



Update on Neonatal Hypoglycemia: Did the PES Recommendations have any effect and where next?

Paul S. Thornton MD
Medical Director Congenital Hyperinsulinism Center
Cook Children's Medical Center



How frequent are the serious hypoglycemic disorders



- Genetic HI 1:25000
- Hypopituitarism 1:25000
- GSD 1:50-100,000
- FAO 1: 6-10,000
- Acquired HI
 - PSHI 1:1200-2500



Rare genetic diseases
1:5000



1:1000



PES Recommendations



- Who to investigate prior to home
 - Neonates with severe hypoglycemia (e.g., an episode of symptomatic hypoglycemia or requiring iv dextrose to treat hypoglycemia)
 - Neonates unable to consistently maintain pre-prandial plasma glucose concentrations > 50 mg/dL by day 3 or > 60 mg/dL thereafter
 - Family history of a genetic form of hypoglycemia
 - Congenital syndromes (e.g., Beckwith-Wiedemann), abnormal physical features (e.g., midline facial malformations, microphallus)



Increase in diagnosis of etiology of hypoglycemia



- Skovrlj, Marks and Rodd:
 - Compared management practices and outcomes pre PES guidelines (2011-2015) to post PES (2016)
 - Results
 - Increase in number of consults to Ped Endo service
 - Average 6 per annum pre versus 33 per annum post
 - 52/58 had HI
 - 86% required IV glucose, 50% diazoxide
 - In 2016 40% of patients detected because of glucose between 46 and 60
 - Conclusion: We postulate that infants diagnosed using the more stringent 2015 guidelines have real disease based on the protracted medical management required



Reduced NICU admissions



- A Quality-Improvement Initiative to Reduce NICU Transfers for Neonates at Risk for Hypoglycemia (LeBlanc et al PEDIATRICS Volume 141, number 3, March 2018)
 - Infants at risk of hypoglycemia were subjected to a QI project
 - 208 baseline and 270 intervention
 - Added Skin to Skin contact, early feeding and glucose test by 90 mins as recommended by AAP protocol;
 - Results:
 - NICU transfer rate dropped from 17% to 3% (national average 10%)
 - 4/5 babies who would have been transferred were not
 - Unnecessary transfers (babies who did not need IV dextrose) dropped from 5% to 0.3%
 - **No change in the number of symptomatic hypoglycemia babies**



Hypoglycemia in low risk babies



- Hypoglycemia in unmonitored full-term newborns—a surveillance study from 04/14 to 03/16.(Flavin et al *Paediatrics & Child Health*, 2018, Vol. 23, No. 8)
- Evaluated the number of healthy term babies not at “traditional” risk of hypoglycemia who developed hypoglycemia over a 2y period
- Inclusion criteria
 - 37 to 42 weeks
 - 2500-bt wt-3999g (AGA)
 - Plasma glu <2mmol/L



Results



- 93 case = 1: 8378 births
- 78% had perinatal stress
- 83% post natal ward or home
- 39% presented in first 6 hours
- 98% had symptoms
 - 35% jitteriness, 28% poor feeding, 25% hypothermia
 - 15% hypotonia, 15% lethargy
 - 12% seizures, 12% apnoea



Canadian study continued



- 20% had major clinical signs of seizure or apnoea
 - Glucose was 0.8 mmol/L (14mg/dL) compared to rest 1.6 mmol/L (29mg/dl)
 - Hypoglycemia detected later (>6 hr of life) compared to rest
- 98% required IV dextrose
- MRI performed on 14% of the babies and 78% of the MRIs were abnormal
- 21% babies at time of discharge were determined to be neurologically abnormal
- 52% (46) had evaluation for cause and 37% (17) had a cause found
 - Hyperinsulinism found in 14/17



Bailey et al: Prolonged transitional hypoglycaemia



- Reviewed the charts of 471 babies with neo hypo and in hospital for >3 days
- Found 39 infants
 - Lasted >3 days
 - Required IV dextrose >8 mg/kg/min and unable to quickly wean
- Evaluated risk factors
 - male sex, IUGR, birth by emergency caesarean, resuscitation at birth, initial respiratory distress



Reality



- Critical samples done in 28/39 patients
 - 100% patients had elevated insulin at time of hypoglycemia
 - 100% had suppressed Beta OHB
 - 100% had suppressed FFA
- Meaning that 100% had acquired PSHI
 - Risk factors are exactly those reported by PES
 - Outcomes in these babies are poor in 20-40% (Avatapelle)
- MRI in 3/5 babies were abnormal with severe restricted diffusion in periventricular white matter



Barrero-Castillero A: J Perinatol Aug 2020



- Glucose concentrations in enterally fed **Pre-term infants in NICU**
 - Prevalence of glucose levels < 70 mg/dL on full enteral nutrition and assess impact on glucose monitoring practices
 - 1717 infants >2 days old and >48 hours off iv fluids
 - 2008-2019
 - compared pre PES to post PES
 - 5917 poc glucose
 - Found glucose levels > 70 mg/dL in 76%
 - 60-69 mg/dL in 16%
 - 50-59 mg/dL in 6% (1.9% babies last glucose pre d/c < 60 mg/dL)
 - < 50 mg/dL in 1.3% (0% babies last glucose < 50 mg/dL)



Results



- Rate of hypo <70
 - SGA 35%, LGA 21% and AGA 19%
- Babies had 1-97 measurement (24% had >3 tests)
- 13 critical samples done in the babies with the highest frequency of tests (13/76 babies)
 - Rate of critical samples 0.4% pre PES v 2% post
 - Proportion of babies with >4 tests increased post PES
 - LOS for those with >4 tests was 2.84 extra days post PES
- Statement
 - More frequent testing leads to longer length of stays
 - No pathological hypoglycemia found



The hidden facts supports PES recommendations



■ Facts

- 3.4 tests per baby with 46% having 1 test
- All 13 critical samples were abnormal (pathological hypoglycemia 9/13 had HI) and all had hypoglycemia resolve prior to d/c but only 4 had fasting study
- When those with pathological hypoglycemia were removed from the analysis no increase LOS
- The baby with 97 glucose measure had hyperglycemia not hypoglycemia



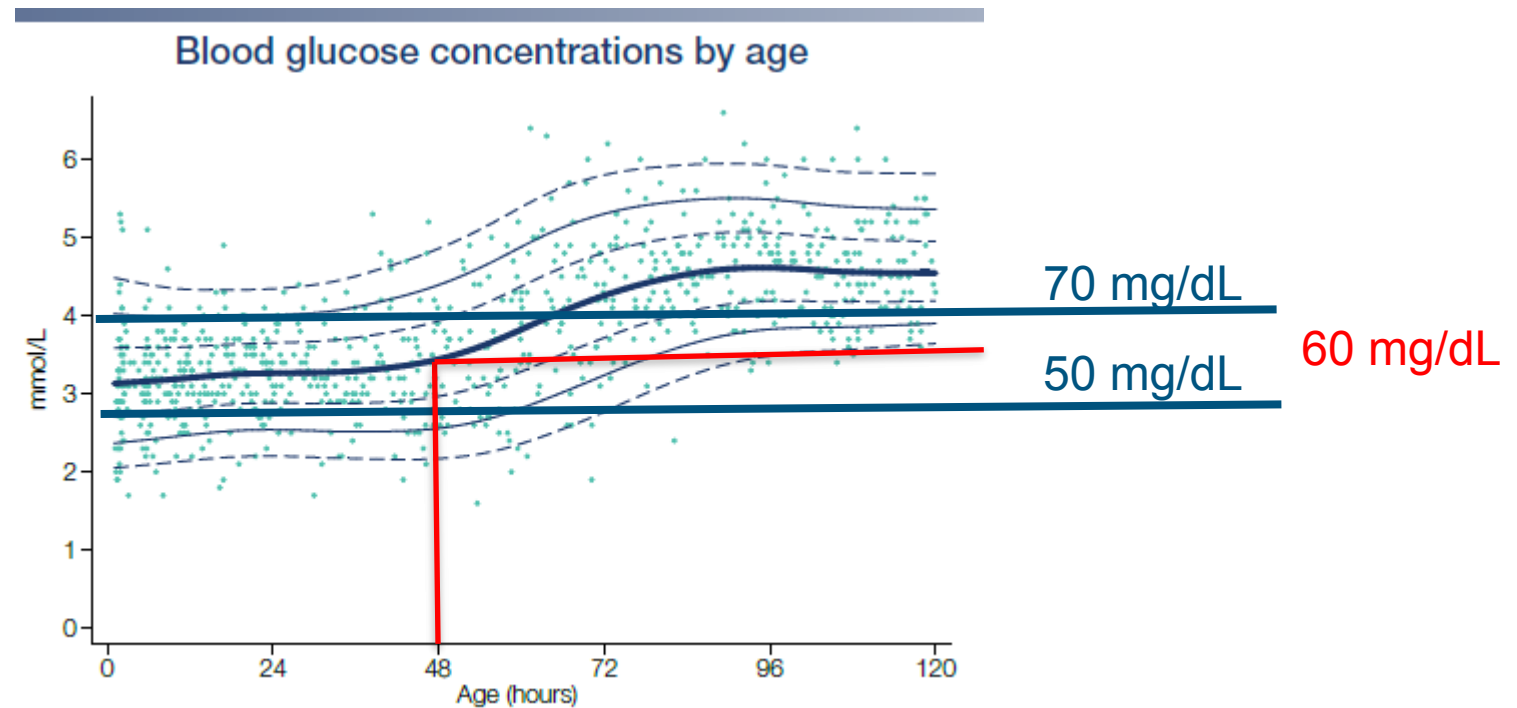
Harris et al GLOW babies



- Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW) Study
 - Plasma glucose and CGM data over 5 days in a group of 67 healthy term breast fed babies
 - Showed glucose profile was very similar to previous studies and that babies normalize their glucose levels by 4 days of age to equal adult levels
 - Confirmed the PES expert working group publication on normal glucose levels in babies transitioning from intra uterine life to the outside world



Glow Study breast fed babies



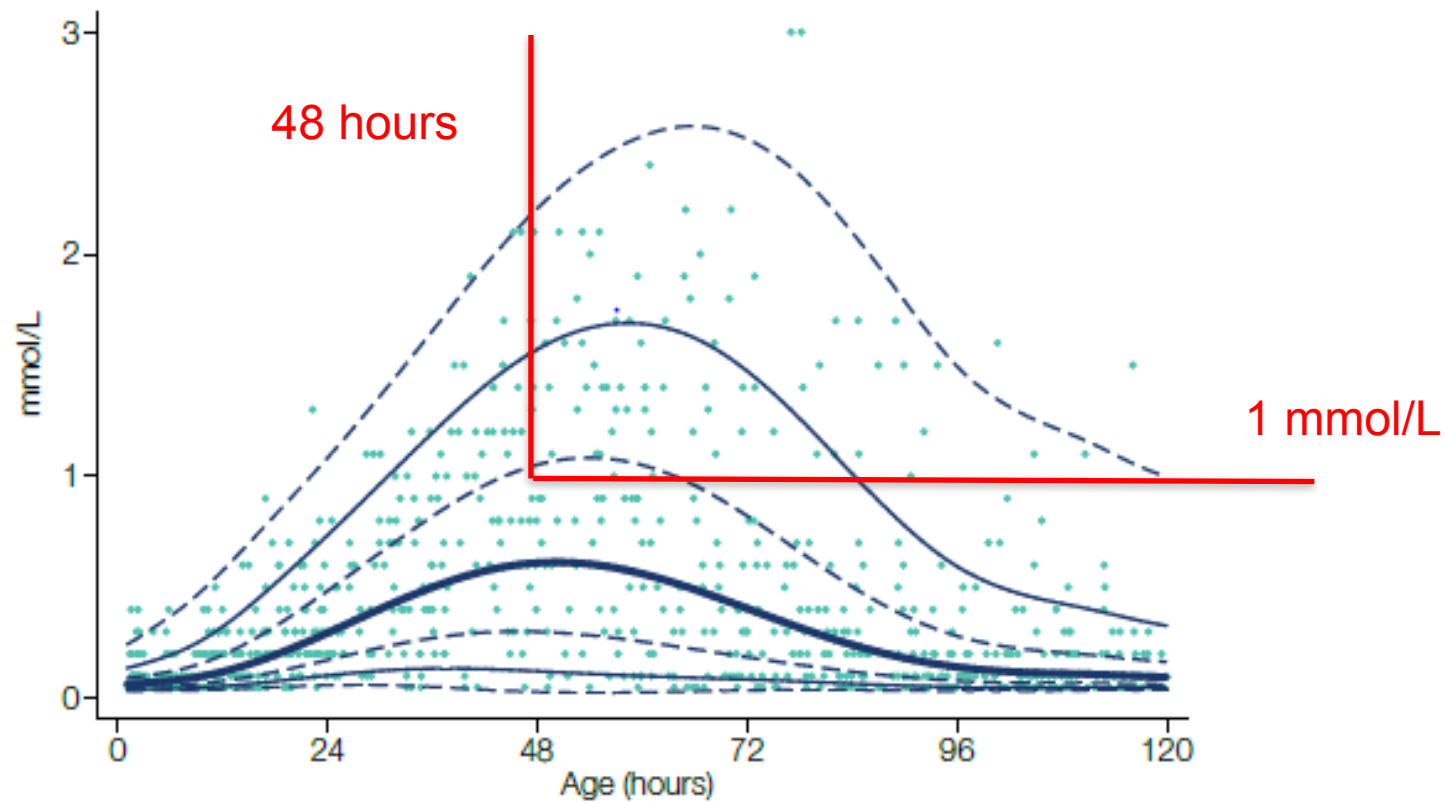
Alternative cerebral fuels in healthy babies: The Glucose in Well Babies (GLOW) Study.
Deborah Harris J Peds 2020



Glow Study breast fed babies Part 2: Alternate fuels.



Beta-hydroxybutyrate concentrations by age



Glow study Implications



- There are two phases of glucose regulation in healthy term breast fed babies
 - Transitional hypoglycemia
 - Hypoketotic hypoglycemia similar to HI
 - Starvation induce hypoglycemia
 - Hyperketotic hypoglycemia
 - Likely not found in most bottle fed infants



New approach to Neo Hypoglycemia



- If:
 - Glucose levels persistently <50 for the first 48 and <60 after that **or**
 - Neuroglycopenic symptoms **or**
 - Required IV glucose to treat
- Measure plasma glucose and ketones
 - If hyper-ketotic and well likely starvation: Feed and safe for home
 - If Hypoketotic need further evaluation



Question Time

- Thank you

