

Outcomes at the Extreme Limits of Viability for Infants Born at 22 to 23 weeks Gestation Managed with a Positive Proactive Approach

2024 TIPQC Annual Meeting, Franklin, TN

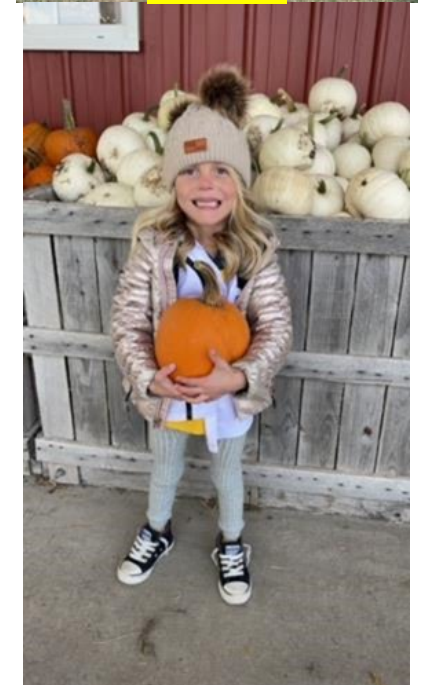
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Faculty Disclosure Information

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- I have permission from the families of all identifiable patients to use the images that they sent me which are displayed within the presentation.





Objectives

- 1) Review single center survival for infants born at 22-23 weeks gestation compared to baseline
- 2) Identify global concepts for the care of periviable infants when utilizing a **proactive**, standardized and balanced approach
- 3) Describe short term morbidity and two-year outcomes for periviable infants born at 22-23 weeks gestation at a single center
- 4) Review Obstetric Interventions at 22 Weeks at the University of Iowa Hospital & Clinics



Survival of Inborn “Perivable Premature” Infants Born at 22 to 24 weeks EGA with a Proactive Approach (2006-2022)



<u>Weeks</u>	<u>22</u>	<u>23</u>	<u>24</u>
Survival	60%	77%	85%
Number of live born infants	79	124	127

15 Months



64% survival at **22 weeks** for NICU admissions (73 admissions with 47 survivors)

Twin IVF Pregnancy:
Twin A NSVD. Twin B born 4 days later
NSVD.

Twin A **22 3/7** wks,
BW 485g AGA 39%

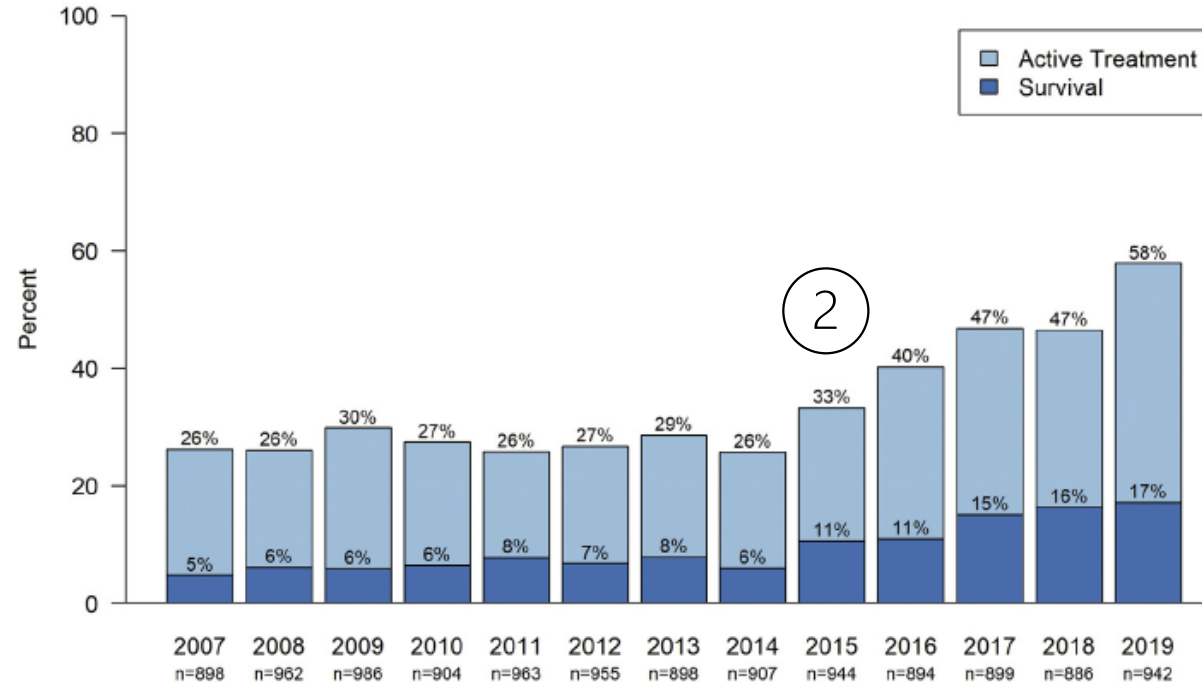
Twin B **23 0/7** wks, BW
630g AGA 87%



Survival is Improving for Premature Infants born at 22 weeks Gestation [1]

2021

MEDICAL PROGRESS



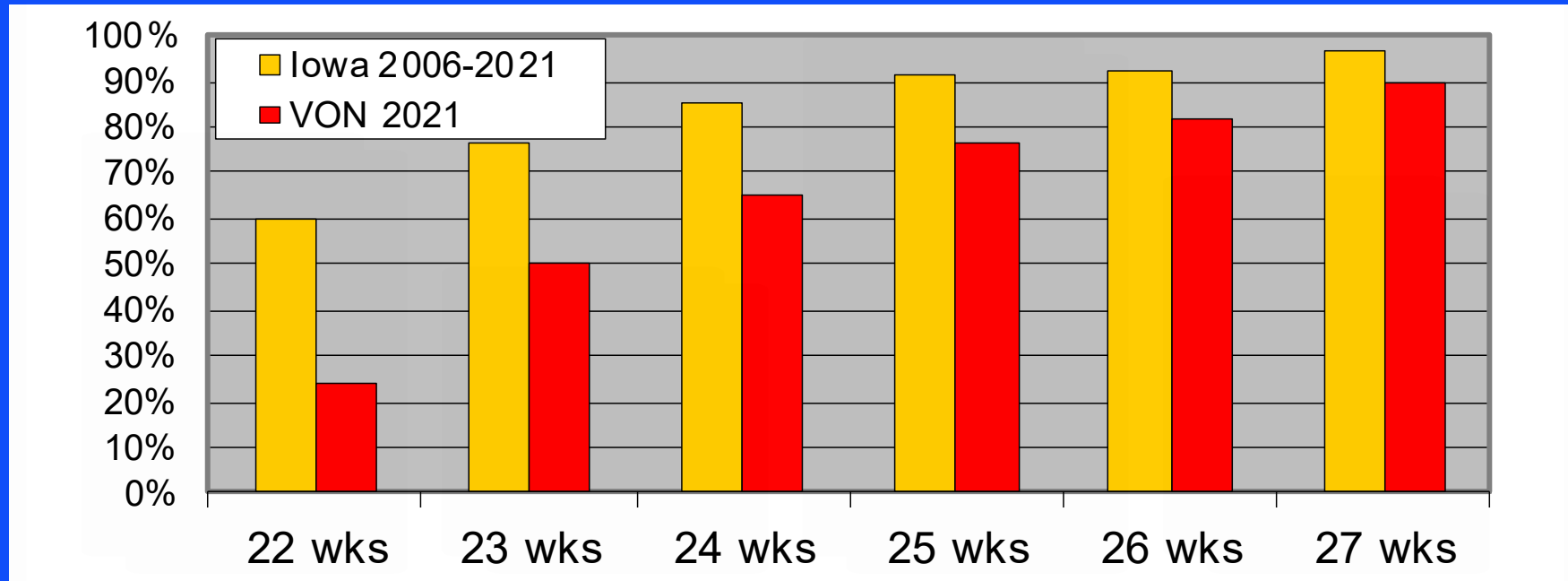
2022 VON Type C:
Survival for all liveborn infants
at 22 weeks was up to 27%.

Figure 1. Active treatment and survival for liveborn infants at 22 weeks in the US. Active treatment is defined as respiratory support (including face mask ventilation, nasal continuous positive airway pressure, endotracheal intubation, surfactant therapy, or mechanical ventilation), chest compressions, or epinephrine. Survival is to hospital discharge or 1 year. The denominator includes all live births, including deaths that occurred in the delivery room. Data are from hospitals participating in the Vermont-Oxford Network.

1) Rysavy MA et al, An Immature Science: Intensive Care for Infants Born at ≤ 23 Weeks of Gestation, *J Pediatr.* 2021;233:16-25.e1.

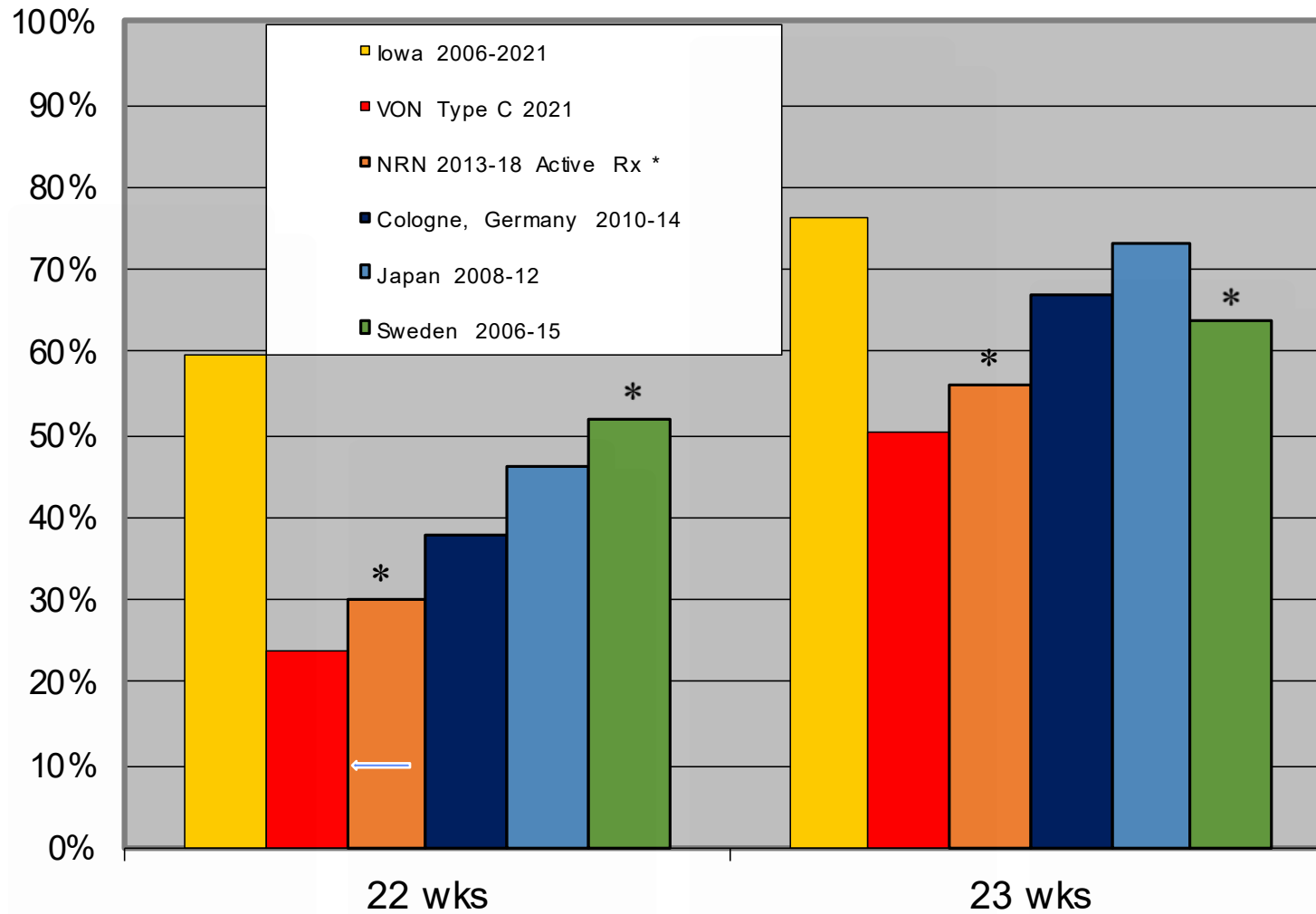
2) Rysavy MA, et al. Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants. *NEJM* 2015;372:1801-1811

Survival of Inborn VLBW Infants 22 - 27 weeks EGA (2006-2021)



Comparison group: VON NICU Type C Mean Data

Survival of Inborn Periviable Infants Born at 22-23 weeks Gestation (live-born)



22-weeks Active Treatment
 (*) **30%** vs all live born **11%**
 NRN] *Bell et al, 2013-2018*
JAMA 2022;327(3):248-263.

Cologne, Germany 2010-14: 22-week **active care Survival 60%**
 (17/28) vs **38%** all live born. *Mehler K et al, JAMA Pediatr 2016*

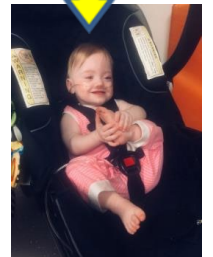
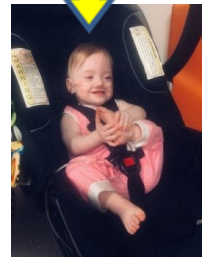
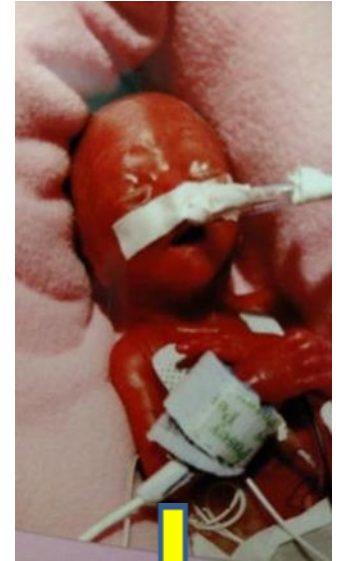
Nagano, Japan 2011-18: 22-week **Survival 81%** (13/16) all live born are resuscitated. *Yanagisawa T et al, American Journal of Perinatology 2022*

Iowa : 22 –week survival all live born:
77% (10/13) 2016
78% (7/9) 2021

Proactive Approach

22 2/7 weeks, 335 g,
SGA < 1%

1. Philosophical expectation that infants born at 22 weeks gestation will survive and thrive.
2. To understand that successfully caring for an infant born at 22 weeks gestation is a constantly changing technological and medical challenge rather than a fixed immutable law of nature.
3. The realization that a large part of successfully caring for infants born at 22 weeks gestation is having a standardized multidisciplinary culture that supports a team approach to the care of these infants both medically and emotionally.
4. Always respecting and supporting the parents' preference to either initiate active treatment or choose comfort care.
5. Mutually supportive interdisciplinary teamwork with the obstetricians to begin treatment before birth with the use of antenatal steroids, even possibly before 22 weeks.
6. To realize that infants born at 22 weeks gestation are not just smaller versions of infants born at 26 weeks and should be treated accordingly; including access to 2.0 ETT.
7. *"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]
8. To understand that *"Three sorts of ethical concerns are generally raised about treatment of babies born so prematurely. One ... is that too many survivors will have severe neurocognitive impairment. Another is that parents do not want such treatment. A third is that it costs too much. Evidence suggests that none of these concerns is valid."* John Lantos, *Ethical Issues in treatment of babies born at 22 weeks of gestation.* ^[2]



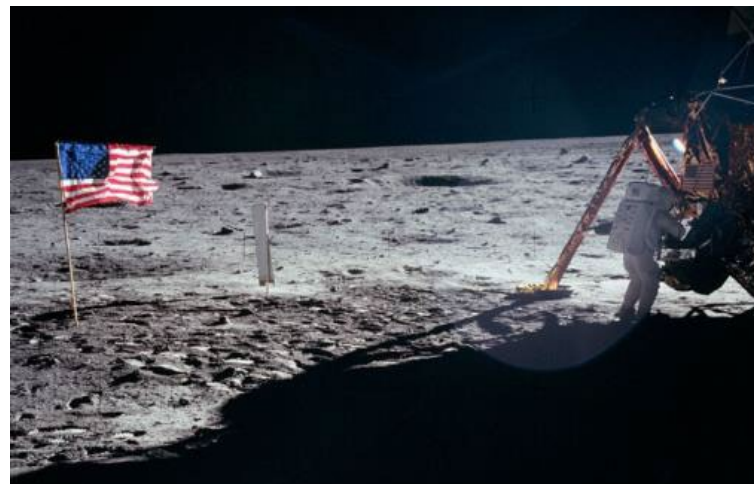
1) Failure is not an option, Gene Kranz, Berkley Books, New York, 2000, p.393.

2) Lantos JD, Ethical issues in treatment of babies born at 22 weeks of gestation. Archives of Disease in Childhood 2021 Dec;106 (12):1155-1157. doi: 10.1136/archdischild-2020-320871

Apollo 11: July 20, 1969

Landing on the Moon

Hard, Difficult and “Impossible”



Philosophy: We expect these infants to survive and thrive

Hard and Difficult, but it is not Impossible

22 1/7
weeks
488 g
AGA 49%



22 6/7
weeks
465 g
AGA 11%



22 2/7
weeks

379 g
SGA 3%





Philosophical Differences [1]



- Rates of active treatment account for 78% of between-hospital variation in survival among children born at 22 or 23 weeks of gestation, but the rates of active treatment did not account for all the variation in among those born at 24 -26-weeks.^[1]
 - For example, among hospitals that treated 100% of infants born at 24 weeks, rates of risk adjusted survival varied from 42–70%.
- Factors other than just the decision to resuscitate contribute heavily to the variation in outcomes!
- Just deciding to offer resuscitation at 22-23 weeks gestation without adjusting management strategies is not the best approach for the care of these delicate patients.

Epidemiology of Extremely Extreme Prematurity

- In 2019, from US birth certificates (live births):
- 22 weeks: **1,799**
- 23 weeks: **2,606**
- 24 weeks: **3,408**
- All births in US: 3,747,540

From the CDC Wonder Data Set

23 6/7 weeks **twin**
507 gm, 10%
Borderline SGA

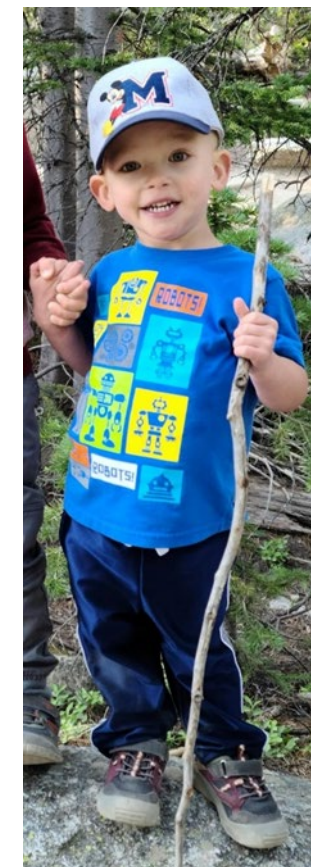
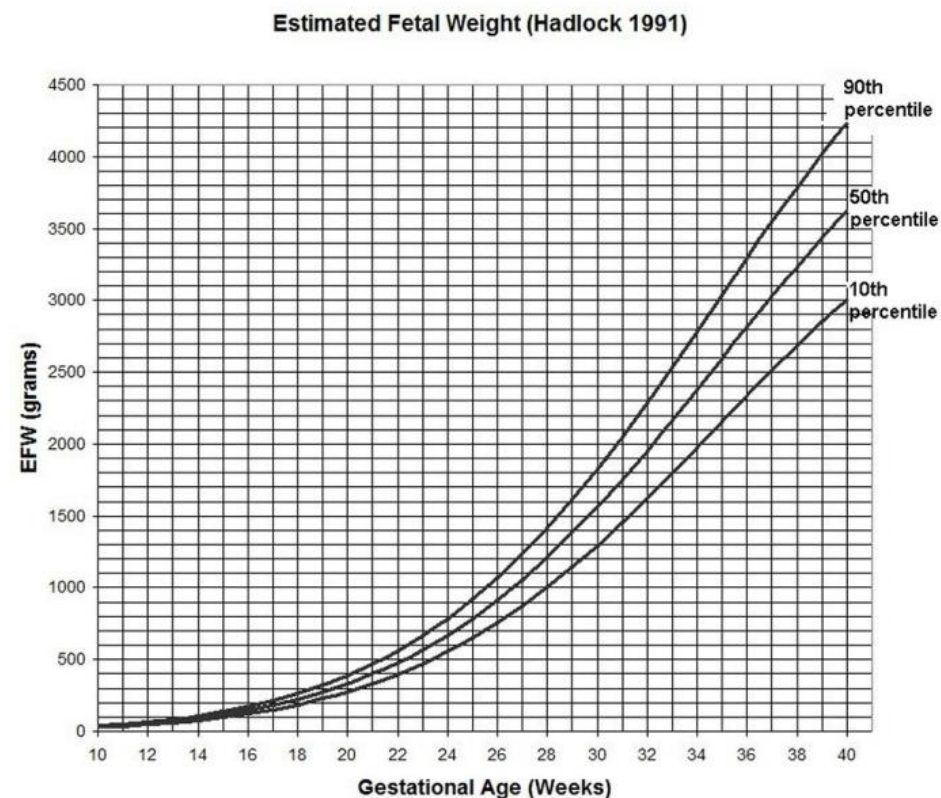


“Periviable” Census on January 8, 2019

517 grams twin
22 6/7 weeks
AGA 29%



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



“Periviable” Census on April 29, 2021

Gestational Age	BW (g)	PMA on 4/29/21
21w3d	410	22w2d
22w0d	600 (94%)	25w2d
22w0d	440	22w0d
22w0d	440	22w0d
22w2d	401	24w6d
22w4d	460	14 months
22w5d	570	31w4d
23w4d	580	29w3d
23w4d	671	29w3d
23w5d	620	24w6d



Discharged Intact at Home:

- 21 3/7-week male 410 g; AGA 20%, No NDI at age 2
- 21 6/7-week female 305 g SGA < 1%
- 21 6/7-week twin female 365 g SGA 2%

Maternal Characteristics Iowa Inborn Cohort (2008-2021)

	22 weeks N = 74	23 weeks N = 109	24 weeks N = 106
Maternal race			
White	78%	67%	67%
Black	18%	20%	23%
Hispanic	2%	8%	6%
Other	2%	5%	4%
C-Section*	6 (8%)*	48 (44%)	75 (71%)
Multiples	29 (39%)	26 (24%)	13 (13%)
Chorioamnionitis	30%	30%	15%
Maternal Hypertension	7%	15%	14%

Inborn 22 Week Survival:

Race:

Black 62%

White 59%

Sex:

Male 56% (24/43)

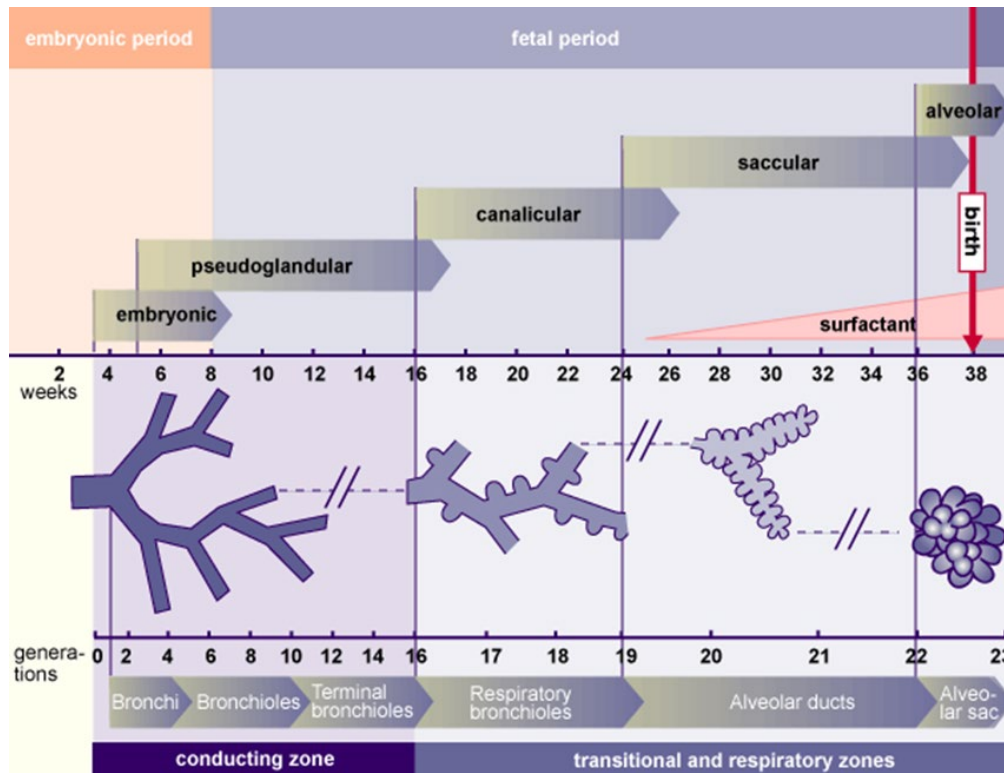
Female 65% (20/31)

*C-Sections at 22 weeks Gestation (University of Iowa) 2016 - 2021; 6/48 (12%) and for maternal indications only

C-Section rate of 0% at 22 weeks in a cohort from Sweden. Outcomes of a uniformly active approach to infants born at 22-24 weeks of gestation. Söderström F, et al. *Arch Dis Child Fetal Neonatal Ed.* 2021 Jul;106(4):413-417.

C-Section rate of 32% at 22 weeks with ANS in US VON. Association of Antenatal Steroid Exposure With Survival Among Infants Receiving Postnatal Life Support at 22 to 25 Weeks' Gestation. Ehret DEY, et al. *JAMA Netw Open.* 2018 Oct 5;1(6):e183235.

Periviable Lungs (< 24 weeks) How is it possible to survive without alveoli?



- Need Alveolar Sacs (thin wall + vascularized) which can begin to form at 24-27 weeks, the cranial segments mature faster than the caudal segments so you can have areas of the lung that are mature enough to support survival at 22 weeks gestation if you accelerate and minimize damage to the lung
- ✓ Need Antenatal Steroids to accelerate lung maturation: differentiation of Alveolar Type I and II cells, thinning of the mesenchyme for gas exchange and increased invasion of the capillaries into the air spaces for oxygen transfer.
- ✓ Need a Lung Protective Strategy to minimize volutrauma !

- 1) At the canalicular stage of lung development (< 24-26 weeks gestation) it is critically important to avoid shear force injury (volutrauma) leading to PIE and Pneumothorax
 - 2) Iowa is a **1st Intention HFV Center**
- ✓ First Intention High Frequency Jet Ventilation is used for all infants at 22-26 weeks gestation who require mechanical ventilation [1]

1) Elgin TG, Stanford AH, Klein JM, First intention high-frequency jet ventilation for periviable infants. Curr Opin Pediatr 2022 Apr 1;34(2):165-169.

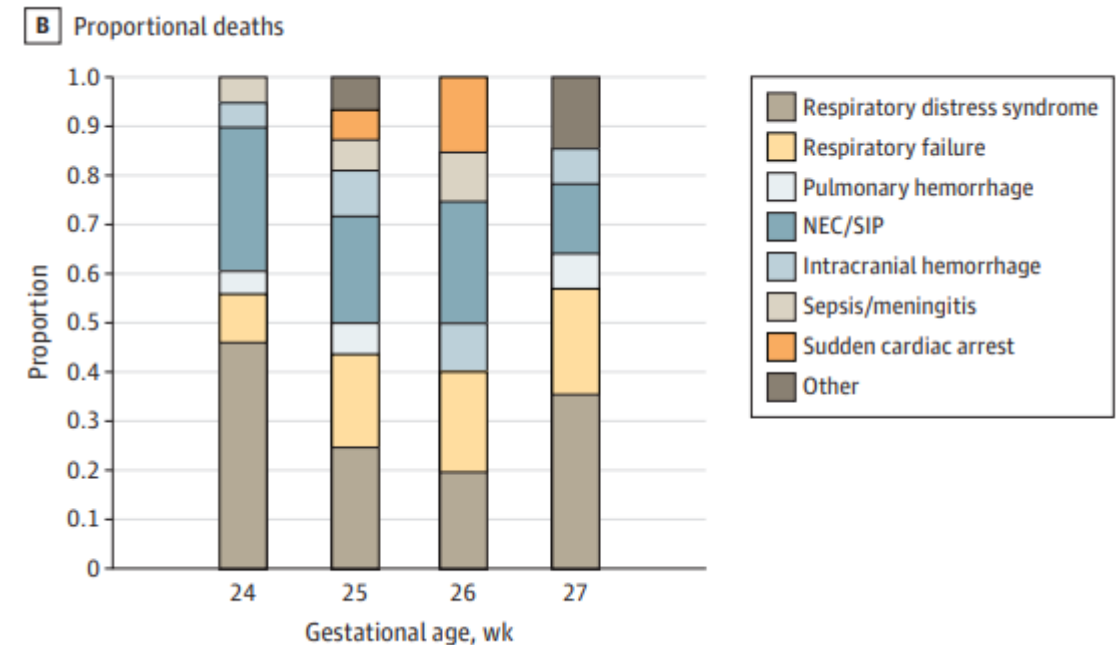
Proportion of Deaths due to a Respiratory Cause for Inborn 22-week Gestation Infants admitted to the University of Iowa NICU (2008-2017) with 1st HFJV

- **Respiratory Causes** Include:

- RDS
- Late Respiratory failure - “(defined as ongoing respiratory compromise after 2 weeks of life)” [1]
- Pulmonary hemorrhage

➤ At Iowa with 1st Intention HFJV, respiratory causes were responsible for only 8% of the deaths of infants born at 22-weeks gestation

➤ In contrast, the leading cause of death in the Preterm Erythropoietin Neuroprotection Trial [19 US sites, n=941, (2013-2016), 24^{0/7} to 27^{6/7} weeks]; were respiratory causes; responsible for 60% of all deaths at 24 weeks and 50% at 25 weeks [1]



1) Juul SE et al., Deaths in a Modern Cohort of Extremely Preterm Infants From the Preterm Erythropoietin Neuroprotection Trial, JAMA Network Open. 2022;5(2):e2146404.doi:10.1001

Respiratory Outcomes for Infants Born at 22 to 23 Weeks of Gestation Treated With First Intention HFV^[1]

Key Respiratory Outcomes: Median GA 23.3 [IQR 22.9-23.6]

- 70 Inborn infants treated with **First Intention HFV:**
 - 65 - HFJV (93%), 5 - HFFI (7%)

Survival

- 22 weeks GA: 14/20 (70%)
- 23 weeks GA: 41/50 (82%)

Median duration of ventilation at 22–23 weeks GA: 63 days (IQR 47–78 days)

Median PMA at time of extubation was **31.0 weeks PMA*** (IQR 29–33 weeks)

Grade 3 BPD at 22–23 weeks GA : Invasive Ventilation at 36 weeks PMA^[2]

- 6% from 2006–2015
- 9% from 2016–2022 (n=87)

Tracheostomy at 22–23 weeks GA

- 1.5%, 3 out of 195 infants (2006-2022)

Supplemental Oxygen at 18-22 months corrected age-17%^[1]

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

2. Jensen EA, et al. *Am J Respir Crit Care Med.* 2019;200(6):751-759.

3. Shalish W, et al. *J Pediatr.* 2022 Aug 24:S0022-3476(22)00760-0.



517 grams twin
22 6/7 weeks
AGA 29%

*31 weeks PMA age at extubation was the same as the APEX cohort PMA **31.3 weeks (IQR 29.8-32.1)** for infants extubated at > 35 days of life and 22-week GA infants were excluded from the APEX cohort. **Median GA 24.1 (IQR 23.8-24.9)**^[3]



Outcomes of Inborn Infants: Acute Morbidity 2006-2022

Outcomes at < 24 weeks gestation are not hopeless

	N	Severe IVH	Cystic PVL	VP Shunt	NEC incidence	ROP Treatment
22-week NICU admissions	73	22%	5%	3%	11%	11%
23-week NICU admissions	122	16%	7%	2%	8%	6%

22 3/7-week twin 544 grams AGA 59%



23 2/7-week twins 1st day of nursery school at age 4 (518 grams AGA 33% and 545 grams 45%)



22 0/7-week twin 440 grams AGA 18%

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



- 1) 11%
- 2) 22%
- 3) 31%
- 4) 36%
- 5) 42%

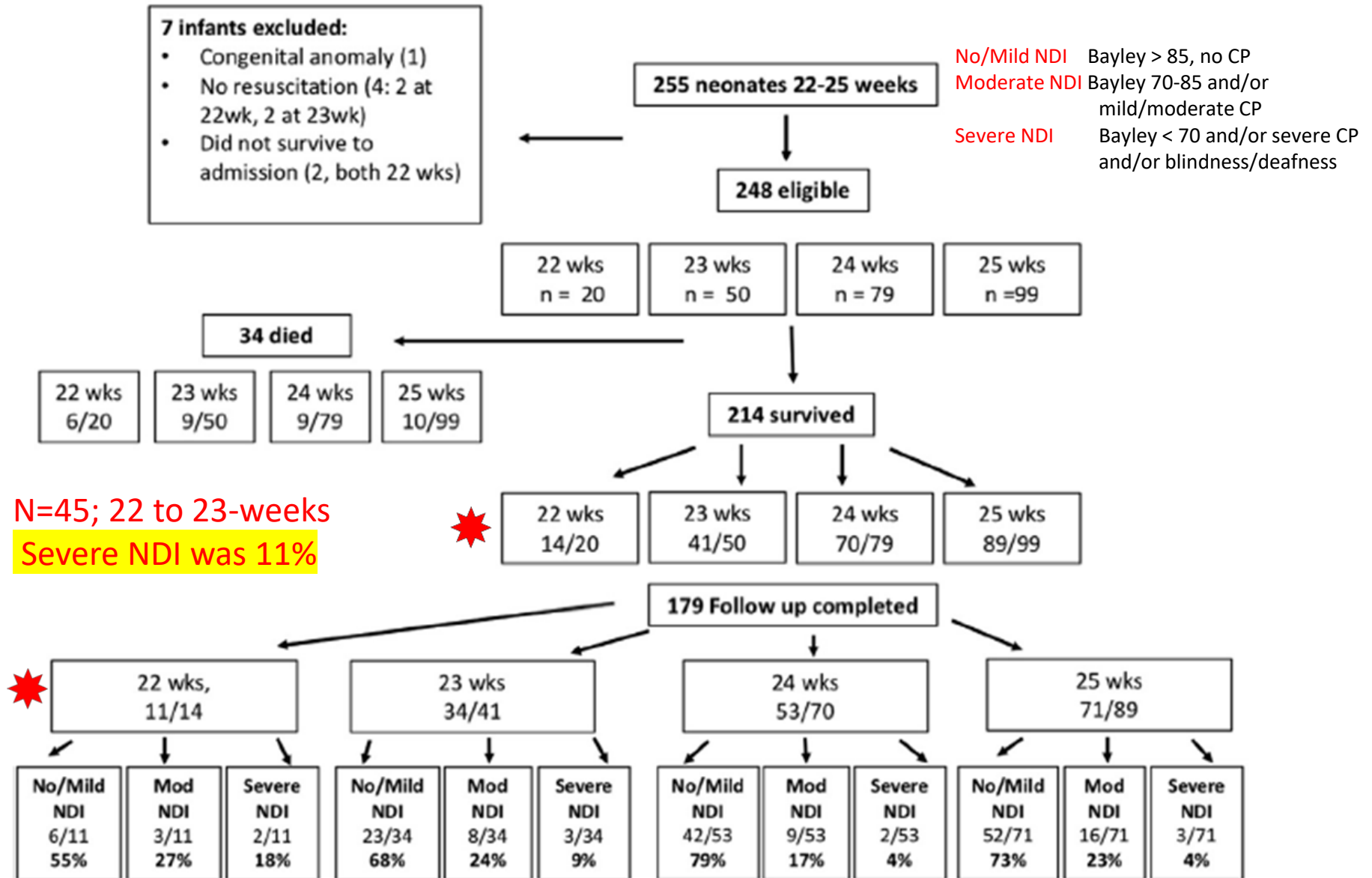
What is the rate of **severe disability** at 18-22 months, defined as a Bayley score of < 70 and/or severe CP and/or blindness/deafness, for inborn infants born during **2006-2015** at 22-23 weeks gestation at the University of Iowa NICU? [1]



- 1) 11% ←
- 2) 22%
- 3) 31%
- 4) 36%
- 5) 42%

N=45; 22 to 23-week premature infants
1) *J Pediatr* 2020;217:52-8

Neurodevelopmental Outcomes at 18-22 months of corrected age in survivors *(J Pediatr 2020;217:52-8)*



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

Patricia L. Watkins, MD, MS · John M. Dagle, MD, PhD · Edward F. Bell, MD · Tarah T. Colaizy, MD, MPH

J Pediatr. 2020;217:52-58.

- Retrospective cohort, 255 admitted infants, inborn, 22–25 weeks of gestation, 2006–2015
- Outcomes at 18–22 months of corrected age in survivors

Outcomes	Infants delivered at 22–23 weeks (n=45)	Infants delivered at 24–25 weeks (n=124)	P-value
Home ventilator	0/42 (0%; 0%–1%)	1/124 (1%; 0%–5%)	.56
Supplemental oxygen	7/42 (17%; 8%–31%)	8/124 (6%; 3%–12%)	.05
Total parenteral nutrition	0/41 (0%; 0%–10%)	0/124 (0%; 0%–4%)	1
Gastrostomy tube	3/40 (8%; 2%–21%)	19/125 (15%; 10%–22%)	.21
Oral diet consisting of solids	41/41 (100%; 90%–100%)	119/124 (96%; 91%–99%)	.19
Autism	0/41 (0%; 0%–10%)	2/89 (2%; 0%–8%)	.34
Vision (normal or corrected with glasses)	35/35 (100%; 88%–100%)	112/114 (98%; 93%–100%)	.58
Hearing (normal or corrected with hearing aids)	34/34 (100%; 88%–100%)	115/115 (100%; 96%–100%)	1
Cerebral palsy (including mild)	7/38 (18%; 9%–34%)	14/124 (11%; 7%–18%)	.02
Tracheostomy	1/42 (2%; 0%–12%)	3/125 (2%; 0%–7%)	.99
Ventriculoperitoneal shunt	3/42 (7%; 2%–20%)	3/121 (3%; 1%–7%)	.56

➤ **Updated VP Shunt placement (2006-2022) for 22-23 weeks Gestation was 2%** (n=195, Inborn admissions)

Difference: **Begin at the Beginning**

Antenatal Steroids are Critical



Interdisciplinary Teamwork with Maternal Fetal Medicine Service is Key

- **ANS at 22 – 25 weeks gestation:**

- ✓ Reduces severe morbidities including IVH and the incidence of NDI at 18 to 22 months and significantly **increases survival**:

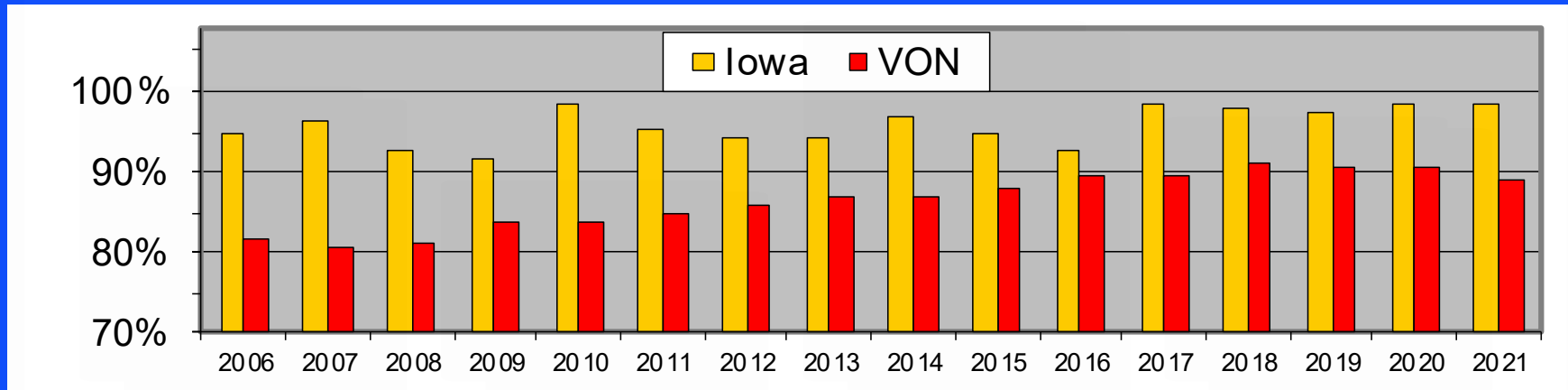
- ✓ 18% to 39% at **22 weeks** gestation^[6]

- ✓ 36% to 54% at **22-23 weeks** gestation^[7]

1. 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.
 2. 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.
 3. Park CK, Isayama T and McDonald SD. Antenatal Corticosteroid Therapy Before 24 Weeks of Gestation; A Systematic Review and Meta-analysis. *Obstet Gynecol* 2016;127:715–25.
 4. Wei1 JC, Catalano R, Profit J, et al. Impact of antenatal steroids on intraventricular hemorrhage in very-low-birth weight infants. *Journal of Perinatology* 2016 ;36, 352–356.
 5. Deshmukh M and Patole S. Antenatal corticosteroids in impending preterm deliveries before 25 weeks' gestation. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F173-176.
 6. 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 Network Open*. 2018;1(16):e183235.
 7. Chawla S, Wyckoff MH, Rysavy MA, et al. Association of antenatal steroid exposure at 21 to 22 weeks of gestation with neonatal survival and survival without morbidities. *JAMA Network Open*. 2022;5(9):e2233331.
- If everyone “already knows” that **ANS therapy**, at ≥ 24 weeks, improves lung maturity and reduces RDS, NEC, severe IVH and mortality ... so

Antenatal Steroids - Inborn

All VLBW Infants (22 to 33 weeks EGA) 2006-2021



2021 All VLBW Infants: Iowa 98.5% vs VON NICU Type C 89.1%

Infants delivered at **22-23 weeks gestation** antenatal steroid use was **91%** (2006-2015 **Iowa Inborn cohort**) Watkins PL, et al. *J Pediatr.* 2020;217:52-8

Updated Guidance Regarding Antenatal Corticosteroid Administration for Threatened and Imminent Perivable Birth by Best Estimate of Gestational Age [1]

ACOG Updated 9/2021	20 0/7 weeks to 21 6/7 weeks	22 0/7 weeks to 22 6/7 weeks	23 0/7 weeks to 23 6/7 weeks	24 0/7 weeks to 24 6/7 weeks
Antenatal Corticosteroids	Not recommended	Consider	Consider	Recommended

1. <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/09/use-of-antenatal-corticosteroids-at-22-weeks-of-gestation>

Obstetric Interventions at 22 Weeks:

Disclosure: I (**Jonathan Klein**) am not a MFM specialist

Mark Santillan MD, PhD is a MFM specialist

Erica Testani DO MFM Fellow PGY-5

UIHC OBGYN Guidelines

Gestational Age (wks)	BMTZ	Latency Antibiotics	Magnesium - Neuroprotect.	Tocolysis	Fetal Heart Rate Monitoring	Delivery Considerations
21 5/7 – 22 6/7	✓	✓	✓ (if contracting)	Mg if contracting for 48-hour steroid window	Handheld doppler	No C-section
23 0/7 – 23 6/7	✓	✓	✓	Mg if contracting for 48-hour steroid window	Doppler vs. NST daily	Vaginal vs. C/S discussion
> 24	✓	✓	✓	Mg if contracting for 48-hour steroid window	NST daily	Vaginal vs. C/S discussion

Antenatal Corticosteroids

- **Current UIHC guidelines:** Administer at 21w5d if delivery is expected within 7 days and if full resuscitation is planned starting at 22w
- Enhances fetal lung maturation and is strongly associated with decreased neonatal morbidity/mortality including respiratory distress, IVH and NEC
- Greatest benefit when delivery is within 7 days of administration
- RCTs have not been conducted in the periviable population but data has been extrapolated from data in pregnancies 25w0d and beyond
- Observational evidence suggests benefit

Magnesium

- **Current UHC guidelines:** *Consider starting at 21w5d if delivery anticipated (no standardized regimen) and if full resuscitation is planned starting at 22w*
- Benefit for the prevention of CP in infants born <32 weeks demonstrated in RCTs and meta-analyses
- Extremely preterm gestations comprise only a small portion of the infants enrolled in sentinel studies of MgSO₄ for neuroprotection
 - The Australasian Collaborative Trial of MgSO₄ study recruited as early as 24 weeks

Latency Antibiotics

- **Current UIHC guidelines:** Consider starting at 21w5d for PROM if full resuscitation is planned starting at 22w
- Broad-spectrum antibiotics prolongs pregnancy, reduces maternal and neonatal infections, and reduces morbidity in the setting of preterm PROM
- Regimen: Total 7-day course of combination of IV ampicillin and erythromycin (2 days) followed by oral amoxicillin and erythromycin (5 days)

Tocolytics

- **Current UIHC guidelines:** Consider starting at 21w5d in cases of PTL during betamethasone administration if full resuscitation is planned starting at 22w
- Medications (**Nifedipine**) used to delay and weaken uterine contractions in the setting of preterm labor
- No benefit to tocolysis after 48hrs
- Contraindications: PPROM*, chorioamnionitis, bleeding

Electronic Fetal Monitoring (EFM)

- Current UIHC guidelines: *Daily fetal heart rate doppler from 22w0d-22w6d*
- Non-stress testing (NST) recommended when full obstetric and neonatal interventions, i.e. starting at 23 weeks
- Diagnosis of fetal compromise by NST is limited given that the parameters of EFM are based on the physiologic responses of a fetus at or near term
- Extrapolation to preterm gestation has been suggested but parameters specific to borderline viability population have not been developed

Route of Delivery at 22 weeks

- ***Current UIHC guidelines:*** *Cesarean section not offered as a mode of delivery from 22w0d – 22w6d*
- Safest mode of delivery for very preterm infants has yet to be determined
- Current research is mixed and does not consistently demonstrate that C-section confers a prognostic/survival benefit to the fetus

Obstetric and Delivery Room Interventions over Time

22-26 6/7 weeks gestation

Current
2018-2022 vs Past
2010-2017

Maternal factors

Antepartum steroids

None

14 (7)

58/421 (14)

0.03

Partial

41 (22)

102/421 (24)

Complete

136 (71)

261/421 (62)

Maternal magnesium sulfate

156/179 (87)

165/336 (49)

<0.001

Delayed cord clamping

101/177 (57)

61/353 (17)

<0.001

Maternal antibiotics

None

30/179 (17)

116/335 (35)

<0.001

Survival at 22-23 weeks gestation is extremely difficult ! But, not impossible and not hopeless !

22 2/7 weeks
335 g SGA < 1%



14 months old

22 6/7 weeks twins
465 g AGA 11% & 395 g SGA 2%



13 months old, normal by age 2

22 1/7-week twins, TTTS,
490 AGA 50% and 449 g AGA 27%



Age 2



Age 3



Age 5



Age 4

Long-Term Outcome



23 2/7 weeks
Candida Sepsis



HS Graduation Photo
Age 18
Attending College

Very Long-Term Outcome

24 0/7 weeks GA



Anchored 4x100-
m relay, Division
3 National Team
Champions 2014



College Graduate
May 2016
Business
Administration and
Writing Major



Wedding July 2023
Age 29 years and 10 months