Vishal Pandey, MD

Dr. Pandey went to Med school in India. He did his Neonatology fellowship and Pediatric residency from Case Western University, Cleveland. During his fellowship his research was focused on the placenta and fetal membranes. He joined the University of Kansas in 2009 and currently is Clinical Associate professor in Pediatrics at UMKC and University of Kansas. His research interest continues to be the effect of placental insufficiency on the long term growth of ELBW infants and to understand how does placental insufficiency lead to hypoglycemia in growth restricted low birth weight neonates.

Gangaram Akangire, MD

Dr. Akangire is currently a Neonatologist at Children's Mercy Kansas City and Associate Professor of Pediatrics at UMKC. He completed his medical school in India and then Master's in Biomedical Engineering at Louisiana Tech University, Pediatric Residency at Texas Tech University in Amarillo, TX and Neonatology Fellowship at Children's Mercy and stayed on staff after fellowship. He has published several peer reviewed publications in reputed journals. He continues to do clinical research on outcomes of infants with BPD needing tracheostomy and neonatal sepsis.

Continuous Glucose monitoring in Newborns- Are we there yet?

Vishal Pandey, MD
Neonatologist, Children's Mercy Hospital,
Associate Professor Pediatrics,
UMKC, School of Medicine,
Kansas City, MO

BEST CHILDREN'S HOSPITALS U.S.News RANKED IN 9 SPECIALTIES 2021-22
MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER
UMKC School of Medicine
KU SCHOOL OF MEDICINE The University of Kansas
LOVE WILL.
Children's Mercy

Objectives

- Describe the physiological and pathological changes in plasma glucose in the Neonatal period and their implications.
- Evaluate the evidence of benefit of Continuous glucose monitoring (CGM) in Newborns
- Identify the risks and shortcomings of monitoring all neonates with CGM
- Compare the various commercially available monitors

Hypoglycemia

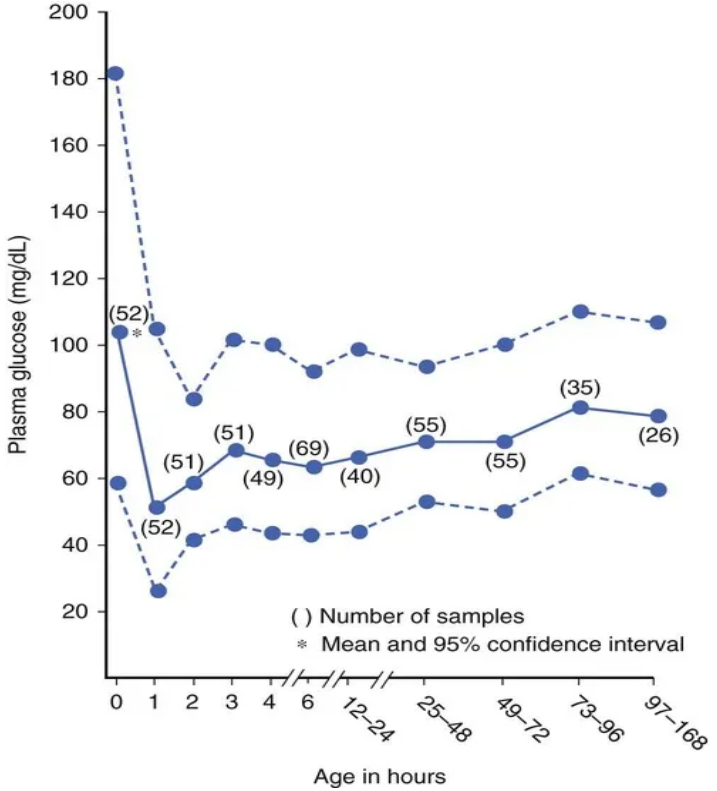
- American Academy of Pediatrics:Birth-4 hours, 4-24 hours

- Pediatric Endocrine Society: >48 hours and beyond

Adamkin DH, Polin RA. Imperfect Advice: Neonatal Hypoglycemia. J Pediatr. 2016 Sep;176:195-6. doi: 10.1016/j.jpeds.2016.05.051. Epub 2016 Jun 11.

Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Levitsky LL, Murad MH, Rozance PJ, Simmons RA, Sperling MA, Weinstein DA, White NH, Wolfsdorf JI; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015 Aug;167(2):238-45.

Postnatal Plasma glucose values in normal neonates



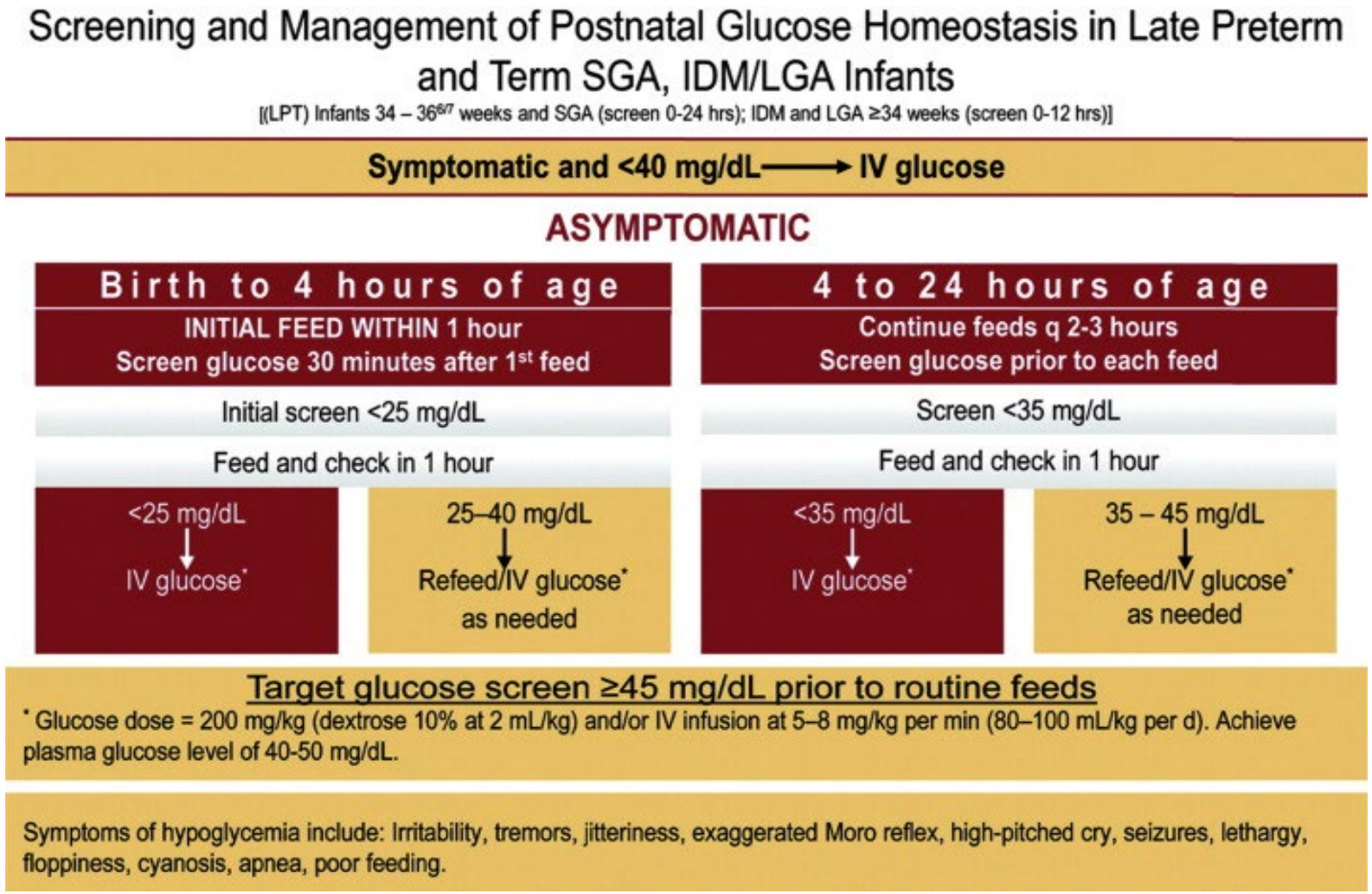
Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. J Pediatr. 1986 Jul;109(1):114-7.

Neonatal Glucose metabolism (Transitional)

- Pre Natal- Maternal supply, transplacental transfer, Glycogen+ Adipose tissue storage, high insulin to glycogen ratio.
- Role of Insulin (glycogen adipose tissue deposits)
- Postnatal- Glycogenolysis, Gluconeogenesis, Lipolysis, Digestion
- Role of glucagon-induces PEP-CK(gluconeogenesis ability by 4-6 hours).
- Role of catecholamines/ epinephrine- Lipolysis-FFA->Glycerol, AA for gluconeogenesis, FA oxidation, Ketone bodies.

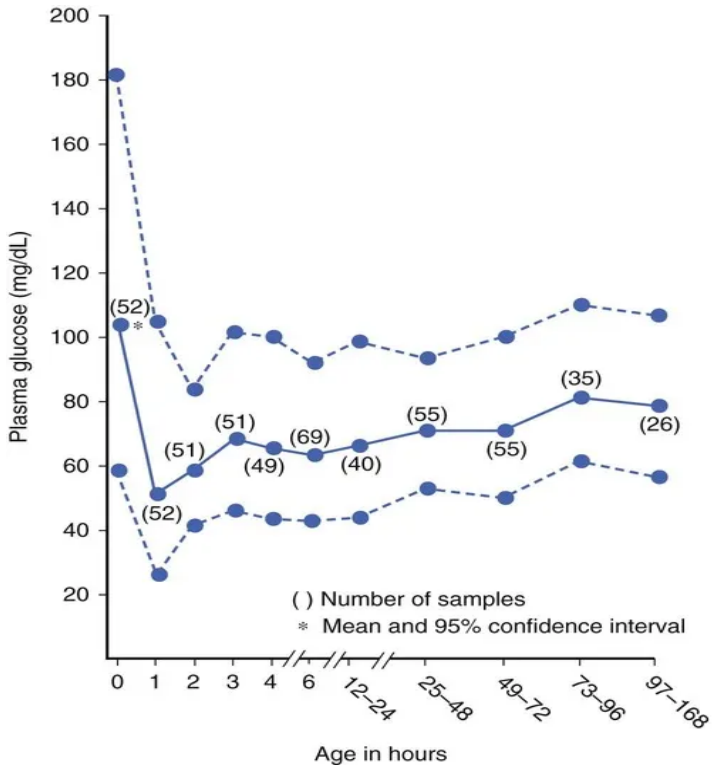
Risk factors for Neonatal Hypoglycemia

- Prematurity (<37 weeks)
- Small for gestational age or IUGR
- Large for Gestational Age
- Maternal Diabetes
- Perinatal stress, post maturity
- Maternal use of oral hypoglycemics or beta adrenergic
- Family history of congenital forms of hypoglycemia
- Congenital Syndromes associated with hypoglycemia (Beckwith Weidman and Kabuki syndrome)



D.H. Adamkin and Committee on Fetus and Newborn Pediatrics, 127 (2011), p. 175

Transitional Hypoglycemia



- Relative hyper-insulinemic
- Low Ketones
- Relatively Preserved Glycogen
- Mean Glucose 55-65 mg/dl

By 72 hours glucose level rise to those observed in older children and adults (>70 mg/dl)

Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. J Pediatr. 1986 Jul;109(1):114-7.

Other causes of Persistent hypoglycemia>48 hours

- Hyper insulinemic states, IDM, Perinatal stress-SGA/HIE/congenital hyperinsulinism
- Iatrogenic (abrupt cessation of high dextrose, UAC placement, Indomethacin, endocrine disorders)
- Inborn errors of metabolism
- Glycogen storage diseases
- Defects in Gluconeogenesis
- Inadequate substrates.

Post transitional blood glucose maintenance

- Feeds
- Glycogenolysis
- Gluconeogenesis

Table. Recognizing and managing neonates at increased risk for a persistent hypoglycemia disorder

Neonates at increased risk of hypoglycemia and require glucose screening:

1. Symptoms of hypoglycemia
2. Large for gestational age (even without maternal diabetes)
3. Perinatal stress
   a. Birth asphyxia/ischemia; cesarean delivery for fetal distress
   b. Maternal preeclampsia/eclampsia or hypertension
   c. Intrauterine growth restriction (small for gestational age)
   d. Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
4. Premature or postmature delivery
5. Infant of diabetic mother
6. Family history of a genetic form of hypoglycemia
7. Congenital syndromes (eg, Beckwith-Wiedemann), abnormal physical features (eg, midline facial malformations, microphallus)

Neonates in whom to exclude persistent hypoglycemia before discharge:

1. Severe hypoglycemia (eg, episode of symptomatic hypoglycemia or need for IV dextrose to treat hypoglycemia)
2. Inability to consistently maintain preprandial PG concentration >50 mg/dL up to 48 hours of age and >60 mg/dL after 48 hours of age
3. Family history of a genetic form of hypoglycemia
4. Congenital syndromes (eg, Beckwith-Wiedemann), abnormal physical features (eg, midline facial malformations, microphallus)

Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

Critical sample!

- Plasma Glucose <50 mg/dl
- Plasma insulin, beta-hydroxybutyrate, cortisol, and growth hormone.
- Bicarbonate, lactate, and free fatty acids

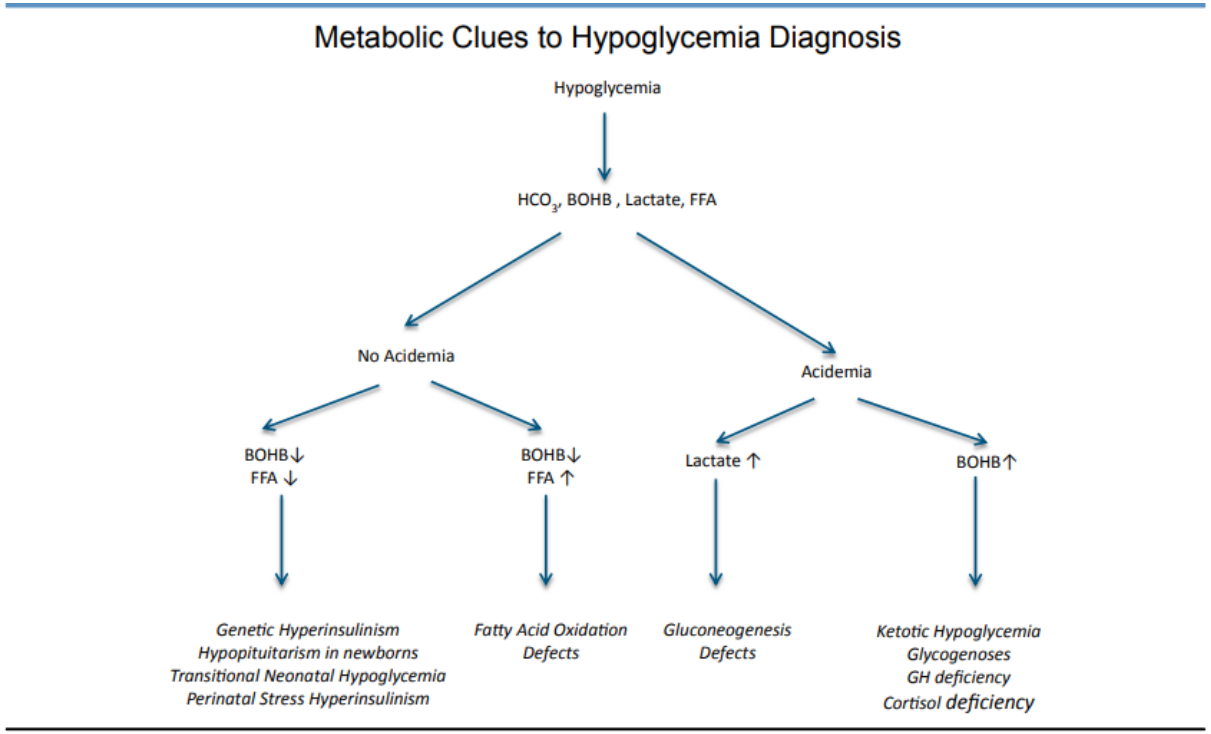
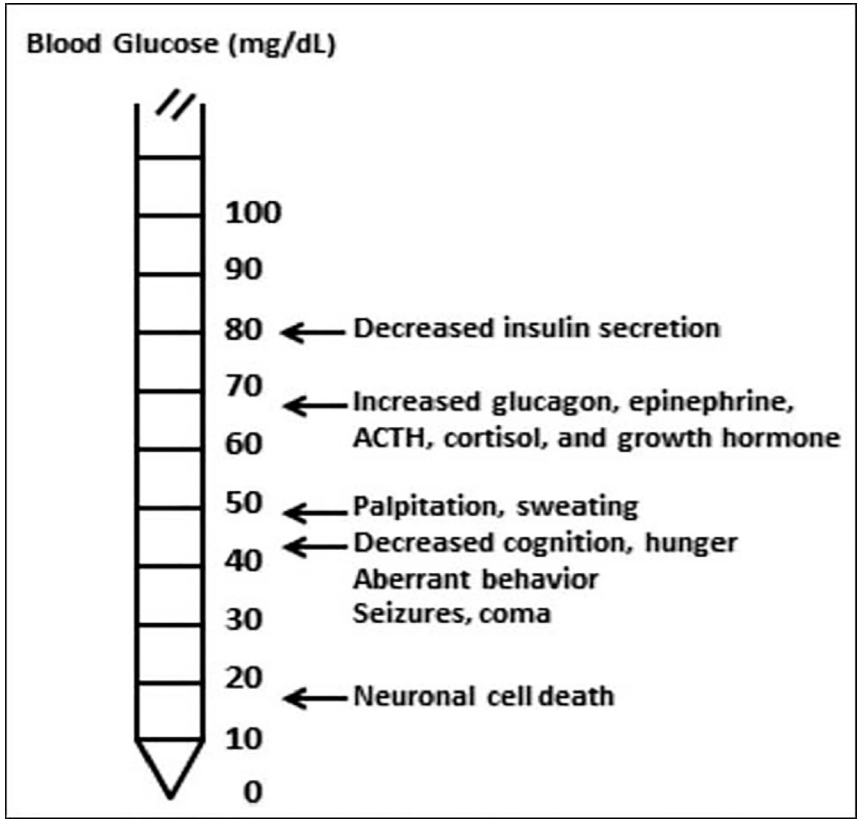


Figure. Algorithm showing how the major categories of hypoglycemia can be determined with information from the critical sample. *GH*, growth hormone.

Thornton PS, Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015 Aug;167(2):238-45.

Acute Hypoglycemia in adults



Moghissi E, Ismail-Beigi F, Devine RC. Hypoglycemia: minimizing its impact in type 2 diabetes. Endocr Pract. 2013 May-Jun;19(3):526-35.

Hypoglycemic brain Injury

- The adult brain accounts for more than one-half of total glucose consumption.
- Because of their disproportionately larger brain size relative to body mass, infants and young children have a 2- to 3-fold higher glucose utilization rate (4-6 mg/kg/min) per kilogram of body weight compared with adults

Hypoglycemic brain Injury Neonatal vs Adults

- Hypoglycemia, Ketone bodies and lactate
- Compensation includes increased Cerebral blood flow but due to low PG less crosses the BBB.
- Insufficient ketone production, lower amount of FFA and limited glycogen stores.
- BBB depends on plasma glucose concentration and activity of carrier medicated glucose transporters on vascular endothelium and cell membranes (Low level in neonates as compared to infants).

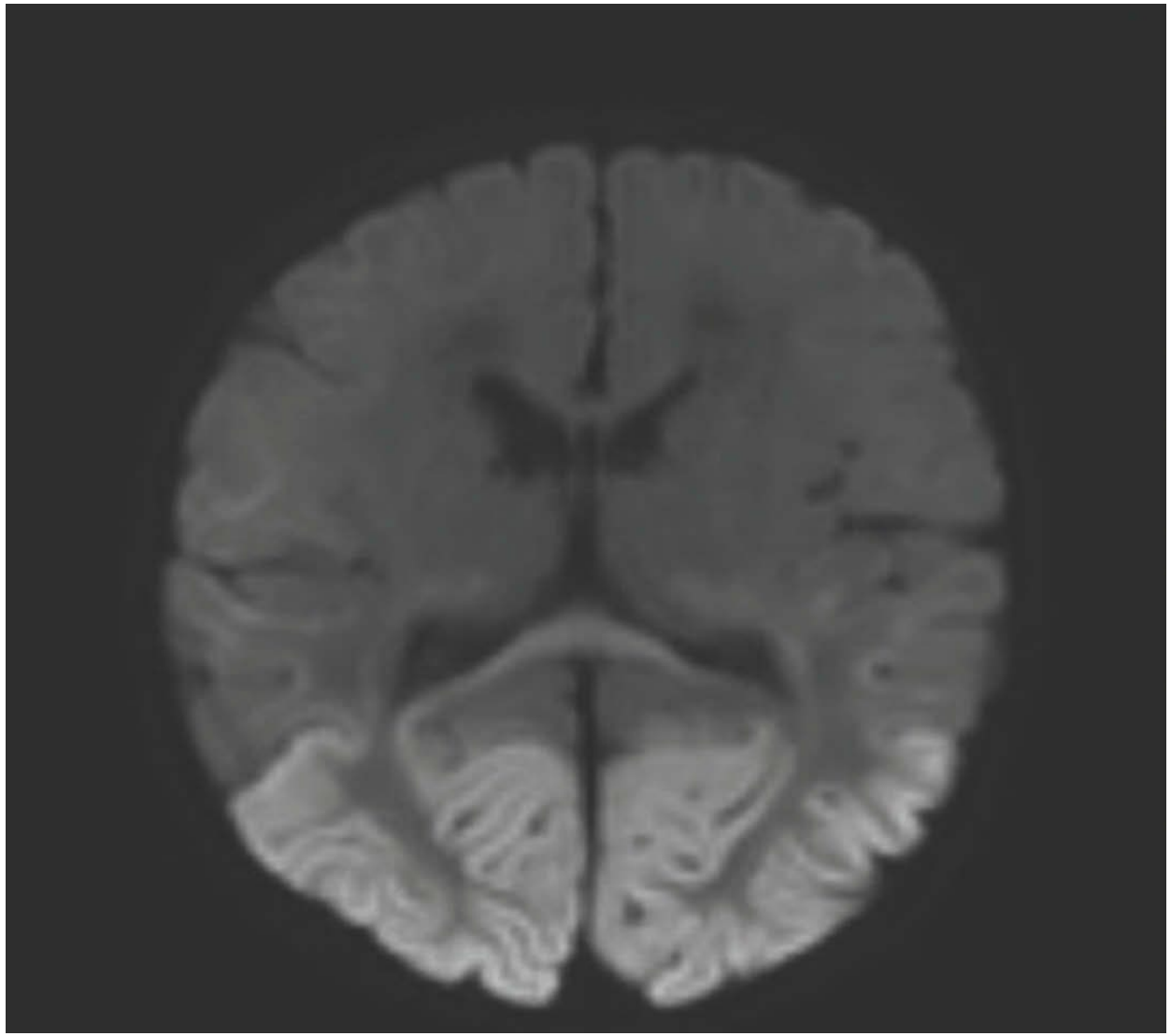
Hypoglycemia induced brain injury

- Decreased electrical activity, cell membrane breakdown and altered amino acid metabolism including the production of glutamate.
- NMDA type receptors ,leads to increased Na and Ca , hypoglycemia induced ATP depletion overwhelms the Na and Ca gradient restoration.
- Excessive Ca leads to cascade of protease, lipases activation. Alter mitochondrial function, free radical formation, changing neurotransmitter synaptic function-neuronal damage and necrosis.

Effects on the Neonatal brain

- Difficult to correlate clinical hypoglycemia with neuropathologic findings.
- MRIs show dilated lateral ventricles, cerebral edema, and loss of white and grey matter differentiation. Occipital and parieto- occipital cortex
- All infants had symptomatic hypoglycemia.
- No clinical corelates of these occipital cortex injuries have been reported.

Murakami Y, et al : **Cranial MRI of neurologically impaired children suffering from neonatal hypoglycaemia.** Pediatr Radiol. 1999 Jan;29(1):23-7.



- MRI diffusion-weight imaging (DWI) after neonatal hypoglycemia. Diffusion restriction in a neonate born at a gestational age of 38 weeks, evaluated with DWI four days after hypoglycemia onset. Showing diffusion restriction in the bilateral cortex of occipital lobes,
corpus callosum, and mesial part of occipital lobe with involvement of right-sided optic radiation—typical finding of neonatal HBI.

Amendoeira S, McNair C, Saini J, Habib S. **Glucose Homeostasis and the Neonatal Brain: A Sweet Relationship.** Neonatal Netw. 2020 May 1;39(3):137-146.

Congenital Hyper-insulinemic Hypoglycemia (25-50%) may be affected.

Table 1 Neurodevelopmental outcomes in the different populations.

Reference Country, years	Participants, *n*	Surgery, %	Abnormal neurodevelopment
Menni *et al.* 2001 [5] France, 1982–1998	90	70	**26%** (8% severe, 18% intermediate) 18% epilepsy
Meissner *et al.* 2003 [6] Germany (and other countries) Participants born 1975–2002	114	55	**44%** (18% severe, 26% mild) 25% epilepsy
Jack *et al.* 2003 [61] Australia, 1972–1998	55	54	**45%** (25% mild, 20% severe) 29% seizures 31% developmental delay +speech delay 18% cerebral palsy
Steinkrauss *et al.* 2005 [62] USA, 1980–2000	68	51	**31%** (16% severe, 15% moderate)
Mazor-Aronovitch *et al.* 2007 [54] Israel, 1982–1997	21	0	38% fine motor problems 33% gross motor problems 29% learning problems 19% hypotonia 4% speech problems
Avatapalle *et al.* 2013 [7] UK	67	18	**39%** (69% severe) 24% epilepsy 37% speech problems 36% motor delay 15% vision impairment 12% lower limb weakness
Lord *et al.* 2015 [8] USA, 1960–2008	121	100	**48%** 21% psychiatric/behavioural problems 18% speech problems 16% learning disabilities 13% seizures 11% physical impairment 10% ADHD, 2% autism
Helleskov *et al.* 2017 [57] Scandinavia, Russia, Eastern Europe, 2013–2016	75	33	**47%** 23% epilepsy 15% microcephaly 13% cerebral palsy 5% visual impairment
Ludwig *et al.* 2018 [9] Germany, 2008–2013	60	37	**46.7%** 39% motor problems 27% speech problems 16% cognitive 9% socio-emotional

Adverse neurodevelopment was observed in 26–48% of cases. The rate of neurodevelopment impairment is not reduced over time, despite the advances in imaging and genetic techniques.
Bold values indicate total percentage of patients with abnoral neurodevelopment. ADHD, attention-deficit hyperactivity disorder.

Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of **congenital hyperinsulinism-induced hypoglycaemia**. Diabet Med. 2019;36(1):9-21. doi:10.1111/dme.13823

Studies thus far on CGM

- Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, Randomised controlled trial
- The Children With Hypoglycemia and Their Later Development (CHYLD) study
- The Glucose in Well Babies (GLOW) Study.
- Sugar Babies Study
- Congenital Hyperinsulinemia

Evidence of benefit of CGM in Hypoglycemia
CHYLD and Sugar Babies study

- 477 at risk infants

- Surprisingly, there were long and undetected periods of hypoglycemia detected only by CGM.

- Neonatal hypoglycemia was not associated with increased risk of combined neurosensory impairment at 4.5 years but was associated with a dose-dependent increased risk of poor executive function and visual motor function, even if not detected clinically, and may thus influence later learning.

McKinlay CJD, Alsweiler JM, Anstice NS, et al. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. *JAMA Pediatr*. 2017;171(10):972-983. doi:10.1001/jamapediatrics.2017.1579

Glucose in Well Babies (GLOW)

- 67 Healthy , AGA during first 5 days.
- CGM showed Half were hypoglycemic at some point.
- Term infants born at <40 weeks gestation had lower plasma glucose concentrations than those born after 40 weeks and were also more likely to have episodes of low glucose concentration.

Table III. Numbers of infants who experienced low and high plasma and interstitial glucose concentrations over the first 120 hours after birth

Postnatal ages (h)	Plasma glucose concentrations (mg/dL [mmol/L])					Interstitial glucose concentrations (mg/dL [mmol/L])				
	Infants (n)*	<27 [< 1.5]	<36 [< 2.0]	<47 [< 2.6]	>144 [>8.0]	Infants (n)*	<27h [< 1.5]	<36 [< 2.0]	<47 [< 2.6]	>144 [> 8.0]
0-120	67	0	7 (10)	26 (39)	0	41	0	10 (24)	30 (73)	4 (10)
0-4	64	0	3 (5)	12 (19)	0	60	0	4 (7)	24 (40)	0
>4-12	62	0	1 (2)	11 (18)	0	63	1 (2)	9 (14)	31 (49)	0
0-12	67	0	4 (6)	18 (27)	0	57	1 (2)	9 (16)	33 (58)	0
>12-24	67	0	2 (3)	8 (12)	0	58	0	3 (5)	20 (34)	0
>24-48	67	0	2 (3)	9 (13)	0	57	0	5 (9)	20 (35)	0
>48-72	67	0	2 (3)	7 (10)	0	56	0	1 (2)	17 (30)	0
>72-96	67	0	0 (0)	1 (1)	0	53	0	0	1 (2)	0
>96-120	67	0	0 (0)	0 (0)	0	49	0	0	4 (8)	4 (8)

Data are number (%).

*For plasma glucose, n is the number of infants with any data in that epoch. For interstitial glucose, n is the number of infants with acceptable data for a minimum of 8 hours in the first 12 hours, 10 hours between 12 and 24 hours of age, 20 hours in each of the following 24-hour periods, and all of these for 0-120 hours.

Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW) Study. *J Pediatr*. 2020;223:34-41.e4. doi:10.1016/j.jpeds.2020.02.079

Unanswered questions

- Can an exact diagnosis of hypoglycemia ever be based on a single level of glucose?
- Why are the clinical signs of neonatal hypoglycemia so variable?
- What are the long-term effects of repeated asymptomatic hypoglycemia?
- How should we treat asymptomatic hypoglycemia in high-risk infants?
- What is the neurocognitive performance at school age of infants who have had the diagnosis of hypoglycemia and does executive function at 4.5 years predict academic outcomes?

Risks vs Benefits of CGM

In Transient, Asymptomatic, Healthy

May result in increased number of investigations, interventions, pain, NICU admissions, separation from mothers, cost, medicolegal implications

- Persistent, Symptomatic, At Risk

- MAY decrease Neurodevelopmental impairment

Hyperglycemia

- Causes , incidence, associations
- Short term and long-term effects-associations?
- Management- Decreasing Glucose Infusion rate vs Insulin therapy
- Side effects of Insulin therapy-hypoglycemia

Hyperglycemia in VLBW infants

- Definition blood glucose >125 or plasma glucose >150 mg/dl (close to renal glucose threshold in VLBW infants)
- Incidence in VLBW: Variable, 15-80% depending on definition. 2 studies using CGM 43-80% in first week of life.
- Typically resolves by 2 weeks likely due to improved insulin secretion. May be reflective of duration of monitoring.
- Recent study where monitoring continued until 28 days showed 20% had >180 mg/dl in 4th week.

Risk Factors

- Gestational age and Birth weight
- Longer duration of parenteral nutrition, higher carbohydrate intake
- Pain , sepsis, higher illness scores
- Medications: steroids, vasoactive agents, Theophylline

Pathogenesis of Hyperglycemia in Preterm infants.

- Relative hyperinsulinism due to defective processing of proinsulin to insulin, less insulin sensitive peripheral tissues, incomplete suppression of glucose release from liver.

- Insulin secretion in response to hyperglycemia is intact , however the secretion of proinsulin (less potent form) predominates 10 folds.

Complications

- Short term: Increased risk of death, IVH, sepsis, NEC, ROP and longer hospital stay in ELBW infants; Association vs causation?

- IVH- Rapid changes in serum osmolarity, however minimal changes in osmolarity with hyperglycemia, suggesting other factors: autoregulation, decreased glucose utilization by injured brain.

- Long term: ? Poor neurodevelopment, growth and metabolic health

Hypoglycemia during Insulin therapy

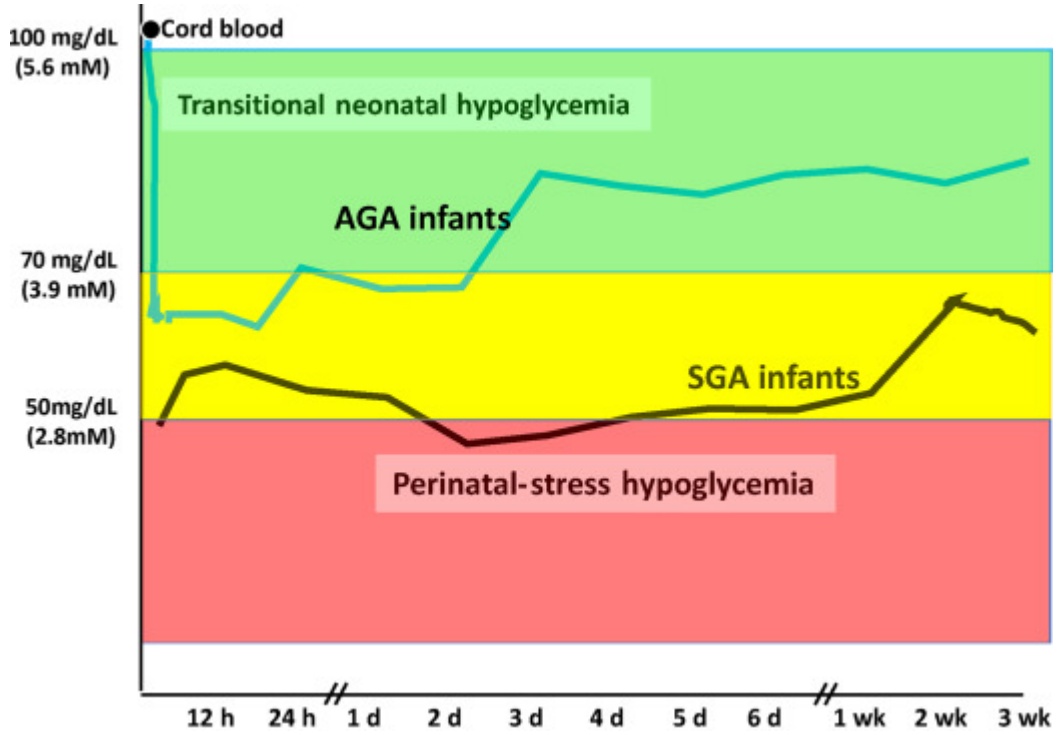
- RCT (N=23) showed decreasing GIR (82% effective) vs insulin therapy (100% effective)
- Low caloric intake
- Insulin therapy is associated with lower mortality in extremely preterm, better glucose tolerance, non-protein intake and weight gain
- Severe hypoglycemia (<40 mg/dl) is rare, but <47 mg/dl increased 27% vs 58%
- But hypoglycemia was not associated with adverse neurodevelopment at school age.

Effects of tight glycemic control

- 88 infants randomized, 11 (13%) died and 57 (74% of eligible children) were assessed at corrected age 7 years.
- Survival without NDI-25 of 68 children (37%), with no significant difference between tight (14 of 35; 40%) and standard (11 of 33; 33%) glycemic control groups (P = .60).
- Children in the tight group were shorter than those in the standard group (121.3 [6.3] cm vs 125.1 [5.4] cm; P < .05) but had similar weight and head circumference.
- Children in the tight group had greater height-adjusted lean mass (18.7 [0.3] vs 17.6 [0.2] kg; P < .01) and lower fasting glucose concentrations (84.6 [6.30] vs 90.0 [5.6] mg·dL−1 ; P < .05), but no other differences in measures of body composition or insulin-glucose metabolism.

Tottman AC, et al. ; PIANO Study Group. Long-Term Outcomes of Hyperglycemic Preterm Infants Randomized to Tight Glycemic Control. J Pediatr. 2018 Feb;193:68-75.e1.

SGA



Diana L. Stanescu, Charles A. Stanley,
Advances in Understanding the Mechanism of Transitional Neonatal Hypoglycemia and Implications for Management, Clinics in Perinatology, Volume 49, Issue 1, 2022,

Asymptomatic growth restricted preterm neonates

Table 1. Patient characteristics, timing of hypoglycemia investigations and outcomes.

Case	Gestational Age (weeks)	Birth Weight (g,%)	DOL of Investigation/ PMA	Blood Glucose(mg/dl)	Insulin Levels (MCU/ml, DOL)	Cortisol (MCG/dL)	BOHB (mmol/L)	FFA (mmol/L)	Glucagon Stim Test Done? (DOL)	Diazoxide (Y/N)	Spontaneous Resolution (Days after diagnosis)/PMA
1	26w0d	527 (5)	36 (31w0d)	34	0.7 (22)	5.8	0.3	N/A	Y (55)	Y	N/A
2	28w3d	898 (17)	52 (35w5d)	35	0.9 (52)	8.2	0.4	0.26	Y (56)	Y	N/A
3	27w5d	667 (5)	65 (36w6d)	44	0.4 (65)	10.8	0.3	0.66	Y (66)	Y	N/A
4	26w1d	695 (25)	52 (33w3d)	35	3.2 (50)	0.4	0.2	N/A	Y (81)	N	29 (37w4d)
5	27w2d	642 (5)	73 (37w4d)	41	1.2 (74)	17.5	0.2	0.2	Y (75)	Y	N/A
6	28w4d	707 (4)	36 (33w4d)	34	0.3 (34)	4.1	0.1	N/A	Y (65)	N	54 (41w2d)
7	26w1d	717 (29)	86 (38w2d)	53	0.3 (77)	14.5	0.2	N/A	Y (89)	N	77 (49w2d)
8	29w3d	995 (15)	36 (34w3d)	42*	0.8 (42)	10.4	0.2	N/A	Y (58)	N	20 (37w2d)

Rodrigues, Megan, Rana, Pratibha, Lee, Gene, Mahajan, Chaitali, Nyp, Michael and **Pandey, Vishal.** "Hyper-insulinemic hypoglycemia in growth restricted convalescent preterm neonates: clinical characteristics and impediments to early diagnosis" *Journal of Pediatric Endocrinology and Metabolism*, vol. 35, no. 3, **2022**, pp. 319-323.

Asymptomatic growth restricted preterm neonates

Table 2. Patient characteristics, Hyperbilirubinemia onset and co-relation with hypoglycemia.

Case	Gestational Age (weeks)	Birth Weight (g,%)	Hypoglycemia in first 48 hours	Maximum GIR in the first 48hours	TPN duration (days)	Direct Hyper-bilirubinemia noted (DOL)	Maximum D. Bili (mg/dl, DOL)	Hyper-bilirubinemia Resolved (DOL)
1	26w0d	527 (5)	Yes	9	19	26	5.4 (46)	115
2	28w3d	898 (17)	Yes	9	17	N/A	N/A	N/A
3	27w5d	667 (5)	No	5.5	14	17	2.5 (33)	94
4	26w1d	695 (25)	Yes	7	12	59	3.2 (59)	96
5	27w2d	642 (5)	Yes	7.7	15	16	6.1 (59)	80
6	28w4d	707 (4)	Yes	12.3	20	12	4.1 (12)	70
7	26w1d	717 (29)	No	4.6	27	31	3.7 (59)	123
8	29w3d	995 (15)	No	10.11	17	N/A	N/A	N/A

Rodrigues, Megan, Rana, Pratibha, Lee, Gene, Mahajan, Chaitali, Nyp, Michael and **Pandey, Vishal.** "Hyper-insulinemic hypoglycemia in growth restricted convalescent preterm neonates: clinical characteristics and impediments to early diagnosis" *Journal of Pediatric Endocrinology and Metabolism*, vol. 35, no. 3, **2022,** pp. 319-323.

Factors leading to delayed diagnosis

1. In the NICU population, HI is usually suspected in neonates who require high GIR to maintain euglycemia. All neonates in this series required GIR less than 12 mg/kg/min.
2. All neonates were **asymptomatic**
3. All responded to **prolongation of gavage feeds** (90minutes-continuous), many were on prolonged duration of gavage feeds for reflux or feeding intolerance.
4. The **hypoglycemia was intermittent** and not very severe.
5. **Use of glucocorticoids** for other clinical conditions. In this series 5/8 infants were treated with hydrocortisone or prednisolone for other clinical conditions and received stress doses. Intermittently low glucoses were sometimes interpreted as signs of adrenal suppression.
6. Lack of consistent guidelines for discontinuation of glucose monitoring in convalescent preterm neonates.
7. **Unfamiliarity** of the clinicians with this form of HI.

Rodrigues, Megan, Rana, Pratibha, Lee, Gene, Mahajan, Chaitali, Nyp, Michael and **Pandey, Vishal.** "Hyper-insulinemic hypoglycemia in growth restricted convalescent preterm neonates: clinical characteristics and impediments to early diagnosis" *Journal of Pediatric Endocrinology and Metabolism*, vol. 35, no. 3, **2022,** pp. 319-323.

PES 2015 recommendations

- Diagnosed: Consultation with a specialist should be considered before planning discharge from the nursery.

- Awaiting specific diagnosis: "safety" fasting test should be done before discharge from the nursery to ensure that PG concentration can be maintained **above 70 mg/dL** if a feeding is missed (ie, a minimum of **6-8 hours**).

- For at-risk neonates without a suspected persistent hypoglycemia disorder and in whom hypoglycemia is considered likely to resolve within a short time, a "safety" fast of **6-8 hours** should be considered before discharge, to determine whether a **PG concentration >60 mg/dL** can be maintained, or whether additional management or investigations may be required.

Potential uses of CGM

- “Fasting Challenge” in at risk infants- PES 2015 guidelines
- Transient Hyperinsulinemia-HIE, SGA, IUGR
- Congenital Hyperinsulinemia
- Persistent Hypoglycemia
- Management of Hyperglycemia- Real time adjustment

Use in research

Absorption of glucose

- Current models for the appearance of glucose from enteral feeding are based on values from adult intensive care cohorts. This study aims to determine enteral glucose appearance model parameters more reflective of premature infant physiology.

- Results: The average half life across all infants for glucose absorption from the gut to the blood was 50 min. This result was slightly slower than, but of similar magnitude to, results derived from literature.

- Breast milk fed infants were found to have a higher absorption constant than formula fed infants, a result which may reflect known differences in gastric emptying for different feed types.

J.L. Knopp, et al. Modelling intestinal glucose absorption in premature infants using continuous glucose monitoring data, Computer Methods and Programs in Biomedicine, Volume 171,2019

• Use in research

Dextrose gel prophylaxis

-Joanne E. Hegarty, et al., Effect of Prophylactic Dextrose Gel on Continuous Measures of Neonatal Glycemia: Secondary Analysis of the Pre-hPOD Trial, The Journal of Pediatrics, Volume 235,2021

Use in research

- Preterm Glycosuria

Jagła M, et al. Preterm Glycosuria – New Data from a Continuous Glucose Monitoring System. Neonatology 2018

Role of CGM

- Sensitivity 88%
- SPECIFICITY 98%
- Positive predictive value 90%
- Negative predictive value 98%

Beardsall K, et al. Validation of the continuous glucose monitoring sensor in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2013 Mar;98(2):F136-40

Technical issues which need to be resolved prior to routine neonatal care

- Calibration
- Sensor drift
- Accuracy
- Plasma interstitial time delay

Continuous Glucose Monitoring in Neonates: Are we there yet?

Sanjay Akangire, MD

Neonatologist, Children's Mercy Kansas City

Associate Professor of Pediatrics

UMKC school of Medicine

4/29/22

Objectives:

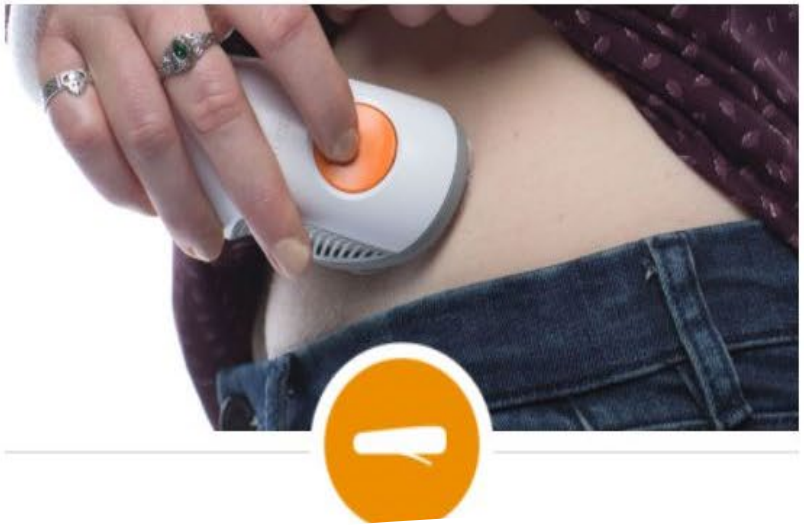
- Discuss current continuous glucose monitoring techniques and sensors available for neonates

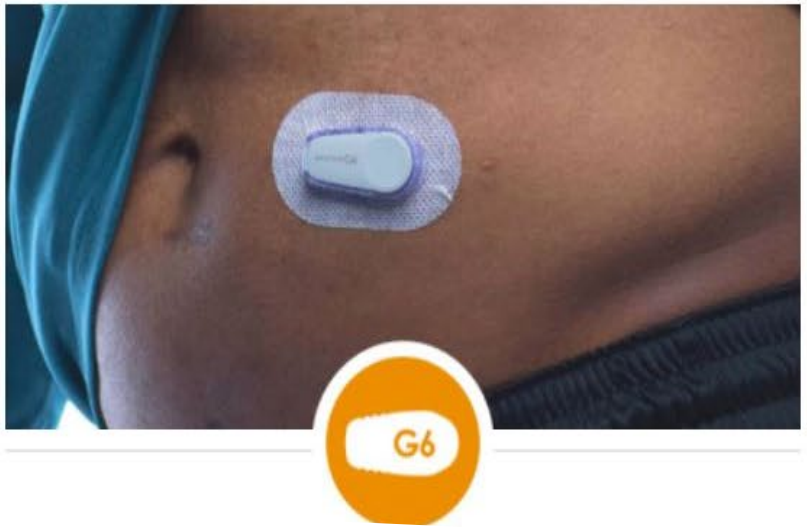
History of CGM devices

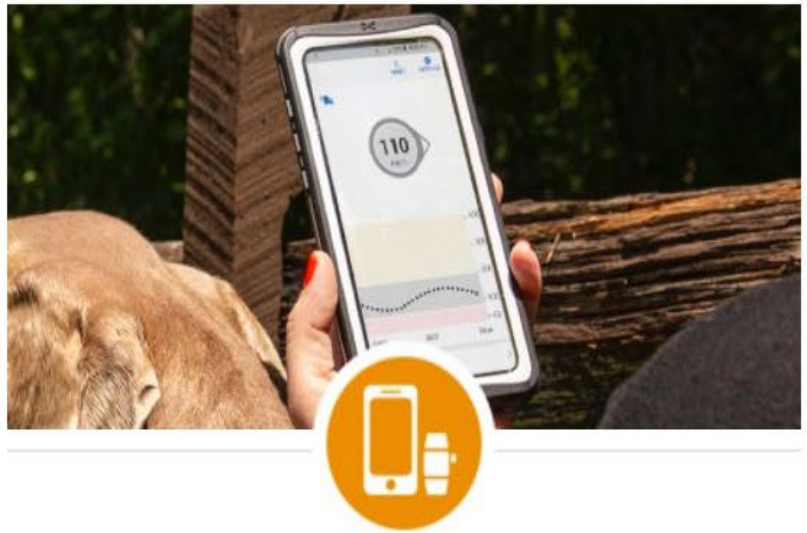
- CGM offers a less painful way for tracking blood sugar
- In 1991, FDA approved first CGM system for home use in adults with diabetes
- It monitors the amount of glucose in interstitial fluid
- CGMs utilize a tiny wire that is inserted below the surface of the skin
- Readings are displayed on a reader
- It does not replace the blood glucose measurement but minimize the pricks

How does a Continuous Glucose Monitor work?

Instead of looking at one glucose number at a single moment in time, a CGM system tracks your glucose levels day and night. Here's how:







CGM for older children and adults

- Freestyle libre
- Dexcom
- Medtronic guardian connect- newest model
- Close loop systems for insulin delivery

Study from UK

- 16 infants' birth to 7 days of age, <1500 grams, median GA of 26.5 w
- Well tolerated and readings close to whole blood
- Concluded that it is feasible in neonates
- Methods:
  - Disposable, glucose oxidase based, platinum electrode sensor that catalyzes interstitial glucose oxidation generating electric current every 10 seconds, that is recorded
  - Monitor averages for every 5 minutes
  - No readings seen real time
  - Minimed sensor (Medtronic, Northridge California, USA)
  - Inserted in subcutaneous tissue of lateral thigh

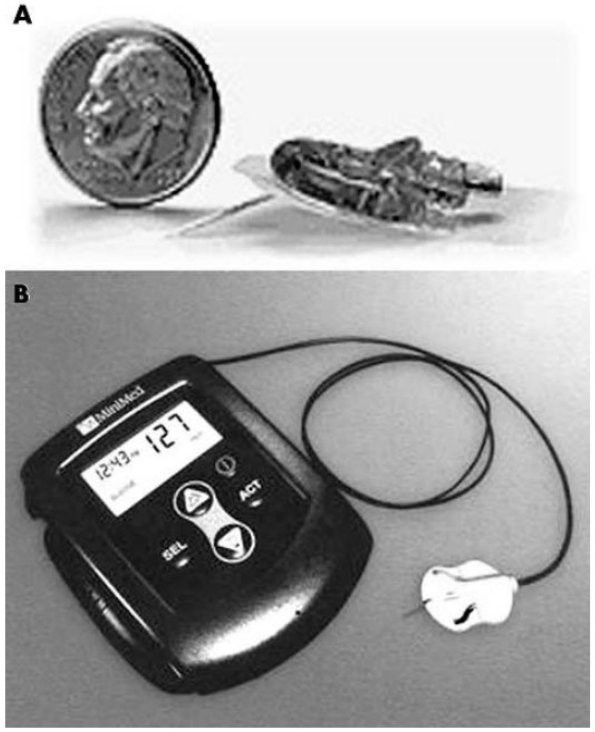


Figure 1 (A) Minimed sensor shown with an American nickel (20 mm diameter) for size comparison. (B) Continuous glucose monitoring sensor (CGMS) monitor with sensor attached (monitor size: 6 × 9 × 2 cm). Reproduced with permission from Medtronic Limited (Sherbourne House, Croxley Business Centre, Watford, UK).

Beardsall et al, Archives of diseases Child fetal neonatal, 2005

Clinical research study

- 50 critically ill 6 weeks to 16-year-old patients
- Mean absolute difference in glucose levels was 15%
- Clinically acceptable correlation
- No site infection, reaction or bleeding

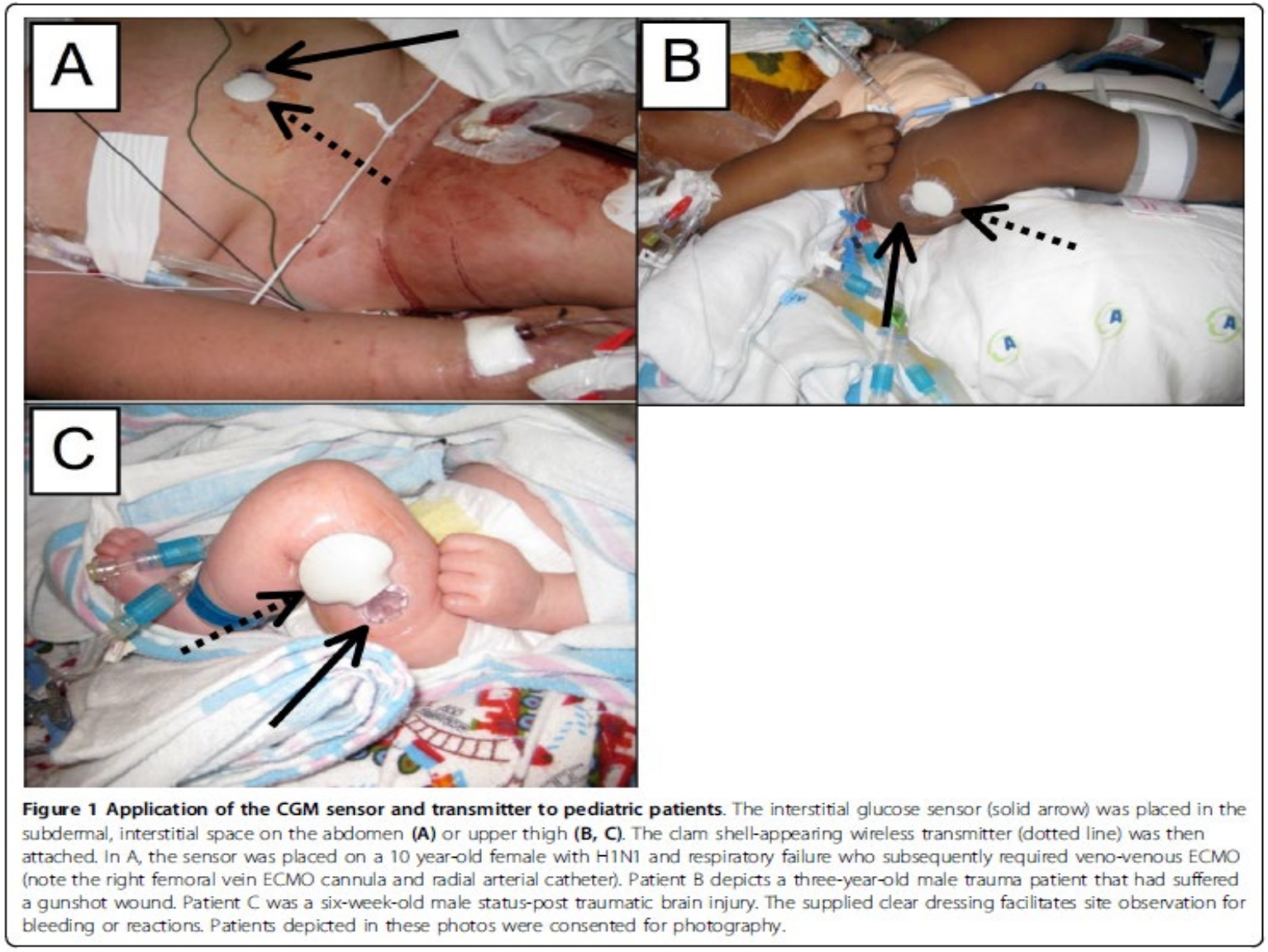


Figure 1 Application of the CGM sensor and transmitter to pediatric patients. The interstitial glucose sensor (solid arrow) was placed in the subdermal, interstitial space on the abdomen **(A)** or upper thigh **(B, C)**. The clam shell-appearing wireless transmitter (dotted line) was then attached. In A, the sensor was placed on a 10 year-old female with H1N1 and respiratory failure who subsequently required veno-venous ECMO (note the right femoral vein ECMO cannula and radial arterial catheter). Patient B depicts a three-year-old male trauma patient that had suffered a gunshot wound. Patient C was a six-week-old male status-post traumatic brain injury. The supplied clear dressing facilitates site observation for bleeding or reactions. Patients depicted in these photos were consented for photography.

Bridges et al, Biomed central 2010

Original Paper

Open-Source Technology for Real-Time Continuous Glucose Monitoring in the Neonatal Intensive Care Unit: Case Study in a Neonate With Transient Congenital Hyperinsulinism

Katarina Braune[1,2], MD; Mandy Wäldchen[3], MSc; Klemens Raile[1], MD; Sigrid Hahn[4], MD; Tebbe Ubben[5]; Susanne Römer[4], MD; Daniela Hoeber[6], MD; Nora Johanna Reibel[4], MD; Michael Launspach[2,4], MD; Oliver Blankenstein[7,8], MD; Christoph Bührer[4], MD

Figure 1. Upper thigh as a suitable rtCGM application site in neonates.

Figure 2. Upper arm as a suitable rtCGM application site in neonates.

2020

Fluid location	Biosensor	Advantages	Disadvantages	Commercial devices in neonates to date
Subcutaneous	• Microdialysis fiber with external amperometric probe • Amperometric needle electrode	• Most accurate • Sensing material is outside skin so biocompatible • Easier insertion	-Subcutaneous inflammation, expensive, long lag time, discomfort, calibration need -Less accurate, sensor issues due to biofouling, poor detection due to edema, discomfort and calibration need	Not available Medtronic Minimed DexCom
Transdermal	Glucose binding protein	No skin penetration Potentially suitable in neonates due to their high trans-epidermal water loss	Accuracy unknown	Not yet available

McKinlay et al, Maternal Health, Neonatology, and Perinatology 2017

Medtronic MiniMed and DexCom

- Retrospective and real time devices
- Not approved for clinical use in neonates
- Needle electrode and transmitters have been placed on the lateral thigh of neonate
- Brief pain but well tolerated
- Complications rare

McKinlay et al, Maternal Health, Neonatology, and Perinatology 2017

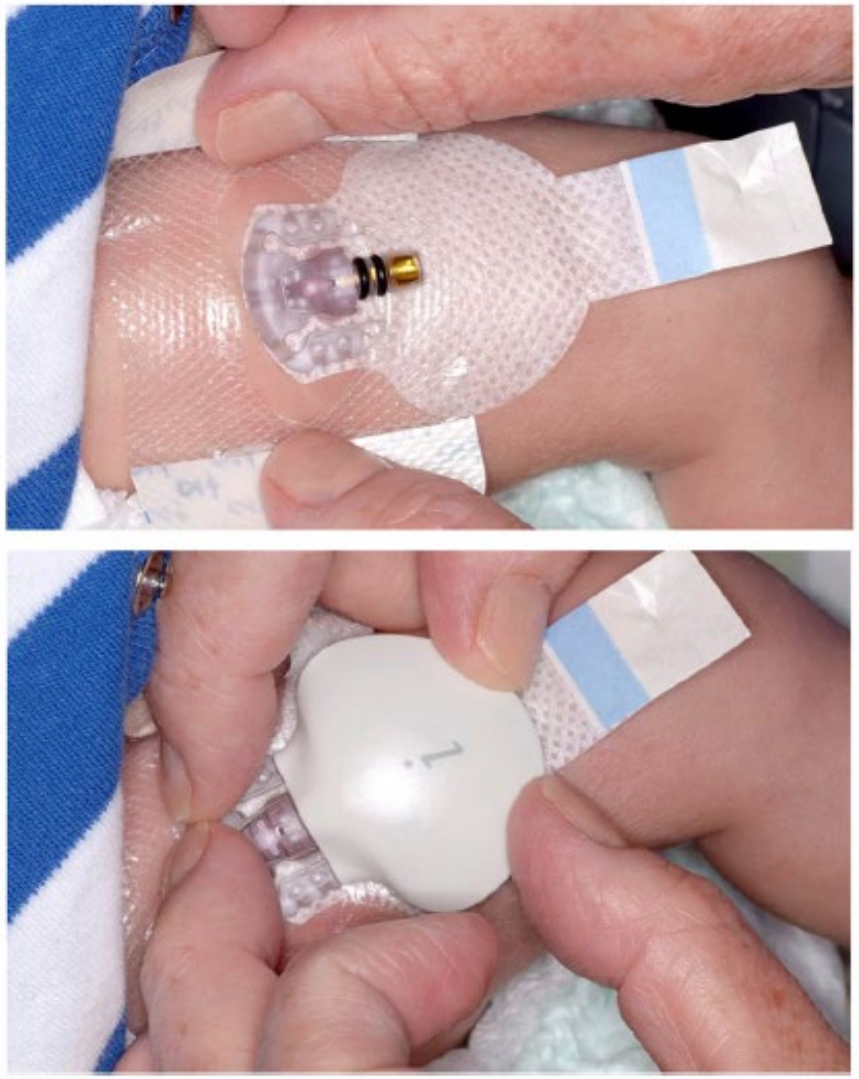


Fig. 1 Insertion of a continuous glucose sensor and attachment of transmitter in the lateral thigh of a newborn infant

Glucose reading

- Raw signal data from the electrode generated every 10 seconds
- Averaged and processed to display reading every 5 minutes
- Data not displayed if glucose fall below 40mg/dl
- Fail to give readings if there is significant skin edema and if patient on vasopressor medications

Accuracy and types of error

- Accuracy is affected by random error or noise
- Standard point of care glucose had zero-mean error of 10-30%
- CGM also contains drift component that may impact accuracy
- Calibration is needed every 12 hours

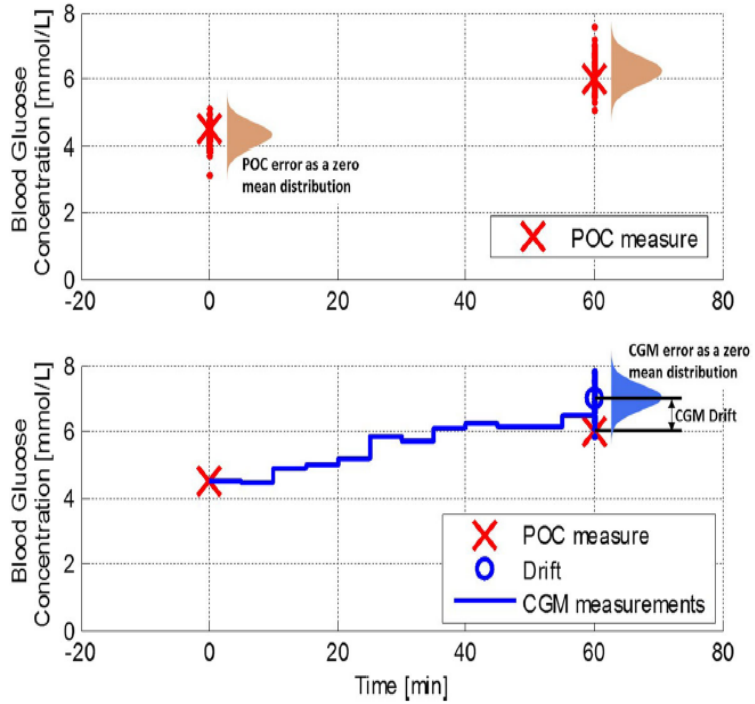


Fig. 2 Comparison of the types of measurement error for point-of-care (POC) and continuous glucose monitors (CGM), where CGMs can be prone to drift as well as a zero-centred noise

Point to point calibration

- Point to point calibration is not employed in current real time CGM devices used in clinical care
- Algorithm interpolates readings between one calibration glucose and the next
- Avoid the problem of multiple point calibration
- Suitable for NICU use

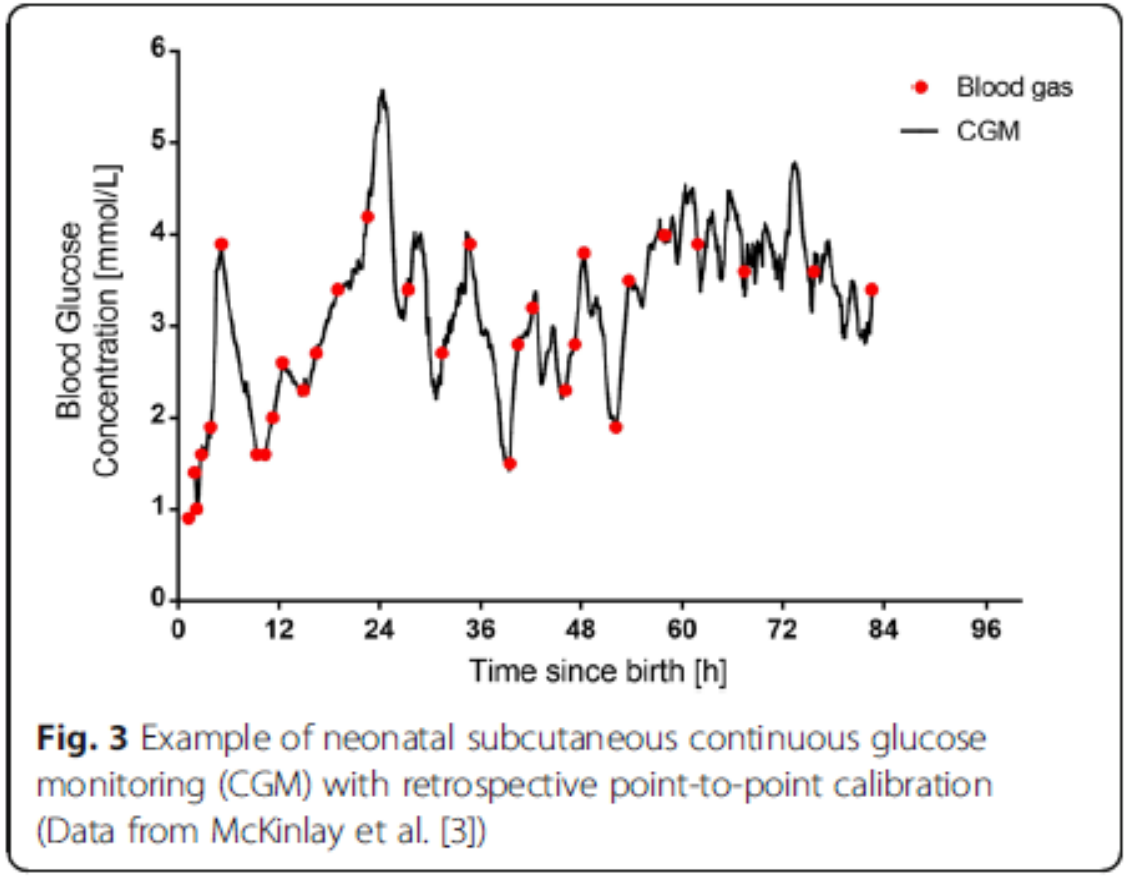


Fig. 3 Example of neonatal subcutaneous continuous glucose monitoring (CGM) with retrospective point-to-point calibration (Data from McKinlay et al. [3])

Analysis and Display of CGM data

- Due to measurement errors in real time CGM, it cannot be relied for accuracy
- Alternative approach to focus on clusters of data points
  - This will minimize impact of random errors
- Possible 4 main types of metrics possible
  - Cumulative quality of blood glucose control
  - Area under the glycemic curve
  - Rising or falling trend
  - Point-to- point change

Insights from CGM about neonatal glucose metabolism

- Term infants- Offers possibility of studying early trends in neonatal hypoglycemia
- Near term infants- can study the trends of glucose levels after birth and after treatment with feeds and dextrose
- Preterm infants-up to 50% preterm infants can have episodes of hypoglycemia that is undetected on intermittent glucose testing but can be picked up on CGM
- NIRTURE trial-early insulin treatment
  - CGM well tolerated
  - Hyperglycemia found

Clinical use of CGM in NICU

- Little direct evidence, benefits and risks
- Small RCT- VLBW infants
  - CGM reduced the hypoglycemic episodes by 50%
  - Number of capillary samples by 25%
- Use of CGM in preterm infants remain uncertain
  - Absence of clinical outcome data
  - Neurodevelopmental status
  - Risks and benefits
- May be important in traditional hypoglycemia, HIE and preterm infants with hyperglycemia

Conclusions and Future directions

- Considerable potential by CGM to optimize glycemic control
- Several issues need to be addressed for real time monitoring in NICUs
- Needs calibration with plasma equivalent whole- blood glucose concentrations
- Current CGM devices use multipoint algorithm that is designed for management of diabetes in older children and adults
- Real- calibration specific to neonates is needed

Conclusions and Future directions

- Potential for sensor drift, needs further research
- Need of research to determine which metric should be targeted for improving long term outcomes
  - Focus on glucose stability
  - Trends of changing metabolic patterns
- Important tool in understanding neonatal glycemia and effects of different treatments on glucose metabolism
- Limited to research studies for now
- Randomized control studies for benefits are needed before introduction in routine clinical care

Questions:

- 3-day old term infant is suspected to have hyperinsulinemic hypoglycemia and started on diazoxide. Infant does not respond to diazoxide, and she remains hypoglycemic. What is potential cause for no response:

A. Hyperinsulinism hyperammonemia syndrome

B. Activating glucokinase mutation

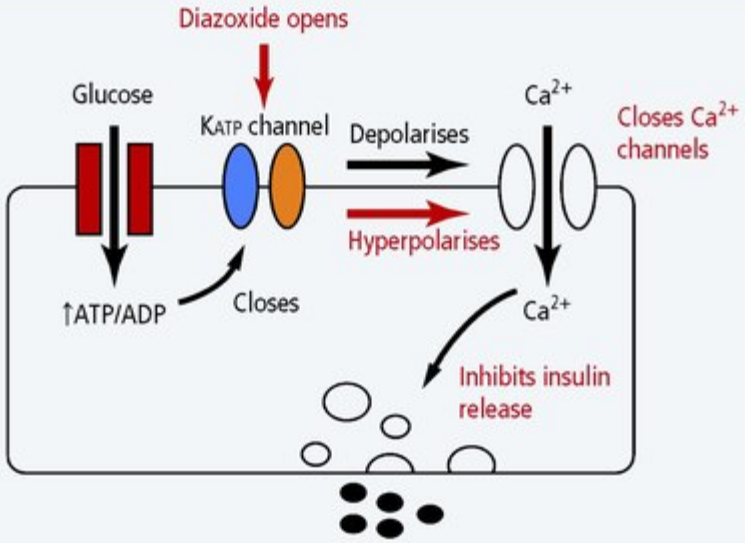
C. Loss of function in mitochondrial uncoupling protein 2 (UCP2)

D. An inactivating mutation in *KCNJ11* gene

Answer D:

- 9 different genes can be affected for hyperinsulinemic hypoglycemia.
- Severe forms- *ABCC8 and KCNJ11* genes
- *KCNJ11* abolishes function of K_{ATP}

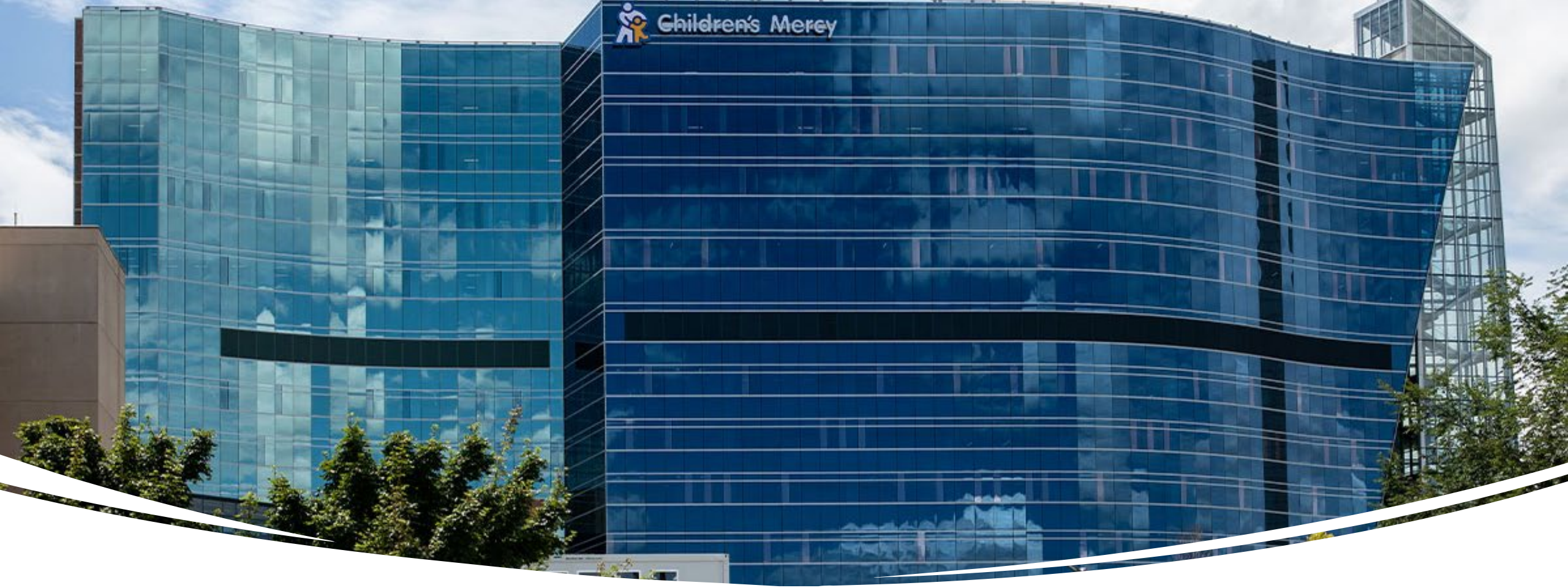
Channel so no response to diazoxide



NOTES. Above is a representation of the beta cell in the pancreas. Glucose enters the cell via the GLUT-2 glucose transporter and is subsequently metabolised, producing ATP. The increase in the ATP/ADP ratio closes the KATP channel. This depolarises the beta cell membrane and leads to opening of voltage dependent calcium channels. The rise in the intracellular calcium triggers insulin granule exocytosis. In contrast, follow red text for diazoxide action. (ATP = adenosine-5'-triphosphate; ADP = adenosine diphosphate; KATP = ATP-sensitive potassium.)

References

- Beardsall K, et al. Validation of the continuous glucose monitoring sensor in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2013 Mar;98(2):F136-40
- Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Levitsky LL, Murad MH, Rozance PJ, Simmons RA, Sperling MA, Weinstein DA, White NH, Wolfsdorf JI; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015 Aug;167(2):238-45. doi: 10.1016/j.jpeds.2015.03.057. Epub 2015 May 6. PMID: 25957977.
- Rodrigues, Megan, Rana, Pratibha, Lee, Gene, Mahajan, Chaitali, Nyp, Michael and Pandey, Vishal. "Hyper-insulinemic hypoglycemia in growth restricted convalescent preterm neonates: clinical characteristics and impediments to early diagnosis" Journal of Pediatric Endocrinology and Metabolism, vol. 35, no. 3, 2022, pp. 319-323.
- J.L. Knopp, et al. Modelling intestinal glucose absorption in premature infants using continuous glucose monitoring data, Computer Methods and Programs in Biomedicine, Volume 171,2019
- -Joanne E. Hegarty, et al., Effect of Prophylactic Dextrose Gel on Continuous Measures of Neonatal Glycemia: Secondary Analysis of the Pre-hPOD Trial, The Journal of Pediatrics, Volume 235,2021
- Jagła M, et al. Preterm Glycosuria – New Data from a Continuous Glucose Monitoring System. Neonatology 2018
- Tottman AC, Alsweiler JM, Bloomfield FH, Gamble G, Jiang Y, Leung M, Poppe T, Thompson B, Wouldes TA, Harding JE; PIANO Study Group. Long-Term Outcomes of Hyperglycemic Preterm Infants Randomized to Tight Glycemic Control. J Pediatr. 2018 Feb;193:68-75.e1. doi: 10.1016/j.jpeds.2017.09.081. Epub 2017 Dec 1. PMID: 29198539.
- Moghissi E, Ismail-Beigi F, Devine RC. Hypoglycemia: minimizing its impact in type 2 diabetes. Endocr Pract. 2013 May-Jun;19(3):526-35. doi: 10.4158/EP13005.RA. PMID: 23425655.
- David H. Adamkin , Low blood sugar levels in the newborn infant: Do changing goal posts matter? Seminars in Fetal and Neonatal Medicine , Volume 26, Issue 3,2021.
- Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW)



Thank you for your attention!!