Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Neonatal Hypoglycemia

Miami Neonatology 2018 – 42nd Annual International Conference

Overview

In this activity, **Paul J. Rozance, MD**, reviews the differences, benefits, and when to use the American Academy of Pediatrics (AAP) and Pediatric Endocrine Society (PES) guidelines for screening, evaluation, and management of hypoglycemia, while highlighting the importance of treating asymptomatic hypoglycemia.

In the companion, *Neonatal Hyperglycemia in the ELBW Infant*, Dr. Rozance discusses strategies to prevent and treat hyperglycemia in extremely low-birth-weight (ELBW) and preterm infants. He identifies risk factors, the long-term effects of hyperglycemia, and the rationale for treating and preventing this biochemical disorder.

Content Areas

- Assessing neonatal glucose concentrations
- Identifying and treating asymptomatic hypoglycemia
- Review of AAP and PES Guidelines
- Fasting challenge

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this module, participants should be better able to:

- Treat asymptomatic neonatal hypoglycemia with buccal dextrose gel
- Develop patient-specific approaches to intravenous dextrose therapy for neonatal hypoglycemia

Faculty

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Paul J. Rozance, MD

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This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 0.5 hour.

This activity was released on February 22, 2019 and is eligible for credit through February 22, 2021.

Neonatal Hypoglycemia

Contact Information

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https://pnce.org/Hypoglycemia

Editor's Note: This is a transcript of a live presentation from Miami Neonatology on November 13, 2018.

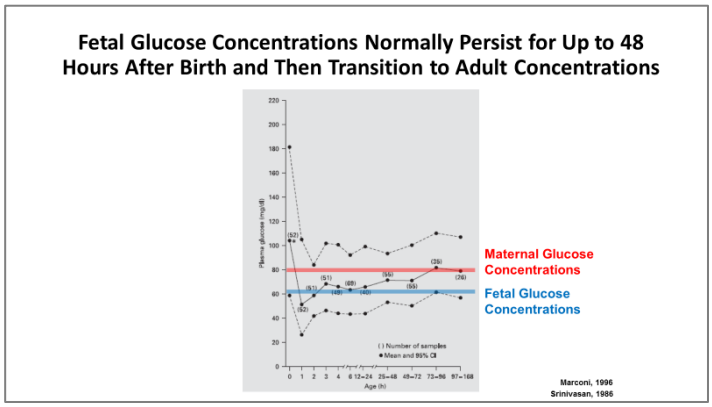
Dr. Paul J. Rozance: Today my talk is about neonatal hypoglycemia, and I'd like to start off the talk by letting you all know, confessing to the fact that I've spent a lot of time working with pediatric endocrinologists discussing neonatal hypoglycemia, and so my take on this has evolved over the last 6 or 7 years. It was in about 2013 that every month or so I would spend an hour or 2 discussing this problem with a group of highly thoughtful pediatric endocrinologists. You'll see why this is important later in the talk.

There are some practical objectives I'd like you to take home after this talk. One is to consider the use of buccal dextrose gel for the treatment of asymptomatic neonatal hypoglycemia. I would like to do maybe an informal poll. How many groups here are using dextrose gel, perhaps in the well-baby nursery, to keep patients out? Okay, so it's not quite half, maybe a third or a quarter. We've adapted that therapeutic, and I'll tell you why and the results that we're finding.

The other thing is I'd like you to consider developing patient-specific approaches to the management of neonatal hypoglycemia. And you'll see at the end of my talk what I mean by that.

My entrance into this field really starts from my background as a fetal physiologist. I spent a lot of time studying insulin and glucose metabolism in the fetus. And for a long time, for the first part of my career, I thought that's what I was really going to focus on. But, as I started learning more about the problem of neonatal hypoglycemia, it became clear to me that my background could actually inform this clinical problem.

What you're seeing here is a graph [Slide 1], essentially of time. On the bottom, we have age in hours, and then age in days of newborns, and on the y-axis, we have plasma glucose concentrations taken from a number of patients intermittently throughout the first hours and days of life.



Slide 1

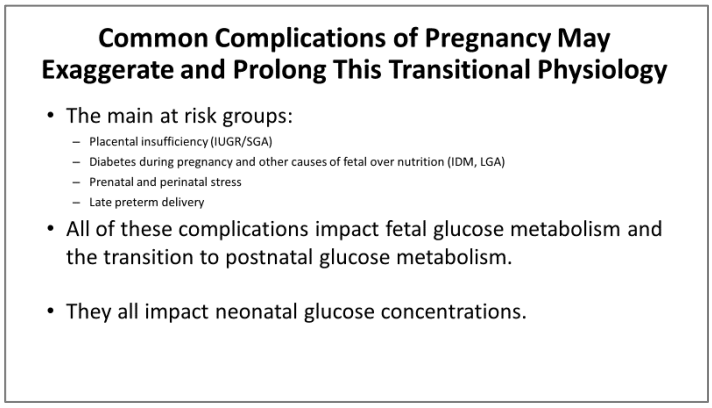
This is a pattern that's been repeated in multiple studies. Right at the time the baby's cord is clamped, we have a fairly, variable, usually high, glucose concentration, likely related to the stress of labor. Mother's glucose concentrations tend to go up, and that is then transferred over to the fetus. Then the glucose concentrations fall in the first hour. After a couple hours, they rise to medians of about 60 mg/dL. Here [3–6 h] they hold at 60 mg/dL. Then over the next two to four days, they rise to means of essentially 80 mg/dL.

As a fetus, it makes a lot of sense to have glucose concentrations here [indicated in blue]. This is data from Anna Maria Marconi, MD[1], that's

superimposed on the graph that I just described. The median concentrations at the end of gestation are about 60 mg/dL. Maternal glucose concentrations [indicated in red] measured in a paired sample are about 80 mg/dL. This concentration gradient has to be there. Without that concentration gradient, the fetus can't get any glucose. It's really that observation, the fact that this is a regulated process in the fetus, which got me interested in this problem.

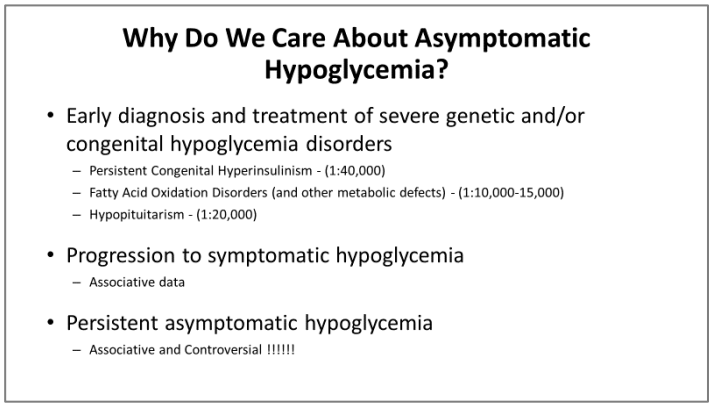
If you give me or any other beta-cell biologist two sets of beta cells and tell them that one is from a fetus and the other is from adult, the easiest functional way to determine which is which is look at the threshold at which glucose causes insulin release. The fetal beta cells always release insulin at a lower glucose concentration than the adult. That drives that concentration gradient. But what you can see is it really takes 2 to 4 days, but after 2 to 4 days, the concentrations go up. And in working with the endocrinologists that I had the fortune of discussing this problem with, it looks like this is a very highly regulated process.

I'm not going to get into the pathophysiology of hypoglycemia in this talk, but I'm happy to discuss it later with any of you who want to know about it. What I will say is the common complications of pregnancy really exaggerate and prolong this transitional physiology. The main at-risk groups for asymptomatic hypoglycemia that we think of are babies who are born following placental insufficiencies, so usually IUGR [intrauterine growth restriction] or SGA [small-for-gestational age]. Diabetes during pregnancy and other causes of fetal overgrowth, so IDM [infants of diabetic mothers] babies, LGA [large-for-gestational age] babies also are at risk. Perinatal and prenatal stress, mild or severe asphyxia can be a significant risk factor for hypoglycemia, and then late preterm delivery. All of these complications impact fetal glucose metabolism and the transition to post-natal glucose metabolism or that rise over the first four days.



Slide 2

Turning away for a second from the pathophysiology to maybe an even broader question: why do we even care about asymptomatic hypoglycemia? Mostly, I think, all the practitioners here, we would likely all be able to define the glucose concentration at which we felt uncomfortable, that we felt the need to intervene and provide exogenous glucose, even if the baby is asymptomatic. I think it's rare that you would find somebody who's willing to not treat hypoglycemia. I think the controversy comes in because we just don't know what the right number is.



Slide 3

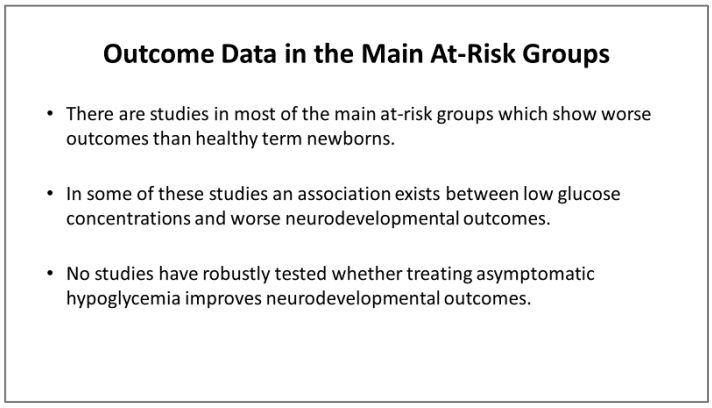
As I started thinking about this problem and preparing talks, I felt it was important to ask the question, "What are our goals around treating

asymptomatic hypoglycemia and identifying it?" And it turns out the endocrinologists, not surprisingly, have a very different approach to this problem and a different background. They're much more worried about this first bullet point [Slide 3], the needle in the haystack. They really want to have an early diagnosis and treatment of severe genetic and/or congenital hypoglycemia disorders. And I've listed the top three classes right there: persistent congenital hyperinsulinism; fatty acid oxidation defects; and other metabolic disorders, as well as hypopituitarism. Some of them are convinced that if we do things the right way, if we develop the right screening strategies, we won't miss these patients. But you can see the incidence of these diseases, and they're really quite hard to identify.

Another reason why we might care about asymptomatic hypoglycemia is the progression to symptomatic hypoglycemia. Most of us, especially after our last talk by Dr. Terrie Inder, would probably not want to allow a baby to become so hypoglycemic that they start seizing. The data to support that practice is associative, but it's still a strong desire for most of us.

Then again, the most controversial is this persistent asymptomatic hypoglycemia. At what point is this injurious to the baby? At what point do we need to intervene on the baby's behalf? And we simply don't have a definitive answer, or this wouldn't be a controversial topic.

If the outcomes were all good for these at-risk groups, I think we also wouldn't have much controversy. To summarize the main outcome data in three bullet points: There are studies in essentially almost all of these at-risk groups that show worse outcomes than healthy term babies. In some of these studies, there's an association that exists between low glucose concentrations and worse developmental outcomes. Finally, no studies have ever robustly tested whether treating asymptomatic hypoglycemia improves neurodevelopmental outcomes.



Slide 4

This is an important point, and you hear people discuss or say things, and I've said it myself, there's no evidence showing that treating asymptomatic hypoglycemia improves outcomes. Is that an absence of evidence or the evidence of absence? In this case, it's really the former. There's an absence of evidence. There's never been a trial, a randomized placebo-controlled trial that's really shown a benefit to treating asymptomatic hypoglycemia. But it doesn't mean that we have a lot of evidence to say that it's irrelevant. We just don't have that study.

Prior to 2011, we talk a little bit about eras of how people view glucose and hypoglycemia as well as blood pressure and seizures. Prior to 2011, I like to think of this era as the *operational threshold era*. This was a phrase coined by Dr. Marvin Cornblath in a seminal article in *Pediatrics*. It was really an opinion piece. It's the *operational threshold era*. I also call it the *era of 47*; 47 mg/dL was one of the most common numbers for a variety of reasons. I think everybody used those numbers maybe more or less.

Then in 2011, the AAP [American Academy of Pediatrics] came out[2], and by this point, I was paying keen attention to the field, and it really generated a lot of controversy. I think for the first

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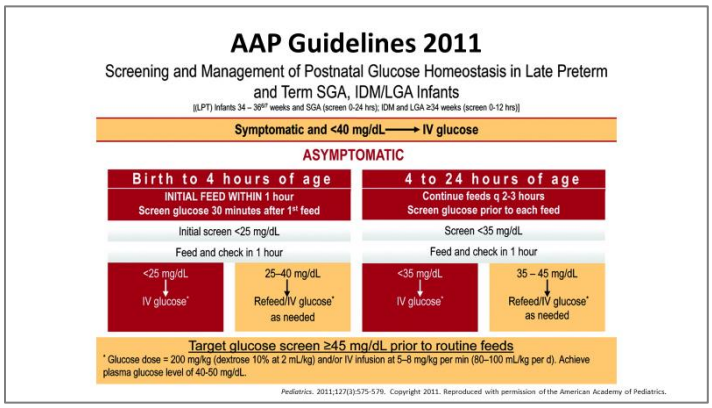
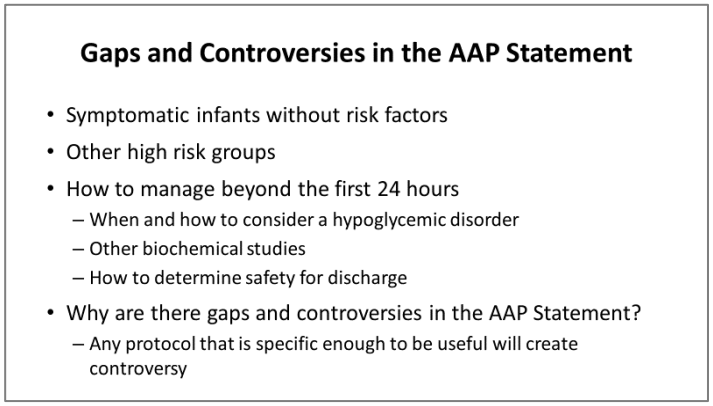
time we had a recognition that in the first 4 hours, a baby's glucose concentration is highly variable and lower than it will be in the next 4 hours. It was one of the first widespread guidelines to not recommend checking of blood sugar until after a baby [is] fed, which I think is fabulous. It also allowed for lower blood glucose concentrations in the first 4 hours of life.



Slide 5

The other thing to note about this statement was that these concentrations were a lot lower than 50 or 47 mg/dL, what had become the norm. So, this did create quite a lot of controversy. Now, over time, people became used to these guidelines, and, in fact, they became so used to the guidelines that I think some problems started to be identified.

These problems relate to some gaps and controversies around this AAP clinical statement. One is it was only designed to look at those four at-risk groups: LGA, IDM, SGA, and late preterm babies. It was never designed to be applied to symptomatic infants without risk factors, but it started being applied that way. It superficially addressed other risk factors. It didn't call any out specifically. We had individuals making choices to not screen for other traditional risk factors that had been in all the textbooks and review articles.



Slide 6

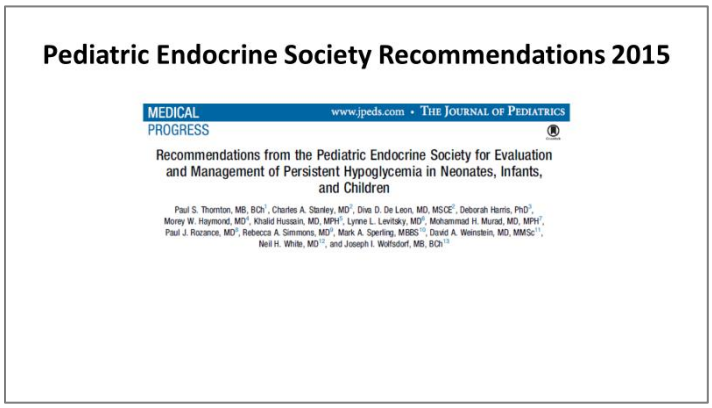
It really became vague after 24 hours [of age]. It became vague in terms of when do you start considering a real hypoglycemic disorder, like the endocrinologists were worried about. It was pretty vague about other biochemical studies. It also was quite vague about determining safety for discharge. For example, the statement was made, "The baby needs to display normal glucose concentrations through three feed-fast cycles." But in that statement, they didn't define what a normal glucose concentration was when a baby was a week of age or 2 weeks of age or 3 weeks of age.

I've just shown you data about the first 4 to 5 days of life. What we found, just by talking to people and those reporting to us, was that people were using these thresholds of 40 or 45 mg/dL for weeks. Again, I can't tell you that a baby who's 3 weeks old, is asymptomatic, and has a glucose concentration of 45 mg/dL is being injured or not. I don't know the answer to that question. But what I do know is that it's not a normal glucose concentration. So, to say that the baby somehow met the AAP clinical guideline for discharge would be wrong. It didn't meet the criteria. Discharging that baby may or may not be wrong, but it didn't meet the AAP criteria.

I came to this last bullet point, and I became acutely aware of this last bullet point, when I joined the Pediatric Endocrine Society's committee to write a different set of guidelines.[3] **Any protocol specific**

enough to be useful will create controversy. By that, I mean, I could tell all of you to use your best clinical judgment and assess babies and make decisions, and I think that would be fine. That's not really a useful protocol to implement at a hospital. When you start putting numbers and times and ages on these protocols, that's when you'll get feedback. I can promise you, you will get feedback that your number is too high or your number is too low, and there'll be debates on both sides. I think that's the nature and the challenge of creating these guidelines.

I've already alluded to this fact, I spent 3 years or so working with mostly pediatric endocrinologists, a couple neonatologists. Deborah Harris, PhD, is a neonatal nurse practitioner who's doing, I think, the best primary research on this topic with Jane Harding, FRACP, DPhil, and others in [University of Auckland] New Zealand.[4] We spent a long time coming up with a different set of guidelines, and here you can read the title [Slide 7].[5] I'll quickly summarize the... well, I want to tell you first the goal wasn't so much just to throw out new numbers to counter the AAP, you know, the AAP's Dr. David Adamkin said one thing and we were going to say something else.

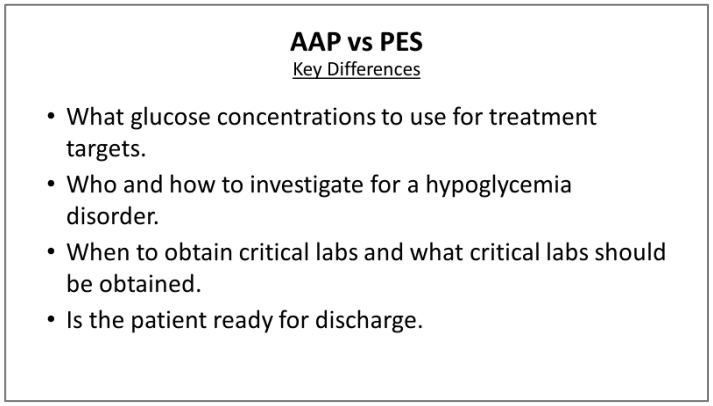


Slide 7

We quickly turned this into a different emphasis. Our emphasis was going to be different than what the AAP's emphasis was. A few of us argued at some point that we should not worry about the first 48 hours. We should just leave that alone and pick up where the AAP statement left off. Those of us who felt that didn't have our consensus adopted by the whole group. But still, this was really the point I wanted to make.

What are some of the key differences? Because now, despite the fact that I wanted to not have that document address the first 48 hours like the AAP document, it did, and so that left us with some conflicting guidelines.

Some of the key differences: what glucose concentrations to use for treatment targets; who and how to investigate for a hypoglycemia disorder; when to obtain critical labs; and what critical labs should be obtained? Meaning you want to know what the cause is or the biochemical cause of this hypoglycemia, and then, is the patient ready for discharge? Those were the key differences.



Slide 8

Then once we published this, then correctly I was tasked by lots of people who would say, "You're a neonatologist. You're not an endocrinologist. You helped create these PES [Pediatric Endocrine Society] guidelines. We want to know how you are putting this into practice. How are you squaring away these two different guidelines?" I think, go back to the title even of the two sets of guidelines and look. That's how I feel we should try to merge these two guidelines.

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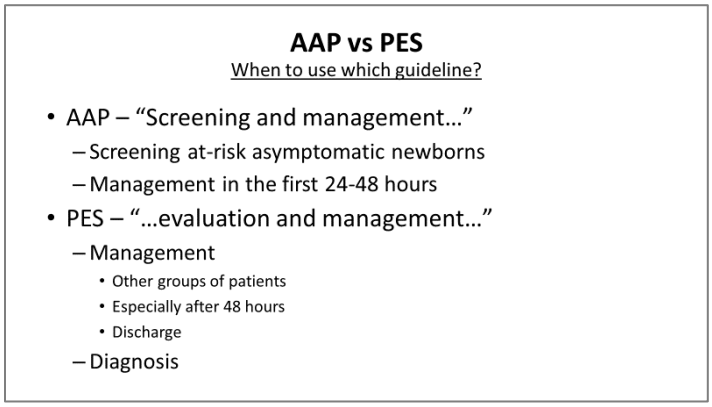
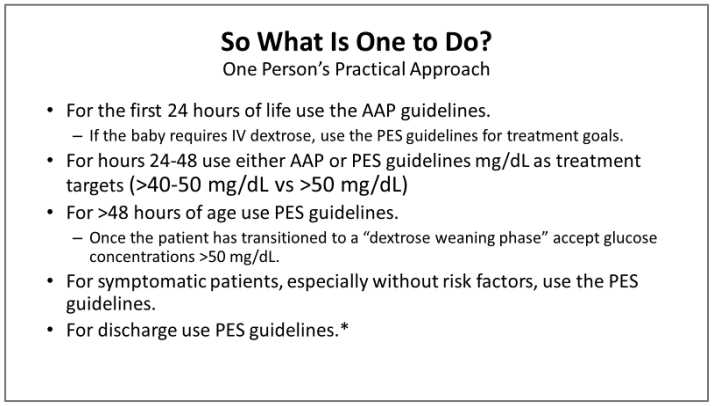
The AAP, even in the title, it says, "Screening and management." It was really designed to focus on screening of these at-risk, asymptomatic newborns. Management was restrictive to the first 24 to 48 hours, whereas you look at the PES title, and it talks about evaluation and management. It's a subtle difference, but I think an important one. The focus there was on other groups of patients, especially after 48 hours, and especially with some attention to discharge. Then diagnosis: What is causing this low blood sugar?



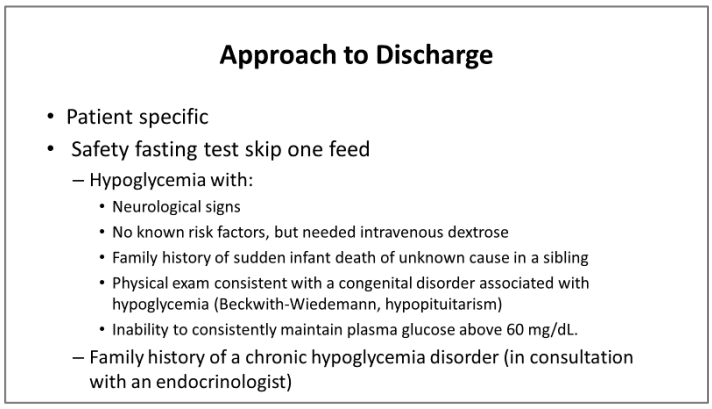
Slide 9

This is simply our practical approach or what I would say should be a practical approach that we use. For the first 24 hours of life, I'm very content using the AAP guidelines or the Canadian Pediatric Network guidelines, any real guidelines you want. Once the baby needs IV dextrose, you've already hit a threshold usually of a NICU admission, of placing an IV, of risking separation from the mother. In that case, I tend to switch to using the PES thresholds. For 24 to 48 hours, there really isn't a big difference if you read the two documents, and I think either would be fine. Then after 48 hours, that's where we felt as a group, the PES, that our guidelines would be more appropriate. Then [for] discharge, we feel our guidelines were more useful. Those from the AAP were vague.



Slide 10

One thing that became quite controversial among our group, and then after we put this out, it's become more and more in practice something called the fasting challenge to either prove the patient's ready for discharge or not. There were those in our group who wanted to say every at-risk baby who ever had a low glucose should get a fasting challenge, meaning they skip one feed and do they maintain their blood sugars above a certain level? We felt that was way too many infants, so we cut that language back, made it much more of a personal choice based on clinician assessment.

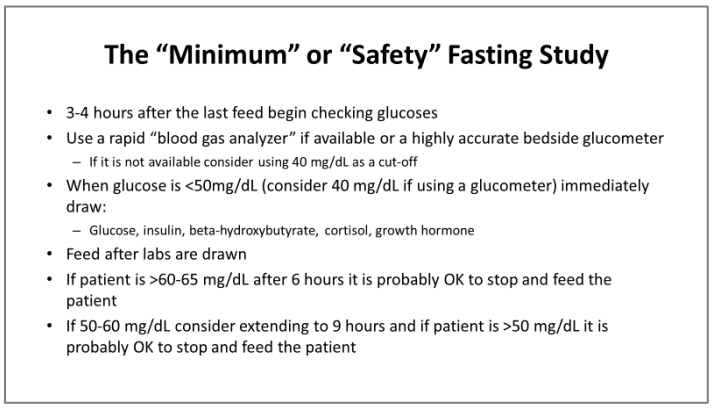


Slide 11

When asked, these are the criteria that I would use to decide which baby I think should get a safety fast: neurological signs, hypoglycemia that needs IV dextrose but no risk factors. This family history I think is important to pay attention to, as well as

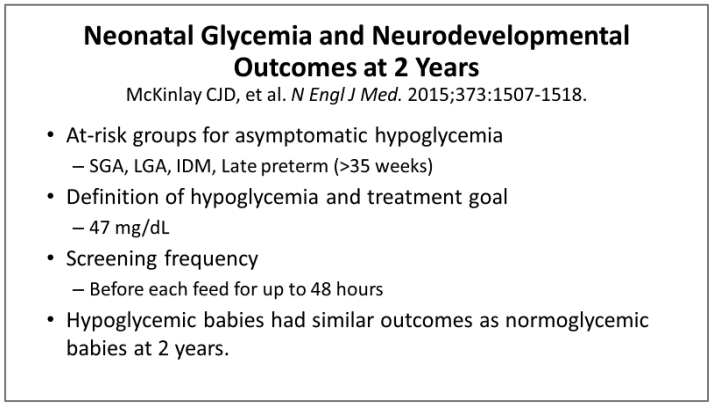
physical exam findings, if you think the baby has hypopituitarism or Beckwith-Wiedemann.

I'm not going to go over what that looks like, but I'm happy to give it to you in the slides [Slide 12] and talk about it at any point later.



Slide 12

I gave you my thee bullet-point summary of outcomes. As we were working with Deb Harris (and we published our PES recommendations in 2015), it turns out Deb Harris with Jane Harding and Christopher J.D. McKinlay, PhD, are working on their own set of primary data, this fantastic set of these same patients we're worried about. Their paper came out in the *New England Journal [of Medicine]*.[6] I don't study BPD [bronchopulmonary dysplasia], and I don't study brain development. I study hypoglycemia, and usually our neonatal hypoglycemia research doesn't end up in the *New England [Journal of Medicine]*. [On publication] this was quite an impressive day for the field of neonatal hypoglycemia.



Slide 13

It wasn't, though, a randomized control trial. It was just an associative study where they took these at-risk groups; said, do you have a glucose less than 47 mg/dL or not? They were screening pretty aggressively, every three hours, essentially for up to 48 hours. What they found was that having had hypoglycemia, by their definition, didn't give you any worse outcomes than if you didn't. This became a Rorschach test, I believe, for people, meaning I got calls from my friends who are holding on to the medical use type research, and they felt like, we never have to measure blood glucose again because it doesn't matter. And I got contacted by my endocrinologist friends who said, "47 mg/dL is way too low. They're obviously not treating the babies to a high enough blood sugar. It needs to go to 70 mg/dL to prevent this kind of damage."

There were a few other associations. At two years, they found that babies who did not have a lower blood sugar, less than 54 mg/dL, did worse, so meaning the opposite of what they were looking for. This difference by continuous glucose monitoring was only 3 mg/dL, but still, that association existed. They also found, that of the hypoglycemic babies, those with the worse outcomes had a steeper rise in their glucose concentrations after treatment with dextrose (I'll show you more about that). Then the third point here [Slide 14], infants who had more time outside this central range of glucose concentrations [54-72 mg/dL] did worse.[6] Glycemic

variability, measuring it's becoming more and more prevalent in the literature, and it's looking like a very important risk factor for outcomes of these babies. But I won't talk more about that unless asked.

Three Associations

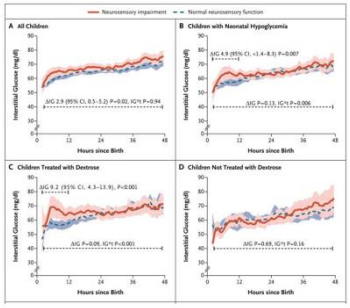
1. Those who did not have glucose lower than 54 mg/dL did worse than those who did.
   - By CGMS those with worse outcomes had a glucose concentration that was 2.9 mg/dL higher on average.
2. Of hypoglycemic infants, those with worse outcomes had a steeper rise in their glucose concentrations after treatment with dextrose.
3. Infants who had more time with glucoses outside the range of 54-72 mg/dL did worse.
   - Glycemic variability

McKinlay CJD, et al. *N Engl J Med*. 2015;373:1507-1518.

Slide 14

Regarding that second bullet point, what you can see here [Slide 15] in the top-left, the red are the babies from their study who had impaired neurosensory outcomes at two years, and those who did not. You can see this 3 mg/dL difference. If you start subsetting that, and looking only at children with neonatal hypoglycemia—here's their age and here's their pattern [Figure B]. You look at only those children treated with dextrose, and you get a sense that it's this early treatment that leads to that steeper rise [Figure C]. If you take away the babies who weren't treated with dextrose, there's complete overlap [Figure D].[6]

A More Rapid Rise After Treatment Was Associated With Worse Outcomes

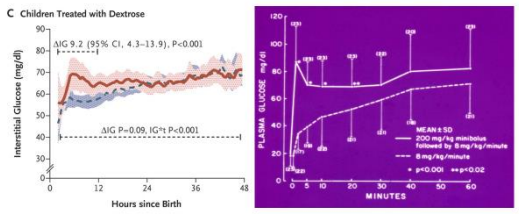


McKinlay CJD, et al. *N Engl J Med*. 2015; 373:1507-1518. Copyright 2015. Reproduced with permission from Massachusetts Medical Society.

Slide 15

We looked at that at my institution, and this graph reminded us a lot of this old graph from 1980 [Slide 16, right].[7] This is the graph that really shows the benefit or the response to the minibolus, the 2 cc/k of D10W [dextrose 10% in water]. In these hypoglycemic babies, they were either started on 8 mg/kg/m of IV dextrose, and this is what happened to their glucose concentrations, or given the minibolus. The minibolus raises the glucose concentrations. It's followed by the continuous infusion, and by minute 20 or 30, you're essentially the same.

Intravenous Treatment of Hypoglycemia:
Skip the 2 ml/kg D10W bolus for asymptomatic SGA, LGA, IDM, and late preterm newborns



Left: McKinlay CJD, et al. *N Engl J Med*. 2015; 373:1507-1518. Copyright 2015. Reproduced with permission from Massachusetts Medical Society.
Right: Lilien LD, et al. *J Pediatr*. 1980;97(2):295-8.

Slide 16

We looked at this graph, and we looked at this graph [Slide 16, left], and we thought, well, since there's really no evidence that using a minibolus is beneficial for asymptomatic hypoglycemia, we stopped using the minibolus. In fact, we are setting out on a QI type project, a before-and-after type project, in our NICU, and one of the metrics going forward was going to be use of the D10W bolus. Our pharmacist just told us that in the last 18 months, we've only done a D10W bolus twice. And that's for all comers, not just for asymptomatic. My recommendation would still be to use it if they have neurological symptoms, but we've essentially eliminated this D10W bolus from our practice for asymptomatic babies based on this associative data only.

Neonatal Hypoglycemia

Well, then, interesting about this Rorschach test that the *New England Journal* article brought out. So, anybody who said we were over-treating or under-treating now has to look at this study [Slide 17],[8] which are the same cohorts of babies studied at 4 1/2 years of age. Now, that association has flipped. So, now their hypothesis was that they would find worse outcomes in babies with glucoses less than 47 mg/dL, and indeed, they did. It was subtle, but they had subtly worse executive function and worse visual motor function compared to babies at 2 years. Really, no significant difference in the parental assessment. They postulated these defects might impact school age, and I think the other associations were not present.

Neonatal Glycemia and Neurodevelopmental Outcomes at 4.5 Years

McKinlay CJD, et al. *JAMA Pediatr.* 2017;171(10):972-983.

- Hypoglycemic (<47 mg/dL) babies had worse executive function and worse visual motor function compared to normoglycemic babies at 2 years.
- There were not significant differences in parental assessment of their children.
- However, the poor executive function and visual motor performance may impact learning and school achievement.
- The other associations reported at 2 years of age were not reported at 4.5 years of age.

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What did this study show, or what does this cohort of babies show? I don't need to repeat what I just said, but the bottom points are important. They don't define one management strategy as better than another. And then the other thing that comes up is it really brings up the idea of long-term follow-up or longer-term follow-up.

What Do These Studies Show?

- Using a screening and treatment strategy to actively increase glucose concentrations to >47 mg/dL, those with a glucose concentration <47 mg/dL:
  - Had equivalent outcomes at 2 years of age, but
  - Had worse outcomes at 4.5 years of age compared to patients that did not have a glucose concentration < 47 mg/dL
- They do not define one management strategy as better than another.
- Importance of longer term follow-up.

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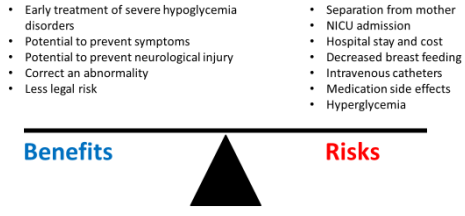
It is probably too early to look at 2 years of age in this group of babies, who universally we think do well. Their problems are probably more subtle than the ELBW [extremely low birth weight], who we can pick up with a Bayley screen at 2 years. This makes it hard to propose studies funded by bodies like the NIH (National Institutes of Health) where the funding is only for 5 years, and you want to look at the babies at 4 ½ years, or even better, at school age, at 10 years or 6 years. I do think we have to be cautious of negative studies around this topic at 2 years of age.

This [Slide 19] is just letting you know there's these potential risks and benefits to under and over-treating or being more aggressive or less aggressive with neonatal hypoglycemia. They all have to be considered.

How Aggressively Do You Diagnose and Treat Hypoglycemia?



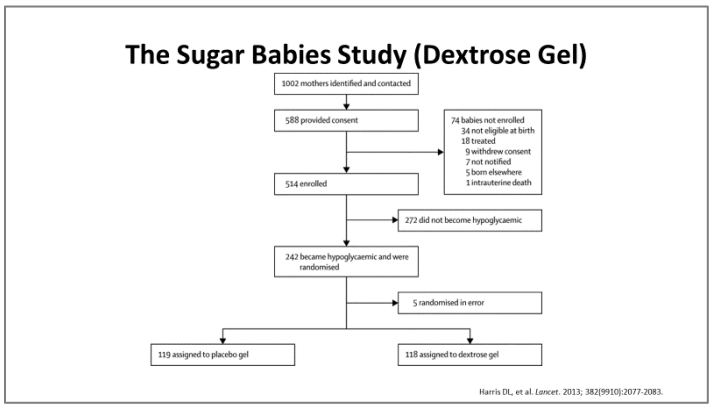
Slide 19

Neonatal Hypoglycemia

Given the fact that there are risks to over-treating, some of those things—like NICU admission, separation from the mother, decreased rates of breastfeeding—are there strategies that we could start to employ that could decrease the potential risks, maximize potential benefits? And this brings me to the dextrose gel study.

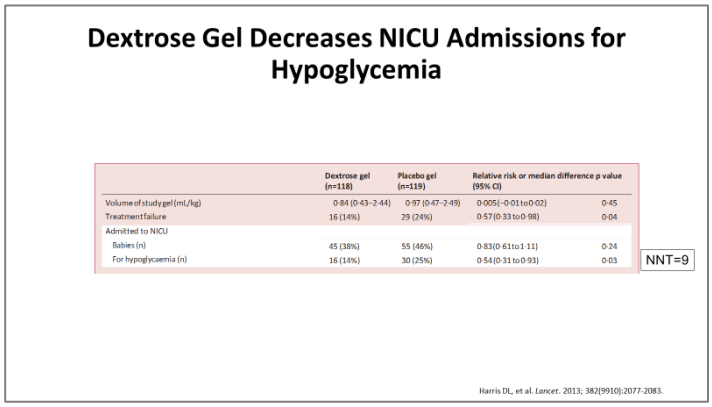
This was a study initially published in *Lancet* in 2013 [Slide 20].[9] This was a placebo-controlled trial of dextrose gel or placebo gel rubbed into the gums of babies who had a blood sugar less than 47 mg/dL (Deb Harris and Jane Harding). It's one of their studies. The primary endpoint was treatment failure defined as a blood sugar less than 47 mg/dL after 2 doses of study gel. Babies could get up to 6 doses of study gel, but most of the time, the physicians caring for the children went to open-label dextrose after 2½ doses.

Before I tell you what they found, I want to make sure when I make this recommendation to you, this is a single-center study. Essentially, 120 patients in each arm. That is not the highest-quality evidence multicenter, international-type trial. This is the evidence, but we've adopted it.



Slide 20

The reason we have adopted it is this: treatment failure, as you might expect, was less in the dextrose gel group; however, what was important to us is that admissions to the NICU were less for hypoglycemia. The number needed to treat was only 9, so not a very high number needed to treat. The overall admission rate to the NICU was not statistically significant, but that is likely due to power. And the absolute reduction seems to be about the same, and the number needed to treat is just a little bit higher. So, that seemed important to us.



Slide 21

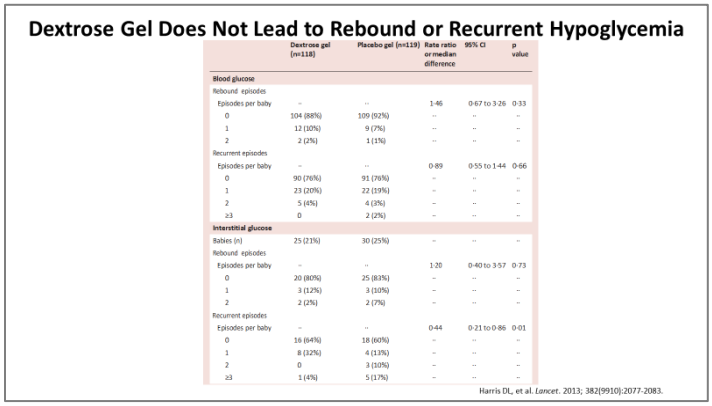
The other thing that seemed quite important to us was that the rate of formula feeding was lower in the group of babies who received dextrose gel. Now, this is just at 2 weeks of age. This is just any formula-feeding. You can see the rates of breastfeeding at Waikato Hospital, where the study was done in New Zealand, are quite high. Nonetheless, those who were in the dextrose gel group at 2 weeks of age were breastfeeding more...were less-likely to have had any formula feeding. This seemed encouraging, as well.

Table 1—Dextrose Gel Facilitates Breastfeeding

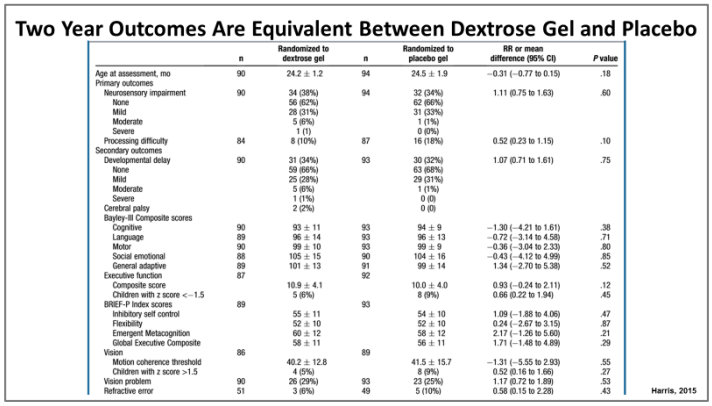
	Dextrose Gel	Placebo
Any Formula Feeding at 2 Weeks of Age		
	4%	13%*

Using both intermittent glucose sampling as well as continuous glucose monitoring, they did not find any rebound or recurrent hypoglycemia.

Neonatal Hypoglycemia



Slide 22



Slide 23

The other thing we can discuss during the Q&A or after is the time taken for that interstitial glucose concentration to be restored above 47 mg/dL was the same in both groups. [It's a] little paradoxical in that there was less treatment failure, but the point here is we may not have quite as rapid a rise as we do with, say, IV dextrose.

Table 2—Dextrose Gel Does Not Correct Hypoglycemia More Rapidly Than Feeding Alone

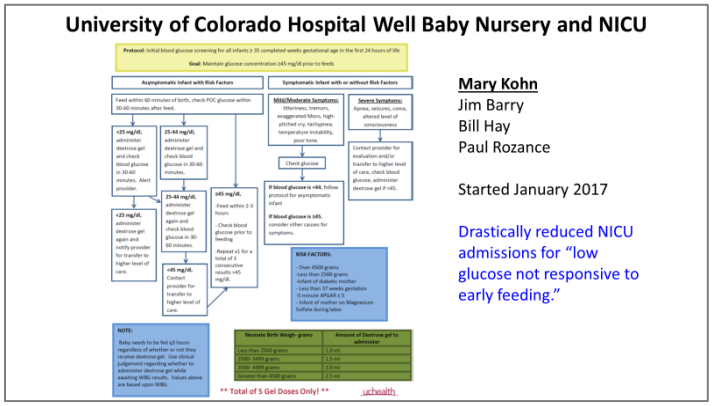
	Dextrose Gel	Placebo
Time taken for interstitial glucose concentration to be restored		
Minutes (Median, 95% CI)	20.3 (0.2-215.4)	22.8 (1.9-165.2)

Finally, I'd like you to take a minute to read every word on this slide [Slide 22]. No, I'm just kidding. Then they published their 2-year outcome. We didn't take up this practice in 2013 when *The Lancet* article came out. There were some real concerns, I think. Even though they had continuous interstitial glucose monitoring, not every event was captured. There might have been more recurrent or rebound hypoglycemia that was unrecognized. That might have impaired outcomes. There might have been a delay in definitive diagnosis, so babies who really needed IV dextrose were not getting it, and so therefore, their outcomes were impaired.

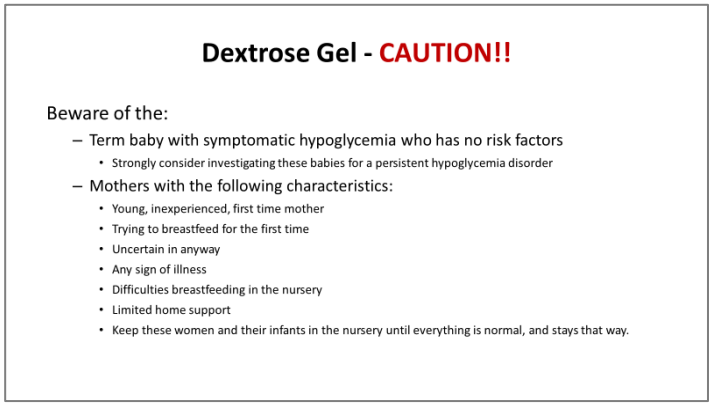
At 2 years, they put out their outcomes, and there was no difference. It didn't improve things, but it also didn't make things worse. Now, I understand I just told you that 2-year outcomes are not the best for this problem. This paper was published before their 4 1/2-year outcome data. So, we were already starting to change our practice based on this 2-year data. I still think it's reasonable if you choose to use dextrose gel to prevent NICU admissions for hypoglycemia.

We went ahead and created this protocol. Mary Kohn, MD was our well-baby nursery medical director. Jim Barry, MD is our NICU medical director. William Hay, MD, and I, we all crafted these together. Mary really finalized it, and it dramatically reduced our admissions for neonatal hypoglycemia by a lot. This has been borne out in numerous case control QI, historically controlled studies that have since been published.

Neonatal Hypoglycemia



Slide 24



Slide 25

When we look at dextrose gel, we have to be careful. One thing is, we don't want to mask a problem and then let that baby be discharged. Always be aware of the symptomatic hypoglycemic baby who had no risk factors. In my experience, quite often, if not well over half the time, you can identify something like panhypopituitarism (it's probably the most common that I'll pick up).

Then the other thing you want to not do is, you don't want to hide some problems with parental bonding or feeding especially (in any case). You have to be aware of young, first-time mothers and families, especially if they're trying to breastfeed for the first time—uncertain in any way, signs of illness, difficulty breastfeeding in the nursery, and limited home support—you can really mask problems by giving too much, too many doses of dextrose gel. That's why most protocols will put a limit somewhere between 2 to 6 of the number of doses you can give.

Other strategies: breastfeeding is best. Deb Harris reanalyzed a lot of their data looking at the change in blood sugar from the low blood sugar to the post-intervention. They found that dextrose gel caused a 3 mg/dL higher rise than if you didn't get dextrose gel. Interestingly, formula causes a 5 mg/dL rise. Breastfeeding was less, so 2 mg/dL. You could think if your goal was to raise blood sugars as fast as possible and as high, you would go with formula and gel. But, breastfeeding was associated with reduced odds of a second treatment of hypoglycemia [Slide 26].[10]

Our goal maybe isn't so much just to raise the sugar acutely if they're not symptomatic, but I think our goal should really be to facilitate that transitional metabolism and get them to a good state. This didn't happen with expressed breast milk. It only happened with breastfeeding. I think there's a lot to the direct breastfeeding that is beneficial to the improved metabolism of these babies.

Neonatal Hypoglycemia

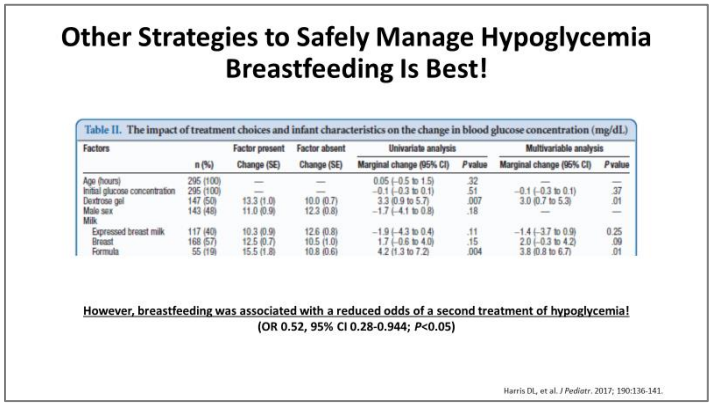


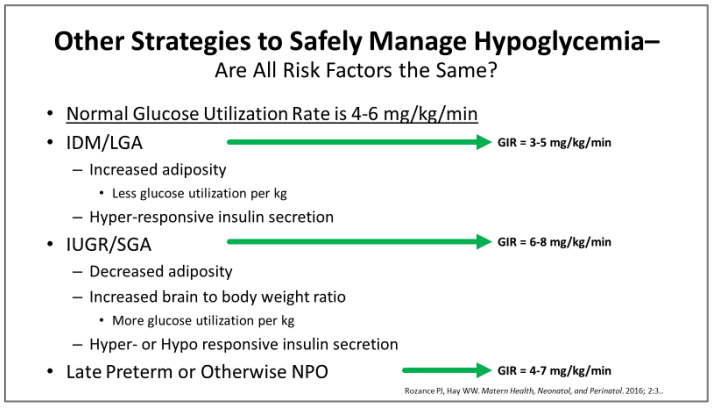
Table II. The impact of treatment choices and infant characteristics on the change in blood glucose concentration (mg/dL)

Factors	n (%)	Factor present Change (SE)	Factor absent Change (SE)	Univariate analysis Marginal change (95% CI)	P value	Multivariable analysis Marginal change (95% CI)	P value
Age (hours)	295 (100)	—	—	0.05 (−0.5 to 1.5)	.32	—	—
Initial glucose concentration	295 (100)	—	—	−0.1 (−0.3 to 0.1)	.51	−0.1 (−0.3 to 0.1)	.37
Dextrose gel	147 (50)	13.3 (1.0)	10.0 (0.7)	3.3 (0.9 to 5.7)	.007	3.0 (0.7 to 5.3)	.01
Male sex	143 (48)	11.0 (0.9)	12.3 (0.8)	−1.7 (−4.1 to 0.8)	.18	—	—
Milk							
Expressed breast milk	117 (40)	10.3 (0.9)	12.6 (0.8)	−1.9 (−4.3 to 0.4)	.11	−1.4 (−3.7 to 0.9)	0.25
Breast	168 (57)	12.5 (0.7)	10.5 (1.0)	1.7 (−0.6 to 4.0)	.15	2.0 (−0.3 to 4.2)	.09
Formula	55 (19)	15.5 (1.8)	10.8 (0.6)	4.2 (1.3 to 7.2)	.004	3.8 (0.8 to 6.7)	.01

Slide 26

One last point: Are all hypoglycemic babies the same? What [is] their risk factor? Should we treat them all the same? Up until now, I think most everybody has treated them the same. We're starting to change that, and this is the new project we're embarking on now.

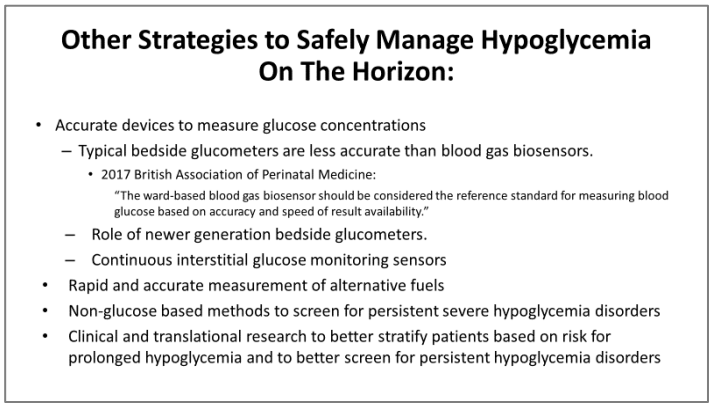
Normal glucose utilization rates for a newborn are 4 to 6 mg/kg/min. That's where we get that starting rate. Babies born to diabetic mothers, they have increased adiposity. They have hyper-responsive eyelids, more insulin secretion, and less glucose utilization per body mass because of that adiposity. Whereas IUGR and SGA babies have decreased adiposity, a higher brain-to-body-weight ratio, so glucose utilization is up, and their eyelids can be hyper- or hypo-responsive.



Slide 27

We've started a process where we used to do 4–6 mg/kg/min to start… Now, we're lowering that for the IDM baby. We're raising that a little bit for the IUGR baby, and we're keeping it essentially the same for others.

Here's what's on the horizon. It's the future directions, and I just want you to be aware of this. I think what you're going to start to see in this field is the need to have accurate devices to measure glucose concentrations—accurate bedside glucometers. Just so you know, typical handheld glucometers for people with diabetes are ±15–20 mg/dL. Blood gas analyzers are ±2–3 mg/dL. And in fact, in 2017, the British Association of Perinatal Medicine made the recommendation that all hospitals in the well-baby nursery should use handheld blood-gas analyzers because they're that much more accurate.[11] You don't have the transport issues getting samples to the central lab. They feel this will decrease admissions.



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There are newer generation blood glucose analyzers that are coming on the market. And then CGMS [continuous glucose monitoring system], you'll be reading a lot more about that. It's point accuracy's not great. It's better for trends. Alternative fuels are being measured. And then we need non-glucose-based methods to screen for those endocrine problems. Things like genome sequencing perhaps, those sorts of things.

Neonatal Hypoglycemia

The last bullet point is my research [Slide 28].[12] With that, I thank you all.

Abbreviations

AAP	American Academy of Pediatrics	**IDM**	infants of diabetic mothers
BPD	bronchopulmonary dysplasia	**LGA**	large-for-gestational age
BWS	Beckwith-Wiedemann syndrome	**LPT**	late-preterm
CGM	continuous glucose monitoring	**IUGR**	intrauterine growth restriction
CGMS	continuous glucose monitoring system	**OFC**	occipital frontal circumference
D10W	dextrose 10% in water	**PES**	Pediatric Endocrine Society
DSMB	Data Safety Monitoring Board	**ROP**	retinopathy of prematurity
ELBW	extremely low birth weight	**SGA**	small-for-gestational age
GLP-1	glucagon-like peptide		

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