How Un

The Conundrum of What to Do for **Transient** Neonatal Hypoglycemia

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Disclosure Statement

• I have no relevant financial relationships with the manufacturers of any commercial product and or providers of commercial services discussed in this activity.
Except that I live in...

The Sweetest Place on Earth
Objectives

1. Normal newborn glucose homeostasis
2. Neonatal transient hypoglycemia-why are newborns more susceptible?
3. Contentious issues
4. AAP vs Pediatric Endocrine Society (PES) guidelines
5. Association between transient newborn hypoglycemia and long-term educational outcomes
6. Do early feedings affect glucose homeostasis?
7. CHYLD-Sugar Babies Study
8. Prophylactic treatment studies
9. Hypoglycemia and neurodevelopmental outcomes
10. Influence of glycemic status and hypocapnia on outcomes in HIE
A Story...

• At the University of Arkansas, universal newborn glucose screening has been in effect since the 1970s
A Story...

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• Peculiar to the University of Arkansas for Medical Sciences
A Story...

- At the University of Arkansas, universal newborn glucose screening has been in effect since the 1970s.
- Peculiar to the University of Arkansas for Medical Sciences.
- 100,000 newborns.
At the University of Arkansas, universal newborn glucose screening has been in effect since the 1970s.

Peculiar to the University of Arkansas for Medical Sciences

100,000 newborns

Let’s study it
Normal Newborn Glucose Homeostasis

- Glucose is the major energy substrate for placental and fetal metabolism
- At term, fetal levels ~10 mg/dL < mother
- Maternal glucose concentrations 70-90 mg/dL
- In normal term newborns, levels reach a nadir to 55-60 mg/dL between 1-2 hours
- Over the first few days, levels steadily increase to >70 mg/dL

Cornblath, *NEJM* 1965;273:378-81

*multiply by 1.15 to convert to plasma levels*
At birth, the continuous utero-placental umbilical infusion of glucose ends and levels nadir during the first several hours.
Breastfeeding in the Normal Newborn

• During the DOL #1, breastfed newborns consume very few calories
  • Average volume of colostrum ingested per feeding is only 0.5-1.6 ml/kg on DOL #1
  • First-day colostrum has 20% of the lactose concentration of mature breast milk
  • Ketones are not elevated in breastfed infants on DOL #2

References:
Hypoglycemia—an Imbalance between Glucose Supply and Utilization

- Decreased substrate (e.g., IUGR)
- Hyperinsulinism
- Endocrine abnormalities
- IEM
Responses of Adults and Newborns to Specific Glucose Concentrations

**Adults**

<table>
<thead>
<tr>
<th>Plasma glucose mg/dl</th>
<th>Clinical presentation</th>
<th>Counter-regulatory response or physical consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>No symptoms</td>
<td>Suppression of insulin release</td>
</tr>
<tr>
<td>70</td>
<td>Autonomic symptoms</td>
<td>Onset of counter-regulatory hormone release</td>
</tr>
<tr>
<td>55</td>
<td>Neuroglycopenic symptoms</td>
<td>Onset of cognitive dysfunction</td>
</tr>
<tr>
<td>25</td>
<td>EEG changes</td>
<td>Seizures Coma</td>
</tr>
</tbody>
</table>

Diabetic Emergencies, 2012
Responses of **Adults** and **Newborns** to **Specific Glucose Concentrations**

- **Adults**
  - **Clinical presentation**
    - 80: No symptoms
    - 70: Autonomic symptoms
    - 55: Neuroglycopenic symptoms
  - **Counter-regulatory response or physical consequence**
    - 80: Suppression of insulin release
    - 70: Onset of counter-regulatory hormone release
    - 55: Onset of cognitive dysfunction
  - 25: EEG changes
  - Below 25: Seizures, Coma

- **Newborns** (Diagram with a large question mark)

---

Diabetic Emergencies, 2012
Why are Newborns More Susceptible to Hypoglycemia?

• The newborn brain uses glucose almost exclusively as an energy substrate, and can account for up to 90% of the total glucose consumption.

• Cerebral glycogen stores are low.

• High brain-to-body weight of newborns result in a proportionately higher glucose demand than adults.

• While alternative fuels such as ketone bodies and lactate can be used by the brain, the immature counterregulatory response limits availability of these molecules, especially early on.

• Thus, newborns are especially vulnerable to problems impairing normal glucose homeostasis during transition from fetal to neonatal life.
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Why are Newborns More Susceptible to Hypoglycemia?

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- Thus, newborns are especially vulnerable to problems impairing normal glucose homeostasis during transition from fetal to neonatal life.
Hypoglycemia

- Transient neonatal hypoglycemia is common affecting up to 15% of healthy infants and up to 50% of at-risk newborns.
- Its incidence may be increasing because of increases in maternal obesity and gestational diabetes.
- **Transient neonatal hypoglycemia** (first 48–72 hours of life)
  - Hypoketotic
  - Due to immature counterregulatory pathways resembling congenital hyperinsulinemia
  - It is associated with a lowered glucose threshold for suppression of insulin secretion
  - Inappropriate preservation of liver glucose stores

*J Pediatr* 2015; 166:1520-5
Hypoglycemia: Evidence- vs Eminence-based

- ...no substantial **evidence-based** progress in defining what constitutes newborn hypoglycemia and its relation to brain injury
- Monitoring, prevention, and treatment of newborn hypoglycemia remains largely empirical, and has been debated for more than 50 years
- Guidelines make practical recommendations for screening and managing neonatal hypoglycemia based on expert consensus (**“eminence-based”**)... rather than evidenced-based long-term follow-up studies
- Some international bodies recommend lower (AAP) and higher (PES) thresholds for treatment and management, which shows the paucity of high-quality evidence. **There is no high-quality evidence to guide the management of transient neonatal hypoglycemia!**
- Neonatal hypoglycemia may be one of the most preventable causes of brain injury, on the other hand, overtreatment may lead to decreased breastfeeding and brain changes from repeated pain from heel lances, and treatment has never been shown to be beneficial

*Pediatrics* 2011; 127:575-9 (AAP); *J Pediatr* 2015; 166:1520-5 (PES)
Clinically Significant Hypoglycemia

• “the definition of clinically significant newborn hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology...”

--Marvin Cornblath, 2000
She Said, He Said
“the experimental and human clinical data are clear that hypoglycemia (<45 mg/dL) is injurious to the newborn brain and must be aggressively managed to avoid adverse consequences.”
• “the experimental and human clinical data are clear that hypoglycemia (<45 mg/dL) is injurious to the newborn brain and must be aggressively managed to avoid adverse consequences.”

• “we strongly disagree. This statement is supported neither by the clinical data in humans nor experimental data from animal studies.”
“that would be a misinterpretation of my commentary. There are, indeed, no data to support such a conclusion.”
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such an unfounded statement has the potential to promote unnecessary invasive interventions, failed breastfeeding, anxiety among parents, and other potential complications from overdiagnosis and overtreatment.”
“the conclusion in my commentary was ambiguous, and such a misinterpretation could lead to overtreatment of healthy infants and medico-legal misinterpretation...”
She Said, He Said

• “the conclusion in my commentary was ambiguous, and such a misinterpretation could lead to overtreatment of healthy infants and medico-legal misinterpretation…”

• If ‘she’ has new objective data to support her statement, we would all welcome the publication of this information. If not, we would be better served if she qualified her statement or, in the absence of any specific information, retracted it completely.”
“In conclusion, I am grateful to ‘him’ for balancing this pendulum with the evaluation of the healthy well infant vs the at-risk newborn. The commentary was focused on the at-risk or “sick” newborn, and should not be extrapolated to healthy newborns, for whom very prolonged and severe hypoglycemia would be required to lead to cerebral injury.”
Knowledge Gaps with Defining Neonatal Hypoglycemia

- Knowledge gaps exist about the definition of neonatal hypoglycemia, specific cutoffs or thresholds (mg/dL), management, and clinical significance ... even after >6,000 articles
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AAP

25

J Pediatr 2009; 155:612-7
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AAP
25

PES
50

Sugar Babies
47

AAP
35
Knowledge gaps exist about the definition of neonatal hypoglycemia, specific cutoffs or thresholds (mg/dL), management, and clinical significance ....even after >6,000 articles
Flaws in the Definition of Hypoglycemia

1. **Clinical:** (“symptoms”), similar non-specific manifestations occur with other neonatal problems

2. **Epidemiological:** cutoff values (<10%-ile, >2 SD) are not necessarily abnormal or cause injury

3. **Physiologic:** effects on CBF, EEG, and hormonal responses

4. **Functional:** (neurodevelopmental outcome), most studies lack non-hypoglycemic controls, do not control for SES and parental education, use different glucose cutoffs, have short follow-up, do not consider other pathologies, and have small numbers of asymptomatic infants
• This report provides a practical guide and algorithm for the screening and subsequent management of neonatal hypoglycemia, in late preterm, and term SGA, IDM/LGA infants
• ...expert panel...
• ...it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed
Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

AAP

2011

Pediatrics 2011; 127:575-9
“Transitional Neonatal Hypoglycemia”

First 48 hours, focus on stabilizing glucose concentrations

“For high-risk neonates without a suspected congenital hypoglycemia disorder, we suggest the goal of treatment to maintain a [pre-prandial] plasma glucose concentration $>50\,\text{mg/dL}$ for those aged $<48\,\text{hours}$”

After 48 hours, persistently hypoglycemic infants should be worked-up to determine etiology
Recurrent, Prolonged, and Severe Neonatal Hypoglycemia is Associated with Poor Long-term Neurodevelopment and Neurocognitive Function (and brain damage)

“substantial controversy, however, remains as to whether asymptomatic [transient] hypoglycemia actually causes brain damage”

- Cornblath et al

- Additionally, many pediatricians and researchers consider transient early asymptomatic hypoglycemia a normal physiologic phenomena that is not associated with harm
Objective

- Evaluate if early **transient neonatal hypoglycemia** is associated with school-age academic performance
  - A large sample size
  - Study sample of all newborns (not just an at-risk infants)
  - Universal newborn glucose screening, since 1970s
  - Adjust for multiple covariates including maternal education and SES
  - Unbiased outcome (4th grade achievement tests)
4th Grade Achievement Tests: “Real World” Assessments

4th Grade Test scores → 8th Grade Test Scores → College → High School → $\text{Money}$
Hypothesis

- Transient neonatal hypoglycemia (a single low value followed by a second value above a cutoff) during the early newborn period is associated with poor long-term academic performance (achievement tests)
  - Glucose cutoffs:
    - <30, <35, <40, <45, and <50 mg/dL
Unique Data and Resources Available in Arkansas

- All newborns had glucose screening during 1\textsuperscript{st} 3 hours (universal glucose screening)
- Plasma glucose with glucose oxidase method
  - NICU lab with turn around time of 25 min
- Glucose values available on >100,000 newborns (from 1970s)
- “No Child Left Behind”
  - Achievement tests in literacy and math 1\textsuperscript{st}–8\textsuperscript{th} grade
  - All Arkansas public school students
  - Arkansas Department of Education longitudinal database, since 1997
- Newborn data conservatively matched to student data: SSN, DOB, and names
Arkansas Dataset

- Newborn data from 1998 (chart review)
  - All newborns 23-42 weeks’ gestation (n=1,943)
  - Exclusions: major congenital anomalies, chromosomal abnormalities, and those with recurrent hypoglycemia
- 4th grade test scores from 2008
  - 10 years of age
  - Matched 1,395 (72%) newborn-test score data
- Matched and unmatched newborns essentially equivalent
Initial Glucose Concentrations in Healthy Term Newborns were Associated with 4th Grade Literacy Achievement Test Scores

- **Definition of “healthy”**
  - Full term (≥37 weeks)
  - AGA (10th–90th %-ile)
  - Apgar score ≥7
  - No maternal DM or substance abuse
  - No polycythemia
Multivariate Logistic Regression

– Primary outcome: proficiency on 4th grade tests

– Covariates used in the final models:
  • Transient hypoglycemia *(using many cutoffs)*, gestational-age group, gender, race, insurance status *(proxy for SES)*, maternal education level, gravidity, and multifetal gestation

• Stepwise backward elimination method

• Other covariates considered for the models: size for gestational age, 5-min Apgar, delivery route, meconium, polycythemia, chorioamnionitis, sepsis, maternal DM, substance abuse, prenatal care, PROM, smoking, and PIH
Multivariable Logistic Regression (<40 mg/dL cutoff)

After adjusting for myriad factors, the odds of being proficient for normoglycemic newborns were about 2 times that of hypoglycemic newborns.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Literacy aOR (95% CI)</th>
<th>P Value</th>
<th>Mathematics aOR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic (&lt;40 mg/dL)</td>
<td>0.43 (0.28-0.67)</td>
<td>&lt;.001</td>
<td>0.51 (0.34-0.78)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*JAMA Pediatr* 2015; 169:913-21
<35, <40, and <45 mg/dL Cutoffs for Transient Hypoglycemia were Significant

<table>
<thead>
<tr>
<th>Glucose Cutoff (mg/dL)</th>
<th>Literacy</th>
<th>Mathematics</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>.385</td>
<td>.103</td>
</tr>
<tr>
<td>&lt;35</td>
<td>.008</td>
<td>.006</td>
</tr>
<tr>
<td>&lt;40</td>
<td>&lt;.0001</td>
<td>.002</td>
</tr>
<tr>
<td>&lt;45</td>
<td>.004</td>
<td>.137</td>
</tr>
<tr>
<td>&lt;50</td>
<td>.102</td>
<td>.419</td>
</tr>
</tbody>
</table>

*JAMA Pediatr* 2015; 169:913-21
Weaknesses

• Retrospective data
• Timing of glucose-specimen collection at discretion of bedside nurses
• Treatment decisions based on neonatologist (and/or residents) *du jour*, no clear management policy
• Did not account for 10 years of personal characteristics, environmental influences, and diagnoses
Strengths

• Universal newborn glucose screening, study not biased by selection of special populations

• Plasma glucose concentration (glucose oxidase) determination routinely performed at a similar time after birth (rapid turn around time)

• Large study sample

• Follow-up 10 years with 72% of newborns

• Objective unbiased outcomes used

• Early transient newborn hypoglycemia was associated with lower achievement test scores at age 10 years
Important Considerations

• Given that the findings are serious and contrary to expert opinion, the results need to be validated in other populations before universal newborn glucose screening should be adopted.

• Perhaps, we can mobilize newborn nurseries (in the future) to maintain iv catheters for glucose infusions.

• Or, perhaps, we should use 40% dextrose gel.
Does Early Feeding Affect Initial Glucose Concentrations?

The Effect of Early Feeding on Initial Glucose Concentrations in Term Newborns

Yin Zhou, MD¹, Shasha Bai, PhD², Joshua A. Bornhorst, PhD³, Nahed O. Elhassan, MD, MPH⁴, and Jeffrey R. Kaiser, MD, MA⁵

(J Pediatr 2017;181:112-5)

Objective To evaluate the influence of early feeding on initial glucose concentrations in healthy term newborns who were not at risk for hypoglycemia.
• Retrospective observational trial
• Initial plasma glucose compared in healthy term infants (not at-risk of hypoglycemia) who were fed:
  • before (early feeders)
  • after (late feeders) their initial glucose screens
• Univariate and multivariate analyses
Glucose Concentrations for Early and Late Feeders in Relation to the Glucose Screen

**Graph:**
- X-axis: Hours from Birth
- Y-axis: Glucose (mg/dL)
- Early Feeder: 0.9
- Late Feeder: 3.8
- Glucose Screen: 1.8-2.2

Breastfed vs Formula-fed
Early vs Late Feeders

• In all infants, breast or formula-fed, initial glucose concentrations were about 3-4 mg/dL lower (and not higher) for early vs late feeders
Conclusion and Speculation

• Early feeding in otherwise healthy term newborns did not increase initial glucose concentrations compared with fasted (i.e., late feeding) infants, irrespective of breast or formula feeding.

• Before direct evidence is available, our observations that early feeding does not increase glucose concentrations in non-at-risk newborns, may be instructive for managing early asymptomatic hypoglycemia in at-risk newborns.
CHYLD Study Group

Children with Hypoglycaemia and their Later Development

Jane Harding, Principal Investigator
Is treatment with 40% dextrose gel (buccally applied) more effective than feeding along for reversal of neonatal hypoglycemia in at-risk babies?

- RCT
- 40% dextrose (n=118) vs placebo (n=119) gel
- 1° outcome: treatment failure—defined as BG concentration <47 mg/dL after 2 treatment attempts
- 2° outcome: NICU admission for the treatment of neonatal hypoglycemia
Sugar Babies Study: Results

% Treatment Failure

% NICU Admission for Hypoglycemia

Lancet 2013;382:2077-83
Does Prophylactic Dextrose Gel Prevent Neonatal Hypoglycemia?
A Pilot Study

Sarah M. Coors, BSN, DO, FAAP
Neonatal-Perinatal Medicine Fellow at Texas Children’s Hospital
• 40% dextrose gel, applied to the buccal mucosa, has been shown in the Sugar Babies Study to safely treat established transient neonatal hypoglycemia

• We wondered if prophylactic dextrose gel provided to at-risk newborns would prevent or decrease transient neonatal hypoglycemia
Hypotheses

Dextrose gel given prophylactically to at-risk newborns, compared to feeding alone, will:

1. Prevent/decrease transient neonatal hypoglycemia

and

2. Decrease NICU admissions for intravenous dextrose
Design/Methods

• Quasi-experimental study design
• Study entry based on researcher availability:
  • After birth, cases (n=75) were given prophylactic dextrose gel after the first feeding
  • Others served as controls (n=188)
• Consent obtained prenatally
• Inclusion: Late preterm, IDM, <2500 g, or >4000 g
• Exclusion: symptomatic, after birth did not meet GA or BW criteria, chromosomal/congenital anomalies
Prophylactic Dextrose Gel Procedure

Birth

Feeding

Dextrose Gel 0.5 ml/kg

BG checked 30 min later

Control Group

Pediatr Res 2018;198:156-61
No Difference in 1st Blood Glucose

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Prophylactic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.79 (Univariate)

P = 0.22 (Multivariate)

Pediatr Res 2018;198:156-61
No Difference in NICU Admission for treatment of hypoglycemia

P = 0.43

11% Prophylactic
15% Control

Pediatr Res 2018;198:156-61
Conclusion/Speculation

• Prophylactic dextrose gel given to at-risk newborns immediately after the initial feeding did not increase blood glucose concentrations, or NICU admission for the treatment of neonatal hypoglycemia compared to feeding alone

• Exogenous glucose may not influence glucose homeostasis during the first hours after birth
Conclusion/Speculation

• Prophylactic dextrose gel given to at-risk newborns immediately after the initial feeding did not increase blood glucose concentrations, or NICU admission for the treatment of neonatal hypoglycemia compared to feeding alone.

• Exogenous glucose may not influence glucose homeostasis during the first hours after birth, i.e.,

• Perhaps, “you cannot fool Mother Nature”
After the Study was Completed, and During Data Analysis...

Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study)

Joanne Elizabeth Hegarty¹,², Jane Elizabeth Harding¹, Gregory David Gamble¹, Caroline Anne Crowther¹, Richard Edlin³, Jane Marie Alsweiler¹,²,⁴*

PLOS Medicine | DOI:10.1371/journal.pmed.1002155  October 25, 2016
Pre-hPOD Study

• RCT
• New Zealand, CHYLD Study Group
• At-risk newborns were provided:
  • Dextrose gel 200 mg/kg (single dose) or 400 mg/kg (double dose)
    • Either once at 1 hour (after breastfeeding)
    • Or, 3 additional doses, pre-prandial, during the first 12 hours
  • Placebo gel: 1 or 4 doses
Pre-hPOD Study

• **1° outcome**: hypoglycemia (<47 mg/dL) during 48 hours
• **2° outcome**: admission to the NICU for hypoglycemia

**Results**

• Newborns randomized to a **single prophylactic dose of 200 mg/kg** had the lowest risk of hypoglycemia ($P=0.04$)
• Newborns who received any **prophylactic doses of dextrose gel** were less likely to be hypoglycemic ($P=0.03$)
• NICU admissions for hypoglycemia were less common (RR 0.46, CI 0.21-1.01, $P=0.05$)
Coors’ Study vs CHYLD Study (Pre-hPOD)

**Coors’ Study**

- Quazi-experimental
- Insta-Glucose®
- n=75 prophylactic, 188 controls
- Given at ~1hour
- Glucometer (glucose dehydrogenase)
- Evaluated 1st glucose concentration

**Pre-hPOD**

- RCT
- Compounded gel
- n=277 dextrose, 138 placebo
- Given at ~1hour
- Glucometer (glucose oxidase)
- Evaluated all glucose concentrations during 48 hours

Neurodevelopment/Cognition after Hypoglycemia
Outcome at 2 Years after Dextrose Gel Treatment for Neonatal Hypoglycemia: Follow-Up of a Randomized Trial

Deborah L. Harris, PhD1,2, Jane M. Alsweiler, FRACP, PhD2, Judith M. Ansell, PhD2, Gregory D. Gamble, MSc2, Benjamin Thompson, PhD3, Trecia A. Woudes, PhD4, Tzu-Ying Yu, PhD3, and Jane E. Harding, FRACP, DPhil2, on behalf of the Children with Hypoglycaemia and their Later Development (CHYLD) Study Team*

% Neurosensory Impairment

% Processing Difficulty

J Pediatr 2016; 170:54-9
Neonatal hypoglycemia was associated with a dose-dependent increased risk of poor executive function and visual motor function at 4.5 years, may influence later learning.
Other Hypoglycemia Development Studies (Observational)

- **Lucas, et al** (1988): PT <1850 g, n=661, ≤45 mg/dL on ≥3 days, lower 18 month Bayley scores
- **Brand, et al** (2005): Healthy Term LGA, <40 mg/dL at 1 hour and <45 mg/dL thereafter, n=75, no difference on 4 year IQ test
- **Tin, et al** (2012): <32 weeks, n=76, ≤45 mg/dL on ≥3 days, no difference in 15 year IQ

*BMJ* 1988;297:1304-8; *Arch Dis Child* 2005;90:78-81; *Pediatrics* 2012;130:e1497-503
Bottom Line

• Eminence-based recommendations from the Pediatric Endocrine Society *(50 mg/dL)*
Bottom Line

• Eminence-based recommendations from the Pediatric Endocrine Society (50 mg/dL)

• Our retrospective study (45 mg/dL)
Bottom Line

• Eminence-based recommendations from the Pediatric Endocrine Society (50 mg/dL)
• Our retrospective study (45 mg/dL)
• Prospective Sugar Babies study (47 mg/dL)
Bottom Line (Opinion)

- Eminence-based recommendations from the Pediatric Endocrine Society (50 mg/dL)
- Our retrospective study (45 mg/dL)
- Prospective Sugar Babies study (47 mg/dL)
- **Opinion**: Maintain newborn glucose concentrations >45-50 mg/dL
Bottom Line (Opinion)

- Eminence-based recommendations from the Pediatric Endocrine Society (50 mg/dL)
- Our retrospective study (45 mg/dL)
- Prospective Sugar Babies study (47 mg/dL)

**Opinion**: Maintain newborn glucose concentrations >45-50 mg/dL

“opinion is the medium between knowledge and ignorance” -- *Plato*
Proposed Randomized Controlled Trial for the Treatment of Asymptomatic Transient Neonatal Hypoglycemia

• During the first 48 hours, at-risk newborns will be randomized to the AAP vs PES treatment guidelines
• Treatment will be with 40% dextrose gel
• 1⁰ outcome: Executive Function, Visual-Motor Integration, and IQ at 3 years (and then at school age)
• RO1 application to be resubmitted
• Please contact me with any ideas
HIE and Glucose and PCO$_2$
Cellular Metabolism

Glucose → O₂ → ATP → CO₂ → H₂O
Cellular Metabolism

Glucose + O₂ \rightarrow ATP, CO₂, H₂O
Hypoxic Ischemic Brain Injury

Glucose

O₂

↓ ATP

↓ CO₂

↓ H₂O
Hypoxic Ischemic Brain Injury

Glucose

$O_2$

$\downarrow$ ATP

$\downarrow$ CO$_2$

$\downarrow$ H$_2$O

$\uparrow$ Lactate
Glycemic Profile in Infants with HIE

- Multi-organ failure
- Liver injury
- Depletion of glycogen stores
  - Gluconeogenesis
  - Hypoglycemia

- HIE
  - With acute brain injury, damaged brain tissue has decreased metabolism
  - Hyperglycemia
Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study.

Hypoglycemia is associated with 6.2 increased risk of unfavorable outcome.

Hyperglycemia is associated with 2.7 increased risk of unfavorable outcome.
Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effect of hypothermia therapy on risk of death and/or severe neurological disability at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of primary outcome</td>
</tr>
<tr>
<td></td>
<td>Cooled n/total (%)</td>
</tr>
<tr>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>54/99 (55)</td>
</tr>
<tr>
<td>12-hour Glucose profile</td>
<td></td>
</tr>
<tr>
<td>Normoglycaemia</td>
<td>23/47 (49)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>27/47 (58)</td>
</tr>
</tbody>
</table>

* The reference group consists of infants that are ‘not cooled’ for all relative risk and RD models.
† The NNT is calculated from the aRD point estimate and presents the number of infants that would have to be cooled in order to prevent one unfavourable 18-month outcome. The NNT is rounded to the next highest whole integer. The NNT is not estimated for the hypoglycaemia group since the point estimate does not reflect a risk reduction conferred by hypothermia therapy.

aRD, adjusted risk difference; aRR, adjusted risk ratio; NNT, number needed to treat.
Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study

Table 3  Effect of hypothermia therapy on risk of death and/or severe neurological disability at 18 months

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate of primary outcome</th>
<th>Relative difference* in risk</th>
<th>Absolute difference* in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cooled n/total (%)</td>
<td>Not cooled n/total (%)</td>
<td>Unadjusted RR (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>54/99 (55)</td>
<td>64/95 (67)</td>
<td>0.81 (0.64 to 1.02)</td>
</tr>
<tr>
<td>12-hour Glucose profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycaemia</td>
<td>23/47 (49)</td>
<td>21/42 (50)</td>
<td>0.98 (0.64 to 1.49)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>4/5 (80)</td>
<td>11/13 (85)</td>
<td>0.95 (0.58 to 1.55)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>27/47 (58)</td>
<td>32/40 (80)</td>
<td>0.72 (0.54 to 0.96)</td>
</tr>
</tbody>
</table>

* The reference group consists of infants that are ‘not cooled’ for all relative risk and RD models.
† The NNT is calculated from the aRD point estimate and presents the number of infants that would have to be cooled in order to prevent one unfavourable 18-month outcome. The NNT is rounded to the next highest whole integer. The NNT is not estimated for the hypoglycaemia group since the point estimate does not reflect a risk reduction conferred by hypothermia therapy.

aRD, adjusted risk difference; aRR, adjusted risk ratio; NNT, number needed to treat.
Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate of primary outcome</th>
<th>Relative difference* in risk</th>
<th>Absolute difference* in risk</th>
<th>NNT†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cooled n/total (%)</td>
<td>Not cooled n/total (%)</td>
<td>Unadjusted RR (95% CI)</td>
<td>aRR (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>54/99 (55)</td>
<td>64/95 (67)</td>
<td>0.81 (0.64 to 1.02)</td>
<td>0.77 (0.63 to 0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>aRR (95% CI)</td>
</tr>
<tr>
<td>12-hour Glucose profile</td>
<td></td>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>aRR (95% CI)</td>
</tr>
<tr>
<td>Normoglycaemia</td>
<td>23/47 (49)</td>
<td>21/42 (50)</td>
<td>0.98 (0.64 to 1.49)</td>
<td>0.95 (0.70 to 1.27)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>4/5 (80)</td>
<td>11/13 (85)</td>
<td>0.95 (0.58 to 1.55)</td>
<td>1.03 (0.52 to 2.00)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>27/47 (58)</td>
<td>32/40 (80)</td>
<td>0.72 (0.54 to 0.96)</td>
<td>0.80 (0.66 to 0.99)</td>
</tr>
</tbody>
</table>

* The reference group consists of infants that are ‘not cooled’ for all relative risk and RD models.
† The NNT is calculated from the aRD point estimate and presents the number of infants that would have to be cooled in order to prevent one unfavourable 18-month outcome. The NNT is rounded to the next highest whole integer. The NNT is not estimated for the hypoglycaemia group since the point estimate does not reflect a risk reduction conferred by hypothermia therapy.
 aRD, adjusted risk difference; aRR, adjusted risk ratio; NNT, number needed to treat.
Rate of Death and/or Disability in Infants with HIE is Increased with Greater Exposure to Hypocapnia

Cumulative exposure (in hours) to hypocapnia (<35 mm Hg)

Lower $\text{PCO}_2$ is Newborns with HIE is Associated with Unfavorable Outcomes

This is Your Baby’s Brain
This is Your Baby’s Brain on Low Glucose
Any Questions?
Management of asymptomatic at risk-newborns: 35-36 weeks, IDMs, SGA, and LGA using AAP vs PES Guidelines

- Feed: breastfeeding, donor breastmilk, or formula
- POC glucose: use Nova StatStrip
- Dextrose gel: 0.5 ml/kg massaged into left and right buccal mucosa
- AAP: If newborn has POC glucose >45 mg/dL (4-48 h) and follow-up value is ≤45 mg/dL, then return to age-based algorithm for management; if remains low, admit to the NICU
- PES: If newborn has POC glucose >50 mg/dL (Birth-48 h) and follow-up value is ≤50 mg/dL, return to algorithm for management; if remains low, admit to the NICU
- May give up to 3 doses of dextrose gel
Achievement Test Scores for Hypoglycemic and Normoglycemic Newborns

Unadjusted
# Comparison of Neurodevelopmental Studies

<table>
<thead>
<tr>
<th></th>
<th>Lucas</th>
<th>Brand</th>
<th>Tin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td>1988 (early ‘80s)</td>
<td>2005 (‘97-98)</td>
<td>2012 (‘90-91)</td>
</tr>
<tr>
<td><strong>Multicenter</strong></td>
<td>Yes, 5</td>
<td>No</td>
<td>Yes, 13</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>LBW &lt;1850 g</td>
<td>Healthy term LGA</td>
<td>&lt;32 weeks</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>661</td>
<td>75</td>
<td>566</td>
</tr>
<tr>
<td><strong>Age at FU</strong></td>
<td>1.5 years</td>
<td>4 years</td>
<td>15 years</td>
</tr>
<tr>
<td><strong>% FU</strong></td>
<td>92%</td>
<td>64%</td>
<td>81%</td>
</tr>
<tr>
<td><strong>Hypoglycemia defn</strong></td>
<td>≤45 mg/dL on ≥3 days</td>
<td>&lt;40 at 1 hr, &lt;45 mg/dL after ≤45 mg/dL on ≥3 days</td>
<td></td>
</tr>
<tr>
<td><strong>N (%) hypoglycemic</strong></td>
<td>104 (16%)</td>
<td>60 (80%)</td>
<td>47 (8%)</td>
</tr>
<tr>
<td><strong>Plasma glucose</strong></td>
<td>Lab (plasma)</td>
<td>? (blood glucose)/plasma DOL #1</td>
<td>Lab (blood glucose)</td>
</tr>
<tr>
<td><strong>Duration of monitoring</strong></td>
<td>9 weeks</td>
<td>10 days</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pre-set sampling</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Prospective data collection</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Prospective observational</td>
<td>Prospective</td>
<td>Prospective case-control</td>
</tr>
<tr>
<td><strong>Adjusted for SES/Mat Ed</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Tests</strong></td>
<td>Bayley</td>
<td>Denver, Behavior, IQ</td>
<td>IQ</td>
</tr>
<tr>
<td><strong>Hypoglycemia: poor outcome</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*BMJ 1988;297:1304-8*
## Comparison of Neurodevelopmental Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Lucas 1988 (early ‘80s)</th>
<th>Brand 2005 (‘97-98)</th>
<th>Tin 2012 (‘90-91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter</td>
<td>Yes, 5</td>
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<td>Population</td>
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<td>81%</td>
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<td>Hypoglycemia defn</td>
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</tr>
<tr>
<td>Plasma glucose</td>
<td>Lab (plasma)</td>
<td>? (blood glucose)/plasma</td>
<td>Lab (blood glucose)</td>
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<tr>
<td>Duration of monitoring</td>
<td>9 weeks</td>
<td>DOL #1</td>
<td>10 days</td>
</tr>
<tr>
<td>Pre-set sampling</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Prospective data collection</td>
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<td>Yes</td>
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<td>Study design</td>
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<td>Prospective</td>
<td>Prospective case-control</td>
</tr>
<tr>
<td>Adjusted for SES/Mat Ed Tests</td>
<td>Yes</td>
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<td>No</td>
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<tr>
<td>Tests</td>
<td>Bayley</td>
<td>Denver, Behavior, IQ</td>
<td>IQ</td>
</tr>
<tr>
<td>Hypoglycemia: poor outcome</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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Arch Dis Child 2005;90:78-81
## Comparison of Neurodevelopmental Studies

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<tr>
<th>Year</th>
<th>Multicenter</th>
<th>Population</th>
<th>N</th>
<th>Age at FU</th>
<th>% FU</th>
<th>Hypoglycemia defn</th>
<th>N (%) hypoglycemic</th>
<th>Plasma glucose</th>
<th>Duration of monitoring</th>
<th>Pre-set sampling</th>
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<tr>
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<td>LBW &lt;1850 g</td>
<td>661</td>
<td>1.5 years</td>
<td>92%</td>
<td>≤45 mg/dL on ≥3 days</td>
<td>104 (16%)</td>
<td>Lab (plasma)</td>
<td>9 weeks</td>
<td>No</td>
<td>Yes</td>
<td>Prospective observational</td>
<td>Yes</td>
<td>Bayley</td>
<td>Yes</td>
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<tr>
<td>Brand 2005 (‘97-98)</td>
<td>No</td>
<td>Healthy term LGA</td>
<td>75</td>
<td>4 years</td>
<td>64%</td>
<td>&lt;40 at 1 hr, &lt;45 mg/dL after</td>
<td>60 (80%)</td>
<td>? (blood glucose)/plasma</td>
<td>DOL #1</td>
<td>Yes</td>
<td>Yes</td>
<td>Prospective</td>
<td>No</td>
<td>Denver, Behavior, IQ</td>
<td>No</td>
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<tr>
<td>Tin 2012 (’90-91)</td>
<td>Yes, 13</td>
<td>&lt;32 weeks</td>
<td>566</td>
<td></td>
<td></td>
<td>≤45 mg/dL on ≥3 days</td>
<td>47 (8%)</td>
<td>Lab (blood glucose)</td>
<td>10 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Prospective case-control</td>
<td></td>
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*Note: *Pediatrics 2012;130:e1497-503
## Comparison of Neurodevelopmental Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Lucas</th>
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<tr>
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<td>Population</td>
<td>LBW &lt;1850 g</td>
<td>Healthy term LGA</td>
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<td>23-42 weeks</td>
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<td>1.5 years</td>
<td>4 years</td>
<td>15 years</td>
<td>10 years</td>
</tr>
<tr>
<td>% FU</td>
<td>92%</td>
<td>64%</td>
<td>81%</td>
<td>72%</td>
</tr>
<tr>
<td>Hypoglycemia defn</td>
<td>≤45 mg/dL on ≥3 days</td>
<td>&lt;40 at 1 hr, &lt;45 mg/dL after</td>
<td>≤45 mg/dL on ≥3 days</td>
<td>&lt;35, &lt;40, &lt;45 mg/dL</td>
</tr>
<tr>
<td>N (%) hypoglycemic</td>
<td>104 (16%)</td>
<td>60 (80%)</td>
<td>47 (8%)</td>
<td>89 (6.4%); 143 (10.3%); 269 (19.3%)</td>
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<tr>
<td>Plasma glucose</td>
<td>Lab (plasma)</td>
<td>? (blood glucose)/plasma</td>
<td>Lab (blood glucose)</td>
<td>Lab (plasma)</td>
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<td>Duration of monitoring</td>
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<td>DOL #1</td>
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<td>3 hours</td>
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<tr>
<td>Pre-set sampling</td>
<td>No</td>
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<td>Yes</td>
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<td>Study design</td>
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<td>Yes</td>
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<td>Achievement tests</td>
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<td>Yes</td>
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<td>Yes</td>
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*JAMA Pediatr* 2015;169:913-21
Blood Ketones After 48 Hours of Age in Breastfed Infants and the Relationship to Glucose Concentrations
Pattern of Glucose Concentrations for ELGAN, PT, LPT, and FT Newborns with 95% CI

Kaiser et al. Neonatology
Aerobic Cellular Respiration

\[ C_6H_{12}O_6 + 6 \text{ (O}_2 \text{)} \rightarrow 6 \text{ (CO}_2 \text{)} + 6 \text{ (H}_2\text{O)} + \text{ ATP} \]

Glucose  Oxygen  Carbon Dioxide  Water  Energy