Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Neonatal Hyperglycemia in the ELBW Infant

Miami Neonatology 2018 – 42nd Annual International Conference

Overview

In this activity, **Paul J. Rozance, MD**, 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.

In the companion, *Neonatal Hypoglycemia*, Dr. Rozance 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.

Content Areas

- Clarifying glycemic variability
- Identifying risk factors of neonatal hyperglycemia
- Treating and preventing hyperglycemia in ELBW infants
- Adverse effects of high glucose concentrations
- Limiting use of insulin in ELBW infants

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:

- Identify risk factors for hyperglycemia in the extremely low-birth-weight (ELBW) and the rationale for treating or preventing this complication
- Employ strategies to minimize hyperglycemia in the ELBW

Faculty

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Paul J. Rozance, MD

Research Support	Nova Biomedical – clinical area: ß-cell survival and function
Consultant	Xeris Pharmaceuticals Data Safety and Monitoring Board – clinical area: congenital genetic hyperinsulinemia

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The following have no significant relationships to disclose:
Erin Allen, MS, RD, LDN (RD reviewer)
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This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the

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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.

Contact Information

For help or questions about this activity please contact Continuing Education:

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https://pnce.org/Hyperglycemia

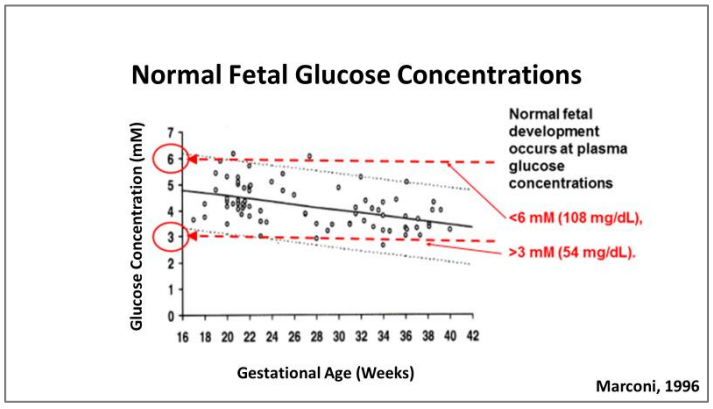
Editor's Note: This is a transcript of a live presentation from Miami Neonatology on November 14, 2018.

Dr. Paul J. Rozance: In today's talk, I'm going to focus on *hyperglycemia*, so glucose concentrations that are too [high], and I'm also going to focus this talk on the extremely low birth weight (ELBW) infant, or the extremely preterm baby. There's a lot of questions about hyperglycemia in other patient populations, which I'd be happy to field, but this again will focus on the preterm baby.

The objectives for this would be for you all to be able to identify risk factors for hyperglycemia in the ELBW, and the rationale for treating or preventing this complication. And then at the end, I'll go over strategies that we can employ to minimize hyperglycemia in the ELBW.

I want to start by saying my interest in this topic came from reading a lot of the randomized controlled trials of tight versus not tight glucose control in intensive care settings. As you may know, that idea made its way down into the neonatal ICU, and it's still an area of active investigation. And what I was struck by was, even in the control groups, the insulin use was quite high, quite a lot more insulin use in those studies than what I was observing in our NICU. We went through the process of identifying why, and this is really the genesis of the talk.

First off, I started yesterday by asking, what is normal neonatal glucose concentrations and the problems defining hypoglycemia? The same problems really occur around defining hyperglycemia. When you ask people, you get quite variable answers. We look at fetal glucose concentrations, and in this case, we think looking at fetal glucose concentrations is appropriate because these babies, as you can see over gestation, really have glucose concentrations that ranged between 54–108 mg/dL. We know on a fairly simplistic level, that over the last third of gestation, fetuses can grow and develop normally at these glucose concentrations. So, this could be used as one justification for a particular range.



Slide 1

However, as I already mentioned, when you asked neonatologists to define hyperglycemia, the definitions are really all arbitrary. They're not really

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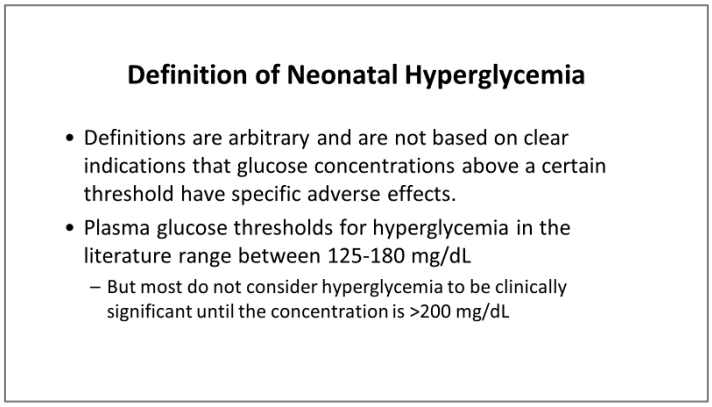
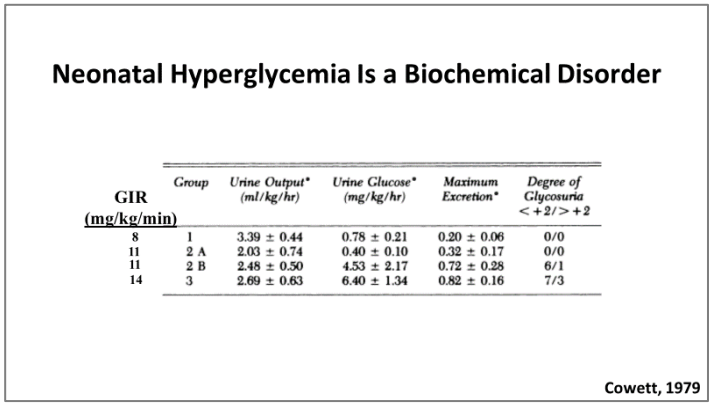
based on any clear indications that glucose concentrations above a specific threshold will have a specific effect. When you get people pinned down to ask where they believe hyperglycemia should be defined or diagnosed, the range is about 125–180 mg/dL. 180 mg/dL is typically, nowadays, the most commonly number in clinical research studies. However, most people don't really act on these high glucose concentrations, or they say they don't act on them until they're over 200 mg/dL.



Slide 2

Neonatal *hyperglycemia* is truly a biochemical disorder. It's really a disorder that's hard to pick up on clinical exam or by doing anything other than measuring the baby's glucose concentration.

This is an old study by Richard Cowett, MD,[1] who created four groups of ELBWs, experimentally infusing different rates of glucose into them: 8 mg/kg/min, 11 mg/kg/min, and 14 mg/kg/min. Then you can see [Slide 3] that they were classified according to whether they had glycosuria or not, off on the far right. What you can say is, even the ones who got the high rate and develop glycosuria, their urine output didn't change. At least with this experimental evidence, contrary to the experience people have with diabetes, you don't develop diabetes. You don't develop a high urine output with hyperglycemia, at least as he defined it.

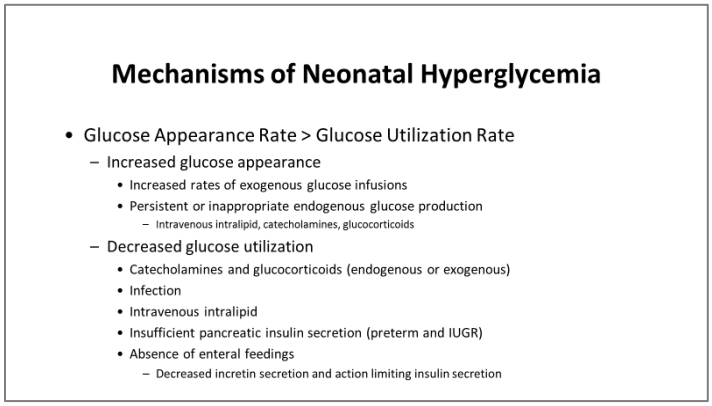


Slide 3

What are the mechanisms of neonatal hyperglycemia? Essentially, you get a high glucose concentration when your glucose rate of appearance exceeds your glucose utilization rate. How might this happen? Increased glucose appearance happens with increased rates of exogenous glucose infusions, also with persistent or inappropriate endogenous glucose production, meaning gluconeogenesis or glycogenolysis by the neonatal liver. This can be made worse with intravenous lipids, catecholamines, and glucocorticoids.

There's also clinical situations we encounter where glucose utilization is decreased. These would include, again, effects of catecholamines and glucocorticoids, either endogenous or exogenous; infections; intravenous lipids also decrease glucose utilization; insufficient pancreatic insulin secretion, which is especially problematic for the preterm baby and the IUGR baby; and then absence of enteral feeds (which I'll get into later). Essentially without enteral feeds, you don't secrete your incretin hormones, and that will limit insulin secretion (as I'll show you).

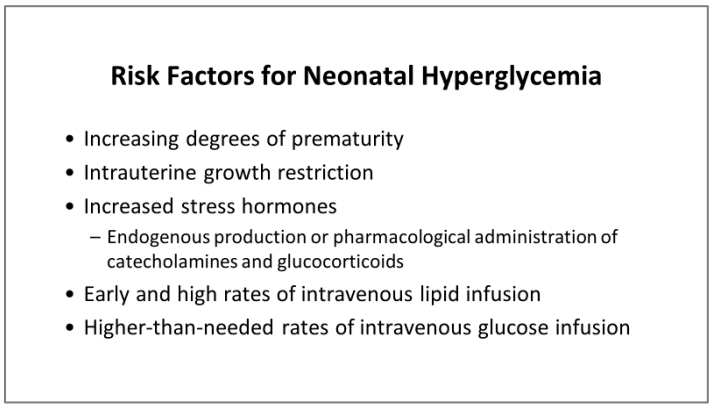
Neonatal Hyperglycemia in the ELBW Infant



Slide 4

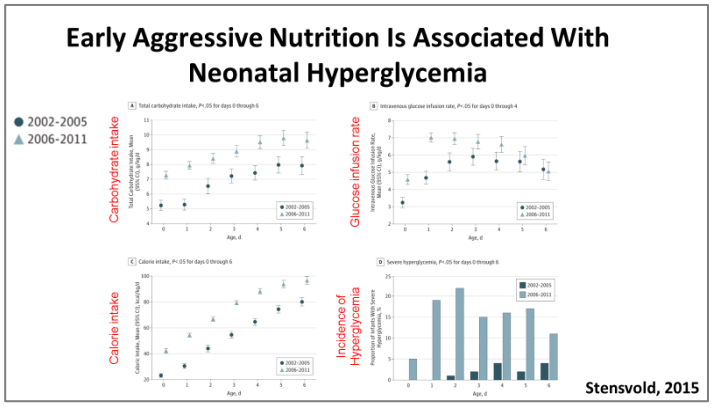
Therefore, having looked at the causes of increased glucose production or rates of appearance and decreased glucose utilization, we can pretty easily understand, now, the well-defined risk factors for neonatal hyperglycemia. These have really been defined in multiple different studies, and are well agreed upon. The more premature you are, the more likely you are to develop hyperglycemia. Intrauterine growth restrictions are a well-defined risk factor for *hyperglycemia*. Increased stress hormones, whether that's endogenous production or pharmacologic administration of catecholamines and glucocorticoids. Both are risk factors.

Early and high rates of intravenous lipid infusions is a risk factor for neonatal hyperglycemia. And then finally, higher-than-needed rates of intravenous glucose infusion is also a risk factor. We'll talk more about each of these.



Slide 5

At the University of Colorado with my mentors, Dr. William Hay, Dr. Patti Thureen, and others, we've really—they really—pushed this idea of early aggressive nutrition. For the most part, of course, we believe that's an appropriate thing to do. However, it's pretty clear to us now that with the advent of this early aggressive nutrition, we get increasing incidence of hyperglycemia. This was documented in a study published in 2015,[2] in which you have essentially a carbohydrate intake, calorie intake, glucose infusion rate, and then the incidence of hyperglycemia. You have that graphed across the first 6 days of life in babies born between 2002 to 2005 compared to 2006, 2011, when this center was adopting this early aggressive nutritional support protocols.



Slide 6

Carbohydrate intake was higher in the later epoch. Calorie intake was higher in the later epoch. The glucose infusion rate also was higher. But, what you notice is this incidence of hyperglycemia was definitely higher in the period when they were using higher rates of glucose and calorie delivery. This is something we have to be aware of because more and more of us are becoming convinced that in the ELBW, hyperglycemia may be not quite as benign as we had once thought.

There's these acute concerns that everybody, I think, shares around hyperglycemia. Most of these are derived from adult diabetic patients. That

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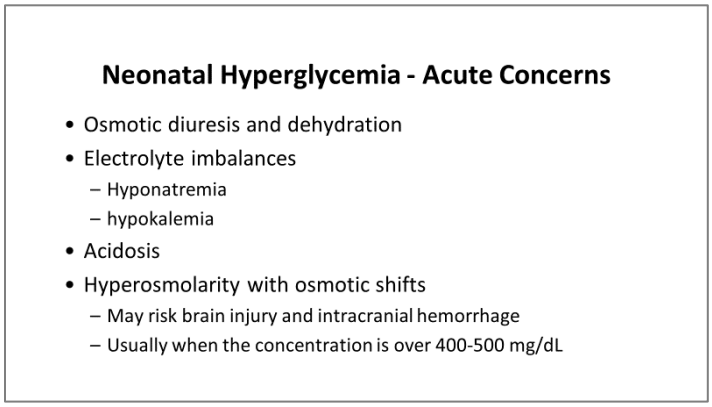
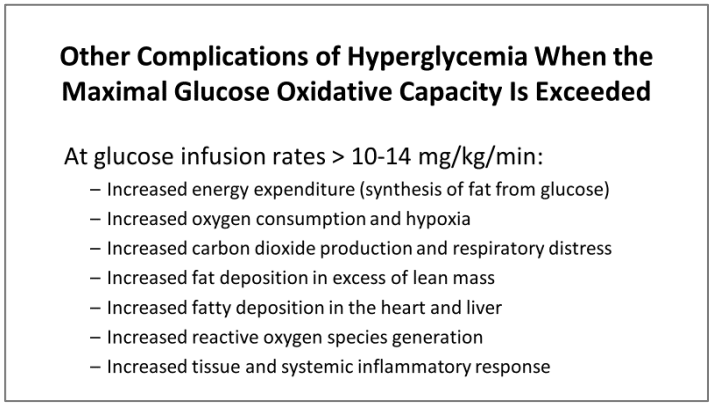
includes osmotic diuresis and dehydration, which may or may not occur in the ELBW neonate. We certainly worry about electrolyte imbalances, like hyponatremia and hypokalemia, metabolic acidosis. Hyperosmolarity with osmotic shifts, which certainly could put you at risk for brain injury, intercranial hemorrhage, perhaps. This is really only seen when the glucose concentrations are extremely high; nonetheless, it's a concern.



Slide 7

There are other complications that we know about when you have hyperglycemia, and these are really exacerbated when the glucose infusion rates are higher than what the baby can handle. Again, you're giving these high rates of glucose; the baby isn't able to utilize them efficiently; and now you start to see some of these adverse effects. This data is taken both from human data, as well as animal data, but it's fairly consistent, not only with humans and animals, but across different animal species. When you start hitting the maximal glucose utilization capacity of a newborn, you start seeing increased energy expenditure. Usually, that's because you're now synthesizing fat from that excess glucose. That's how the individual tries to cope with this excess glucose.



Slide 8

You get increased oxygen consumption, which sometimes can lead to hypoxia. Increased carbon dioxide production, and a need to ventilate that CO2 down, so you get some signs of respiratory distress. Increased fat deposition, this would be an excess of lean mass growth. Increased fatty deposition into the heart and liver, which are particularly worrisome for short- and long-term effects. And then there's biochemical evidence of increased reactive oxidative species generation, increased tissue in systemic inflammation, which we don't think are good.

Given these problems, it's not surprising that hyperglycemia in the ELBW has been associated with a number of adverse effects. Probably the best associations are with increased mortality, impaired neurodevelopment, and retinopathy of prematurity.

I'm just going to show you one slide for each of these—basically picking an illustrative figure or table to make the point. Here's one study that looked at both death, as well as white matter injury,[3] and essentially showed that hyperglycemia is associated with an increased risk of death, as well as with white matter injury.

This is just one of a handful of studies that's made this association in the ELBW, and it follows all the data from adult and pediatric literature, as well. The

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associations with death and impaired neurodevelopment are clear.

Hyperglycemia Is Associated With Death and White Matter Injury

TABLE 3 Factors Associated With Death and WMR Among EPT Infants

Variable	$B \pm SE$	Wald χ^2	P	OR (95% CI)
Death				
Intercept	6.3 ± 6.6			
Hyperglycemia	1.3 ± 0.54	6.0	.01	3.7 (1.3–10.6)
GA	−0.38 ± 0.25	2.2	.13	0.68 (0.41–1.1)
Gender	−0.15 ± 0.53	0.08	.78	0.86 (0.30–2.4)
WMR				
Intercept	0.18 ± 7.0			
Hyperglycemia	1.1 ± 0.58	4.1	.04	3.1 (1.0–9.2)
GA	−0.11 ± 0.26	0.19	.66	0.89 (0.96–1.3)
Gender	1.1 ± 0.49	5.6	.02	3.1 (1.2–8.1)
CRIB score	0.11 ± 0.08	2.0	.16	1.1 (0.96–1.3)

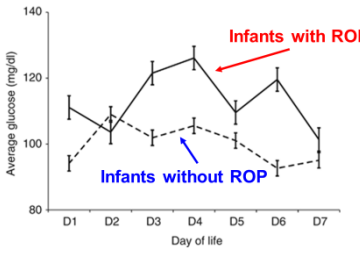
The hyperglycemia cutoff value at 24 hours was 8.3 mmol/L. P values of $<.05$, according to logistic regression models, were considered significant.

Alexandrou, 2010

Slide 9

The association with retinopathy of prematurity is also present in a handful of studies. In this graph [Slide 10], we essentially see day of life down here [x-axis], [and] average glucose concentration. The infants were stratified to either the group who had retinopathy of prematurity or didn't.[4] As you can see, those with a retinopathy of prematurity had higher glucose concentration. This is a nice figure representation of a phenomenon that's been documented in a number of studies.

Hyperglycemia Is Associated With Retinopathy of Prematurity

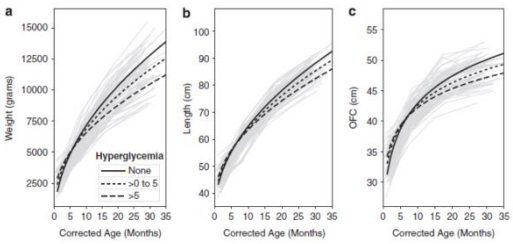


Mohsen, 2014

Slide 10

Finally, there are a few less studies, but talking about long-term growth, or at least growth within the NICU, and evidence of hyperglycemia. This is one [Slide 11] of a nice series of studies out of the University of Minnesota where they categorized babies as either never having had hyperglycemia in this top line, having had hyperglycemia on 0 to 5 days, or having had hyperglycemia for greater than 5 days.[5] Then, they look at their growth based on corrected age over months, so now we're talking long-term effects. Those with more hyperglycemia ended up not gaining as much weight—essentially not growing as well for weight, for length, or for OFC—for head circumference.

Hyperglycemia Is Associated With Poor Long-Term Growth



Ramel, 2013

Slide 11

If I've just told you that hyperglycemia is associated with all these bad outcomes, now the question is what can we do to stop it, to prevent it? Clearly, one of the obvious answers is to provide exogenous insulin. It's a great agent for lowering blood sugar concentrations, and so this has been contemplated and actually tested in a few different [academic] centers, looking at treating neonatal hyperglycemia in the ELBW with insulin. I'll go over one really interesting study, and then I'll go over a second study about prophylaxis.

This is a study by Jane Alsweiler, PhD, MBChB, from the New Zealand group in Auckland [Slide 12].[6] In here, they took babies who had hit a threshold of above 180 mg/dL, and then randomized them not so much to insulin or no insulin, but to tight glycemic control versus a standard of care. This idea of tight glycemic control in intensive care settings, as I've said, has a long history in the adult and pediatric literature. This was a trial of tight glycemic

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control in the ELBW. All the babies in the tight group received insulin. Over half the babies in the control group did, but it was less, but clearly the group in that tight glycemic control arm got a lot more insulin, both time and dose.

Treatment of Neonatal Hyperglycemia With Insulin

	72-108 mg/dL	144-180 mg/dL	
	Tight Group	Control Group	*P* Value
n	43	45	
Treated with insulin	42 (98)	29 (64)	<.0001
Total insulin dose, U/kg	13.5 (4.0–30.0)	1.8 (0–9.7)	<.0001
Daily mean dose of insulin,* U/kg/hr	0.06 (0.05–0.07)	0.04 (0.04–0.05)	.002
Time on insulin, h	168 (80–413)	44 (0–179)	<.0005

Alsweiler, 2012

Slide 12

What did they find? Clearly, they were able to reduce glucose concentrations in the tight group. That was the aim of the study. They also, though, uncovered more hypoglycemia in the tight group, so that's also not too surprising. They really wanted to look at whether tight glucose control improved growth in the NICU.

Treatment of Neonatal Hyperglycemia With Insulin

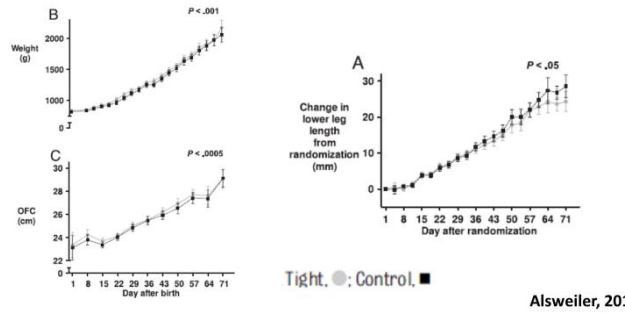
	Tight Group	Control Group	*P* Value
BGC, all measurements, mmol/L			
Daily maximum	6.5 (5.2–8.4)	6.9 (5.2–9.5)	<.0005
Daily mean	5.7 (4.8–6.7)	6.5 (5.1–8.2)	<.0001
Daily minimum	4.7 (3.7–5.9)	5.7 (4.7–7.1)	<.0001
BGC, while receiving insulin, mmol/L			
Daily maximum	7.7 (6.3–9.6)	10.8 (9.3–12.7)	<.0001
Daily mean	5.8 (5.1–7.1)	8.5 (7.5–10)	<.0001
Daily minimum	4.2 (3.4–5.5)	6.5 (5.1–7.8)	<.0001
Hypoglycemia[d]			
No. of infants[e]			
<2.6 mmol/L	25 (58)	12 (27)	<.005
<1.5 mmol/L	7 (16)	2 (4)	.06
No. of episodes			
<2.6 mmol/L	1 (0–2)	0 (0–1)	<.005
<1.5 mmol/L	0 (0–0)	0 (0–0)	.08
Recurrent hypoglycemia[f]	7 (16)	2 (4)	.06

Alsweiler, 2012

Slide 13

With the caveat of more episodes of hypoglycemia, here's what they found [Slide 14].[18] These graphs are interesting. The statistics are run on cumulative data, so even though the tight glycemic control is barely heavier than the comparative group, the *P*-value is quite significant for a small, but consistent, increase in weight [plot B]. They found the same thing for OFC [plot C]. Then what we found quite interesting, they found it interesting as well and concerning, was that the length didn't follow the trend of height and head circumference. The babies had lower leg limb growth throughout their days after randomization [plot A].

Treatment of Neonatal Hyperglycemia With Insulin



Alsweiler, 2012

Slide 14

Again, it's subtle, but statistically significant, and what I should let you know is that Anna Tottman, PhD [University of Auckland] recently looked at these subjects who, at the time she looked at them, were now 7 years old. Those 7-year old babies who were randomized to the tight glycemic control group were shorter than the control group, than the comparative group.[7] This drop in lower limb length growth, we think is real. I don't know the significance of that. There were other features of the subjects that make you wonder whether they're going to have long-term metabolic changes either positively or negatively. We certainly know this leg growth phenomena, we think is real.

Instead of treating these babies that develop hyperglycemia with insulin, what about trying to prevent the hyperglycemia from ever happening? This was a study, it was published in the *New England Journal of Medicine* by Kathryn Beardsall, MRCP,[8] and she built up to this multicenter international randomized trial of insulin versus no

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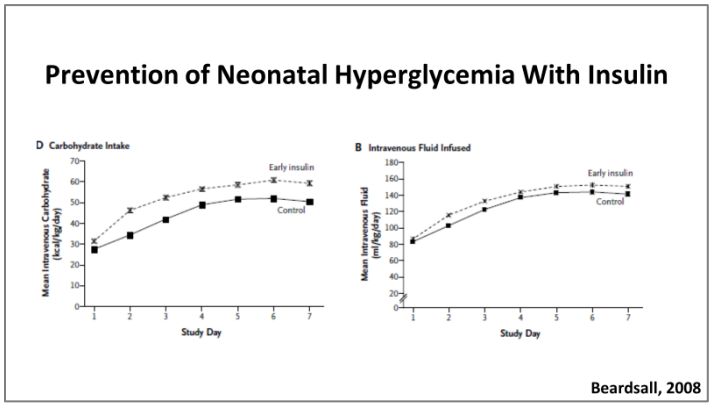
insulin in the ELBW with the primary goal of decreasing mortality at the expected due date. Again, decreasing mortality, at the time, seemed like obviously one of the most important outcomes you can measure, and it seemed like a reasonable hypothesis given what was happening in some of the adult ICU literature at the time.

In this study [Slide 15], here's the glucose concentrations, this is the early insulin group. These would be the control group, and so they obviously were able to lower insulin concentrations over the first week of study, which was completely anticipated.

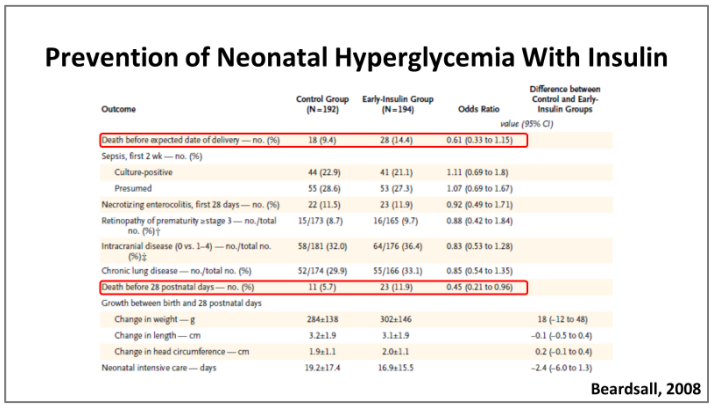


Slide 15

This was the percent of time spent in hyperglycemia. So, that was another one of their outcomes, and the group who was in the prophylactic insulin arm had less hyperglycemia. They also had a higher percentage of time in the low glucose concentration range, so perhaps not surprisingly, in hindsight, more time spent being hypoglycemic.

They were able to deliver a higher carbohydrate load to the infants in the insulin arm, without really big changes in the fluid administered. But their primary outcome was survival to estimated due date, estimated day of delivery. The trial was stopped early because there were concerns of futility of the treatment. The DSMB didn't think this study was going to be able to show a positive benefit to the insulin, and also [there were] some concerns around adverse effects. They stopped the trial early for those reasons. When all the patients were finally analyzed, death before the expected rate of date of delivery was 9.4% percent in the control group and 14.4% in the early insulin group. This didn't reach statistical significance.

However, they also looked at death before 28 days, and that did reach statistical significance. And so these concerns around harm were real, and they were probably born out in the final analysis, as well as the concern around hypoglycemia. For those reasons, the trial was stopped early, and really, we didn't hear much about prophylactic insulin for quite a while after that study, until the New Zealand group started taking it up. [Dr. Beardsall's] group is also now taking it up with more refinements, which I'll talk about in a minute.

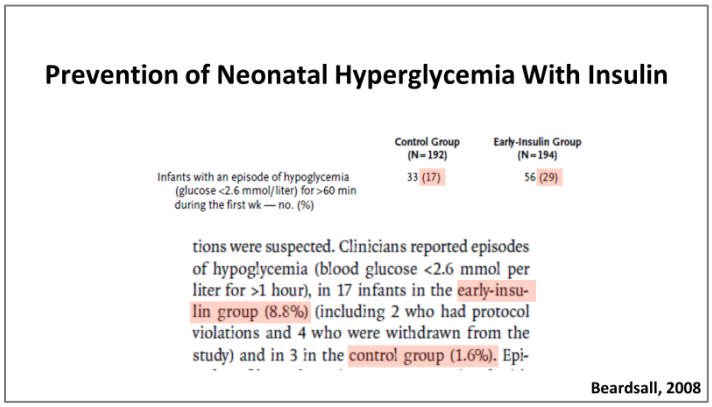


Slide 16

The other problem was this hypoglycemia in the early insulin group, but more important than that is, this study didn't use an open, continuous glucose monitoring system. They used CGM, but it was blinded, as they all have been until very recently. If you just take even the control group, they clinically, by intermittent sampling, only documented hypoglycemia in 1.6% of the control group. Seventeen percent, based on the continuous glucose monitoring, had hypoglycemia; same with the early insulin groups. They're using these insulin

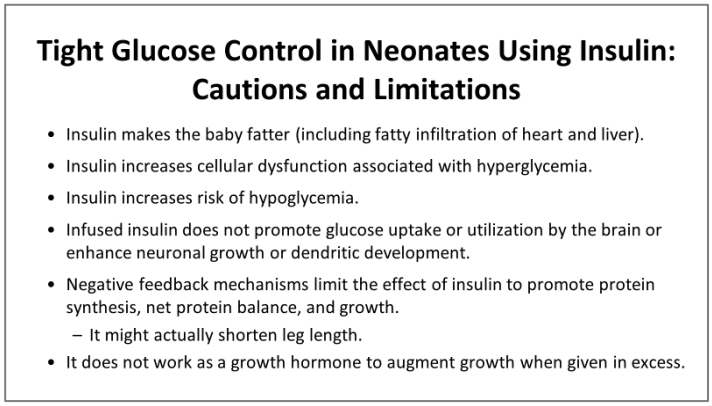
Neonatal Hyperglycemia in the ELBW Infant

infusions and their standard of glucose monitoring. There was a lot of occult hypoglycemia that was missed during the trial, and this holds for a lot of different trials in different ICU situations.



Slide 17

The cautions and limitations around tight glycemic control in the neonate using insulin—again, some of this comes from human data, some from animal data—but it's pretty consistent across humans to animals and different animal species. Insulin makes the baby fatter, and this includes making things worse in the heart and the liver, so increased fatty infiltration of the heart and liver. It increases cellular dysfunction. Cellular dysfunction we see with hyperglycemia is made worse when you add insulin to the system. Obviously, it increases the risk of hypoglycemia. The infused insulin doesn't promote glucose uptake or utilization by the brain or enhance neuronal growth or dendritic development. I think this is a really important point that I'm going to repeat here. **Giving a baby insulin increases the baby's glucose utilization, but it does not increase cerebral glucose utilization. That's almost solely dependent on the concentration of glucose in the plasma.**



Slide 18

There are negative feedback mechanisms that limit the effect of insulin to promote protein synthesis, net protein balance and growth, so it might actually shorten leg length. We saw that from the clinical study, and we've seen evidence of this in our animal models; therefore, it's not surprising that it does not work as a growth hormone to augment growth when given in excess. You certainly need insulin, if a fetus is insulin deficient, experimentally or through genetic abnormalities. In humans, they don't grow well. You can correct that growth by giving insulin, but you can't get excess growth by giving more insulin because of these negative feedback mechanisms.

Can insulin therapy be improved? I think this is what Dr. Beardsall's group is working on and Dr. Alsweiler's group is working on. They're trying to improve the way they use insulin to make it a better, more effective therapy, and a safer therapy. The ways, I think, we'll see improvements here are by the use of accurate glucometers. Eventually, I think the continuous interstitial glucose monitoring sensors will develop the point accuracy that's needed, or at least we'll learn how to use them appropriately. Then, what I think is also going to be really key are computer-determined dosage of insulin with specific neonatal protocols. So, neonate's insulin sensitivity, secretion, and glucose metabolism change rapidly over the course of hours in that first week of life. What Dr. Alsweiler is finding

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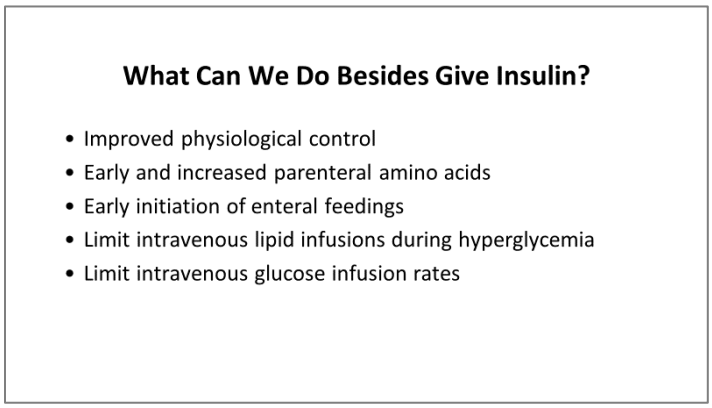
is that maybe there's computer programs that are better at predicting those changes than we are. I think this is really going to help our field a lot.

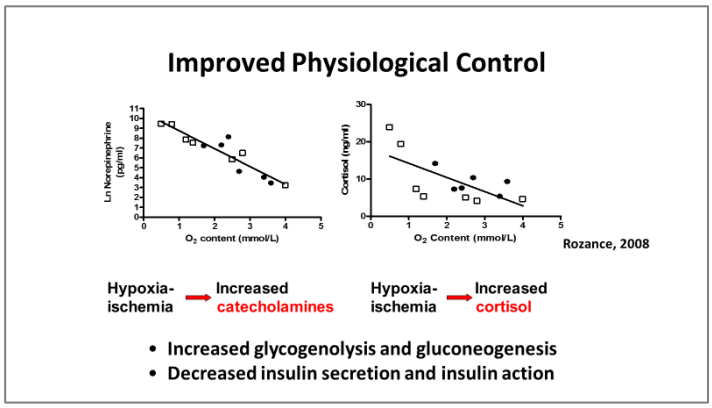
What can we do besides give insulin? I've just told you that hyperglycemia is bad. It's associated with bad outcomes. Insulin may not actually help the situation and it may actually be harmful. Are there are other things we can do besides give insulin to either prevent or treat neonatal hyperglycemia?

Here's the five bullet points that I think, when I looked at what our practice was, to me, these sort of explained at Colorado why we don't typically use insulin. It's a very rare event in our ELBWs. Of course, we all think we can improve physiological control, and that's the goal, whether it's related to hyperglycemia or not. Early and increased parenteral amino acids. We think by pushing for this aggressive parenteral amino acid infusion of higher rates earlier in life that we've seen less hyperglycemia. Early initiation of enteral feedings. I'll talk about the incretin hormones and their role. Limiting intravenous lipid infusions during hyperglycemia, we think has an important role. Then limiting intravenous glucose infusion rates, (which I'll talk about at the very end).



Slide 19

This is a graph from our animal lab [Slide 20], where we graph oxygen content on the x-axis, and then on the left graph, we're graphing norepinephrine (the log concentration of norepinephrine). In this graph, it's cortisol. This is simply to make the point that in the perinatal period, lower oxygen concentrations in the blood are associated with higher elevations of these stress hormones. These stress hormones, both catecholamines and cortisol, have the effect of increasing glycogenolysis and gluconeogenesis. They increase liver's production of glucose. They also decrease insulin secretion and inhibit insulin action in the non-hepatic tissues.



Slide 20

Improving physiological control is great. Limiting exogenous steroids or pressors is great. I think we all want to do that no matter what. If a baby is hyperglycemic, maybe just reassess what level of support you're providing to these babies; see if you can decrease the exogenous use of these medicines or whatever else you can do to improve physiological control.

The one that I think was a most exciting, when I started at University of Colorado, was the idea of early aggressive parenteral nutrition with amino acids. This was work by Patti Thureen at Colorado with Bill Hay. It remains one of my most favorite publications. It's in 2003 in *Pediatric Research*.[9] What they did in 2000, 2001, they took babies who were about 1 kg, 2-days of age, and they randomized them to our standard amino acid infusion rate. Back then it was 1 g/kg/d at 2-days of age, or what they were calling at the time, a high-dose amino acid

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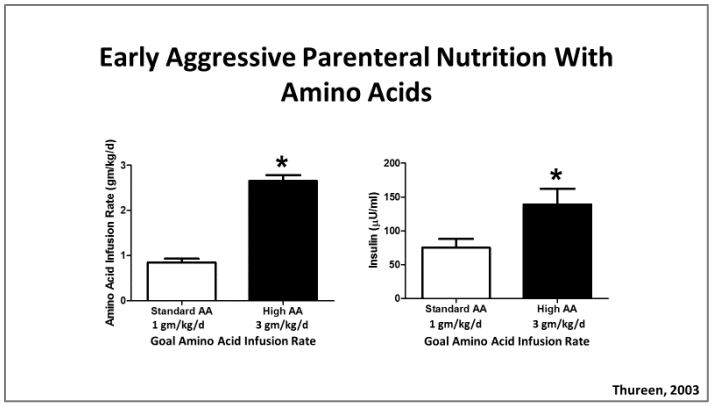
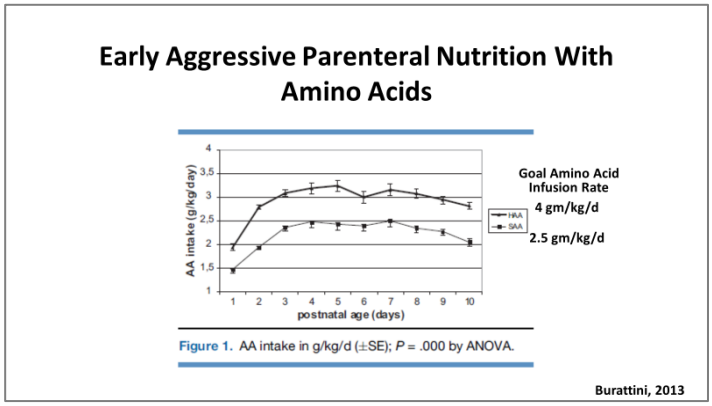
infusion rate of 3 g/kg/d. These were the actual rates.

Among a lot of other things, they measured insulin concentrations. But this is one of the first times that I'd seen in the literature from human data showing that amino acids increase insulin concentration. The idea, our idea, was if we gave these high rates of amino acids, we might increase endogenous insulin, and perhaps endogenous insulin is released in a way that's different than an infusion, obviously. Perhaps it works differently and perhaps more safely to lower glucose concentrations. We felt for a long time that was one of the reasons why we didn't see much insulin use in our unit at all compared to what we were reading about in the literature.



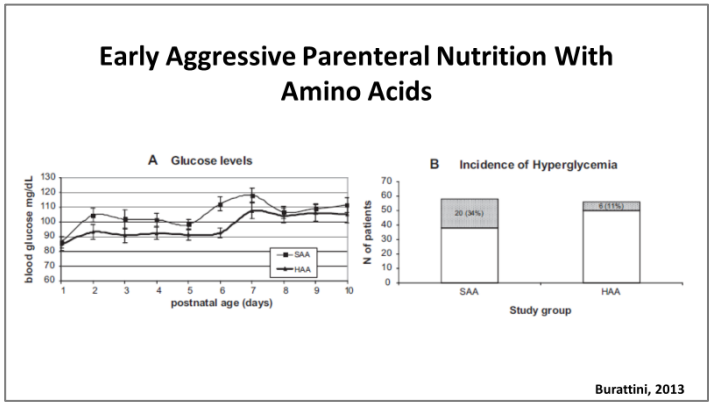
Slide 21

We never did the big study, that showed it reduced rates of hyperglycemia. Fortunately, there was a study in 2013 published that did.[10] In this case, by 2013 the standard of care had become 2.5 g/kg/d, and the high dose being tested was 4 g/kg/d. We'd made a lot of progress, we think, in the amino acid infusion rate use.



Slide 22

Here they had a true difference of about 0.5–0.75 k/kg/d over the course of 10 days, and here's what the glucose concentrations look like. The high amino acid group had significantly lower glucose concentrations throughout that first 10 days of life compared to the standard amino acid infusion rate. The incidence of hyperglycemia, not surprisingly then, was lower. This was the first clinical evidence that we had to support what Patti had been thinking when she and Bill published that study.



Slide 23

Another important aspect of preventing or treating hyperglycemia is early initiation of enteral feedings. Why might early initiation of enteral feedings help? The physiological rationale has to do with the incretin hormones. Incretin hormones are the hormones your stomach and small intestine secrete after you ingest a meal. When secreted, what they

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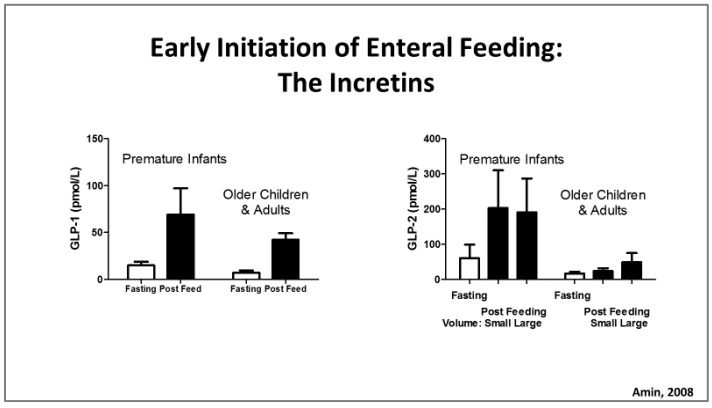
do is they increase the amount of insulin secretion for any given glucose concentration in the system.

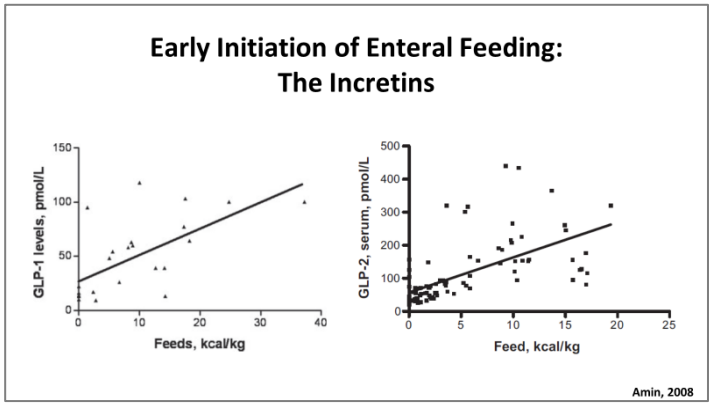
It's the reason why, if I inject myself with a bolus of 50 g of dextrose, I'll get this kind of insulin rise, a standard insulin rise. But if I ingest it into my stomach instead of injecting it into my vein, I get a much bigger insulin response for the exact same stimulus. That's without glucose concentrations being higher. These incretins potentiate glucose stimulated insulin secretion. So, if a person is feeding, they'll secrete more insulin for any given calorie load.

This was a nice study in 2008 [Slide 24] that showed this is a phenomenon that's occurring in premature infants.[11] GLP-1 is one of the best characterized incretins. It's as pronounced, if not more, than for older children and adults. In GLP-2, which has similar mechanisms of action, the response is quite a bit bigger than in these older children and adults.



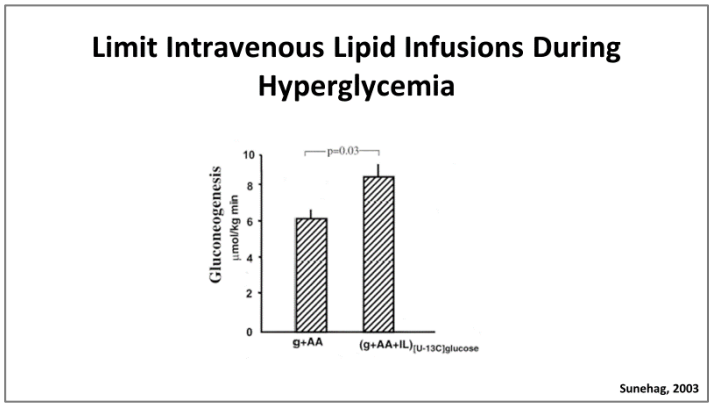
Slide 24

In fact, you might want to think when you're starting these feeds, at what point is the feeding so small that it may not matter? There are these positive associations between the amount of calories ingested by these preterm babies and their incretin levels post feed, so we think earlier is better. The more you can safely provide enterally is better, and we think it'll help prevent hyperglycemia in your babies.



Slide 25

This is just a nice study from Agneta L. Sunehag, MD, PhD, [Slide 26], who is measuring gluconeogenesis in ELBWs, using glucose tracers.[12] Here [left bar] the babies are getting only glucose and amino acids, and here they're getting glucose, amino acids, and intralipids [right bar]. What you can see is that when you don't have the intralipids, your rate of gluconeogenesis is a lot lower. That's because the glycerol backbone from the triglyceride feeds directly into gluconeogenesis, and then the energy produced by the intralipid inhibits glucose utilization in the liver, causing you to release more glucose. We will limit our intravenous lipid infusion during hyperglycemia.



Slide 26

Let me just summarize these strategies to prevent and treat hyperglycemia and then make a few closing comments. The goal glucose concentration that most of us in our group adopt is between 60–

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125 mg/dL. That's pretty arbitrary. We use some of those fetal numbers. We use statistical norms. Both Dr. Hay and I now start changing the way we care for babies when they hit 108 mg/dL. Prior to a few years ago, I would've figured 108, 120, we're all okay. Now, if I see 108 or higher, we start looking at limiting the glucose infusion rate or balancing with more amino acids, or we start really paying attention to strategies that we can employ to start... In that case, it's more to keep the glucose from going up, but there's a range, if you would like to use it.

We certainly look for improved physiological control, so that's limiting those exogenous catecholamines and steroids. Thinking about infection, temperature, oxygen delivery. We are always initiating early enteral feeds, and we advance as rapidly as tolerated, so we think that's an important part of our strategy.

Summary Of Strategies To Prevent And Treat Hyperglycemia In the ELBW

- Goal glucose concentrations – 60-125 mg/dL (Arbitrary)
- Improved physiological control
  - Limit exogenous catecholamines and steroids
  - Oxygen delivery, infection, temperature, pain
- Early initiation of enteral feedings with advancement as rapidly as tolerated

Slide 27

With specific respect to the parenteral nutrition. With the glucose infusion rate, we'll undertake a stepwise reduction in the glucose infusion rate until we're in our target glucose concentration range, or we achieve the lowest possible glucose concentration in the fluid. This is a really important point. The idea of how low can you go on the glucose infusion rate. I've talked to a couple of the academic centers where they've published high rates of insulin infusion, so I believe there's room for academic argument here. They believe there's a limit to how low you can go on your glucose infusion rate. Maybe it's 4 or 5 mg/kg/m, and they don't want to go any lower than that.

Our approach is that we will happily go lower than that. Usually, you can't go too much lower because you have to deal with water issues in the baby, and you have to deal with the safety of the fluid. But in our minds, if this baby is hyperglycemic—and typically the hyperglycemia lasts 1 to 2 days max—we think you can safely go down to 2–3 mg/kg/m. And the brain, because that is concentration dependent, will still get the glucose needed. We may be sacrificing energy for something like growth, but we don't think the babies can grow well anyway. And if you give them insulin to lower the glucose to give a higher glucose infusion rate, you are sacrificing length growth.

Then, we'll also limit lipid infusions, as I've said, and we'll try to achieve our goal amino acid concentration as quickly as possible.

Summary Of Strategies To Prevent And Treat Hyperglycemia In the ELBW

- Parenteral nutrition
  - Glucose – stepwise reduction in the GIR until target glucose concentration is achieved or the lowest possible glucose concentration in the fluid is achieved
    - There is not a minimum GIR required for supporting cerebral metabolism. Cerebral glucose uptake is dependent on glucose concentration and cerebral blood flow.
  - Lipid – reduce or even stop the intralipid infusion during hyperglycemia
  - Amino acids – goal of 4 gm/kg/d, achieved in 1-3 days (faster if hyperglycemic)

Slide 28

We reserve insulin therapy for severe and unresponsive hyperglycemia. We start at the low dose. We don't want to go lower than that 150–180 range. That's the comparative group, the control group in most of the trials. We will use frequent blood glucose measurements. We will use a reliable blood glucose measuring device in these patients.

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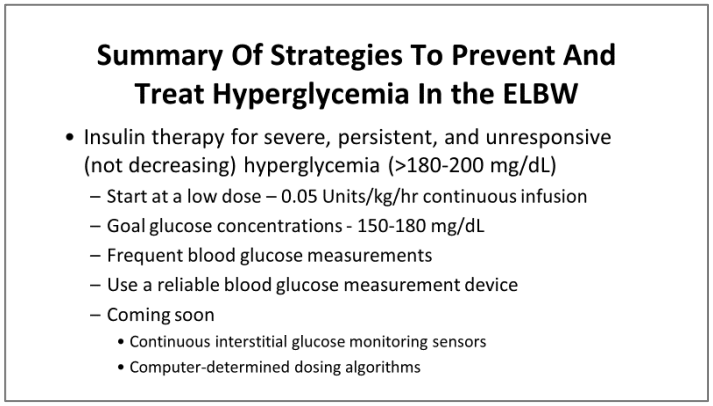
I think coming soon, what you'll see are application of open, so unblinded, continuous, interstitial glucose monitoring sensors, and these computer-determined dosing algorithms. With that, I'd like to thank you all. Thanks to Bill Hay, who has been wonderful in helping me with this topic.



Slide 29

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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