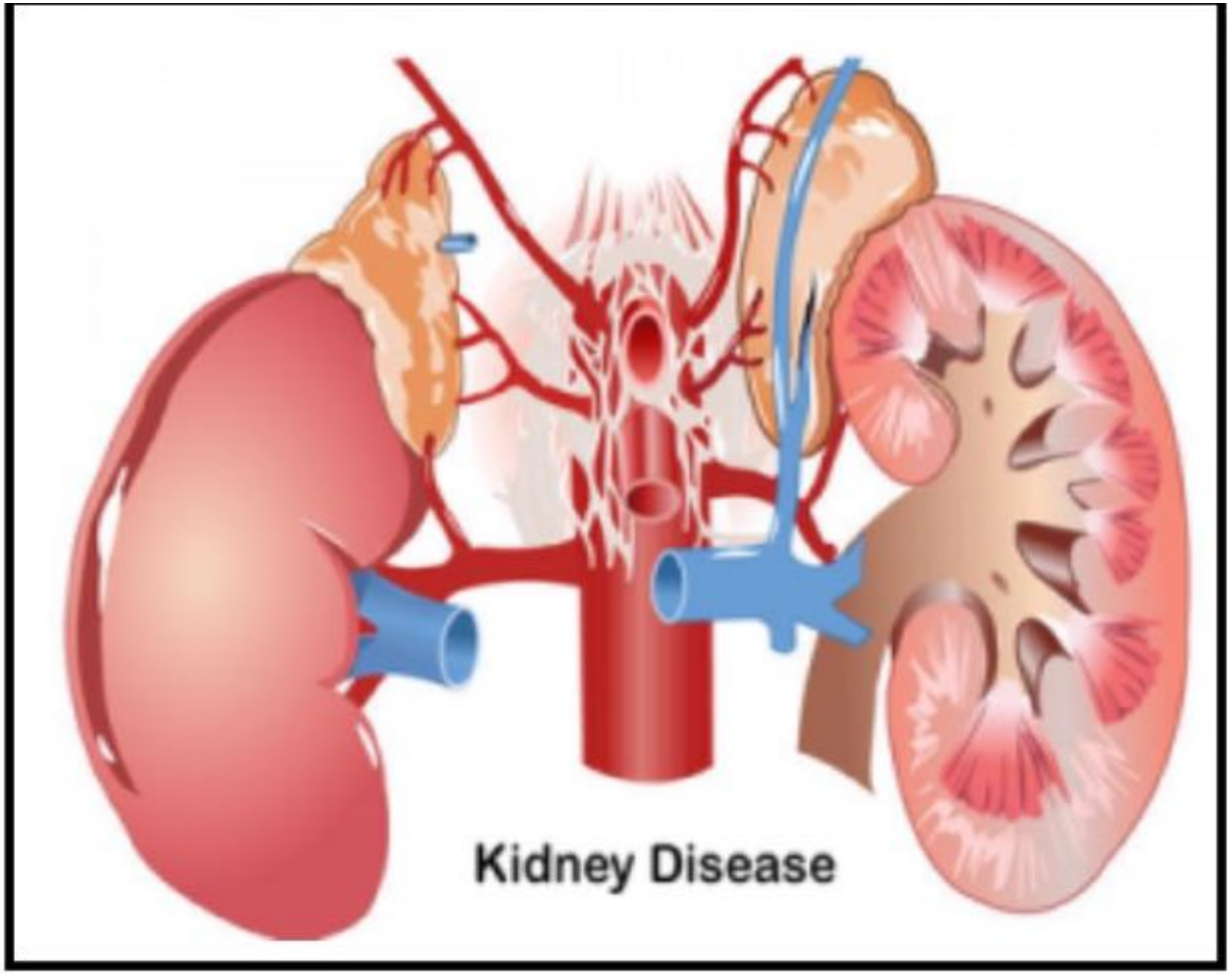
- It is now clear that hypoxic-ischemic insults may lead to necrosis or apoptosis, or more commonly a continuum, dependent principally on the severity of the insult and the maturational state of the cell.

Glucose

- The primary determinant of weight gain in the neonate is energy intake, as carbohydrate and fat, that exceeds resting energy expenditure in a protein-sufficient environment. Carbohydrates, particularly glucose, are the main fuel source for the brain. The human has a peculiarly high brain energy demand among mammals, accounting for an estimated 50% of total body oxygen consumption.

Sara E. Ramel · Michael K. Georgieff Preterm Nutrition and the Brain Koletzko B, Poindexter B, Uauy R (eds): Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2014, vol 110, pp 190–200 (DOI: 10.1159/000358467)

- d. The ATP generated by the citric acid cycle and the electron transport system is transported from the mitochondrion by a specific carrier and ultimately is used in the brain primarily for transport processes (especially of ions and neurotransmitters for impulse transmission and for the prevention of dangerous increases thereof; e.g., extracellular glutamate, cytosolic Ca2+) and for synthetic processes (especially of neurotransmitters, but also lipids and proteins, particularly in the developing brain). The principal ions involved in ATP consumption are sodium (Na+), potassium (K+), and Ca2+ ; in the adult brain (under normal conditions), approximately 60% to 75% of ATP is used for maintenance of membrane gradients of these three ions, especially Na+ and K+



FOLLOW UP

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REVIEW
published: 07 April 2022
doi: 10.3389/fped.2022.842544

Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- **Follow up**

All neonates with an identified AKI episode should have longitudinal follow-up.

KDIGO guidelines recommend patients with a history of AKI have a CKD evaluation 3 months after their AKI event

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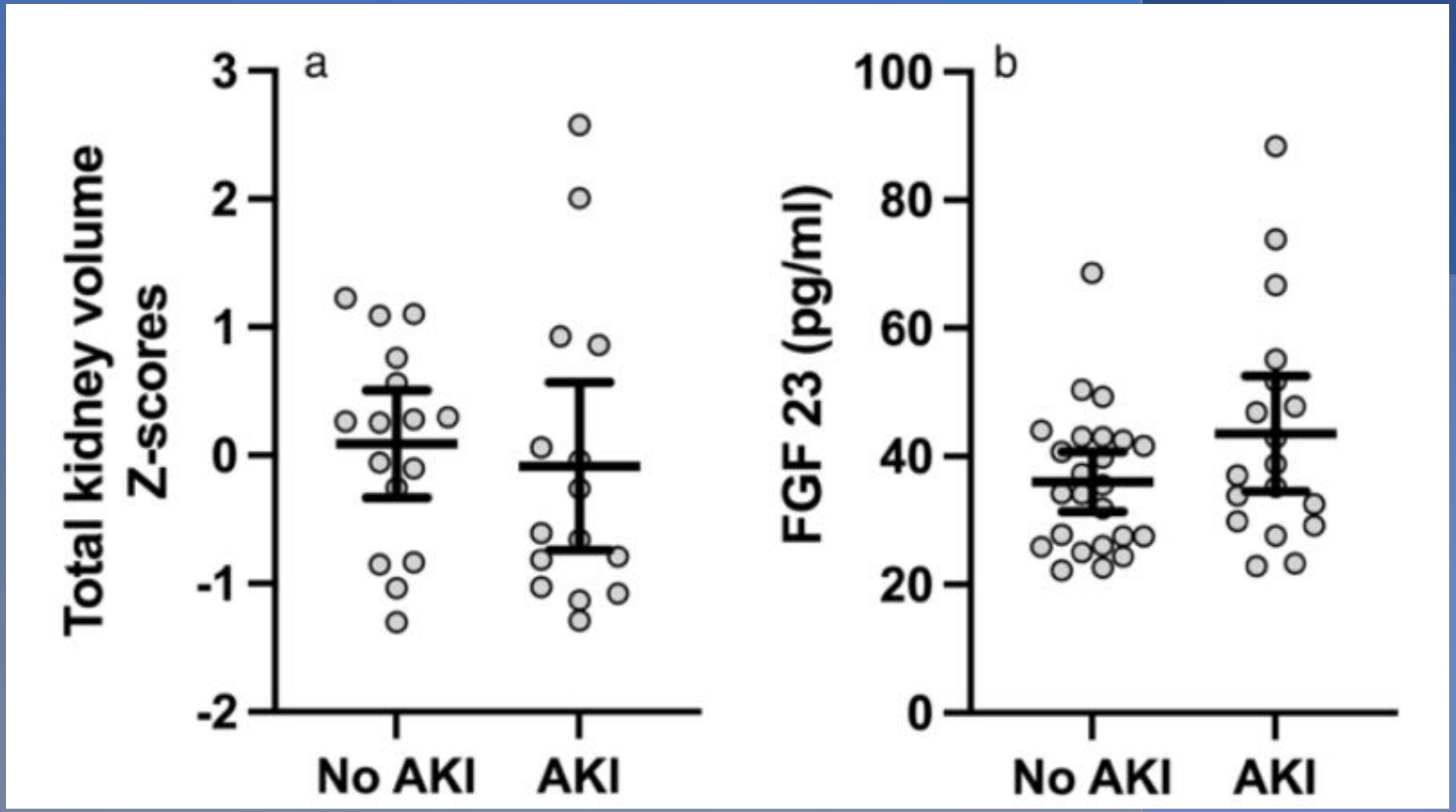
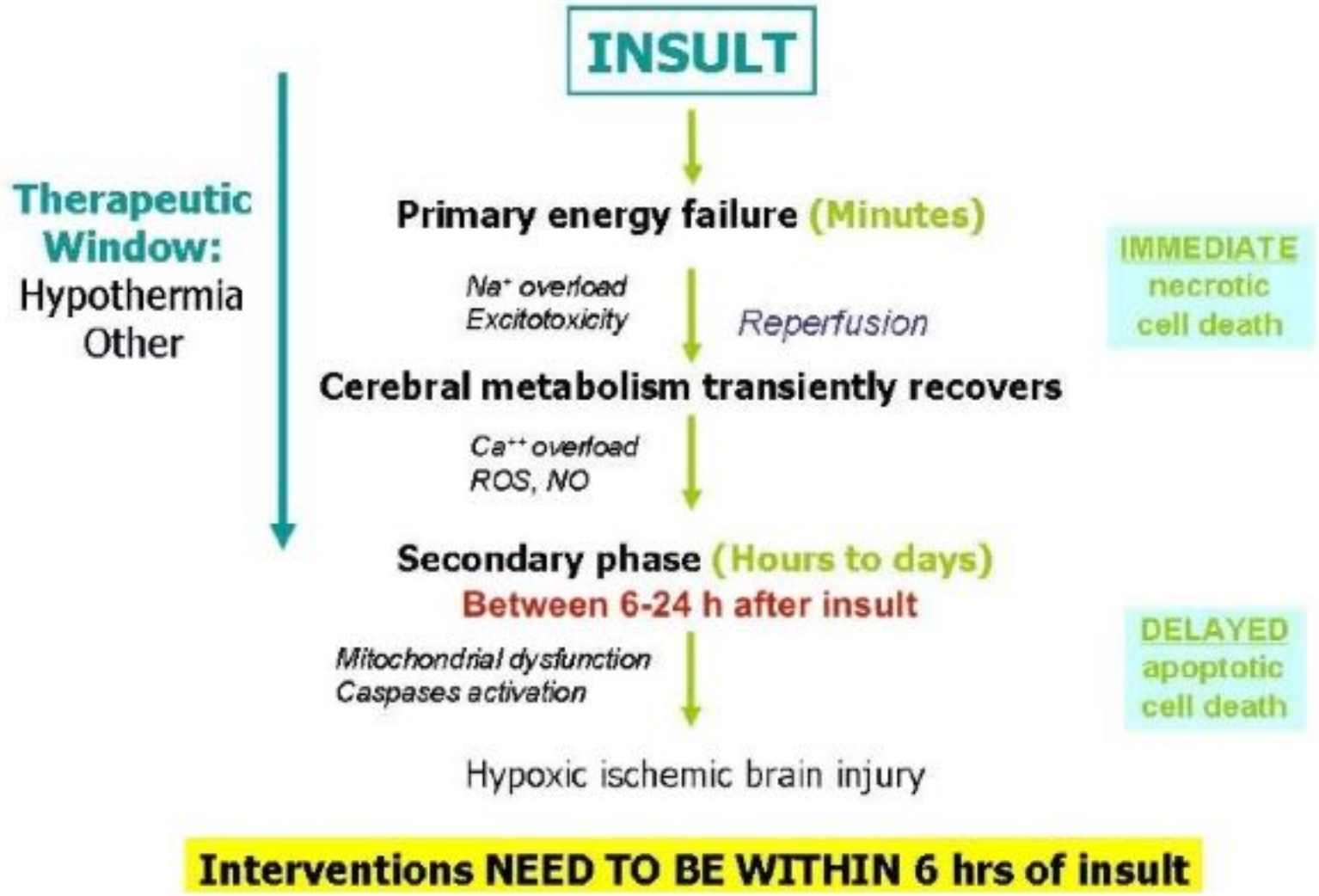
Neonatal Acute Kidney Injury

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	Increase ≥26 μmol/l within 48 hours or increase ≥1.5 to 1.9 x baseline SCr	<0.5 ml/kg/hour for 6–12 hours
2	Increase 2–2.9 x baseline SCr	<0.5 ml/kg/hour for ≥12 hours
3	Increase ≥3 x baseline SCr or increase 354 μmol/l or commenced on renal replacement therapy, irrespective of stage	<0.3 ml/kg/hour for ≥24 hours or anuria for ≥12 hours

KDIGO (2012)



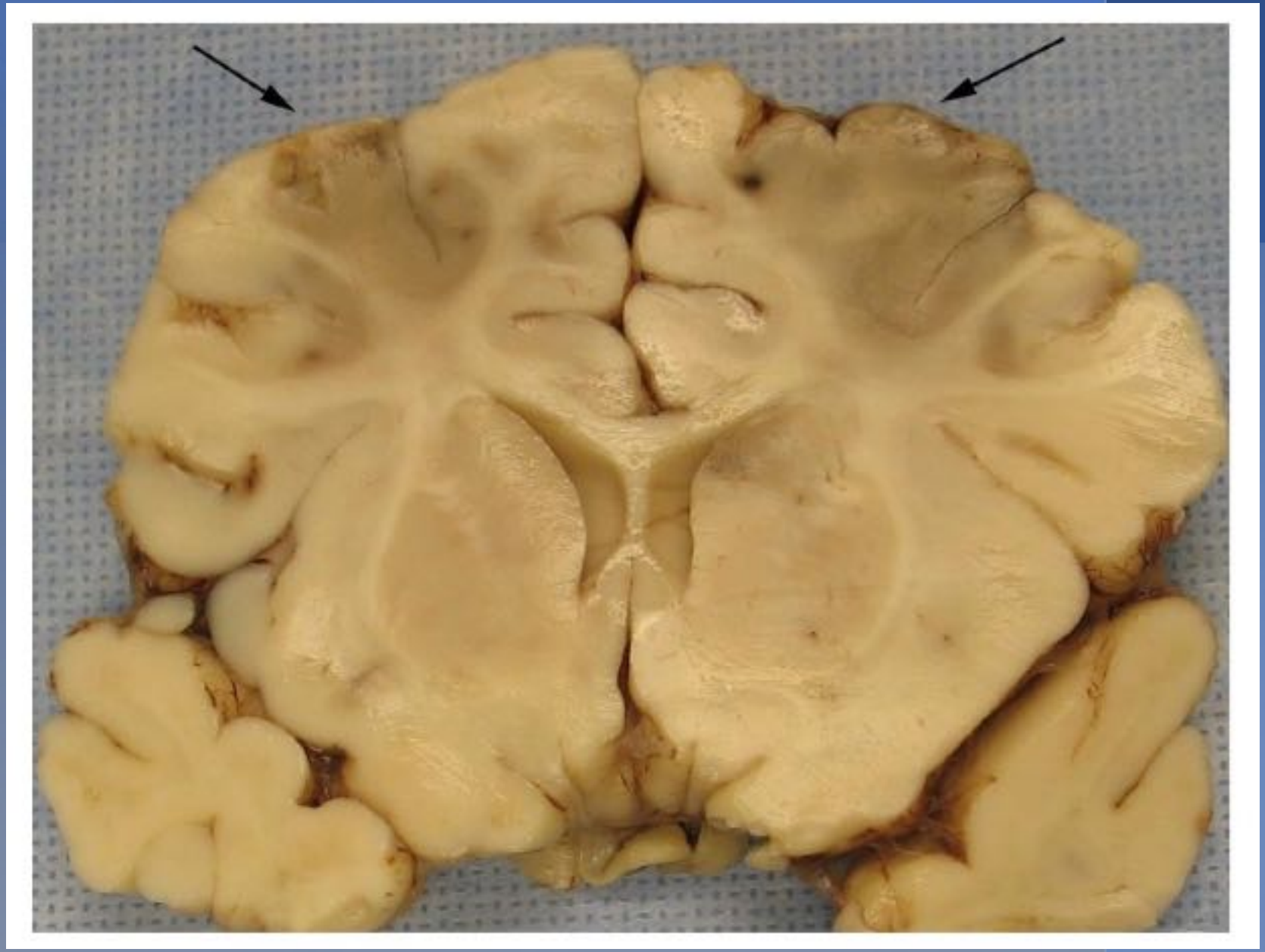
a Total kidney volume Z-scores at age 10–12 years according to neonatal AKI-status, shown with mean and 95% CI bars. b Individual FGF 23 levels in pg/ml at age 10–12 years according to neonatal AKI-status, shown with median and IQR bars. AKI, acute kidney injury; FGF, fibroblast growth factor; IQR, interquartile range. No significant difference was detected between the two groups for either variable


INSULT
Therapeutic Window:
Hypothermia
Other
Primary energy failure (Minutes)
Na+ overload
Excitotoxicity
Reperfusion
IMMEDIATE
necrotic
cell death
Cerebral metabolism transiently recovers
Ca++ overload
ROS, NO
Secondary phase (Hours to days)
Between 6-24 h after insult
Mitochondrial dysfunction
Caspases activation
DELAYED
apoptotic
cell death
Hypoxic ischemic brain injury
Interventions NEED TO BE WITHIN 6 hrs of insult

Study	Enrollment criteria	Method	Duration of cooling	N	Time of Follow-up	Results
Gluckman et al (2005)	< 6h pH<7.0, BE≥16 Apgar≤5 @ 10′ Encephalopathyby aEEG	Head cooling	72h 34-35°C Rectal	110 (H) 108 (N)	18 mth	No effect in most severe aEEG Death or severe disabilty: 66% (N) vs 48% (H) *; NNT= 6 Severe neuromotor disability: 28% (N) vs. 12% (H) * MDI: 77 (N) vs. 85 (H) * PDI: 85 (N) vs. 90 (H) *
Eicher et al (2005)	< 6h pH<7.0, BE≥14 Apgar≤5 @ 10′ Clinical enceph	Whole body cooling	48h 33-33.5°C Rectal	32 (H) 33 (N)	12 mth	Death or mod/severe disability: 84% (N) vs. 52% (H) * PDI <70: 64% (N) vs 24% (H) * Mortality: 42% (N) vs 31% (H)
Shankaran et al (2005)	< 6h pH<7.0, BE>16 Clinical enceph	Whole body cooling	72h 33-33.5°C Esophageal	102 (H) 106 (N)	18 mth	Death or mod/severe disability: 62%(N) vs. 45%(H) ** NNT=6 Mortality: 36% (N) vs. 24%(H)

H= hypothermia group, N= normothermia group

* p<0.05 vs. N; ** p<0.01 vs. N



Strategies	Interventions
↓ cerebral metabolic rate	Hypothermia
Block NMDA receptor channel	Magnesium
↓ glutamate release	Adenosine Adenosine agonists Adenosine uptake inhibitors
Inhibit voltage-sensitive Ca++ channels	Calcium channel blockers
↓ free radical reactions	Free radical scavengers Allopurinol Vitamin C, E Super oxide dismutase (SOD)
Prevent free radical formation	Indomethacin Iron chelators Allopurinol NOS inhibitors
↓ inflammatory response	Allopurinol Inflammatory antagonists (blocking IL-1 and TNF-α, steroids)
Attenuate apoptosis pathway	Caspase inhibitors

- Perinatal asphyxia is the condition resulting from lack of oxygen (hypoxia) or lack of perfusion (ischemia) to fetus or newborn to cause various organ dysfunction of sufficient magnitude and duration (1). The burden of birth asphyxia in neonates is so high that every hour 104 children die due to the disease, and the condition is alarming in India as between 250,000 to 350,000 infant deaths are reported annually, mostly within the first three days of life (2). The birth asphyxia affect almost every organ of the body and the most frequently affected organs are kidneys (50%), central nervous system (28%), cardiovascular (25%) and pulmonary system (23%) (3). In absence of perinatal record, it is very difficult to diagnose and grade the asphyxia after delivery (4),(6). There is a need to identify neonates with asphyxia who will be at risk for hypoxic ischemic encephalopathy and multi-organ dysfunction. Kidney is one of the most important organs commonly involved in the multiple organ dysfunction caused by perinatal asphyxia. Renal injury in birth asphyxia is a potential consequence of an adaptive mechanism (6). Amongst the recognised complications, Acute Renal Failure (ARF) is the most common and carries a poor prognosis and even 40% of survivors may develop permanent renal damage (7). The novelty of this study is that it compared renal dysfunction in different stages of HIE (Levene staging) and also assessed the renal function on postnatal day 1, 3 and 10. Literature regarding comparison in HIE staging is not much and very few studies have shown the renal derangement as the disease progresses (8),(9). We should keep a high index of suspicion of renal dysfunction in asphyxiated neonates. By this way, we can recognise early derangements of renal function in asphyxiated neonates according to their HIE stage which can be helpful in management of perinatal asphyxiated neonates, so we can reduce the mortality and morbidity in perinatally asphyxiated term neonates. Hence, the present study was conducted with an aim to study renal functions in perinatal asphyxia and various stages of HIE in term neonates.

Hospital Neonatal Database

INDIAN JOURNAL of NEONATAL MEDICINE and RESEARCH

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IN THIS ARTICLE

ORIGINAL ARTICLE / RESEARCH

Year : 2020 Month : July-September Volume : 8 Issue : 3 Page : PO07 - PO11

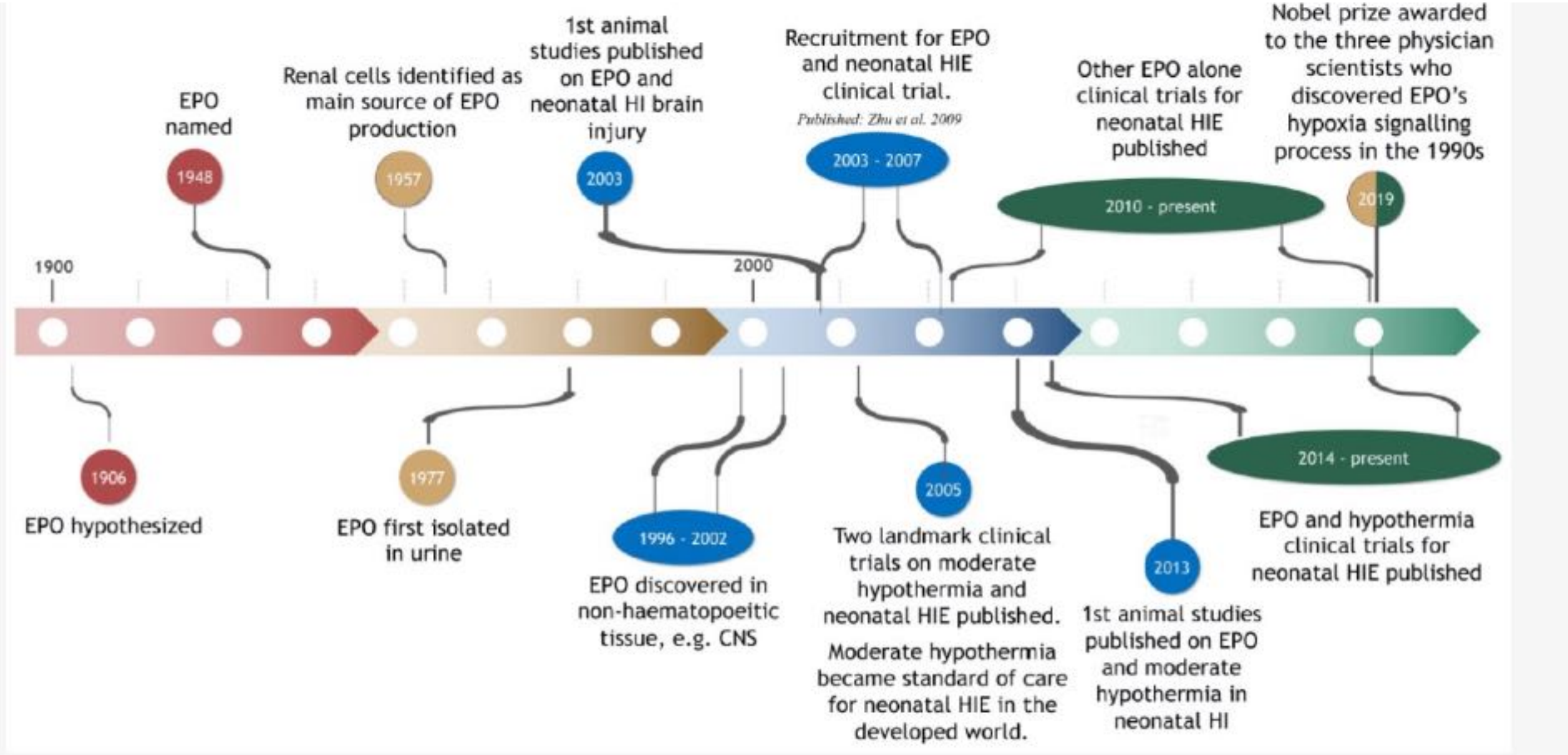
Renal Functions in Relation to Severity of Perinatal Asphyxia in Term Neonates

Dinesh Kumar, Mukesh Vir Singh, Niraj Kumar, Durgesh Kumar, Krishan Mohan Shukla, Kalbe Jawad

1. Associate Professor, Department of Pediatrics, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India. 2.

- Renal oximetry for early acute kidney injury detection in neonates with hypoxic ischemic encephalopathy receiving therapeutic hypothermia
- Jennifer A. Rumpel, Beverly J. Spray, Adam Frymoyer, Sydney Rogers, Seo-Ho Cho, Saritha Ranabothu, Richard Blaszak, Sherry E. Courtney & Valerie Y. Chock
- *Pediatric Nephrology* **volume 38**, pages2839–2849 (2023)Cite this article
- Abstract
- Background
- Neonates with hypoxic ischemic encephalopathy (HIE) receiving therapeutic hypothermia are at high risk of acute kidney injury (AKI).
- Methods
- We performed a two-site prospective observational study from 2018 to 2019 to evaluate the utility of renal near-infrared spectroscopy (NIRS) in detecting AKI in 38 neonates with HIE receiving therapeutic hypothermia. AKI was defined by a delayed rate of serum creatinine decline (< 33% on day 3 of life, < 40% on day 5, and < 46% on day 7). Renal saturation (R_{sat}) and systemic oxygen saturation (SpO2) were continuously measured for the first 96 h of life (HOL). Renal fractional tissue oxygen extraction (RFTOE) was calculated as (SpO2 – R_{sat})/(SpO2). Using renal NIRS, urine biomarkers, and perinatal factors, logistic regression was performed to develop a model that predicted AKI.
- Results
- AKI occurred in 20 of 38 neonates (53%). During the first 96 HOL, R_{sat} was higher, and RFTOE was lower in the AKI group vs. the no AKI group ($P < 0.001$). $R_{sat} > 70\%$ had a fair predictive performance for AKI at 48–84 HOL (AUC 0.71–0.79). RFTOE ≤ 25 had a good predictive performance for AKI at 42–66 HOL (AUC 0.8–0.83). The final statistical model with the best fit to predict AKI (AUC = 0.88) included RFTOE at 48 HOL ($P = 0.012$) and pH of the infants' first postnatal blood gas ($P = 0.025$).
- Conclusions
- Lower RFTOE on renal NIRS and pH on infant first blood gas may be early predictors for AKI in neonates with HIE receiving therapeutic hypothermia.

Timeline of the history of EPO in the context of its discovery, hypoxia-induced signalling processes (and the associated Nobel Prize), its use in animal studies on perinatal hypoxia-ischemia (HI) and its use in clinical trials on neonatal hypoxic-ischemic encephalopathy (HIE).



Immediate effect

- In response to hypoxia, astrocytes, oligodendrocytes, microglia, endothelial cells and neurons produce EPO. EPO improves oxygen consumption and storage in the hypoxic brain.

Effects contributing to neuroprotection*

- EPO decreases the hypoxic-induced nitric oxide surge and increases antioxidants.
- EPO inhibits glutamate release and inhibits brain cell death (i.e. is anti-apoptotic).
- EPO decreases inflammation.

Effects contributing to the restoration of neurons and glia*

- EPO promotes neurogenesis and oligodendrogenesis.
- EPO enhances revascularization of the ischemic brain.

• The effects of EPO are dose- and timing-dependent.

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REVIEW
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Neonatal Acute Kidney Injury

*Cassandra Coleman[1], Anita Tambay Perez[2], David T. Selewski[2] and Heidi J. Steflik[1]**

- Neonates with perinatal asphyxia, also known as HIE, often develop multiorgan failure, which impacts virtually every organ system. AKI has been shown to occur commonly in infants with HIE with an incidence ranging from 38 to 72% (27–32). In a single center study of 96 neonates with HIE undergoing therapeutic hypothermia, AKI occurred in 38% of neonates and independently predicted prolonged duration of mechanical ventilation and NICU stay (28). In a follow-up study, AKI during therapeutic hypothermia was found to be associated with the development of abnormal magnetic resonance imaging (MRI) findings at 7–10 postnatal days (33). The impact of therapeutic hypothermia on the incidence of AKI in HIE remains unclear, with trials and retrospective studies demonstrating conflicting results (34, 35).

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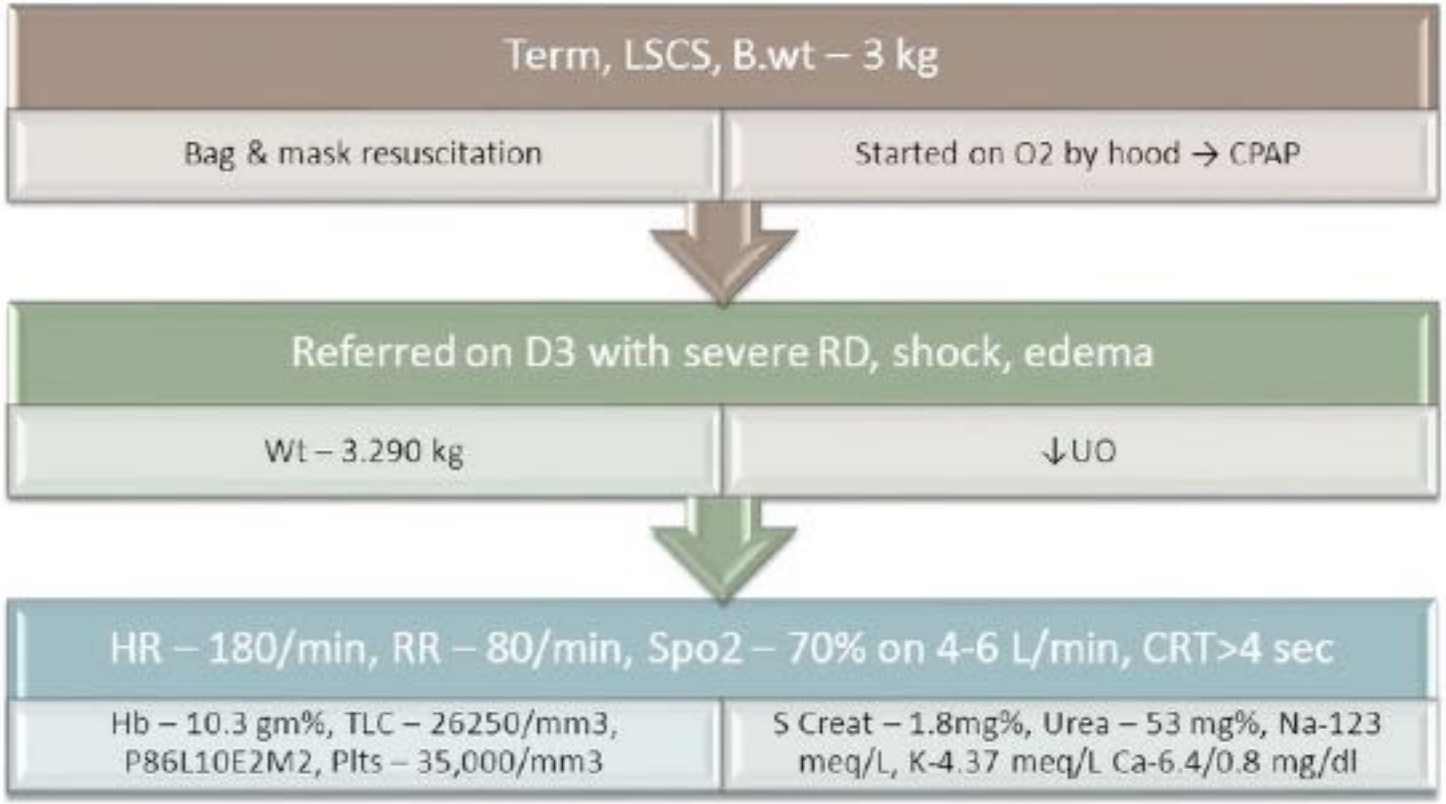
ADVANCES IN DIAGNOSIS, PREVENTION AND MITIGATION, AND TREATMENT OF SEQUELAE

- There are currently no proven treatments for established AKI. Despite multiple clinical trials across critical care nephrology, no therapeutic interventions have been shown to be effective in patients once AKI has occurred. As a result, efforts to advance the field have shifted toward improved diagnostics, prevention and mitigation strategies, and treatment of sequelae in neonatal AKI.

Epidemiology of high risk populations for neonatal acute kidney injury

NICU sub-population	Study details	AKI incidence	Significant findings
Hypoxic ischemic encephalopathy (HIE)	Kirkley et al. (*n* = 113) (91)	41.6%	• Outside hospital birth, IUGR, and meconium at delivery associated with increased odds of AKI • Infants with AKI had longer duration of stay compared to those without AKI
	Chock et al. (*n* = 38) (92)	39%	• Those with AKI had higher renal artery saturations (Rsat; *via* NIRS) compared to those without AKI after 24 h of life • Rsat > 75% by 24–48 h predicted AKI with sensitivity 79% and specificity 82% (AUC 0.76)
	Tanigasalam et al. (*n* = 120) (35)	32% in TH; 60% in standard tx	AKI incidence in TH vs. standard tx groups: • Stage 1: 22 vs. 52% • Stage 2: 5 vs. 5% • Stage 3: 5 vs. 3%
	Sarkar et al. (*n* = 88) (33)	39%	• AKI independently associated with abnormal brain MRI
	Selewski et al. (*n* = 96) (28)	38%	• AKI predicted prolonged duration of mechanical ventilation and length of stay

Case


Term, LSCS, B.wt – 3 kg
Bag & mask resuscitation
Started on O2 by hood → CPAP
Referred on D3 with severe RD, shock, edema
Wt – 3.290 kg
↓UO
HR – 180/min, RR – 80/min, Spo2 – 70% on 4-6 L/min, CRT>4 sec
Hb – 10.3 gm%, TLC – 26250/mm3, P86L10E2M2, Plts – 35,000/mm3
S Creat – 1.8mg%, Urea – 53 mg%, Na-123 meq/L, K-4.37 meq/L Ca-6.4/0.8 mg/dl

What Next?

- Bolus ? Volume ? Repeat ?
- Inj Frusemide – Bolus / Continuous infusion :
- Low dose Dopamine ?
- Any other drug for AKI ?
- RRT ?

Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Low hemoglobin levels are independently associated with neonatal acute kidney injury: a report from the AWAKEN Study Group

- Neonatal acute kidney injury (AKI) used to be an under-recognized morbidity among neonates. Single-center studies1–3 and reports from a recent multicenter study, Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN), suggest that AKI occurs in up to 30% of critically ill neonates admitted to the neonatal intensive care unit (NICU) who receive intravenous (IV) fluids for at least 48 h. Neonates with AKI have 4.6 times higher independent odds of mortality.4

Pediatric RESEARCH

SPRINGER NATURE

CLINICAL RESEARCH ARTICLE

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Pediatric RESEARCH

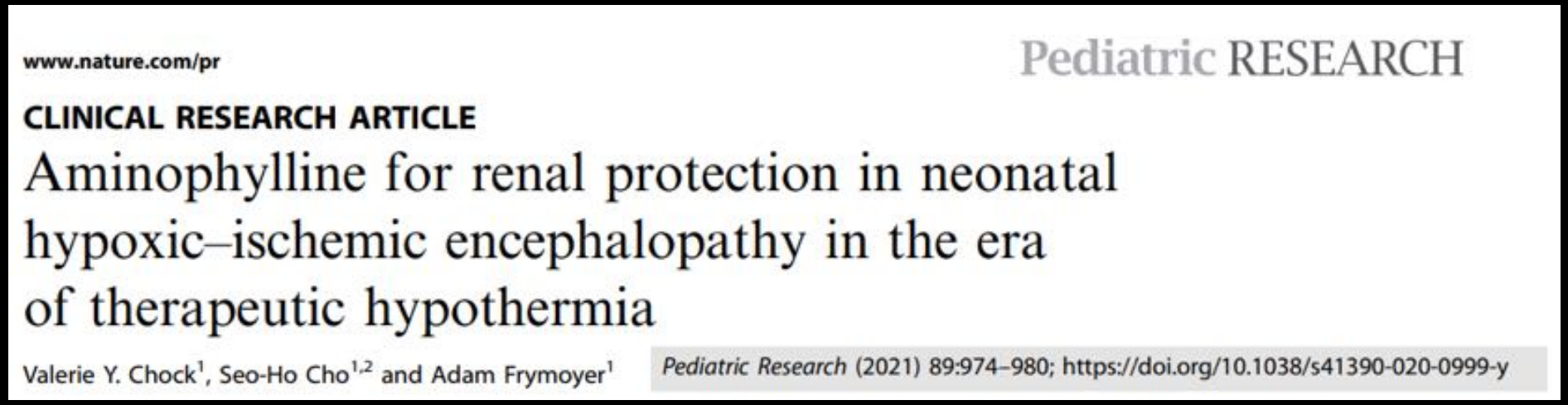
CLINICAL RESEARCH ARTICLE

Aminophylline for renal protection in neonatal hypoxic–ischemic encephalopathy in the era of therapeutic hypothermia

Valerie Y. Chock[1], Seo-Ho Cho[1,2] and Adam Frymoyer[1]

Pediatric Research (2021) 89:974–980; https://doi.org/10.1038/s41390-020-0999-y

- Neonates with hypoxic–ischemic encephalopathy (HIE) are at high risk of acute kidney injury (AKI) with several reports of an incidence as high as 40%.1–3 Antenatal and postnatal hypoxia, hypotension, and use of nephrotoxic medications may contribute to ongoing renal insult. The occurrence of AKI in neonates with HIE is an independent risk factor for adverse outcomes, including prolonged mechanical ventilation, prolonged length of hospital stay, injury on magnetic resonance imaging (MRI), and increased risk of long-term neurodevelopmental impairment.1,4–6



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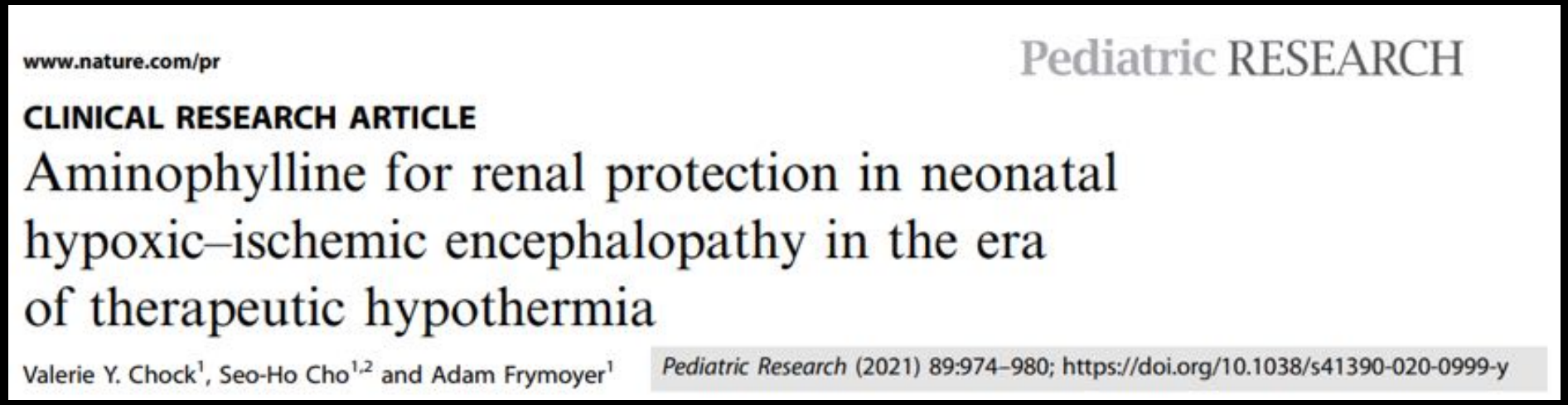
- Theophylline and aminophylline (the ethylenediamine salt formulation of theophylline and same active molecule) are potentially targeted therapeutic agents for AKI through action as non-selective adenosine receptor antagonists. During hypoxia/ ischemia, intrarenal vasoconstriction occurs as a consequence of higher adenosine levels with a subsequent reduction in renal blood flow and fall in glomerular filtration rate (GFR) and filtration fraction.8 In newborn animal models, administration of low-dose theophylline prevented hypoxemia-associated reductions in GFR and filtration fraction.8,9 Theophylline or aminophylline for renal protection has been studied in infants with congenital heart disease after cardiac surgery,10,11 neonates on extracorporeal membrane oxygenation support,12 and preterm infants with apnea of prematurity,13,



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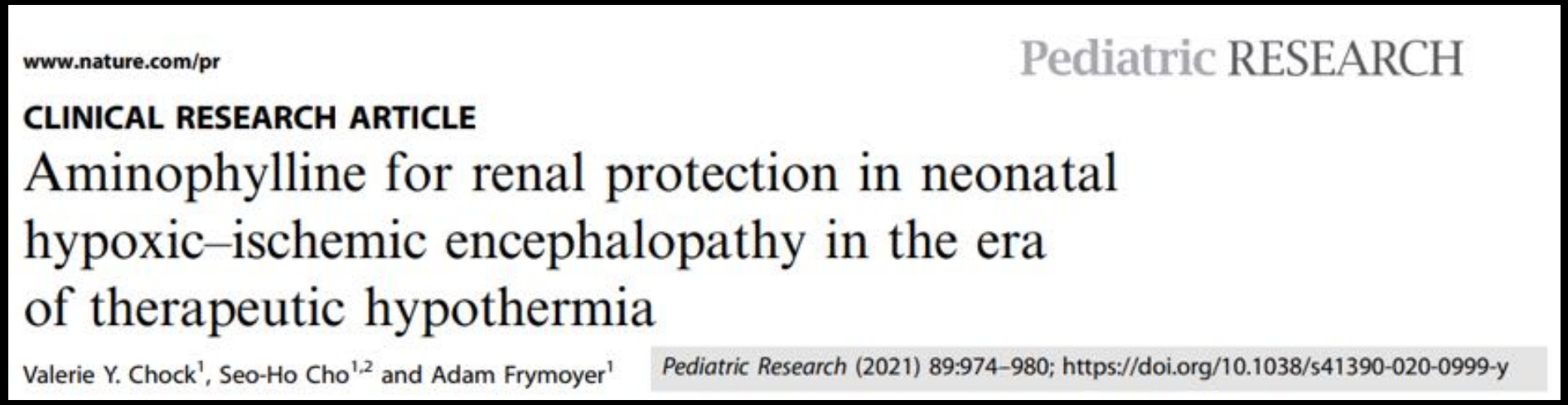
- However, the physiologic effect of theophylline on renal function in the HIE population remains unclear. Neonates being cooled for HIE with AKI have higher renal saturation measures compared to those without AKI,15 possibly reflecting decreased extraction of oxygen by an injured kidney. Theophylline may increase renal blood flow post-hypoxic insult and lead to improved renal saturation measures.



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Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Aminophylline for renal protection in neonatal hypoxic–ischemic encephalopathy in the era of therapeutic hypothermia

Valerie Y. Chock[1], Seo-Ho Cho[1,2] and Adam Frymoyer[1]

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- In single-center, randomized controlled trials, a single dose of theophylline shortly after birth has also been shown to improve UOP and reduce the incidence of severe renal dysfunction in neonates with severe perinatal asphyxia.16–20 Based on available evidence, the 2011 Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest a single dose of theophylline to be considered for prevention of AKI in the HIE population (moderate quality of evidence).21 However, all theophylline clinical studies to date were conducted before the widespread use of therapeutic hypothermia (whole-body cooling) for HIE, and the therapeutic benefit of theophylline (or aminophylline) in the context of hypothermia remains unknown.

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Maternal risk factors for neonatal AKI.

Pregestational	Gestational	Peripartum
Socioeconomic factors	In vitro fertilization	Nephrotoxic medications
Age	Maternal nutrition	Chorioamnionitis
Bodyweight	Alcohol consumption	Abruption
Environmental stress	Smoking	Cord prolapse
Interpregnancy interval	Hypertensive disorders	Illicit drug use
CKD	Nephrotoxic medications	Perinatal asphyxia
Hypertension	Fetal growth restriction	
	Oligohydramnios and unexplained polyhydramnios	

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High-risk neonates.

Population
Preterm birth <28 weeks
Small for gestational age
Birth weight <1500 grams
Congenital anomalies of the kidney or urinary tract (CAKUT)
Congenital heart disease
Undergoing cardiopulmonary bypass
Single ventricle physiology
History of heart transplant
Extracorporeal membrane oxygenation (ECMO)
Hypoxic-ischemic encephalopathy
High risk of dehydration
Unrepaired gastroschisis
Inherited cutaneous conditions

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High-risk procedures and states.

High-risk procedures
Cardiopulmonary bypass
Complex birth (or hemodynamic instability during birth)
ECMO
Radiologic studies and procedures utilizing iodinated contrast
Major surgical procedures (NEC, CDH repair and Cardiac repair)
Cancer treatment
High-risk states
Dehydration
At risk for sepsis or culture-positive sepsis
Necrotizing enterocolitis
Decreased oncotic pressure
Increased intra-abdominal pressure
Hypotension requiring vasopressors
High nephrotoxic medication exposure
Hemodynamically significant PDA

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Neonatal AKI bundle.

Evaluation of potentially modifiable risk and complications of AKI
Monitoring volume intake and output and daily weights
Calculate and track cumulative fluid overload
Evaluation of medications for nephrotoxic potential
Evaluation of underlying AKI cause/physiology
Treatment of hypoalbuminemia, hypotension, high abdominal pressure, hypoperfusion, bladder obstruction
Evaluation of nutrition/electrolyte composition of fluid intakes
Multidisciplinary approach: pharmacy, dietitian, bedside nurses

- Acute kidney injury (AKI) is a common occurrence in the neonatal intensive care unit (NICU).
- In recent years, our knowledge of the incidence and impact of neonatal AKI on outcomes has expanded exponentially.
- Neonatal AKI has been shown to be associated with adverse outcomes including increased length of mechanical ventilation, prolonged length of stay, and rise in mortality.
- There has also been increasing work suggesting that neonates with AKI are at higher risk of chronic kidney disease (CKD).

- Acute kidney injury (AKI) is it common?
- Is it increasing?
- Is it benign?
- Does it have long term consequences?
- Is it avoidable?
- Is there any specific treatment?In recent years, our knowledge of the incidence and impact of neonatal AKI on outcomes has expanded exponentially. Neonatal AKI has been shown to be associated with adverse outcomes including increased length of mechanical ventilation, prolonged length of stay, and rise in mortality.

- . In the past, AKI had been defined multiple ways.
- The utilization of the neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria as the standard definition for neonatal AKI in research and clinical care has driven the advances in our understanding of neonatal AKI over the last 10 years.
- This definition has allowed researchers and clinicians to better understand the incidence, risk factors, and outcomes associated with neonatal AKI across populations through a multitude of single-center studies and the seminal, multicenter Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study.

- identifying those at highest risk, protocolizing AKI surveillance, improving prevention and diagnosis, and expanding kidney support therapy (KST) for neonates has occurred. These efforts also include improving risk stratification (identifying high risk populations, including those with nephrotoxic medication exposure) and diagnostics (novel biomarkers and diagnostic tools).

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- protocolizing AKI surveillance,
- improving prevention
- improving diagnosis, and
- expanding kidney support therapy (KST) for neonates has occurred.
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- diagnostics (novel biomarkers and diagnostic tools).