



Care of Periviable Infants

Overview

Survival for periviable infants is improving. Neonatal intensive care specialist, **Jonathan Klein, MD**, shares his expertise and strategies to care for these extremely premature infants at 22–24 weeks' estimated gestational age. Multidisciplinary teamwork and standardization of practice are essential strategies to allow extremely preterm infants the potential to survive and thrive. Join Dr. Klein's examination of the survival, morbidity, and 2-year outcomes for periviable infants at a center with a proactive philosophical approach, as well as his review of NICU practice improvements, including the critical use of antenatal corticosteroids prior to 24 weeks.

Target Audience

This activity was developed for neonatologists, nurses, advanced practice clinicians, dietitians, and other healthcare providers with an interest in preterm infants.

Learning Objectives

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

- Describe the cultural factors that impact survivability and neurologic outcomes for periviable infants born at 22–23 weeks' gestation
- Understand differences in management strategies when caring for periviable infants born at 22–23 weeks' gestation
- Review survival, morbidity, and 2-year outcomes for periviable infants born at 22–23 weeks' gestation at a center with a proactive philosophical approach.

Faculty

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Editor's Note: This is a transcript of an online presentation broadcast on July 23, 2021. It has been edited and condensed for clarity.

FACTORS THAT INFLUENCE SURVIVAL RATES OF PERIVIAIBLE INFANTS



Dr. Jonathan Klein: In this talk, I'm going to cover many topics. Initially we're going to start with the factors that influence survival rates of periviable

infants. And when we talk about the factors that influence survival, the main issue is whether we believe this is possible or impossible. Certainly, over 20 years ago we would think that survival at 22 weeks certainly wasn't possible. Even currently, many people would think this is impossible.

This is a set of twins we cared for over 2 years ago. There was twin-twin transfusion, which led to complications in the early delivery. They were born at 22-1/7 weeks. One was 490 g; one was 449 g. So basically, these were AGA [appropriate for gestational age] for 22 weeks.

Survival at 22 Weeks Gestation – Possible or Impossible?

TTS: twins born at 22 1/7-weeks

490 g

449 g

TTS, Twin to Twin Transfusion Syndrome.

Slide 1 - Survival at 22 Weeks Gestation - Possible or Impossible

Their mother was very social media savvy, and she realized these weren't the smallest, but these were the most premature surviving twins in the world. She hooked them up with the *Guinness Book of World Records*. You can see in

the corner of this slide the girls holding their book.

As we think about this topic, I'm going to ask a few questions, and this is the first of the survey questions. I want people to think, **What is the mean survival of all live-born, 22-week gestation infants born in US hospitals that participated in the Vermont Oxford Network in 2019?** Would you think that would be 9%, 17%, 22%, 27%, or 32%. Feel free to answer—we want to get an idea of what you think is happening.

What is the mean survival of all live-born 22-week gestation infants in US hospitals that participated in VON in 2019? ^[1]

a) 9%
 b) 17%
 c) 22%
 d) 27%
 e) 32%

Impossible: All VON Type C NICUs, **Median Survival** in 2019 is 0.0% (IQR: Q1, Q3 is 0.0, 25.0)

Possible: VON Centers in the US that offered active treatment in 2019, **Mean Survival** was 29% ^[1]

VON, Vermont Oxford Network.

1. Rysavy MA, et al. J Pediatr. 2021;233:P16-25.E1.

Slide 2 - Audience Response Question

Of course, this is an incredibly intelligent and well-informed audience because you got the answer exactly right, which is 17%.

So, when you look at a 17% survival, many people would say, well, that falls kind of in the impossible category because a lot of people feel that for something to be possible, they want to be closer to 50%. If you looked at the median survival rather than mean survival, it's actually 0.0%. If you're looking at median survival, you'd say this certainly is impossible. Now, if you're on the viewpoint of this being possible, more importantly, you should look at the centers that offered active treatment in 2019, in which case

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mean survival was 29%. The possibility of survival is clearly there. And hopefully this type of knowledge gets spread further. We published on that recently in 2021, so that can impact the care that's being offered.¹

Now, why are we talking about this from Iowa? The next question would be **What is the survival of all live-born, 22-weeks' gestation infants delivered at University of Iowa NICU?** I'm doing cumulative survival because there's not a lot of 22-weekers born every year. This is from 2006 all the way to 2019. If we're thinking about cumulative survival of all live born, which even includes babies that the family does not wish to resuscitate, would you think it'd be 14%, 24%, 33%, 45%, or 59% survival?

What is the survival of all live-born 22-week gestation infants delivered at the University of Iowa NICU from 2006-2019?

- a) 14%
- b) 24%
- c) 33%
- d) 45%
- e) 59%**

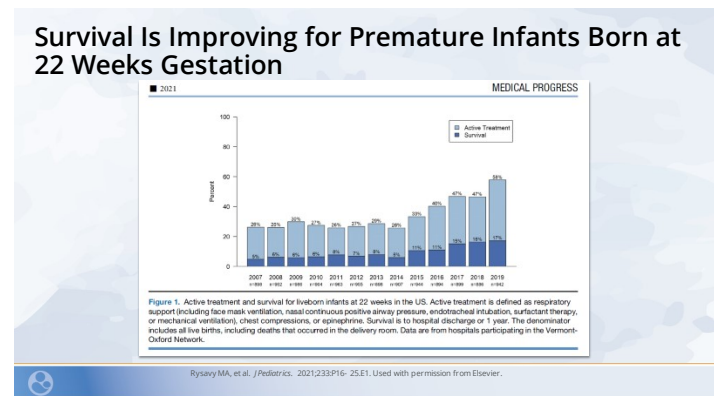
University of Iowa Stead Family Children's Hospital

Rysavy MA, et al. J Pediatr. 2021;233:P16-25.E1.

Slide 3 - Audience Response Question

The interesting thing is, in this case, the audience didn't get it because you felt the majority of survival would be 45%. But if we look at our current survival at the University of Iowa, we're at 50% cumulative survival, and this is all live-born, including infants that do not want resuscitation. It clearly is over 50%.¹ So, it's certainly possible to truly have survival at this gestational age.

Now, if we think about it, is it just Iowa? No, it's certainly not. And on this slide, you can see that survival is improving for premature infants born at 22 weeks' gestation. This has started to occur beginning in 2015. If you go from 2007 to 2014, you can see survival hovered between 5% and 8%. And then, in 2015, 2 major things happened. One, survival of all live-borns, at all centers in the US and VON, started going up from 11% and up to the 17% which we talked about. At the same time, [the number of] centers that actually offered active resuscitation at 22 weeks, dramatically increased. You can see in 2014 there was only 26%, which more than doubled by 2019;¹ 58% of all centers are now offering active resuscitation.



Slide 4 - Survival Is Improving for Premature Infants Born at 22 Weeks Gestation

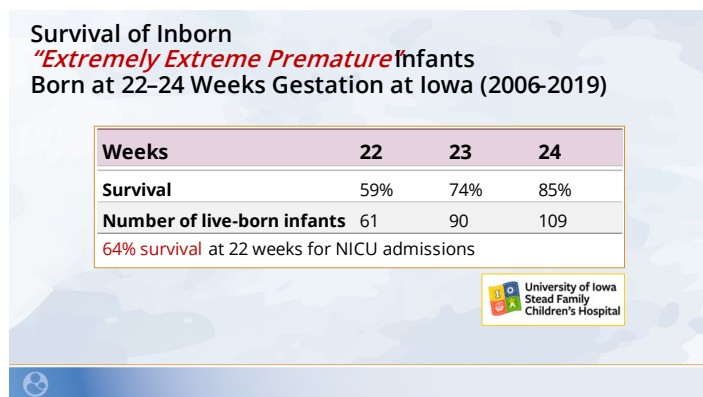
In 2015, a couple of things happened. One, there was a *New England Journal* article published, with the lead author being one of our former fellows, that looked at survival that was occurring,² and it started to change people's minds. Then we also began to discuss this and present more on what are approaches that can impact survival. If you looked at the centers that offered active treatment, 29% of those 22-weekers would survive if you looked at

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just the centers that offered acute treatment and 17% for all live-borns .

University of Iowa Strategy

Now if you look—with our Iowa approach—what we're talking about is survival of inborn. I'm going to concentrate on inborn because it's much harder to impact the outborn survivors. I'm looking at what I call **extremely extreme premature**. To me, extremely premature is just less than 28 weeks, and that's really not the issue. The issue really is what's considered periviable, which is basically less than 24-, 22-, and 23-weekers—or some may include 24-weekers—at that. And these are the tables that we would use for a consultation prior to delivery. If we look at all live-born, we took care of 61 infants in that time period of 22 weeks, 59% survival; 90 infants at 23, 74% survival; and 109 24 weeks at 85% survival. Now, the neonatologists would say, well, this is unfair because you're including patients that the family wish to redirect care at birth and not go to active resuscitation.



Slide 5 - Survival of Inborn "Extremely Extreme Premature" Infants

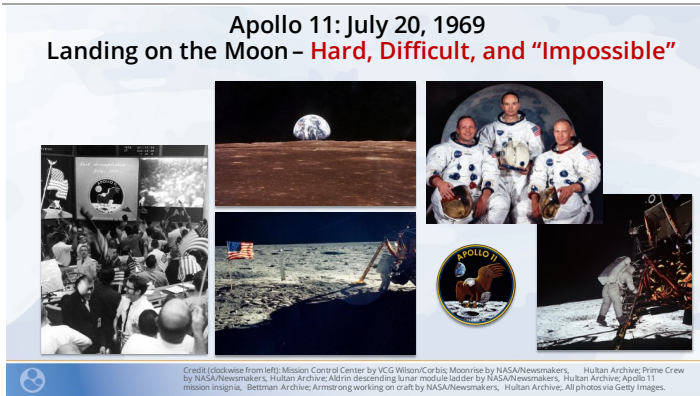
They want to know if you did admit in the NICU, what is the survival. Their current survival for this time period would be 64% survival at 22 weeks for NICU admissions. I always like to look

at live-born because there's always a concern of obstetricians [who ask] are we just cherry picking? Are we going back and saying, "Okay, this 22-weeker is really vigorous, we'll resuscitate; this one is not vigorous, we won't resuscitate." We don't make a decision based on level of vigor; **we make a decision that's family centered, with the parents directing our approach.**

Hard, Difficult, But Not Impossible

Now, when I always think about caring for 22-week babies, it reminds me of something that happened over 52 years ago, which was the Apollo 11 landing on the moon. Back then, most people would say this is impossible. And many people still think it's impossible. However, we know it was very hard and it was very difficult, but it was not impossible. The key thing with this moon landing wasn't the 3 main astronauts, Neil Armstrong and Michael Collins and Buzz Aldrin, but in reality, **this occurred because of hundreds of thousands of people in mission control**, as well as throughout the entire United States and the world helping to support this mission. That **same concept of teamwork is very critical when we talk about caring for 22-week babies**. One of the things I always took away from the Apollo program was looking at how they approached what was considered something that was impossible.

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Slide 6 - Apollo 11: July 20, 1969, Landing on the Moon - Hard, Difficult and "Impossible"

This is from their mission statement, the Foundations of Mission Control and their motto is, “Achieve through excellence.” Obviously, we would all agree with that for the NICU.

I pulled 2 other things out that I thought were very relevant to NICU care, especially of the 22-week infant. One is “competence, there being no substitute for total preparation and complete dedication for space,” and then I added, “or the NICU will not tolerate the careless or indifferent.”

Now, we all say we're not careless, but we're not all indifferent. And the problem is it's very easy to say, "Well, this is an extremely extreme profoundly premature baby. They're gelatinous. It's impossible. And why are we doing this?" If you're indifferent, it's certainly not going to work, and it's not whether everyone's indifferent. It only takes a few people to be indifferent, and the care that has to be fine-tuned for many days, weeks, months will not occur.

Foundations of Mission Control¹

- **Achieve Through Excellence**
- **Competence:** There being no substitute for total preparation and complete dedication, for **space (or the NICU)** will not tolerate the careless or indifferent.
- **Teamwork:** Respecting and utilizing the ability of others, realizing that we work toward a common goal, for success depends on the efforts of all.
- *“To recognize that the greatest error is not to have tried and failed, but that in trying, we did not give it our best effort.”*
— Gene Kranz, NASA Flight Director



¹ Failure is not an option, Gene Kranz, Bantam Books, New York, 2000, p.393. Images: top: Bob McCall; bottom: by Dorling Kindersley via Getty Images.

Slide 7 - Foundations of Mission Control

The next thing is for all the physicians to realize that it's not all about them, but it's about the team. The same thing was also realized in the Apollo 11 missions. **You have to have teamwork** which is recognized, respecting, and utilizing the ability of others. Realizing we work toward a common goal for success depends on the efforts of all. This is critically important.

I showed you a set of 22-1//7-week twins on the first slides. Those twins are both alive because one of the nurse practitioners was concerned that the glucose level one day was normal, but it was lower than expected. And before I said something dumb like, "Well, it's still normal, does it really matter?" I kept my mouth closed, and she said, "And I thought that was unusual, so I sent screening labs, and I sent blood cultures and started antibiotics. And that blood culture came back positive for E. coli within 12 hours." So, she saved that baby's life and saved it because I did not stand in their way; I allowed them to care for the babies without the physician trying to interfere. The same thing...many times the parents or the bedside staff nurse will say the baby is not behaving right. Rather than not listening to that, you need to listen to it, and then figure out why the baby is not looking right. We had other times where

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a mom recognized the baby was infected with E. coli. The key thing is starting the therapy early, and that's the only way you'd overcome sepsis. Now, the next thing is a quote from the NASA flight director, which is, *"To recognize that the greatest error is not to have tried and failed but in trying we did not give it our best effort."*

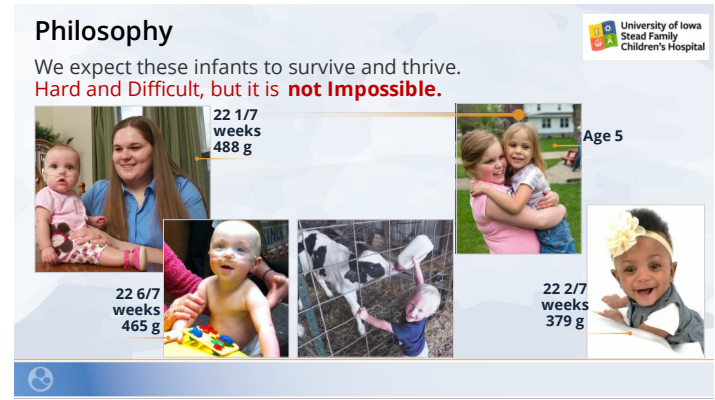
Again, it's very hard to give your best effort in this population. They take a lot of work. This is not just a plug-and-play group. There's a lot more fine-tuning that has to be done at 22 weeks than there has to be done, for example, at 26 or 27 weeks. That takes a lot of effort, and you're doing a lot of fine-tuning, a lot more in the first couple of days of life than you normally will do for most patients. And it can be emotionally and physically taxing, but if we're going to do this, we've got to push hard on this.

Philosophical Differences

Our philosophy at Iowa regarding the periviable population is we don't expect these babies to die; we expect these infants to survive and not only survive, we expect them to survive intact and thrive. We know it's hard, and we know it's difficult, but we know it's not impossible.

This is 3 22-weekers [see slide 8]. This one was at another hospital. Mom was there pregnant. They said 22-week babies can't survive. She called our hospital, and the OB [obstetrician] said, "Well, that's okay. If you want us to resuscitate, then the neonatologist and I will resuscitate." This one, I happened to be at the birth. The interesting thing was how she was so gelatinous—you could see her heartbeat through the chest wall. And, of course, she responded very well when she was intubated and bagged. This is from her, from the *New York Times* article, which came out in 2015 as a

follow-up to the *New England Journal of Medicine* article that helped to stimulate the change that's been happening at 22-weeks' survivors.



Slide 8 - Philosophy

This is another 22-weeker, who's actually 379 g. He just sailed through. This 22-weeker had severe pulmonary hypoplasia, actually had pneumothorax in the delivery room, which was recognized because I was there, but more importantly, one of the transplant nurses said, "Hey, the baby's not responding." She pulled out her transilluminator flashlight and said, "Look, there's a pneumo[thorax]." We needled it. Even then, we *just* got the heart rate over a 100, but that was enough to get back onto the high-frequency jet and start ventilating this baby. These 2 children are doing perfect. He is in elementary school. He does have a chronic seizure disorder, but he's doing relatively well. He did also have NEC [necrotizing enterocolitis], but did not require surgery for that.

Now, when we talk about philosophical differences, this again is from that paper published in the *New England Journal* in 2015 from one of our former fellows.² If you look at the rates of active treatment, account for 78% of between-hospital variation, and in survival among children born at 22- or 23-weeks' gestation, you do have to make a decision to

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resuscitate, but that's not the only thing that's going on... and, even, just 22% for those born at 24 weeks. Importantly, the rates of active treatment do not count for any of the variation and outcomes among those born at 25 or 26 weeks. So, what that means is, yes, you can decide to resuscitate, but you have to have an approach that's going to work, otherwise, you will not have good survival. Importantly, differences in hospital rates of active treatment did not account for all variation and outcomes, which is what we're going to talk about through much of the presentation.

Philosophical Differences

- Rates of active treatment account for 78% of between-hospital variation in survival among children born at 22 or 23 weeks of gestation and just 22% for those born at 24 weeks, but the rates of active treatment did not account for any of the variation in outcomes among those born at 25- or 26-weeks' GA.^[1] **Importantly, differences in hospital rates of active treatment did not account for all variation in outcomes.**
 - For example, among hospitals that treated 100% of infants born at 24 weeks, rates of risk adjusted survival varied from 42–70%.
- Therefore, factors other than just the decision to resuscitate contribute heavily to the variation in outcomes!
- Of note, hospitals where active treatment was more often initiated had higher rates of risk-adjusted survival than hospitals where active treatment was less frequently initiated.

GA, gestational age.

¹ Rysavy MA, et al. *NEJM* 2015;372:1801-1811.

Slide 9 - Philosophical Differences

In that paper, they showed [that] in hospitals that make the decision to treat all 24-weekers, rates of risk-adjusted survival vary dramatically from as low as 42% to (in that paper) as high as 70%.² Obviously, we showed you that our survival is about 85% at 24 weeks. Therefore, factors other than just the decision to resuscitate contribute heavily to variation in outcomes. And importantly, **hospitals where active treatment was more often initiated had higher rates of risk-adjusted survival** than hospitals where active treatment is less frequently initiated. So, as you start to care for younger and younger and more and more

developmentally immature babies, your care of the older babies constantly improves.

Epidemiology of Extremely Extreme Prematurity

- In 2016, from US birth certificates (live births):
 - 22 weeks: 1,857
 - 23 weeks: 2,944
 - 24 weeks: 3,719
- All births in US: 3,945,875

23 6/7 weeks twin
507 gm



Age 5



CDC Wonder Data Set: Premature Birth. <https://www.cdc.gov/reproductivehealth/features/premature-birth/>. Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. Last reviewed: October 30, 2020.

Slide 10 - Epidemiology of Extremely Extreme Prematurity

One of the things is, is this a major problem? As you start caring for 22-weekers, is this going to overwhelm the United States? And the answer is, no.

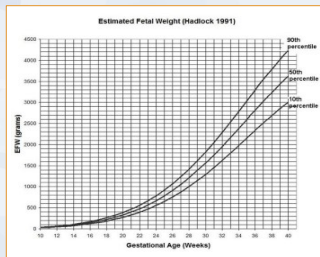
This is data from 2016.³ There were about 4 million births back then. There were only about 2000 live 22-weekers born, 3000 live 23-weekers, and 4000 live 24-weekers. So, you're certainly not going to be overwhelming the unit with hundreds of these babies.

This is a former 23 twin. (We'll talk about why there's so many twins.) He's now actually 12 years old and has a podcast. But importantly, when his sister was born, she was at 22 weeks, and the parents did not want to resuscitate. We respected the decision. But we said, "Gee, at 23 weeks, this is our survival, and certainly we've gotten the antenatal steroids in, are you okay with us resuscitating?" And they were.

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"Perivable" Census on January 8, 2019

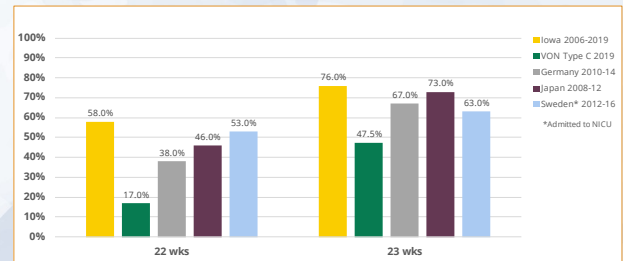
GA (baby)	BW (g)	PMA (baby) on 1/8/19
22w1d	490	28w4d
22w1d	449	28w4d
22w2d	545	22w6d
22w5d	550	28w3d
22w6d	517	28w3d
23w0d	510	36w6d
23w0d	512	36w6d
23w2d	634	29w5d
23w2d	580	38w4d
23w3d	660	26w5d



BW, birth weight; GA, gestational age; PMA, postmenstrual age.

Hadlock FP, et al. Radiology. 1991;181:129-33.

Possible – Survival of Inborn Perivable Infants Born at 22-23 Weeks Gestation (all live-born)



EGA, estimated gestational age; NRN, Neonatal Research Network; VLBW, very low birth weight; VON, Vermont Oxford Network.

Slide 11 - "Perivable" Census on January 8, 2019

The father was a physician, so he was okay, but not gung-ho. He kept waiting for something to happen, and all that's happened now that the child is age 12, is they do a father and son podcast, and he's done extremely well! So, there is a lot of prejudice that's been built in the system because a lot of the data lags 10, 20 years behind.

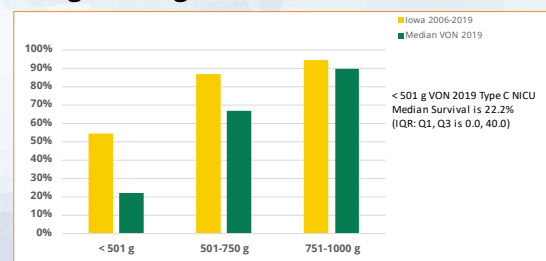
Perivable Census

This is a look from a few years ago, of what I call a perivable census. On that day, January 8, 2019, there were 10 babies in the main unit that were between 22 and 23 weeks—90% or 89% were all AGA. It isn't that our 22-weekers are misdated and all [eligible] infants, they all fit basically where they should be in terms of the 22-week AGA range and the 23-week AGA range.

Slide 12 - Possible - Survival of Inborn Perivable Infants Born at 22-23 Weeks Gestation (all live-born)

This is the postmenstrual age at the time on that day. Now, importantly, we talked about survival being about 60%. Two of these 5 22-weekers did pass away. And you have to realize, even if you think you're doing everything as well as humanly possible with about 60% survival, 4 out of 10 of these babies still can pass away. If those 4 out of 10 come all in a row, it tends to be an emotionally difficult time for the unit. And I ask that what they need to focus on is the babies who they gave a try at life to, who've survived, and who are coming back for follow-up in the clinic, and are going on to thrive.

Survival of Inborn ELBW Infants ≤1000 Grams Birth Weight Categories 2006-2019



VON, Vermont Oxford Network.

Slide 13 - Survival of Inborn ELBW Infants ≤1000 Grams Birth Weight Categories 2006-2019

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Worldwide Survival Data

Is this just Iowa? Of course not. This is happening at other places around the world. This is 58% survival at 22 weeks at Iowa. Here is the VON data. We talked about 17%. This is Cologne, Germany, which does a great job with these patients; this is Japan, which also obviously does a great job with 22-weekers; and this is Sweden, also doing a great job. Obviously as you go from 22 to 23 weeks, everything goes up for everyone. But the important thing is that this is happening worldwide, and it's been happening worldwide for a while. There will be [a paper] coming out shortly, looking at similarities and differences between the approaches of Japan and Sweden and Iowa, that we've put together.

I also like to show the birth weight. There are still people that feel this is a gestational-age dating issue, even though OBs date babies in Iowa the same as any of the other states or places in the world. So, this is based on birth weight. We look at less than 501 g. Our survival is over 50%. The median survival in VON is a little over 20%. There are some places that will not resuscitate babies based on this size. This is a better fair comparison, 501 to 750. If you looked at mortality, we're about 12% and the VON is about over 30%. So, we have about 2½ times less mortality. I think some of the approaches have a lot of utility.

STRATEGIES TO INCREASE SURVIVABILITY

Let's talk about the strategies to increase survivability in the periviable population. I think one of the most critical things is that you have to have a **"small baby" system**. There can't be a lot of random variation, and it's hard for every

single person who works throughout any NICU to become an expert in every single thing. **You have to create a dedicated integrated structure and culture for extremely premature infants.** You have to realize the system is the star. It's not any individual. You have to have a robust system. Our system is that we have a separate dedicated unit of 14 beds. We call it Bay 1. We call it the Neonatal Critical Care Unit (NCCU). We admit all infants—definitely less than 28 to 30 weeks for the most part—as well as those critically ill term infants.

"Small Baby" System
Dedicated Integrated Structure and Culture
for Extremely Premature Infants
"The System is the Star"



Separate dedicated unit of 14 beds: Bay 1, NCCU- Neonatal Critical Care Unit

- All infants **<28-30 weeks** admitted here, as well as the most critically ill term infants
- Separate **nursing staff**
- Separate location **integrated with labor and delivery**
- Separate **Critical Care Lab** just for the NICU
- Separate medical team for just these 12-13 patients
 - Separate Attending service ("**Neonatal Intensivists**"), Fellow, NNP, 2 Residents, Dietician, Pharmacist, Respiratory Therapist

Slide 14 - "Small Baby" System

It's not classically a small baby unit only, but all the small babies are admitted there. We like having all the critically ill term infants there, because we want to make sure that the nursing staff and the physicians working in that unit have a wide breadth of experience in respiratory and cardiopulmonary failure of all infants, not just the extremely small babies. But the extremely small babies are not admitted to anywhere else in the unit. They may eventually transition over there as they become more stable.

There's a separate nursing staff, for the most part, that just works in those 14 beds. It's very hard to become great at caring for the skin of a 22-weeker if you care for 1 22-weeker every 2

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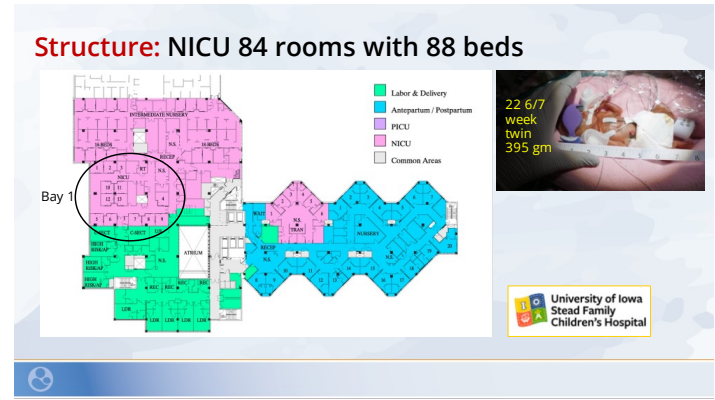
or 3 years vs caring for 22-weekers every month. Now that nursing staff... There are some nurses that are floats, who will float through other areas of the units, so we can always have new learners coming in; but predominantly, the vast majority of nurses specialize in that unit.

We have a separate location integrated with Labor and Delivery, so that these babies can get back for their 10-minute Apgar, to the unit; a separate critical care lab just for the NICU, because it has to be a lot of fine-tuning of glucose and CO₂; and importantly, a separate medical team for just these 12 to 13 patients. Rounds on these 12 to 13 patients, because of their level of complexity, takes just as long as someone rounding on 28 to 36 step-down patients.

We have a separate attending service. Not all attendings want to be at that level of intensity, and some that don't want to be there are not there. And we can have people with a positive attitude. There are always fellows, and critically, there's always neonatal practitioner at least 7 days a week—and some of the nights—residents, dieticians, pharmacists, respiratory therapists ... It's a **big team approach**.

This is an example (see slide 15). The structure for us—we have 84 rooms with 88 beds. The important thing of this slide, as you can see, Bay 1 is located right next to the green Labor and Delivery, and that's important. The idea is you have the 5-minute Apgar; you have a good heart rate; the stats are climbing; baby's shown to mom; mom kisses the baby, and the baby gets—for us—right on the jet before 10 minutes of life. You can see there's another 22-6/7th week twin, 395 g, looks about 8 in long in that

picture. This was taken by a new faculty, who was amazed at that baby, who, at 22 weeks and under phonograms, could do okay.



Slide 15 - Structure: NICU 84 Rooms with 88 Beds

Exposure to Antenatal Steroids

So, next survey question: **Exposure to antenatal steroids and given postnatal life support significantly increases survival at 22-weeks' gestation by how much?** As the question comes out ... do [you] think the steroids don't do anything at 22 weeks/are not effective, [or do they increase survival] by 10%, by 30%, by 50%, or by 100%, so it doubles survival? Let's look at that survey and see what you think. This audience is obviously way smarter than any other audience because it looks like you are clearly getting the correct answer, which is the majority of you are saying the results are coming in showing that it doubles survival.

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Exposure to antenatal steroids and given postnatal life support significantly increases survival at 22 weeks gestation by how much?^[1]

- a) 0% (not effective)
- b) By 10%
- c) By 30%
- d) By 50%
- e) By 100% (doubles survival)**

VON, Vermont Oxford Network.

1. Ehret D, et al. *JAMA Netw Open*. 2018;1(16):e183235.

**Difference: Begin at the Beginning
Antenatal Steroids Are Critical
Interdisciplinary Teamwork with MFM**

- ANS at 22–25 weeks gestation:
 - Reduces death, reduces severe IVH, reduces the incidence of NDI at 18–22 months, increases survival from 18% to 39% at 22 weeks gestation!

- Carlo W, McDonald S, Fanaroff A, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks gestation. *JAMA*. 2011;306(21):2348-2358.
- Mori R, Kusuda S, Fujimura M. Antenatal corticosteroids promote survival of extremely preterm infants born at 22 to 23 weeks of gestation. *J Pediatr*. 2011;159(1):110-114.
- Park CK, Kayama T, and McDonald SD. Antenatal corticosteroid therapy before 24 weeks of gestation: A systematic review and meta-analysis. *Obstet Gynecol*. 2016;127:715-25.
- Wei J, Catalano R, Proffitt J, et al. Impact of antenatal steroids on intraventricular hemorrhage in very-low-birth-weight infants. *J Perinatol*. 2016;36:352-356.
- Deshmukh M and Patole S. Antenatal corticosteroids in impending preterm deliveries before 25 weeks' gestation. *Arch Dis Child Fetal Neonatal Ed*. 2018;103:F1731-76.
- Ehret D, Edwards E, Greenberg L, et al. Association of antenatal steroid exposure with survival among infants receiving postnatal life support at 22 to 25 weeks' gestation. *JAMA Netw Open*. 2018;1(16):e183235.

- If everyone "already knows" ANS therapy, at ≥ 24 weeks, improves lung maturity and reduces RDS, NEC, severe IVH, and mortality, so...

ANS, antenatal corticosteroids; IVH, intraventricular hemorrhage; MFM, maternal fetal medicine; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome.

Slide 16 - Audience Response Question

It doubles survival. This is just so critical to this population. One of the things that is responsible for our good outcomes is our OBs willingness to give antenatal steroids to this population. If you look at this, one of the differences—if we're going to care for a 22-week population—is that you always have to begin at the beginning, which is before delivery, **antenatal steroids are critical**. You must have interdisciplinary teamwork with maternal fetal medicine. If the OBs want us to start caring for 22-weekers, and we want to care for 22-weekers, and parents want us to care for 22-weekers, our OBs will give steroids at 21-5/7 weeks.

We're now looking at the literature that antenatal steroids—at this 22- to 25-week range—reduces death, reduces severe IVH [intraventricular hemorrhage], reduces the incidence of neurodevelopment impairment, increases survival, as we talked about, from 18% to 39% at 22-weeks' gestation.

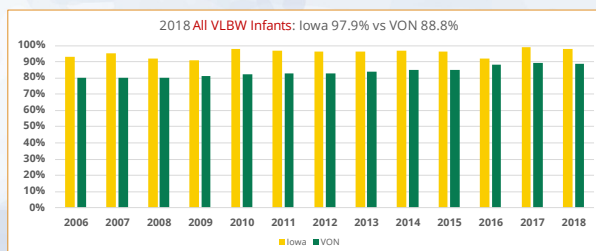
Slide 17 - Difference: Begin at the Beginning

There are many papers that talk about this from 2011, 2016, and one of the most recent papers from 2018 is the one that showed the more than doubling of survival.⁴⁴⁻⁹

If we all know that any necessary therapy, certainly a greater than or equal to 24 weeks, improves lung maturity and reduces RDS [respiratory distress syndrome], NEC, severe IVH mortality—so clearly everyone must be giving antenatal steroids. Well, as you can see (slide 18), unfortunately, that's not true. Iowa is here in gold. Our OBs have been helping us tremendously because they always get close to a 100% of getting antenatal steroids in 97.9%. And currently at VON it was 88.8%. You can see back in 2006, VON was around 80%, and then over 15 years, they're getting much closer to 90%. One of the keys is that if you looked at the infants delivered at 22 to 23 weeks, which are in a recent publication by one of our fellows in 2020,⁵ antenatal steroid use was 91% in our inborn babies.

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Antenatal Steroids: Inborn Deliveries All VLBW Infants (22 to 33 Weeks EGA) 2006–2018



Infants delivered at 22-23 weeks gestation antenatal steroid use was 91% (2006-2015 Iowa Inborn cohort)^[1]

1. Watkins PL, et al. J Pediatr. 2020;217:52-8.

Slide 18 - Antenatal Steroids: Inborn Deliveries All VLBW Infants (22 to 33 weeks EGA) 2006-2018

This 91% at 22 to 23 weeks helps, dramatically, to have survival improve and morbidities diminish. **It's very hard, as a neonatologist, for us to be aggressive resuscitating at the lower gestations if our OBs aren't helping us with antenatal steroids.** At the same time, the OBs don't want to start giving it if you're just going to walk away from the baby. So, this has to be a **multidisciplinary team approach.**

Some other interesting things to look at, this is both inborn and outborn infants at Iowa. There have been 12 22-weekers outborn at Iowa. Six out of 12 survived, so that's 50%. Not as good as 59 to 64, but it's not hopeless.

Maternal Characteristics Iowa Cohort Inborn and Outborn Infants Admitted 2004–2015

Mean ± SD on N (%)	22 weeks N=34	23 weeks N=76	24 weeks N=138
Maternal age	25.32 ± 4.7	28.04 ± 6.8	26.55 ± 6.1
Maternal race			
White	25 (74%)	46 (65%)	101 (76%)
Black	5 (15)	11 (15)	20 (15)
Other	4 (11)	14 (20)	12 (9)
C-Section	0	37 (49%)	102 (75%)
Multiples	17 (50%)	19 (25%)	23 (17%)
Hypertension	2 (6%)	2 (3%)	13 (10%)
Chorioamnionitis	7 (21%)	7 (9%)	13 (10%)
Diabetes	1 (3%)	1 (1%)	4 (3%)
Pre-eclampsia	0	1 (1%)	9 (7%)

Slide 19 - Maternal Characteristics Iowa Cohort Inborn and Outborn Infants Admitted 2004-2015

You can see (slide 19) the majority of our patients at 22 weeks were White, but certainly 26% were not. This is not unique to the White population. What tends to be unique is we don't routinely do C-sections at 22 weeks. It's a very difficult choice. It's difficult enough for term babies for OBs to decide when they should C-section or not. It's a 1000-fold more difficult at 22 weeks. In this cohort, there were no C-sections at 22 weeks. More recent cohort, there have been about 4 C-Sections, almost all for maternal reasons.

We don't routinely do a C-section for fetal distress, and we don't do fetal monitoring at 22 weeks. Once they are 23 weeks, fetal monitoring is done, and therefore you can see 49% of those 23-weekers are by C-section, actually 75% of 24-weekers because we are detecting that fetal distress.

The other issue is... we talked about twins and this cohort; half [of] these babies were multiples, twins and one triplet 22-weeker. It's not normal to be born at 22 weeks, and that's why multiples end up causing preterm labor. At 23 weeks, that drops to 25%, and at 24 weeks drops to 17%. The other thing I want you to see here is chorioamnionitis. We know a lot of issues are premature and prolonged rupture of membranes, and chorioamnionitis is a major reason why some of these babies are being delivered.

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Differences: Delivery Room Part 1

- Minimize **Hyperoxia and Hypoxia** during resuscitation
 - Delivery room Oximeter Protocol
 - Initiate resuscitation with oxygen ⁽¹⁾ not RA and not 30% oxygen; we start with **50%** and titrate per saturation protocol
- Oei JL, Saugstad OD, Lui K, et al. **Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial.** *Pediatrics.* 2017;139(1):e20161452.
 - Mortality <28 weeks: Resuscitation with RA, 22% vs 6% with 100% O₂

Time after Birth	Productal Target Saturation
1 minute	60 - 65%
2 minutes	65 - 70%
3 minutes	70 - 75%
4 minutes	75 - 80%
5 minutes	80 - 85%
10 minutes	85 - 95%

2010 AHA JM Klein 1/1/12

NRP, Neonatal Resuscitation Program; RA, room air.

1. Oei JL, et al. *Pediatrics.* 2017;139:e20161452.

Slide 20 - Differences: Delivery Room Part 1

Delivery Room Oximeter Protocol

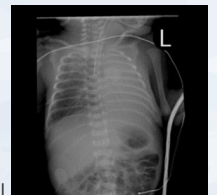
The next thing is there are some differences that should be practiced in the delivery room so that we can optimize survival. You always want to minimize hyperoxia and hypoxia during resuscitation. We have the delivery room oximeter protocol. We initiate resuscitation with oxygen—not room air—and that's 30% oxygen. **We start at 50% titrate per saturation protocol.** Why don't we want to start with oxygen, and that's barely room air, or maybe 30%? Well, the reason is here's a randomized control trial published in 2017 targeted oxygen resuscitated preterm infants randomized clinical trial.⁶ The fascinating thing, this is a practice we've done for a long time, and here is additional proof of the value of it. We looked at babies under 28 weeks that were resuscitated with room air. Mortality was 22% vs 6% with a 100% oxygen. So, 3-4-fold difference in mortality on how you approach the first few minutes of life.

Now, we don't recommend using a 100%. We've been very successful with 50%. And most of the time, we begin to wean pretty quickly, because here is the NRP guidelines (see slide 20).⁷ You really don't have to be glowing pink really until basically 5 to 10 minutes. It's not like long ago

when you'd want babies to be pink within seconds. Most of the time we're able to wean the oxygen quite successfully before we even get out of the delivery room. In patients in which people did not follow this—we've certainly had cases where people try to start with 25% or 30%—and then those babies end up developing issues with pulmonary hypertension. These babies are at high risk of pulmonary hypertension because many of them have chorio [chorioamnionitis], many of them have pulmonary hypoplasia due to prolonged rupture of membranes, and V/Q mismatch is very high because there's no of alveoli.

Differences: Delivery Room Part 2

- Minimize **Hypothermia**
 - Plastic wrap (polyethylene blanket and hat), delivery room temperature 25 °C, trans-warmer mattress for transport
- Intubate with 2.0 ETT at 22 weeks GA, 2.0/2.5 at 23 weeks:
 - ETT depth **5.5–6.0** cm at the lip
 - Transfer to NICU with gentle bagging via ETT, PEEP of 5 cm
 - Start on 1st Intention HFJV within 10 minutes of life
- Surfactant given within 20-30 minutes after initial chest radiograph



ETT, endotracheal tube; PEEP, positive end expiratory pressure.

Slide 21 - Differences: Delivery Room Part 2

Minimize Hypothermia

The next thing is you can't allow these babies to get hypothermic. We have plastic-wrap polyethylene blankets and hat. We try to get the delivery room temperature to 25C or 77F. But we always have a transwarmer mattress for transport because sometimes it's hard to get the room temperature turned up in a reasonable time.

The next difference, when you're dealing with babies at this small gestation, we intubate almost every 2weeker with 2.0 ETT tube. This is

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the same as Japan and Sweden. We might use a 2.0 or 2.5 at 23 weeks. We usually start with the 2.5 by 23, unless the baby looks incredibly small.

The other unique thing is you can't use the 6 cm plus the weight in kilos, and in this population will be right mainstem [intubation], as you can see in that chest X-ray. ETT depth at 22-weekers tends to be 5.5 to 6.0 cm at the lip, not 6 plus the weight in kilos.

Our approach is that we transfer to the NICU with gentle bagging by the ET tube. That's our approach. The key thing is not to get these babies hyperinflated, so we always use a PEEP [positive end expiratory pressure] of 5 cm, and we go right on. For us, our first intention is high-frequency, and we use the jet ventilator within 10 minutes of life. We also try to give surfactant within 20 to 30 minutes of the initial chest radiograph. And again, why do we get chest radiograph? It's very easy to get these babies right mainstem, and you want to make sure you're not giving the surfactant only to one lung.

to use the jet ventilator for all infants. We use the jet ventilator for infants who require ventilation of less than 27 weeks. Does it have to be the jet? No, I think this one when minimizing volutrauma. I'm a proponent of high frequency. Certainly, you can try to do this with some volume guarantee, like they do in Sweden for the 22-weekers, but when those fail, they end up going to a high-frequency device. The initial rate with the jet on these babies needs to be at 300 [BPM], which is I:E ratio 1:9, which avoids air trapping. And again, initially you want to start a lower PEEP than you think, because you want to avoid over distension, and you'll recruit with the surfactant.

It's **critical to avoid volutrauma to sheer-force injury because you're at the canalicular stage of lung development**, as this diagram shows (see slide 22), the canalicular stage at 22-24 weeks. The terminal bronchioles branch to respiratory bronchioles, which branch alveolar ducts, which terminate into alveolar sacks with a thin wall, and vascular beginning at 24 weeks.

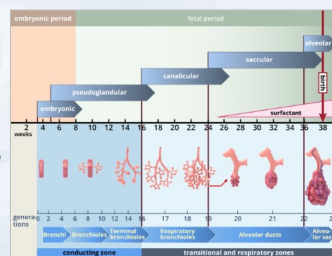
So, how can you survive before 24 weeks? Well, you can because the lung doesn't develop in a homogeneous fashion. The cranial segments, which are faster than caudal segments, they're always a few areas the lung will mature enough for survival at 22 weeks, if you don't damage it. You need the antenatal steroids to accelerate maturation of the type 2 cells, and you need the lung protective minimal volutrauma strategy.

Post-Surfactant Slump Management

Another difference is 20% of these babies will develop something called post-surfactant slump. That's what showing this diagram (see slide 23). Eighty percent of babies who have

Differences in the NICU: Ventilator Issues Prime Directive: Minimize Risk of Pneumothorax and PIE

- Iowa is a **1st Intention HFV** Center
 - HFJV** for all infants <27 weeks at birth
 - Initial rate 300 BPM at 22-23 weeks GA (I:E of 1:9)
 - Initial PEEP 5 cm to avoid overdistention
- Critical to avoid volutrauma (shear force injury) to the lung at 22 to 23 weeks GA
 - At the **canalicular stage** of lung development: terminal bronchioles branch to respiratory bronchioles which branch to alveolar ducts which terminate into alveolar sacs (thin walled and vascularized) beginning at 24 weeks, however cranial segments mature faster than caudal segments so there are a few areas of the lung mature enough for survival at 22 weeks gestation if you don't damage the lung.
 - Need antenatal steroids to accelerate maturation and a lung protective strategy



HFV, high frequency ventilation; HFJV, high frequency jet ventilation; PIE, pulmonary interstitial emphysema.

Slide 22 - Differences in the NICU: Ventilator Issues

It's important to minimize pneumothorax and PIE [pulmonary interstitial emphysema], while first intention high-frequency center you want

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RDS get better with the absence of surfactant, first or second dose, but 20% will go on to slump. Post-surfactant slump is the lack of endogenous surfactant production. You'll usually notice that they get worse between day [of life] 7 and day [of life] 10. You can see when we gave repeats surfactant, we ablated this progression to death or severe lung disease in this population. You can almost predict who was going to get post-surfactant slump, because these babies needed 2 or more doses of initial surfactant. And once again, **antenatal steroids reduce the risk of developing post-surfactant slump.**

NICU Difference: Treat Post Surfactant Slump With Repeat Surfactant Therapy [1]

- 20% of infants <1000 g with RDS develop post-surfactant slump after DOL 6
- PSS is the lack of endogenous surfactant production
- More than 70% of infants with PSS have an improvement in the Severity of their Respiratory Disease with treatment
- 2 or more doses of initial SRT for RDS was predictive of developing PSS (RR 2.4, 95% CI [1.2, 4.9], P=0.02)
- Controlling for GA: Antenatal steroids significantly reduced risk of developing PSS (OR 0.22, 95% CI [0.07, 0.67], P=0.008)
- Either calfactant or poractant alfa treats post-surfactant slump
- Always R/O a hemodynamically significant PDA as well as sepsis/pneumonia and atelectrauma leading to surfactant dysfunction and inactivation

CI, confidence interval; DOL, day of life; GA, gestational age; RR, odds ratio; PSS, post-surfactant slump; RDS, respiratory distress syndrome; RR, respiratory rate; SRT, surfactant replacement therapy; RSS, respiratory severity score = $\text{FI} \times \text{MAP}$ (mean airway pressure).

1. Katz LA, Klein JM. *J Perinatol.* 2006;26(7):414-22.

Slide 23 - NICU Difference: Treat Post-Surfactant Slump With Repeat Surfactant Therapy

Now, you always have to make sure, if there's something between day [of life] 7 and day [of life] 10, that's not due to a hemodynamically significant PDA [patent ductus arteriosus] because if it is, you deal with the PDA. You have to make sure if there's slump due [to] sepsis or pneumonia, you want to treat that. Most of the time it's due to people over wean the baby, sometimes too aggressively, or extubating too early, and they get atelectrauma, leading to surfactant dysfunction.

The next thing that's unique about this population, again, you don't want to treat them

as a 28-weeker or 29-weeker that you're going to extubate, if they require intubation within a day or two; or a 26-weeker that you might extubate within the first week. If you push them off too quickly, you get severe atelectrauma.

So, here you can see (slide 24), you want to extubate only when ready, to have a sustainable respiratory drive. You don't push them off. If you look at some of the data on this, if you fail extubation in the first weeks of life... In this population, and in this study they looked at babies from 24-27 [gestational age], the mortality—failing extubation—was significantly associated with increased death before discharge, 28% vs 6% mortality, as well as worsened severe IVH [intraventricular hemorrhage] and BPD [bronchopulmonary dysplasia].⁸ This is why we control it 100%. This is almost a 5-fold increase in mortality. You could predict who, and this is why we control elective extubation. It's pretty much easier to predict who is going to fail in the first 2 weeks, because it was basically who was in this study, the 24- and 25-weekers, not the 26- and 27-weekers.

NICU Difference: Standardized Extubation Support

1. **Avoid Atelectrauma**
 - Extubate "only when ready" to have a sustainable respiratory drive. "Don't push them off!"
 - Failed extubation in the first weeks of life in this population (mean GA 25.8 weeks) is significantly associated with increased death before discharge: **28% vs 6% mortality** as well as increases in severe IVH and BPD.¹
 - Minimize multiple failure attempts
 - Extubate to noninvasive ventilation (>800-850 grams); we use NAVA for noninvasive ventilation.
2. **Nasal Intermittent PPV vs Nasal CPAP** [2]
 - **NIPPV group:**
 - Decrease rate of extubation failure, (23% vs 58%)
 - Lower rates of clinical (21% vs 39%) and physiologic BPD (11% vs 46%)

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; NAVA, neurally adjusted ventilatory assist; NIPPV, neonatal nasal intermittent positive pressure ventilation; PPV, positive pressure ventilation.

1. Chawla S, et al. *J Pediatr.* 2017;188:113-119.e2.
2. Ramaniathan R, et al. *J Perinatol.* 2012;32:338-43.

Slide 24 - NICU Difference: Standardized Extubation Support

The same CO₂ that's fine extubated at 26- or 27-weeker is not valid to use to extubate these tiny babies. Especially as you go down to 22 and 23,

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it's even more important not to have those failed extubations. You want to minimize multiple failure attempts. And one of the things we do is when they are ready, a month or two of life, you want to extubate to noninvasive ventilation. Now, we use a NAVA [neurally adjusted ventilatory assist] device, but use what works for your center.

When we look at some of the studies, here's a study by Dr. Ramanathan that showed if you extubate straight to nasal ventilation, you cut your rate of extubation failure in half, and you have lower rates of clinical and physiological BPD.⁹

NVN Strategies

NVN [neonatal venous nutrition] strategies have to be a little bit different. You have to minimize both hyperglycemia and hyperlipidemia. Hyperglycemia and hyperlipidemia are associated with not surviving. So, we keep the glucose levels...and higher morbidities. We keep the glucose levels tight, 50 to 150, [and] try to keep sodium [levels] tight, 135 to 150. This may **require** quite **frequent labs in the first few days**. This is not the population in which you say, "Well, I'm going to try to do minimal labs." In a 22-weeker, you're not going to have good outcomes. You need a lot of fine-tuning in that first 3-7 days of life.

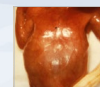
And the total fluids are often more than you expect. They're not going to do okay at 80 per kg even with full humidity. They're going to need more fluids than you expect.

Differences: Standardized NVN Strategies Minimize Hyperglycemia and Hyperlipidemia

- Glucose levels 50-150, Na levels 135-150**
 - Initially, requires frequent labs
 - Total fluids, often up to 250-350 ml/kg/day, use 3 fluids: UAC fluid without dextrose, NVN at 80-100 ml per kg/day for optimal protein, calcium, phosphorus and D2.5 W carrier fluid
 - No or minimal humidification to accelerate keratinization
 - Strict regulation
 - Initial GIR may be <4 mg/kg/min
 - Buffer with sodium and potassium acetate to compensate for renal losses to avoid need for aggressive ventilation to maintain pH >7.25
- Start Intralipids **slowly**, not <12 hours of life, @ 0.5-1.0 gm/kg/day; do not exceed 2 gm/kg/day (liver protective strategy)
 - Minimize NVN cholestasis
 - Mortality rate** (pulmonary hemorrhage) increased significantly in 600 to 800 gm infants receiving Intralipid at <12 hours of life vs controls (48% vs 24%, $p = 0.032$)^[1]
- Goal NVN protein 3.5-4.0 gm/kg/day, starter NVN at birth
- Photoprotection** of NVN^[2]

GIR, glucose infusion rate; NVN, neonatal venous nutrition.

¹ Scainko R et al. *J Pediatr*. 1993;123:975.
² Croese P, et al. Shielding parenteral nutrition from light improves survival rate in premature infants. *PENJ Parenter Enteral Nutr*. 2017;41:378-383.



Slide 25 - Differences: Standardized NVN Strategies

We don't use humidity, so sometimes we require transiently up to 350 mL/kg/day. We always use 3 fluids. The advantage of 3 fluids is we can get NVN going, trying to get, close to 80-100 mL/kg/day, so we can maximize the protein at 4 g/kg/day, and maximize all the vitamins, optimal protein, calcium phosphorus. We have a UAC [umbilical artery catheter] fluid without any dextrose so we can manage insensible fluid losses without getting hyperglycemic. We'll use some D2.5 carrier fluid that's wide in, and in which case we want to give... If the sodium is rising, we don't want to give more sodium through the UAC. We would give it with the sodium-free carrier fluid.

Now we don't use humidification. Sweden also doesn't humidify because it also accelerates keratinization much quicker. **The sooner you get keratinized, the less risk of infection.** The other thing is the initial GIR [glucose infusion rate] can't be the classic 4 to 6 [mg/kg/min], it's got to be less than that. These babies don't require much dextrose to maintain normal glucose, because you're supporting the ventilation at 100%. You're supporting their energy needs 100% with heat and/or humidity. So, you've got to give them time. You can't get the perfect calories in that first week of life.

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They're not ready, yet, because they're not needing it yet. We also buffer with a lot of acetate to compensate for renal losses to avoid the need for aggressive ventilation with the goal of keeping a pH over 7.25.

Now, start intralipids [slowly]. You want to start them not before 12 hours of life. You want to start them slowly. You won't exceed 2/g/kg [per day]. It's liver-protective because you don't want to be in cholestasis.

Here's a great randomized control trial that was done in the early '90s. It showed the mortality rate increased significantly in 600-, 800-g infants who got Intralipids before 12 hours life vs controls; 48% death vs 24%.¹⁰ But this study was designed to show the benefit of giving lipids early. And they actually found that the Intralipids caused significant doubling of death in this population. So, none of these kids are starting intralipids at birth. However, we know protein is good, so they're all starting on NVN at birth. We try to get anywhere between a 0.5 and 1.5 g/kg of NVN protein; 1.5 g/kg of protein at birth to start on NVN with the goal over the next few days to get to 3.5-4 g/kg/day.

We also [use] photo-protector [of] NVN. There's meta-analysis of randomized controlled trials showing that photoprotection of NVN reduces mortality.¹¹ You can see we photo protect it all the way through the hospitalization.

Gut Protective Strategies

We have to have gut protective strategies. You've got to minimize instances of spontaneous intestinal perforation as well as necrotizing enterocolitis. These babies are very high risk for both of these. We don't do prophylactic indomethacin. Recent work by

Nationwide showed, again, that there was no benefit. We know there's a 5% incidence of SIP [spontaneous intestinal perforation] with early indomethacin alone. You combine that with, in this case, dexamethasone in one study from 2001, which was an RCT study that incidence left at 19%.¹²

**Standardization of Gut Protective Strategies:
Minimize the Incidence of Spontaneous Intestinal Perforation (SIP) and Necrotizing Enterocolitis (NEC)**

- Avoid prophylactic Indomethacin:
 - 5% incidence of SIP with early Indomethacin alone
 - 19% incidence of SIP with the combination of Indomethacin plus Dexamethasone in ELBW patients (*NEJM* 2001 Jan 11; 344(2):95)
 - Hydrocortisone alone was not associated with an increase in SIP, however combined with Indomethacin the risk significantly increases (OR 9.37, 2.02-43.49, Shaffer ML et al, Meta-Analysis *J Pediatr* 2019; 207:136)
 - Avoid the combination of indomethacin and steroids**
 - Address the PDA, after the 1st week of life or use a Targeted Neonatal Echocardiographic Hemodynamics Approach
- Reduce NEC and focal intestinal perforation:
 - Early trophic feeds (10 ml/kg/day) within 24 -36 hours
 - Maternal breast milk or donor
 - Advance slowly 10 -12 ml/kg/day only if tolerating
 - Bolus when > 5 ml by pump over 1 hour
 - Probiotics
 - Early detection of meconium obstruction of prematurity¹³ to minimize meconium relative ileus/intestinal injury

1. Siddiqui MMF, et al. Arch Dis Child Fetal Neonatal Ed. 2012;97:147-150.

Slide 26 - Standardization of Gut Protective Strategies

Hydrocortisone alone is not associated with increase in SIP, but when you combine it with indomethacin, the risk goes up 9-fold. So, you try not to give steroids plus indomethacin together.¹¹ You avoid that.

Now, people are concerned, what about the PDA? Do we need prophylactic? We deal with it. Usually, the PDA can either be addressed after the first week of life, [which] is one approach. That's the Swedish approach. At Iowa, we're using more of a targeted hemodynamics approach, and looking to see if we have a PDA that is hemodynamics significant, [if so,] we will address it. But in the first week, we would use acetaminophen and not indomethacin. If it happened to be in the second week, we'll make sure we're not on hydrocortisone, and then we would use indomethacin.

The next thing is you have to figure out ways not to have NEC and or focal intestinal

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perforation. We believe in early trophic feeds. We prefer breast milk as much as possible. We try to get them going within the first day or 2 of life, but trophic for us is 10 mL/kg/day, and you just use that. It's not for nutrition; it's for gastrointestinal peptide, cholecystokinin; get the gut, prepare itself for neuro nutrition. You have to advance very slowly. If you're in a big rush to get the lines out, you're going to end up pushing the baby into an NEC state. We also, when the babies are getting up to 4 to 5 mL, rather than having random gravity flow of a bolus, we'll give it by pump over 1 hour. We also do probiotics, not at birth, but certainly by the time they're 23 weeks and more than a few days old, postmenstrual age.


The other main issue is many of these babies do have meconium obstruction of prematurity. The risk of inspissated meconium leading to a perforation.¹³ So, you've got to minimize meconium-relative ileus or intestinal injury because they don't have the developmental maturity [to] move the meconium through. Many of these babies need glycerin suppositories, and occasionally, if things aren't moving and there's still evidence of the meconium stools and ileus and obstruction, in the first 7 to 14 days, you might have to do a contrast enema to get all that meconium out.

Other differences in management strategies: you want to **prevent fungal infection**. So, these babies get nystatin, and when they're on antibiotics, and they also get fluconazole for at least the first 2 weeks, and the skin is keratinized. We know there's an RCT that shows 6 weeks of fluconazole reduces the risk of invasive candidiasis.¹⁴ We don't go for the full 6

weeks. Like I said, at least 2 weeks in the skin is keratinized.

Endocrine issues: these babies are at risk of hypothyroidism, which is not detected on the initial screen. So, they're all re-screened at a month of age.¹⁵ The other endocrine issue is some of these babies do need hydrocortisone to maintain blood pressure. Most of them get 4 days or less of hydrocortisone. A few of them, if they deteriorate when their hydrocortisone is weaned off in those 4 days, they might need days, weeks, months, depending on blood pressure stability.

Other Differences in Management Strategies



22 1/7-week twin 394 g

1. **Infectious Disease**
 - Prophylactic Nystatin for all patients on antibiotics
 - Prophylactic Fluconazole for at least the first 2 weeks and the skin has keratinized
2. **Endocrine**
 - Repeat thyroid screening at 1 month of age¹¹ Based on TSH and free T4 values will be placed on **thyroid replacement**
 - Use stress dose and physiological **hydrocortisone** replacement for days to months depending on BP stability
3. **Cardiopulmonary Failure**
 - Rescue with **inhaled NO** if O₂ requirement > 60 ~70% with appropriate mean airway pressure, usually patients with PROM, pulmonary hypoplasia and/or pulmonary hypertension
4. **Management changes since 2014**
 - Probiotics
 - Delayed Cord Clamping
5. **Use of Aggressive Phototherapy**, significantly reduces overall NDI as well as profound impairment²

BW (g)	1d	2d	3d	4d	5d	6d	7-14d
<1000	5	5	5	5	5	5	7
6. **Targeted Neonatal Echocardiography since 2018**
 - During 1st week of life to detect hemodynamically significant PDA shunts, pulmonary hypertension and assessment of ventricular function
 - Since 2018, Acetaminophen treatment for a hemodynamically significant PDA during the 1st week of life (40% efficacy at Iowa) then indomethacin

1. Kalarachchi DC, et al. J Perinatol. 32:277-282, 2017
2. Morris BH, et al. N Engl J Med. 2008; 359:1885.

T4, thyroxine; TSH, thyroid stimulating hormone.

Slide 27 - Other Differences in Management Strategies

Cardiopulmonary failure: If we find evidence of pulmonary hypertension on Echo, they will be on inhaled NO [nitric oxide]. These are often patients with PROM [premature rupture of membranes] and pulmonary hypoplasia. We do probiotics. We do delayed cord clamping. We do aggressive phototherapy, which reduces neurodevelopmental impairment.¹⁶ And, like we talked about, targeted neonatal echocardiography.

PROGNOSIS ASSESSMENT

If I asked you, **What is the leading cause of death for 22-weekers at Iowa?** Would you think it's IVH? Do you think it's respiratory

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failure? Do you think it's birth trauma or perinatal asphyxia? Would you think it's infection?

I'll let you guys think about this. I wouldn't expect you to know the answer because this isn't easily known, but what do you think 22-weekers die from? I don't believe it's using prematurity as a cause of death. Prematurity is nothing a neonatologist can do something about, but we can do something about all those other issues. Let's see what you are thinking.

What is the leading cause of death for inborn 22-week GA infants admitted from 2006-2017 to the University of Iowa NICU?

- a) IVH - 31%
- b) Respiratory failure - 8%
- c) Birth trauma/perinatal asphyxia -15%
- d) Infection - 46%**

IVH, intraventricular hemorrhage.

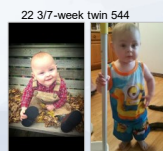
Slide 28 - Audience Response Question

So, right now it's trending between respiratory failure and infection. Let's see what we have for the answer. It's actually infection. The point of this slide was to say, if you have an approach that tries to minimize volutrauma, respiratory failure is not the leading cause. And infection, it's not late-onset sepsis, which was the issue with the infection; it's the early onset sepsis, because why are they being born? We've had babies born with multi-drug resistant E. coli. We had babies born at 22 weeks with GBS [group B *Streptococcus*] septic shock. We've had babies with *Klebsiella pneumoniae* that's beta-lactamase positive. Now, also in infection, I will include NEC, and that is also a challenge. So, **infection is the primary challenge**, and we certainly have been working on that more and

more. We talked about fluconazole. And some other things we're doing now is we don't routinely give IVIg [intravenous immunoglobulin]. [RCT] didn't seem super strong about it, but if the IgG levels are below 200 in the first month of life, they will get some IVIg. IVH is always a struggle, and that's where the antenatal steroids help. And obviously we will redirect care if there's a severe IVH. It's very hard to do a lot about it—asphyxiant birth trauma—unless we're going to then talk about C-sections, which is again controversial.

Outcomes of Inborn Infants: Acute Morbidity 2006–2018

	N	Severe IVH	Cystic PVL	NEC incidence	ROP Laser therapy
22-week NICU admissions	45	22%	7%	18%	14% in survivors (29)
23-week NICU admissions	78	17%	8%	11%	2% in survivors (60)



Extremely extreme prematurity (< 24 weeks GA) is not hopeless

23 2/7-week twins 1st day of nursery school at age 4 (518 and 545 gm)



IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Slide 29 - Outcomes of Inborn Infants: Acute Morbidity 2006-2018

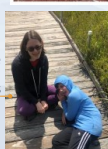
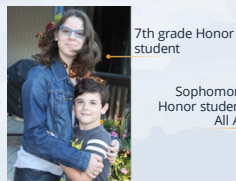
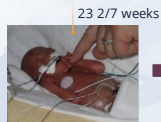
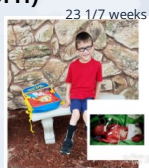
Outcomes of Inborn Infants

Let's look at some outcomes that are extremely important (see slide 29). Acute morbidity is not 100% of this population. You can see here (slide 29) that at 22 weeks, severe IVH is 22%; it's not at 100%. PVL, 7%, NEC, like I said, it's an issue at 18%, and ROP laser's not 50% or 60%, it's only 14% in our approach. [At] 23 weeks, severe IVH dropped to 17%, NEC dropped to 11%, and even ROP laser drops to 2%. This twin here 22-3/7-week male twin, his twin did develop NEC at a few weeks of life and died. So, you can see that is a challenge in this population.

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Infant Characteristics (Inborn and Outborn) Admitted 2004–2015

Baseline Characteristics	22 weeks N = 34	23 weeks N = 76	24 weeks N = 138
Gestational age (median)	22 3/7	23 3/7	24 3/7
Survived to discharge	16 (47%)	53 (70%)	114 (83%)
Birthweight (grams)	486 ± 69	584 ± 83	649 ± 129



Slide 30 - Infant Characteristics (Inborn and Outborn) Admitted 2004-2015

This is looking at the baseline characteristics (see slide 30). The important thing is, again, the 22-weekers were all AGA 46, the 23-weekers, 584; and the 24-weekers at 649. It's not like our 22-weekers have average birth weight of 649. They're exactly where they should be. This is a 23-weeker who did have invasive candidiasis, and she did well and is [now] an honor student.

Other factors associated with survival: It's always better to be more mature. It's better to be bigger. It's better not to be males. Males have a higher risk of death. It's better to have antenatal steroids. It's better not to have severe IVH because, again, care will be redirected to the family wishes. And it's better for the older moms, and I don't have the pathophysiology for that. Again, the reason that we want to use the jet or any type of minimized volutrauma approach is we want to avoid what I call lethal BPD, which is grade 3A. It was talked about by Higgins and Jobe a few years ago.¹⁷ And more importantly, the most recent definition is called grade 3 BPD, which is invasive respiratory support at 36 weeks, which is the brilliant work of Eric Jensen.¹⁸ He showed that if you have grade 3 BPD, you have a 2-fold higher rate of late death, serious respiratory morbidity, and

moderate-to-severe neurodevelopmental impairment among infants receiving invasive rather than noninvasive support, which strongly supports distinct classification of infants treated with invasive mechanical ventilation.

So, when you look for BPD, we need to get away from the oxygen at 36 weeks and concentrate on invasive mechanical ventilation, because this is what correlates with a bad outcome. For infants at the canalicular stage of lung development, you want to focus on the 21st-century clinical definition of BPD, which is Jensen's and base the mechanical ventilation at 36 weeks instead of the 20th-century definition, which is supplementary oxygen at 36 weeks, which came about in the '80s.

We look at some outcomes at Iowa. If we looked at the duration of ventilation for 22- and 23-weekers at 63 days, you'd say, "Well, that's really long." Well, but in reality, the post [mass] rates time of extubation for over half the babies was 31 weeks, clearly 5 weeks before you would have been considered to have grade 3 BPD, which is the only one that correlates, really, with a problem.

Univariate Factors Associated With Survival 22–24 Weeks GA Inborn and Outborn (Admitted 2004–2015)

	Alive (n= 316)	Dead (n=83)	Pvalue	OR for survival	95% CI
Gestational age	24.6 ± 0.9	23.9 ± 1.1	<.0001	2.1	(1.6, 2.7)
Birth weight (grams)	684 ± 141	585 ± 156	<.0001	1.0	(1.0, 1.0)
Male sex	152 (48%)	50 (60%)	0.049	0.6	(0.4, 1.0)
Antenatal steroids	271 (86%)	60 (72%)	0.007	2.3	(1.2, 4.3)
Severe IVH	48 (15%)	23 (26%)	0.003	0.2	(0.1, 0.5)
Maternal age (years)	27.7 ± 6.0	26.4 ± 6.4	0.038	1.0	(0.9, 1.0)

After adjusting for multiple variables, survival was associated with higher gestational age, appropriate fetal growth, lack of severe IVH, and older mothers.


CI, confidence interval; GA, gestational age; IVH, intraventricular hemorrhage; OR, odds ratio.

Slide 31 - Univariate Factors Associated With Survival 22-24 Weeks GA

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The interquartile range was 22 to 33 weeks. So, the vast majority were off. We looked at our grade 3 BPD incidence and base of ventilation for 22- and 23-weekers. This isn't for all the VLBWs, only 22- and 23-weekers—6% in this study that we published. More recently when I looked at the data, it was up to 11%. And again, we're getting more babies referred with prolonged ruptured membranes. Tracheostomy, which is one of the outcomes that grade 3 BPDs correlated with, we had 2%—3 out of 144 infants.

Goal of 1st Intention HFJV Is to Avoid Lethal BPD [Grade III(A)] [1] and **Grade 3 BPD** - Invasive Respiratory Support at 36 weeks PMA [2]



- **Diagnosis of Grade 3 BPD**
 - "twofold higher rates of late death, serious respiratory morbidity, and moderate to severe neurodevelopmental impairment among infants receiving invasive rather than noninvasive positive airway pressure at 36 weeks' PMA, strongly supports the distinct classification of infants treated with invasive mechanical ventilation..."
 - Serious respiratory morbidity: tracheostomy, supplemental oxygen for >2 years,

BPD Severity Definition at 36 weeks PMA (2)

Grade 1: Nasal Cannula ≤ 2 LPM
Grade 2: Nasal Cannula > 2 LPM, Nasal CPAP, or NIPPV
Grade 3: Invasive Mechanical Ventilation

Therefore, for infants born at the canalicular stage of lung development, focus on 21st century clinical definition of BPD (Jensen, Invasive Mechanical Ventilation at 36 weeks PMA) instead of the 20th century definition (supplemental oxygen) at 36 weeks PMA

BPD, Bronchopulmonary dysplasia; LPM, liters per minute; PMA, postmenstrual age.

1. Higgins R, et al. *J Pediatr*. 2016;197:303-308.
 2. Jensen EA, et al. *Am J Respir Crit Care Med*. 2019;200(6):751-759.

Slide 32 - Goal of 1st Intention HFJV is to Avoid Lethal BPD [Grade III(A)] and Grade 3 BPD

Long-term outcomes: obviously one of the most important is neurodevelopmental outcomes.

[Here is] another survey question: **What is the rate of severe disability at 18 to 22 months corrected, defined as a Bailey score less than 70 and severe CP [cerebral palsy] and blindness or deafness for infants born at 22 to 23 weeks at Iowa?** For this timeframe would it be 11% or severe 20% to 31%, 36% or 42%? We'll look at that survey and see what you think, 11, 22, 31, 36 or 42.

What is the rate of severe disability at 18 -22 months, defined as a Bailey score of <70 and/or severe CP and/or blindness/deafness, for inborn infants born at 22 -23 weeks gestation from 2006-2015 at the University of Iowa NICU?

- a) 11%
- b) 22%
- c) 31%
- d) 36%
- e) 42%

N=45; 22 to 23-week premature infants
CP, cerebral palsy.

Watkins PL, et al. *J Pediatr*. 2020;217:52-8.

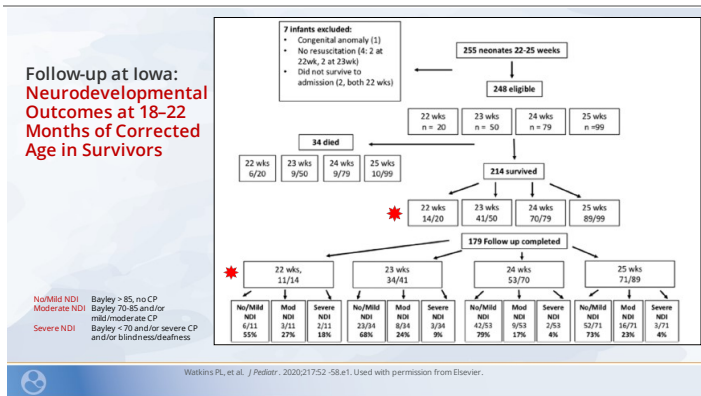
Slide 33 - Audience Response Question

What's very impressive is you are answering the questions. A lot of you must have read the paper because a good portion of you feel it's only 11%, and another good portion of 22%, but importantly, you can see it is not an overwhelming dismal outcome.

If we go to that slide (see slide 34), you can see it's only 11% of 22- and 23-weekers. I think with the right approach, you can have very good outcomes. And we know from more recent data that was published, when you compare age 2 to age 10, almost two-thirds of the babies that would be severe at age 2 are now normal to mild.⁵

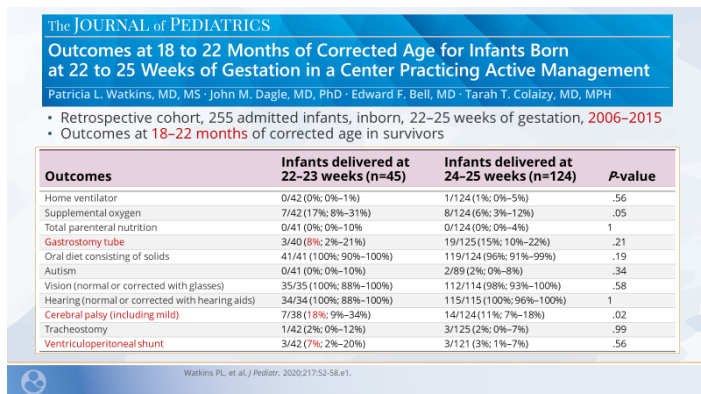
Now, if we look at that paper from Dr. Watkins, you can see the 22-weekers, their severe NDI was 18%, 11% is combining 22 and 23, but no or mild was 55%. We know all of these get dramatically better by age 10. We usually talk to most parents that we expect 60%, at a minimum, of these babies to be basically normal.

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Slide 34 - Follow-up at Iowa: Neurodevelopmental Outcomes at 18-22 Months of Corrected Age in Survivors

The next thing to think about [is] what are the long-term outcomes on the 8% of the 22- and 23-weekers who needed a G-tube. Now CP, that was severe CP, mild CP, for example, a little bit of increased tone in the lower extremities would be about 18%. And the need in a severe IVH [is] bad enough to require some, was only 7% of 22- and 23-weekers. So, there's not a 100% morbidity.



Slide 35 - Outcomes at 18 to 22 Months of Corrected Age for Infants Born at 22 to 25 Weeks of Gestation in a Center Practicing Active Management

In conclusion, we believe survival at 22 to 23 is extremely difficult, but it's not impossible and it's not hopeless. I remember when this baby was born, the 22-2/7-something weeker, 335 grams, I couldn't believe the amazing care done by the nurses for this gelatinous, incredibly tiny

baby. And there she is at 14 months, and since she is actually much older. And those are the twins I showed you. This is the 22-weeker, the 395 g. And in this case, the male twin actually did better than she did.

The key takeaways would be you want to develop a dedicated, integrated structure and culture for extremely premature infants. Antenatal corticosteroids are encouraged prior to 24 weeks to promote infant survival in extremely preterm infants. We strongly encourage them.

Conclusion: Survival at 22-23 weeks GA is Extremely Difficult! But not impossible and not hopeless!

22 2/7 weeks 335 g

22 1/7-week twins, TTS, 490 and 449 g

22 6/7-weeks twins 465 and 395 g

14 months

2 years old

13-month-old, Normal at 2-year F/U

Slide 36 - Conclusion: Survival at 22-23 weeks GA is Extremely Difficult! But not impossible and not hopeless!

We feel the literature strongly encourages them. We're hoping maternal fetal medicine societies and ACOG will start to shift that from not recommended to consider. I think that will make a big difference in a lot of survival. It's important that the lungs of the canicular stage of fetal lung development are at high risk of mechanical injury. It's critically important to minimize both volutrauma with whatever mode of high frequency you're considering or with very targeted, very specific conventional, but be very open, if any volutrauma is developing, to going to high frequency.

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
Then you also want to avoid atelectrauma, because if you extubate and fail, the lungs collapse down, and when you re-intubate them, things are vastly worse than those first few weeks. So, you want to extubate when developmentally appropriate for that gestation.

You want to think about a 22-weeker who is 7 weeks old. Now that baby is 29-1/7 [weeks]. Now, I think about that baby as a 1 day old 29-weeker, who actually is a 49-, 50-day old, 22-weeker.

Obviously you want competence. You need multidisciplinary teamwork, and you need standardization of practice, [which] are essential to allow extremely preterm infants the potential to survive and thrive. Thank you very much.

Key Takeaways

- Develop a dedicated, integrated structure and culture for extremely premature infants.
- Antenatal corticosteroids are encouraged prior to 24 weeks to promote intact survival in extremely preterm infants.
- Lungs at the canalicular stage of fetal lung development are at high risk of mechanical injury so it is critically important to minimize both volutrauma with HFV and atelectrauma by extubating when developmentally appropriate.
- Competence, multidisciplinary teamwork and standardization of practice are essential to allow extremely preterm infants (22-24 weeks EGA) the potential to survive and thrive.

Slide 37 - Key Takeaways

AUDIENCE QUESTION & ANSWER

Editor's Note: This is a transcript of audience questions together with presenter responses from the July 21, 2021 audio webcast.

Dr. Klein, any thoughts on preventing spontaneous GI preparations?

Dr. Jonathan Klein: My thoughts revolve around 2 areas. One is to avoid the use of prophylactic indomethacin. I feel Nationwide has also published on this very recently that

there's really no benefit from using that. The TIP trial also showed it did not improve long-term neurodevelopment outcomes. And the risk of spontaneous perforation is very high in these babies. So, one is to minimize the use of indomethacin in that first week of life, if at all possible, which is why we use the acetaminophen approach to decrease the PDA shunt. Two, spontaneous meconium is a very high problem in this population and that often leads to perforation. So, you can't really advance feeds until you feel like you've made the transition from meconium stools to transitional stools. If that's not happening, you have to think about doing a lower GI contrast study, which is difficult, but you need to work with your radiologists to consider this. And that's something that's done in Korea and Japan and elsewhere to avoid this problem.

Which probiotic do you use?

We use Ultimate Flora, which is a combination of 3-4 different strains of *Bifidobacteria* and *Lactobacillus*. We chose that. There was a study that came out of Canada using that, which cut their risk of the rate of NEC in half.¹⁹ It's one that the Canadian, their version of the FDA, standardized this. There is quality assurance from that. Then we've also, twice on our own, cultured it to make sure that the *Bifidobacteria* and *Lactobacillus* are present are in there.

I know there's other more standardized probiotics coming out, and I know there's a lot of controversy with probiotics. The AAP [for] the fetus and newborn, is still waiting, but we feel that with 30-40 randomized controlled trials, if you try to wait for the perfect probiotic that it will go on forever, and we always feel it's much better to have friendly bacteria in your stool

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rather than unfriendly bacteria, like *E. coli* and *Klebsiella* and or *Lactobacillus*. It's something that we've been doing since 2014.

Do you ever use liquid glycerin or do you just use suppositories?

That's a really great question. We do this: a sliver of the suppository, but one of our surgeons has talked to me about using a tiny liquid glycerin enema and feels that it works quite successfully and efficaciously. So, we're thinking pretty hard about adding that as an option because it's so important to get this inspissated meconium out of there. I'm wondering if it's become a problem more in the last 10-15 years, because we're using antenatal magnesium as a neuroprotective strategy, and the side effect being it slows down gut motility. So that's certainly a great idea.

Are there any differences in survival and IVH rates between breech vs vertex 22-week vaginal deliveries?

That's a very controversial topic, and I would say most people would say that it's probably better not to be trying to have that breech delivery at 22 weeks. Then there's some more recent papers that have just come out promoting better outcomes at C-section, but then I think it's a very difficult decision because you're taking care of 2 patients at the same time, and this is not an easy thing for the obstetricians to do. I find their job is incredibly challenging, especially when we're talking about... Even if everything works perfectly, you're still talking about potentially 40% mortality. So, I am not trying to promote that at all. I support whatever the OBs and the family decide to do. The C-sections that our OBs have done at 22 weeks were to save the mother's life

related to severe preeclampsia. And that was the mom's decision. At this point, I would always be concerned about the mother's health. Like I said, even at term, where there's still an issue of knowing when to do C-section. So, it's a tremendous challenge.

At Iowa, do you have a goal CO₂ level in the first days of life, aside from keeping pH greater than 7.25?

Yes. So, the goal would be to keep the CO₂ ideally in that 45-55 range. That is to try to manage cerebral blood flow. If you allow the CO₂, as they start to get high 50s into the 60s in the first 3-7 days of life, you're going to increase cerebral blood flow, and you're going to increase the risk of IVH. There is a good paper by Jeff Kaiser and others showing the association with higher CO₂s.²⁰ In the first week of life you want to be neuroprotective. It's not the time to be lung protective. You've got to protect the brain before you protect the lung. At the same time, you also don't want to over ventilate because we know as the CO₂s get below 35 and action in the 20s, that's when people show that high frequency causes a problem because it wasn't the high-frequency device, it was having CO₂s in the 20s that can lead to cerebral ischemia from lack of autoregulation of cerebral blood flow.

Iowa keeps those CO₂s quite tight, which does require, in the first 3-7 days of life, a lot of blood gasses, but the goal is to protect the brain at *all* costs because that's something that's very hard to recover from. The lungs will keep growing at least to age 8.

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To avoid hyperlipidemia, what is the max triglyceride level you will tolerate?

That's another great question. We found, a long time ago, that if we never exceeded 2 g/kg/ day, and we give our intralipids over 20 hours, that we've not had any problems with hyper triglycerides. We don't follow triglyceride levels. I mean, the people that want to follow them are ones that are trying to push hard on the lipids, to use the lipids as a way to increase caloric intake. In my mind, what we're trying to do with the lipids, one, is essential fatty acids, number one, and obviously that would be the first sort of 0.6 g/kg. And then the other 1.6-2 g/kg is additional calories.

So, we don't track triglycerides anymore. Once we just stopped trying to get lipids over 2 g/ kg, we stopped having any issues with/by lipemic samples. So, I can't give you the answer to that because we don't follow that, but we just don't exceed 2 g/kg. Now with the intralipids, I know there's issues with SMOF, and if we occasionally get a baby sent to us that has short gut, we'll do a combination of [fish oil triglycerides] and intralipids.

How do you tolerate a glucose infusion rate less than 4 mg/kg per minute before considering insulin?

The only time we would consider insulin is if we're requiring basically under 2 mg/kg per minute. If we have to go that low, then we talk about using a transient insulin drip. And most of the time we take much more than 12 hours, and then they reset. But we know there were RCTs a long, long time ago showing that all that happened if you tried to max calories right away using insulin drips, you didn't get good linear growth. You didn't put on muscle, basically, you just increased adiposity.

So, when the babies will... when they're ready, they'll tolerate the adequate calories. You can't think, in the first week of life, I need to be on a 100 cal/kg. You might be on 45, then you might be on 50, and then it might be 50ish, and then you work your way to 60. But by the second week, third week of life, then you'll be up to the calories you need for the next 4 months. **The key thing is protein.** We don't want any patients to become protein malnourished. So, we try to get the 3.5-4 g/kg very quickly in the first, second day, or third day of life.

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Abbreviations

AGA	appropriate for gestational age	NRP	Neonatal Resuscitation Program
BPD	bronchopulmonary dysplasia	NVN	neonatal venous nutrition
CP	cerebral palsy	OB	obstetrician
ETT	endotracheal tube	PDA	patent ductus arteriosus
GBS	group B <i>Streptococcus</i>	PEEP	positive end expiratory pressure
GIR	glucose infusion rate	PEI	pulmonary interstitial emphysema
IgG	immunoglobulin G	PROM	premature rupture of membranes
IVH	intraventricular hemorrhage	PSS	post-surfactant slump
IVIg	intravenous immunoglobulin	PVL	periventricular leukomalacia
NAVA	neurally adjusted ventilatory assist	RDS	respiratory distress syndrome
NEC	necrotizing enterocolitis	ROP	retinopathy of prematurity
NCCU	Neonatal Critical Care Unit	SIP	spontaneous intestinal perforation
NDI	neurodevelopment impairment	UAC	umbilical artery catheter
NICU	neonatal intensive care unit	VON	Vermont Oxford Network

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