Management of Premature Infants Born at the Extreme Limits of Viability

The Iowa Way

2024 TIPQC Annual Meeting, Franklin, TN

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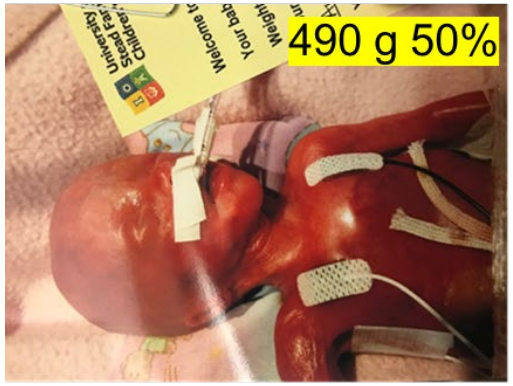

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Age 4 years, 10 months

22 1/7-week twins, Twin to Twin Transfusion Syndrome

Faculty Disclosure Information

1. I, Jonathan Klein, MD, have no relevant financial relationships with any manufacturer of any commercial interests to disclose.
2. I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.
3. I have permission from the families of all identifiable patients to use the images that they sent me which are displayed within the presentation.

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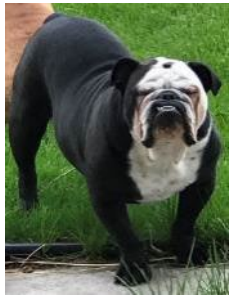

Learning Objectives

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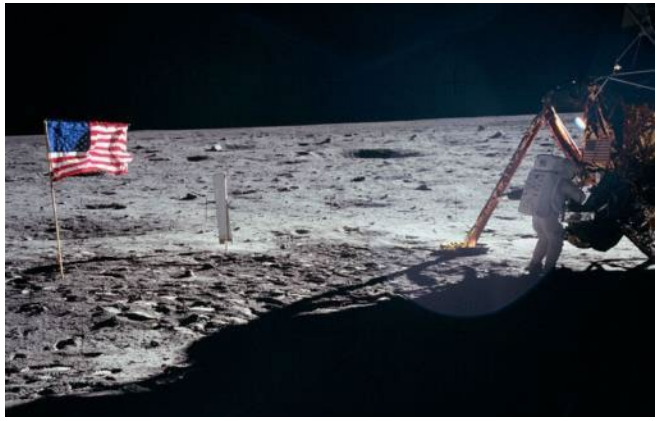
When caring for infants born at 22 to 23 weeks gestation:

1) Identify the importance of differences in culture and philosophy
2) Examine the need for differences in management strategies
3) Describe how to balance competing outcomes in a proactive and standardized manner

Apollo 11: July 20, 1969
Landing on the Moon
Hard, Difficult and “Impossible”



Survival of Inborn "Periviable Premature" Infants Born at 22 to 24 weeks GA with a Proactive, Standardized, and Balance Approach (2006-2022)

Weeks	22	23	24
Survival	60%	77%	85%
Number of live born infants	79	124	126

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

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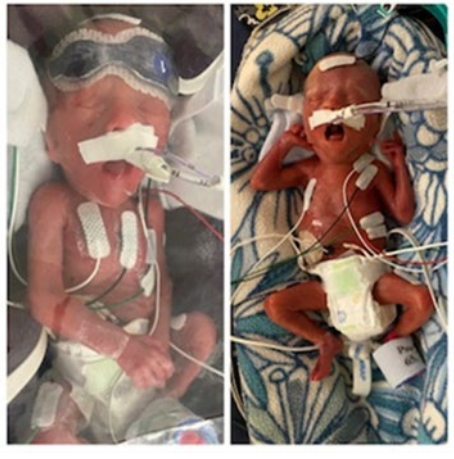
Twin IVF Pregnancy: Twin A NSVD. Twin B born 4 days later NSVD.

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

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



Foundations of Mission Control [1]

- **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, Berkley Books, New York, 2000, p.393.

"Small Baby" System

Dedicated, Integrated, Standardized Structure and Culture for Extremely Premature Infants [1]

"***The System is the Star***"

Separate Dedicated Unit of 14 Beds - Bay 1

- ✓ All infants < 29 weeks are admitted here as well as the most critically ill term infants (NCCU-Neonatal Critical Care Unit)
- ✓ Separate Nursing Staff
- ✓ Separate location Integrated with L&D
- ✓ Separate Critical Care Lab just for the NICU
- ✓ Separate Medical Team for just these 12-14 patients
  - ➢ Separate Attending Service ("Neonatal Intensivists"), Fellow, NNP, Residents, Dietician, Pharmacist, Respiratory Therapist

1) **Care from Birth to Discharge of Infants Born at 22 to 23 Weeks' Gestation**. *Crit Care Nurs Clin North Am.* 2024 Mar;36(1):23-33. doi 10.1016/j.cnc.2023.08.007. John M Dagle, Stephen K Hunter, Tarah T Colaizy, Steve J McElroy, Heidi M Harmon , Patrick J McNamara, and Jonathan M Klein

Structure: NICU 84 rooms with 88 beds

Bay 1

HLM Design

Development of Replacement Perinatal and Obstetrical Patient Care Units
Level 6 - John Pappajohn Pavilion

University of Iowa Health Care

Exposure to Antenatal Steroids and given Postnatal Life Support significantly increases survival at 22 weeks gestation by how much?

Ehret D et al, JAMA Network Open.2018;1(6)e183235

1) 0% (not effective)
2) By 10%
3) By 30%
4) By 50%
5) By 100% (Doubles survival)

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Difference: Begin at the Beginning

Antenatal Steroids are Critical

Interdisciplinary Teamwork with Maternal Fetal Medicine Service is Key

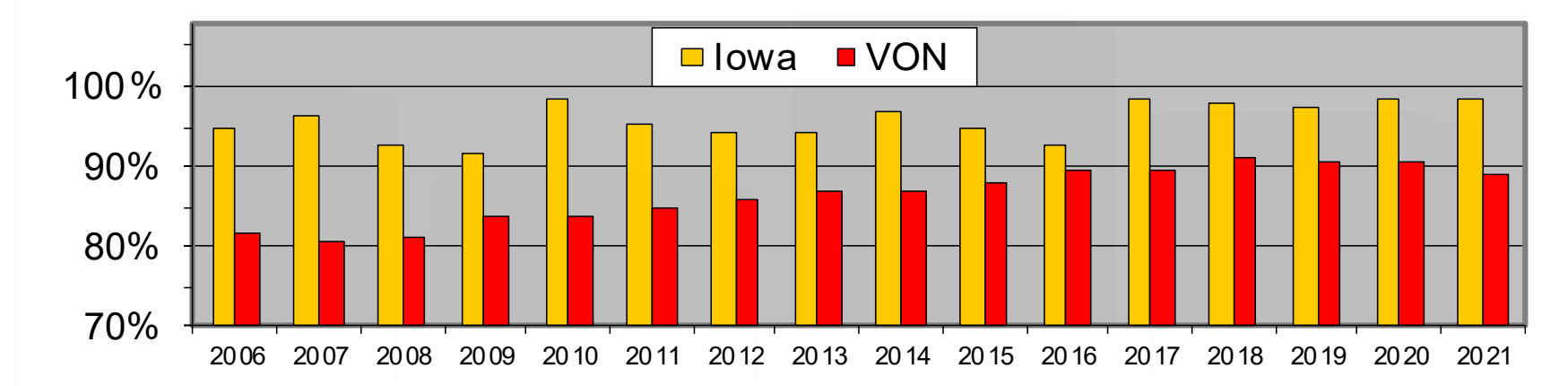
- ANS at 22 – 25 weeks gestation:
  - ✓ Reduces severe morbidities including IVH and the incidence of NDI at 18 to 22 months and significantly increases survival:
    - ✓ 18% to 39% at 22 weeks gestation[6]
    - ✓ 36% to 54% at 22-23 weeks gestation[7]

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. *Wei 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 Periviable 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

Balanced Approach to Delivery Room Resuscitation for Infants Born at 22 to 23 Weeks Gestation

- Initiate resuscitation with 50% oxygen and titrate per goals to minimize hypoxia and hyperoxia
  - **Mortality < 28 weeks**: When resuscitated with RA was 22% vs 6% with 100% O_2 [1]
- Intubate with 2.0 ETT for 22 weeks GA, 2.0/2.5 for 23 weeks GA[2]:
  - At birth: Invasive compared to noninvasive respiratory support in the delivery room reduces severe IVH and death at 22 to 23 weeks gestation (OR 2.20, CI, 1.07-4.51) [4]
  - ETT depth **5.5-6.0 cm** at the lip.
- Transfer to NICU with gentle bagging focused on heart rate and saturations via ETT using a PEEP of 5 cm. (SAIL Trial: significant increase in early death in the sustained inflation group 7.4% vs 1.4% in the controls with 11/16 SAIL deaths occurring in the *"23- to 24-week stratum")* [5]
- Start within 10 minutes of life on **1st Intention HFJV**
- Surfactant given within 10 minutes after initial chest radiograph
- **Minimize Hypothermia during resuscitation**: Plastic wrap (polyethylene blanket and hat), delivery room temp 25°C, trans-warmer mattress for transport

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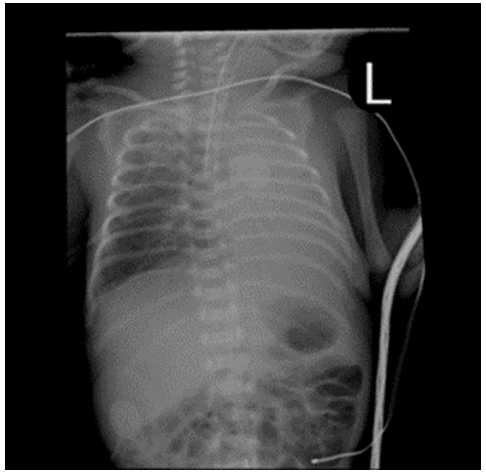
NICU Delivery Room NRP Oximeter Protocol

Time after Birth	Preductal 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%

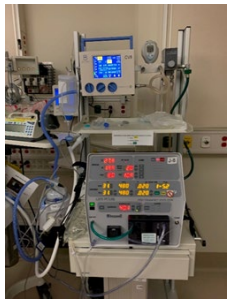
2010 AHA JM Klein 1/1/12

Not reaching ≥ 80% by 5 minutes is associated with greater risk of death/major NDD by 2 years[3]



1) *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*
2) *Berger J et al,* Survival and short-term respiratory outcomes of < 750g infants initially intubated with 2.0mm vs 2.5mm endotracheal tubes, *J Perinatol 42, 202, 2022*
3) *Oei JL et al.* Neurodevelopmental outcomes of preterm infants after randomization to initial resuscitation with lower or higher initial oxygen levels. An individual patient meta-analysis. *Arch Dis Child Fetal Neo Ed 2022.*
4) *Shukla VV et al,* Hospital and Neurodevelopmental Outcomes in Nano-Preterm Infants Receiving Invasive vs Noninvasive Ventilation at Birth, JAMA Network Open 2022;5(8):e2229105
5) Kirpalani H et al. Effect of Sustained Inflations vs Intermittent Positive Pressure Ventilation on Bronchopulmonary Dysplasia or Death Among Extremely Preterm Infants The SAIL Randomized Clinical Trial, JAMA 2019;321(12):1165-117

Use of 2.0-mm ETT in Patients < 750 g on HFJV [1]



- 2.0-mm (n=69) compared to 2.5-mm ETT (n=75)
  - 2.0 ETT patients were more premature median GA 23 vs 24 weeks and smaller median birth weight 545 vs 648 grams (smallest 2.0 ETT patient was 279 grams vs 463 grams for the 2.5)
  - 2.0 ETT patients require significantly higher Jet PIP: 27 vs 22 cm H_2O to achieve a similar pCO_2 at both day of life 1 and 7
  - Upsizing of the ETT was more frequent (56% vs 12%) in the 2.0 group but no significant difference in the median age (27 vs 24 days)
  - **Importantly, no difficulty in maintaining effective ventilation and oxygenation with a 2.0 ETT on HFJV**
- Overall survival was 77% of patients initially intubated with a 2.0-mm ETT (median BW 545 grams and GA 23 weeks), so the need for a 2.0 ETT is not a marker of viability
- 2.0 ETT also used successfully in Sweden, Japan and Cologne Germany (CV & HFOV) [2]

1) *Berger J et al,* Survival and short-term respiratory outcomes of < 750g infants initially intubated with 2.0mm vs 2.5mm endotracheal tubes. *J Perinatol 42:202-208, 2022.*
2) *Rysavy et al,* Use of 2.0-mm endotracheal tubes for periviable infants. *J Perinatol 42:1275-1276, 2022.*

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In the NICU
Standardization of Care
Golden Hour Protocol

Golden Hour Goals:

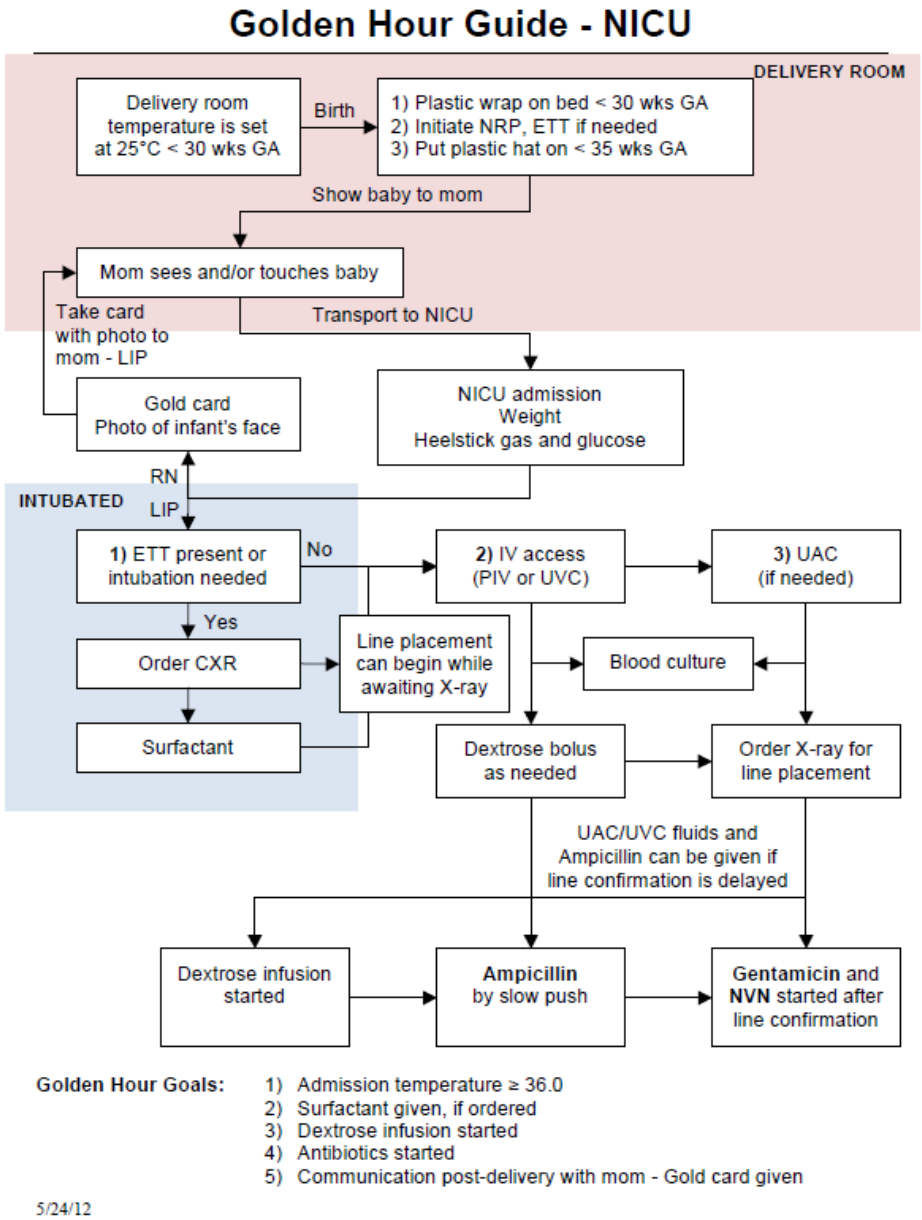
1) Admission temperature ≥ 36.0

2) Surfactant given

3) Dextrose infusion started

4) Antibiotics started

5) Communication post-delivery with mom



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In the NICU Standardization of Care: Computerized Physician Order Entry

- Order Sets

Order Sets

Order Sets

Suggestions

- ☐ BLD:NICU - Blood Products
- ☐ NICU - Acute Lab Panels
- ☐ NICU - Admission
- ☐ NICU - AKI Protocol
- ☐ NICU - Antibiotics
- ☐ NICU - Antivirals
- ☐ NICU - Cardiac Medications and Infusions
- ☐ NICU - CCHD
- ☐ NICU - Circumcision
- ☐ NICU - Continuous Drips
- ☐ NICU - Cooling/Total Body
- ☐ NICU - COVID Vaccination
- ☐ NICU - Custom IV Infusions/Boluses
- ☐ NICU - Discharge Orders
- ☐ NICU - Diuretics
- ☐ NICU - Double Volume Exchange Transfusion
- ☐ NICU - ECMO Daily Management
- ☐ NICU - ECMO Daily Management Labs Reorder
- ☐ NICU - ECMO Initiation
- ☐ NICU - Endocrine
- ☐ NICU - Extreme SGA Term Infant (<1900 gram)
- ☐ NICU - GI
- ☐ NICU - Glucose Protocol
- ☐ NICU - Heparin Line Orders
- ☐ NICU - Hypertension Work-up
- ☐ NICU - Immunizations
- ☐ NICU - Intubation Premedication
- ☐ NICU - IV Infiltrates
- ☐ NICU - Level 6 Admission
- ☐ NICU - Liver Function Tests
- ☐ NICU - Lumbar Puncture
- ☐ NICU - NAS Screening
- ☐ NICU - NEC
- ☐ NICU - Neonatal Abstinance Syndrome Orders
- ☐ NICU - Neurology
- ☐ NICU - Newborn Disorder of Sexual Differentiation Consults
- ☐ NICU - NVN and LIPIDS Orders
- ☐ NICU - Pain / Sedation Medications and Infusions
- ☐ NICU - PDA Bedside Ligation/Cardiac Catherization Closure
- ☐ NICU - Phototherapy
- ☐ NICU - PICC Insertion
- ☐ NICU - PICC/UVC Removal
- ☐ NICU - Post Operative Pain Management
- ☐ NICU - Procedural Pain and Sedation (Bedside)
- ☐ NICU - Residual Management
- ☐ NICU - Respiratory Medications
- ☐ NICU - Respiratory Orders
- ☐ NICU - ROP Procedures
- ☐ NICU - Routine Weekly Labs
- ☐ NICU - SCID
- ☐ NICU - Seizure Medications
- ☐ NICU - Sepsis
- ☐ NICU - Support Services
- ☐ NICU - Surfactant
- ☐ NICU - Torch Labs

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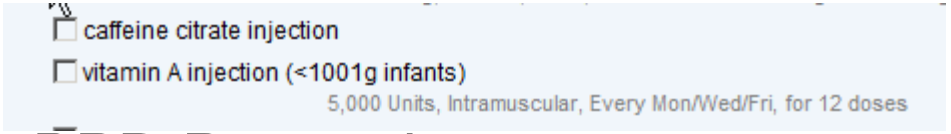
Standardization of Care: Medical Respiratory Issues

1) Admission Order Set

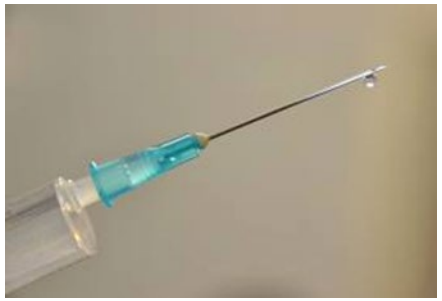


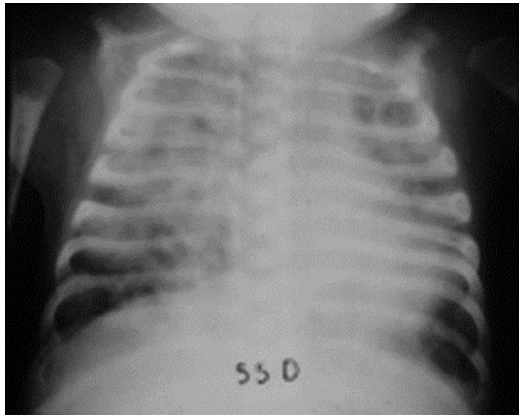
2) Caffeine for BPD Prevention

- All patients < 1250 grams; Schmidt B, (NEJM 2006, 2007), OR 0.63, CI: 0.52, 0.76, p<0.001

3) Vitamin A for BPD Prevention

- All patients < 1001 grams; Tyson JE, (NEJM 1999), [RR 0.87 (0.77, 0.98)], Use a 29/30-gauge needle





In the NICU: Standardization of Care – Paper Guidelines

Neonatal Reference Card

- Fellow Card - Original author Dan Ellsbury M.D. during Fellowship
- Topics:
  - Initial Fluids
  - Transfusion Guidelines
  - Phototherapy Guidelines for Premature Infants
  - Ventilation Goals
  - Initial Respiratory Settings: HFOV, HFJV, SIMV (PC/PS), SIMV (PRVC/PS), Nasal CPAP, NP-IMV, Noninvasive NAVA, etc…
  - Outcome Data
  - Feeding Guidelines
  - Antibiotic Dosing Guidelines
  - Cardiac Medications
  - Respiratory Medications
  - And so forth

Fellows Reference Card

NEONATAL REFERENCE CARD

Updated July 2014 BY Rabe/Klein

Bay 1 Staff #5791 Bay 1 RT #8447
Bay 1 Fellow #3792 Bay 1 Fax 353-6084
Bay 1 PL-2/Mole #4556 Bay 5 PNP #7795
Bay 2/3 NP/On-Call #5557 Lounge code 4513
NNSY PL-1 #4555 Office Xerox 2484
Transfer pager #6256
To set up a transport: Dispatch 22808/(800) 272-6440
Transport RN Pager #3210

INITIAL FLUIDS

GA	Total Fluids (ml/kg/day)	
≥34	60-70	D10 0.2 NS
30-33	70-80	
29	80-90	$D_{10}W$*
28	90-100	
27	100-120	
26	130-140	D_4W
25	140-150	
24	150	
22 - 23	200	$D_{10}W$

**D may be required w/Starter NVN, to give ≥4 mg/kg/min glucose*

UVC fluids:
Starter NVN (D10, 5% AA) for Infants < 30 weeks GA
<27 wk run at 30 ml/kg/day (1.5 g/kg/d protein, gir 2.1)
27 – 29 wk run at 60 ml/kg/day (3 g/kg/d AA, gir 4.2)
Carrier for Starter NVN (see above chart)
_____ + ¼ unit/ml heparin tra _____ ml/h

Goal blood sugar 50 – 150

UAC *SW w/40 mEq/L Na acetate + ½ (<34 wks) - ½ (≥34 wks) unit/ml heparin TRA 1.5-2 ml/h; if no UVC, can run $\frac{1}{2}D_{10}S$ in UAC)*

RAL NS + 1U/ml heparin + 120 mg/L **Papaverine** TRA 2 ml/h (If < 2 kg, use 0.5 units/ml heparin)

Keep total daily heparin <100 units/kg/day

LINES, CATHETERS AND TUBES

UVC 5 Fr OR 3.5 Fr *(<500g)*; Single, double OR triple lumen
Depth: 2/3 shoulder to umbilicus, want at RA-IVC junction
UAC 5 Fr, 3.5 Fr *(<1500g)* OR 2.8 Fr *(<500g)*; Single lumen
Depth: Shoulder to umbilicus + 1 *(PT)* - 2 cm *(T) (OR 3(kg)+9)*
want at T6-10 *(High position) (Low position: L3-4 = 3/3 S to U)*
PICC 26g/2 Fr *(<40 mln)* OR 28g *(<12 mln)*
RAL NS + 1U/ml heparin + 120 mg/L **Papaverine** TRA 2 ml/h (If < 2 kg, use 0.5 units/ml heparin)
CHEST TUBE 12 Fr *(T)*, 10 Fr *(PT*, 8 Fr *(micropremie).*
8.5 Fr pigtail
FOLEY 5 Fr *(T)* OR 5 Fr *(PT)*
MISCELLANEOUS 24g thoracentesis/bladder tap,
22g LP/pericardiocentesis, 20g paracentesis, 18g IO

SAFETY OF SPECIFIC MEDS GIVEN THROUGH UAC

Safe	*Discuss w/Staff*	*Not Recommended*
$\frac{1}{2}D_{10}S$	*$\frac{1}{2}D_{15}$*	*K >40*
Heparin	*Lipids*	*high dose Ca*
Na ≤150	*PGE1*	*Na bicarbonate*
Na acetate	*Caffeine*	*pressors*
Morphine	*Ampicillin/ Gent*	*Vancomycin*
	Cefotaxime	*Ativan*
	Fentanyl	*anticonvulsants*
	K ≤40	*Pavulon*

TRANSFUSION GUIDELINES

Hb *(g/dl)*	Considerations
< 15	ECMO with SVO_2 < 60%
<13	Ventilated on ≥70% O_2, ECMO, CHD, sepsis, NEC
<11.5	Ventilated on < 70% O_2 or NPCPAP ≥ 40% O_2
<10	NPCPAP <40% O_2 or NC 100% O_2 before surgical procedure, even if not on O_2
<8	NC < 100% or without O_2, but w/ clinical signs of anemia: excessive apnea, sustained tachycardia *(>180)* or tachypnea *(>80)*, poor growth
<7	without supplemental O_2 & clinically well

PHOTOTHERAPY: INFANTS ≥35 wks *(2004 AAP)*

Risk*	24h	36h	48h	60h	72h	4d	≥5d
Lower	11.5	13.5	15	16.5	17.5	20	21
Medium	10	11.5	13	14.5	15.5	17	18
Higher	8	9.5	11	12.5	13.5	14.5	15

12h: *Lower 9, Medium 7.5, Higher 6*
work-up: BT, DAT, CBC w/smear, D bili ± retic

EXCHANGE: INFANTS ≥35 wks *(w/failure of Intensive PRx)*

Risk*	24h	36h	48h	60h	72h	≥4d
Lower	19	21	22	23	24	25
Medium	16.5	18	19	20	21.5	22.5
Higher	15	16	17	18	18.5	19

**Lower = ≥38 wks & well*
Medium = ≥38 wks + risk factors OR 35-37 wks & well
Higher = <37 wks + risk factors (alloimmune hemolytic disease, G6PD deficiency, asphyxia, sepsis, acidosis, ↓ albumin)

PHOTOTHERAPY: INFANTS <35 wks (NEJM 2008)

BW (g)	1d	2d	3d	4d	5d	6d	7-14d
<1000	5	5	5	5	5	5	7
1000-1250	6	6	6	7	7	7	8
1250-1500	7	7	7	8	8	8	10
1500-2000	8	8	10	10	12	12	12
>2000	8	10	12	13	14	15	15

PARTIAL VOLUME EXCHANGE TRANSFUSION

$$\text{Volume (ml)} = \frac{(80 \times \text{wt (kg)}) \times (\text{Hct}_{\text{actual}} - \text{Hct}_{\text{desired}})}{\text{Hct}_{\text{actual}}}$$

Est. Blood Volume = 80 ml/kg; $\text{Hct}_{\text{desired}}$ **= 50-55%**

ET TUBE SIZES (depth = 6 + wt (kg))

Wt (g)	GA	ETT
< 500	< 24 wks / IUGR	2.0 (or 2.5)
500 – 1000	24 - 28 wks	2.5
1000 – 2000	28 – 34 wks	3.0 (or 2.5)
2000 – 3000	34 – 38 wks	3.5 (or 3.0)
> 3000	> 38 wks	3.5 (or 4.0)

VENTILATION GOALS

	pH	pCO_2	SaO_2
RDS	≥7.25	45-60	80-93% *(≤26 wks)*
BPD/ airleak	≥7.25	50-65 *(~7d)* 55-70 *(>7d)*	80-95% *(27-31 wks)* 85-98% *(≥32 wks)* ≥90% *(≥32 wks on NC)*
PPHN	≥7.40-7.55	35-50	≥90%

Note: *pCO_2 <35 ↑↑ risk of PVL, airleak; ΔpCO_2 5 = ΔpH 0.04*

INITIAL RESP SETTINGS

High-flow NC (1 – 6 lpm) *to generate CPAP 6 cm: flow (L/min) = 0.02 × 0.58 (wt in Kg)*
NPCPAP or RAM: 5-7 (RDS), 8 -14 (BPD)
NPIMV: **PIP** = PEEP + 10, **Rate** 20-40, **IT** 0.3 – 0.4
NAVA: Initial NAVA 0.4 – 2.2 cm/uv (range 0-5; wean NAVA by 0.1-0.3 per change to adjust pCO2), Back-up for apnea – rate 60, it 0.4-0.5, PIP 26 - 32, PEEP same as NPCPAP, apnea time start at 2-5 sec and increase by 5 sec intervals as apnea resolves
SIMV PC/PS: PIP = 14-24*(28)*, **PEEP** = 4-6*(8)*, **Rate** = 30-40 *(15-30 in apnea; minimal rate = 10)*, **IT** 0.4-0.5, **PS** 6-10
SIMV PRVC/PS: TV = 7-10 cc/kg, **PEEP** = 4-6*(8)*, **Rate** = 30-40 *(15-30 in apnea; minimal rate = 10)*, **IT** 0.4-0.5, **PS** 6-10
HFJV (Jet):
Initial Jet settings for pt < 1000 g for RDS
Jet PIP 22 – 24, **Jet Rate** 360 bpm **Jet IT** 20 msec
IMV PEEP 5, **IMV PIP** 8+PEEP, **Rate** 0-4, **IT** 0.4
Conversion from SIMV to JET
Set Jet PIP = SIMV PIP + (0 to 4)
Set PEEP = SIMV PEEP + 1 to 4 *(adjust to maintain MAP post-conversion)*, **Jet Rate** 420 bpm, **Jet IT** 20 msec
Conventional PIP = PEEP + 6, **Rate** 4, **IT** 0.4
Airleak Settings
↓JET Rate by 60 bpm to a low of 240 bpm as tolerated
↓Conventional rate to 0
Typical Adjustments on Jet
↑ Jet PIP by 1 - 2 ⇒ ↓ pCO_2 by 2 - 4 mmHg *(& vice versa)*
↑ Jet PIP by 2 - 4 ⇒ ↓ pCO_2 by 5 - 8 mmHg *(& vice versa)*
Jet Rate range: *240 – 660* bpm – increased rate can improve oxygenation and ventilation
↑ oxygenation by ↑ Jet PIP, Conv. PIP & PEEP by 1 -2 cm at the same time
HFOV MAP 2-4 >MAP on SIMV, **IT** 33% *(30% OR 33%)*,
Power start at 3, "↑ until shaking well" *(1-10)*, 10 **Hz** *(8-15; 15 in PT ≥2.5 kg) (settings w/airleak: minimal MAP, IT 30%, 15 Hz)*
↑ Power by 0.3 ⇒ ↓ pCO_2 by 3-5 mmHg *(& vice versa)*
↓ Hz ⇒ ↑ TV (& ↑ V_A), ↑ IT *(& vice versa)*

MAP = (PIP - PEEP) x ((Rate)(IT) ÷ 60) + PEEP
OI = (MAP)(FiO_2)(100) ÷ PaO_2 *(≥40 "80% risk of mortality")*
$AaDO_2$ = (FiO_2)(713) - PaO_2 - $PaCO_2$ *(≥500 "potential ECMO")*

PREMATURE INFANT OUTCOMES AT UICH

GA	% Survival (2006-2013)
22	48
23	71
24	88
25	90
26	90
≥ 27	>97

Long-term follow-up of infants born in 2005:
Infants < 1000 g and ≥ 24 weeks have 15% chance of impairment.*
If 23 wks gestation, 30% chance of impairment.*

*CP, blindness, deafness, or severe developmental delay.

Morbidities in Survivors <1500 grams (2004 – 2008):
9.2% with Severe IVH
6.6% with Severe ROP (≥ stage 2)
3.1% with Necrotizing Enterocolitis

SCREENING

HEAD U/S *(≤32 wks OR 1500g) Initial U/S on DOL 7; if IVH present, repeat weekly until resolves. Late U/S at 36 wks PMA to assess for PVL*

INITIAL ROP EXAM

All infants with **BW<1500g OR** all infants with gestational age ≤ **30 6/7 weeks**.
Plus, select infants 1500 to 2000 g who are ≥ 31 wks with unstable cardiorespiratory course deemed at high risk by the staff neonatologist

Timing of first exam as follows:
If ≤27 6/7 wks: at 31 wks PMA
If > 27 6/7 wks: at 4 wks of age

FEEDING GUIDELINES FOR ELBW (< 1 kg) INFANTS

- Add HMF (24 kcal/oz) when > 25 ml per day & > DOL 5
- When feed volume > 5 ml, put feeds on a pump over 1 hour until greater than 1 month of age and > 1.2 kg. May return to routine bolus feeds after this.
- For infants ≤ 1500 g, increase feeds by 10 – 15 ml/kg/d

ROUTINE CONSULTS:

- On DOL 7, consider palate plate consult if infant will likely remain intubated greater than a week.
- ENT consult prior to discharge on infants s/p PDA ligation to assess vocal cord movement

ANTIBIOTICS

Acyclovir 20 mg/kg IV Q8h over 1h
Amoxicillin 20 mg/kg QHS for UTI prophylaxis
Ampho B 1 mg/kg IV Q24h over 4h
Ampicillin 100 mg/kg/dose IV
≤29 wks PMA: Q12h *(≤28d)*, Q8h *(>28d)*
30-36 wks PMA: Q12h *(≤14d)*, Q8h *(>14d)*
37-44 wks PMA: Q12h *(≤7d)*, Q8h *(>7d)*
≥45 wks PMA: Q6h
Cefazolin 25 mg/kg IV ***(Ancef)*** *(Intervals as for* **Cefotaxime***)*
Cefepime 50 mg/kg IV Q12h OR Q8h *("meningitis interval")*
Cefotaxime 50 mg/kg IV *(hepatic metabolism)*
≤29 wks PMA: Q12h *(≤28d)*, Q8h *(>28d)*
30-36 wks PMA: Q12h *(≤14d)*, Q8h *(>14d)*
37-44 wks PMA: Q12h *(≤7d)*, Q8h *(>7d)*
≥45 wks PMA: Q6h *(Q8h:* **Ceftazidime***)*
Ceftazidime 30 mg/kg IV *(Intervals as for* **Cefotaxime***)*
Clindamycin 5-7.5 mg/kg IV
(NEC w/pneumatosis **(Metronidazole** *preferred))*
≤29 wks PMA: Q12h *(≤28d)*, Q8h *(>28d)*
30-36 wks PMA: Q12h *(≤14d)*, Q8h *(>14d)*
37-44 wks PMA: Q12h *(≤7d)*, Q8h *(>7d)*
≥45 wks PMA: Q6h
Fluconazole 12 mg/kg LD, then **6 mg/kg** IV
≤29 wks PMA: Q72h *(≤14d)*, Q48h *(>14d)*
30-36 wks PMA: Q48h *(≤14d)*, Q24h *(>14d)*
37-44 wks PMA: Q48h *(≤7d)*, Q24h *(>7d)*
≥45 wks PMA: Q24h
OR 6 mg/kg LD, then 3 mg/kg PO QD *(thrush)*
Gentamicin
√ Trough ≤ 2nd dose; *if tr > 1,* **re-√ in 12h. If <0.3, discuss with fellow/staff. If septic/bacteremic, √ peak with goal 5 -12**
≤29 wks PMA: **5 mg/kg** IV Q48h *(≤7d)*
4 mg/kg IV Q36h *(8-28d)*, Q24h *(>28d)*
30-34 wks PMA: **4.5 mg/kg** IV Q36h *(≤7d)*
4 mg/kg IV Q24h *(>7d)*
≥35 wks PMA: **4 mg/kg** IV Q24h
Metronidazole 7.5 mg/kg IV over 1h, *may load w/***15 mg/kg**
≤29 wks PMA: Q48h *(≤28d)*, Q24h *(>28d)*
30-36 wks PMA: Q24h *(≤14d)*, Q12h *(>14d)*
37-44 wks PMA: Q24h *(≤7d)*, Q12h *(>7d)*
≥45 wks PMA: Q8h
Nafcillin 50 mg/kg IV *(Intervals as for* **Zosyn***)*
Nystatin 0.5 *(PT)* - 1 ml *(T)* PO QID
Vancomycin 15 mg/kg IV over 90 minutes
Pk 25-40, **Tr 15-10** *(↑Tr & 2nd (<30 wks) OR 3rd dose (≥30 wks))*
≤29 wks PMA: Q18h *(≤14d)*, Q12h *(>14d)*
30-36 wks PMA: Q12h *(≤14d)*, Q8h *(>14d)*
37-44 wks PMA: Q12h *(≤7d)*, Q8h *(>7d)*
≥45 wks PMA: Q6h
(see Vancomycin trough guidelines for details)
Zosyn 100 mg/kg IV **(Piperacillin-Tazobactam)**
≤29 wks PMA: Q12h *(≤28d)*, Q8h *(>28d)*
30-36 wks PMA: Q12h *(≤14d)*, Q8h *(>14d)*
37-44 wks PMA: Q12h *(≤7d)*, Q8h *(>7d)*
≥45 wks PMA: Q8h *(Q6h:* **Piperacillin***)*

BLOOD PRODUCTS

Cryo 10 ml/kg IV over 1h *(fibrinogen <100)*
FFP 10 - 15 ml/kg IV over 1h *(PT > 20, PTT >100)*
pRBC 15 ml/kg over 4 hours
platelets 10 – 15 ml/kg IV over 1 hour
<100K if < 32 wks GA or < 7 days, or on Indocin
< 75K if ≥ 32 wks GA or ≥ 7 days
< 50K if term or PMA > 40 weeks

CARDIAC MEDS

Adenosine*(3mg/ml)* 0.05 mg/kg IVP, ↑ by 0.05 mg/kg Q 2 min PRN to 0.25 mg/kg
Atropine *(0.1 mg/ml)*0.02 mg/kg IV/IM, may repeat
Captopril 0.01-0.05 mg/kg PO Q8-12h *(Initial dose)*
Dobutamine drip 2 – 20 mcg/kg/min
Dopamine drip 2 – 20 mcg/kg/min
Digoxin 5 mcg/kg PO BID *(4 mcg/kg IV)*
Epinephrine **IV:** 0.1-0.3 ml/kg *(1:10,000)*
ET: 0.3-1 ml/kg *(1:10,000) (NRP 2006)*
Epinephrine drip 0.1 – 1 mcg/kg/min
Hydralazine 0.1-0.2 mg/kg IV Q4-6h PRN
Hydrocortisone 2-6 mg/kg/day IV – BID-QID
Indomethacin DOL 2 – 7: 0.2 mg/kg IV Q12h x 3 doses
>DOL 7: 1st dose 0.2 mg/kg, then 0.25 mg/kg for doses 2 & 3
(follow BUN/Cr, platelets; UOP >0.5 ml/kg/h)
Isradipine 0.1 mg/kg/day ÷ Q 8 hr
Lidocaine 1 mg/kg IV, then drip *(V-tach)*
Methylene Blue 1 mg/kg IV
Milrinone 0.5 – 1 mcg/kg/min
Neoprofen 10 mg/kg *(Initial dose)*, then *(24h later)* 5 mg/kg IV Q24h x 2 doses *(follow BUN/Cr, platelets; UOP >1 ml/kg/h; use w/caution in hyperbilirubinemia)*
Nicardipine 0.5 mcg/kg/min (initial) to 2 mcg/kg/min (adjust by 0.1-0.2mcg/kg/min)
Norepinephrine 0.05 – 0.5 mcg/kg/min drip
Propranolol 0.25 mg/kg PO Q6h OR 0.01 mg/kg IV Q6h for SVT
Prostaglandin E_1 0.02 - 0.1 mcg/kg/min
Sildenafil (Revatio)1 mg/kg PO Q6h– *do NOT give with feeds* (may ↑ to 1.5 mg/kg/dose)
Sildenafil (IV) 1.6 mg/kg/day (continuous infusion)
Vasopressin 0.1 -0.5 milli-units/kg/min

DIURETICS

Acetazolamide 5 mg/kg PO daily
Chlorothiazide 10-40 mg/kg/day PO ÷ BID
5-20 mg/kg/day IV ÷ BID
Lasix 1-2 mg/kg IV *(OR drip 0.1-0.4 mg/kg/h)*
Metolazone 0.2-0.4 mg/kg/day PO QD or ÷ BID
Spironolactone 1-3 mg/kg/day PO QD or ÷ BID

NRP MEDS

Epinephrine **IV:** 0.1-0.3 ml/kg *(1:10,000)*
ET: 0.3-1 ml/kg *(1:10,000) (NRP 2006)*
Narcan 0.1 mg/kg *(0.1ml/kg)* IV/IM/ET

PAIN / SEDATION MEDS

Ativan 0.05-0.1 mg/kg IV Q1-2h PRN
Dexmedetomidine 0.2 – 1.2 mcg/kg/hr
Fentanyl 2-5 mcg/kg IV Q1h PRN
Ibuprofen 5-10 mg/kg PO Q6-8h
Morphine drip 10 - 50 mcg/kg/h
Morphine 0.05-0.1 mg/kg IV Q1h PRN
Rocuronium 0.5-1 mg/kg IV Q1h PRN
Tylenol 10-15 mg/kg PO *(15-30 PR)* Q6h PRN
Tylenol (IV) > 39 wks, 1-28 days: 7.5 mg/kg Q6h
>43 wks, 29 d-1yr: 10-12.5 mg/kgQ6h
Vecuronium 0.1 mg/kg IV Q1h PRN
Vecuronium drip 0.05 - 0.1 mg/kg/h

RESPIRATORY MEDS

Azithromycin 5 mg/kg PO BID x 7 d, then 5 mg/kg PO QD x 5 wks
Bosentan 1 mg/kg PO Q12h
Caffeine citrate 20 mg/kg LD, then 5-7 (6) mg/kg IV/PO QD
Convert to PO when ≥ 30ml/kg feeds
Dexamethasone 0.1-0.25 mg/kg IV/PO Q12h x 6 doses *(follow BG, TG, CXR BID)*
Duoneb 1.5 ml Q 12 (inhaled)
Inhaled NO **Term:** 20 ppm, wean by 2 – 5 ppm Q12/24, until 1 -2 ppm then off
Preterm: 20 ppm (2-4 days), then 10 (x1 wk), 5 (x 1 wk), 2 (x1 Wk), then off (NEJM 2006)
Prednisone 2 mg/kg IV/PO BID x 5d
Pulmicort 0.25 mg INH BID
Q-VAR (40 MCG) 1 - 2 puffs BID
Theophylline 5-6 mg/kg LD, then 2 mg/kg IV/PO Q8h *(Pk 5-15 (A), 10-20 (BPD))* *(1 mg/kg LD will ↑ level by 2)*

SURFACTANTS

Survanta *(beractant)* 4 ml/kg ET in 4 aliquots *(<700g)*
Curosurf *(poractant)* 2.5 ml/kg ET in 2 aliquots *(≤700g)*, give 1.25 ml/kg *for repeat doses.*
Infasurf *(calfactant)* 3 ml/kg ET in 2 aliquots

OTHER COMMON NICU MEDS

ADEKs 1 ml PO QD
Afrin *(0.025%)* 2 gtts/nare BID x 3d
5% Albumin 10 ml/kg IV over 1h
25% Albumin 4 ml/kg *(1g/kg)* over 4h
Amicar 100 mg/kg over 1 hr as load, then 25 mg/kg/hr x4 hr, extend as needed
Bicitra PO, dose varies *(1 ml = 1mEq Na citrate)*
Calcium chloride 20 mg/kg IV over 30-60 min
Calcium gluconate 100 mg/kg IV over 30-60 min *(preferred)*
Cyclomydril 1 gtt OU Q 5 min x 2, 1h ā ROP exam
D_5W 2 ml/kg IVP, then 8 mg/kg/min
Elemental Fe 3-6 mg/kg elemental Fe PO QD
Factor VIIa (Novo-7) 90 mcg/kg IV *(refractory PT/bleeding)* , may repeat every 2h until hemostasis achieved
Famotidine 0.5 mg/kg IV QD
Fosphenytoin 15-20 mg PE/kg LD over 10 min
G-CSF 10 mcg/kg SQ QD x1, then recheck
HBIG 0.5 ml IM within 12 hrs of birth
Heparin flushes if ≤ 1kg: 0.5ml of 1 U hep/ml q8h & prn
if > 1kg: 0.5ml of 10 U hep/ml q8h & prn
Keep total daily heparin <100 units/kg/day
Heparin 100 units/kg load, then drip range 25 – 125 units/kg/hour, adjust per ACT values on ECMO
Hyaluronidase (Vitrase) 15 units/ml, as SC injections, give as 0.2 ml for 5 injections around site of extravasation, may use up to 24 hr out
IVIG 500 mg/kg IV over 3h
Kayexalate 1 g/kg PR *(K>5.5-7)*
Na bicarbonate 1-2 mEq/kg IV over 1h *(OR 0.3(kg)(BD))*
NaCl ≥0.5 mEq/kg PO QID
Narcan 0.1 mg/kg *(0.1ml/kg)* IM/IV/ET
Normal Saline 10 ml/kg IV over 1h
Omeprazole 0.5 – 1 mg/kg/day daily or divided BID
Phenobarbital 20 mg/kg LD over 15-20 min, then 3-5 mg/kg/day IV/PO ÷ BID **(level 20-40)**
Phentolamine (for DA infiltrate) 0.1 – 0.2 mg/kg (max 5 mg) into existing IV or SC inj into affected area (typical amount 1-5 mg)
Polycitra PO; *(1 ml = 1mEq Na & K, 2mEq citrate)*
Polycitra K PO, dose varies *(1 ml = 2mEq K, 2mEq citrate)*
Potassium bolus 0.5 mEq/kg IV over 1 hour for K < 2.5, discuss with fellow prior to ordering!
Reglan 0.1 mg/kg PO/IV Q8H
Synagis 15 mg/kg IM *(Qm (from 10/31 to 3/31) to inpatients ≤28 wks (≤28d) or w/severe CLD)*
Tri-Vi-Sol 1ml PO Daily
TobraDex 2 gtts/nare Q 8 hr x 5 days
Ursodiol 10-15 mg/kg PO Q12h
Vitamin A 5000 IU IM MWF x 12 doses (BW ≤ 1 kg)
Vitamin E 30 IU/kg in 2 ml SW NG *(~1250g)*
Vitamin K 0.5 *(<1500g)* - 1 mg *(≥1500g)* IM/SQ (IV)

INTUBATION PREMEDICATION

1. Morphine 0.05 - 0.1 mg/kg IV (if ≤ 1.5 kg use 0.05)
2. Ativan 0.05 - 0.1 mg/kg IV (if ≤ 1.5 kg use 0.05)
Wait 5 – 10 minutes, then
3. Atropine 0.02 mg/kg IV, *(0.1 mg/ml)*

REPLACEMENT FLUIDS

Replace losses > 30 ml/kg/day (10 ml/kg/8 hour shift)
VL output: ½ NS + 30 meq/L KCl
Ostomy output: NS + 20 meq/L KCl

PDA LIGATION ORDERS

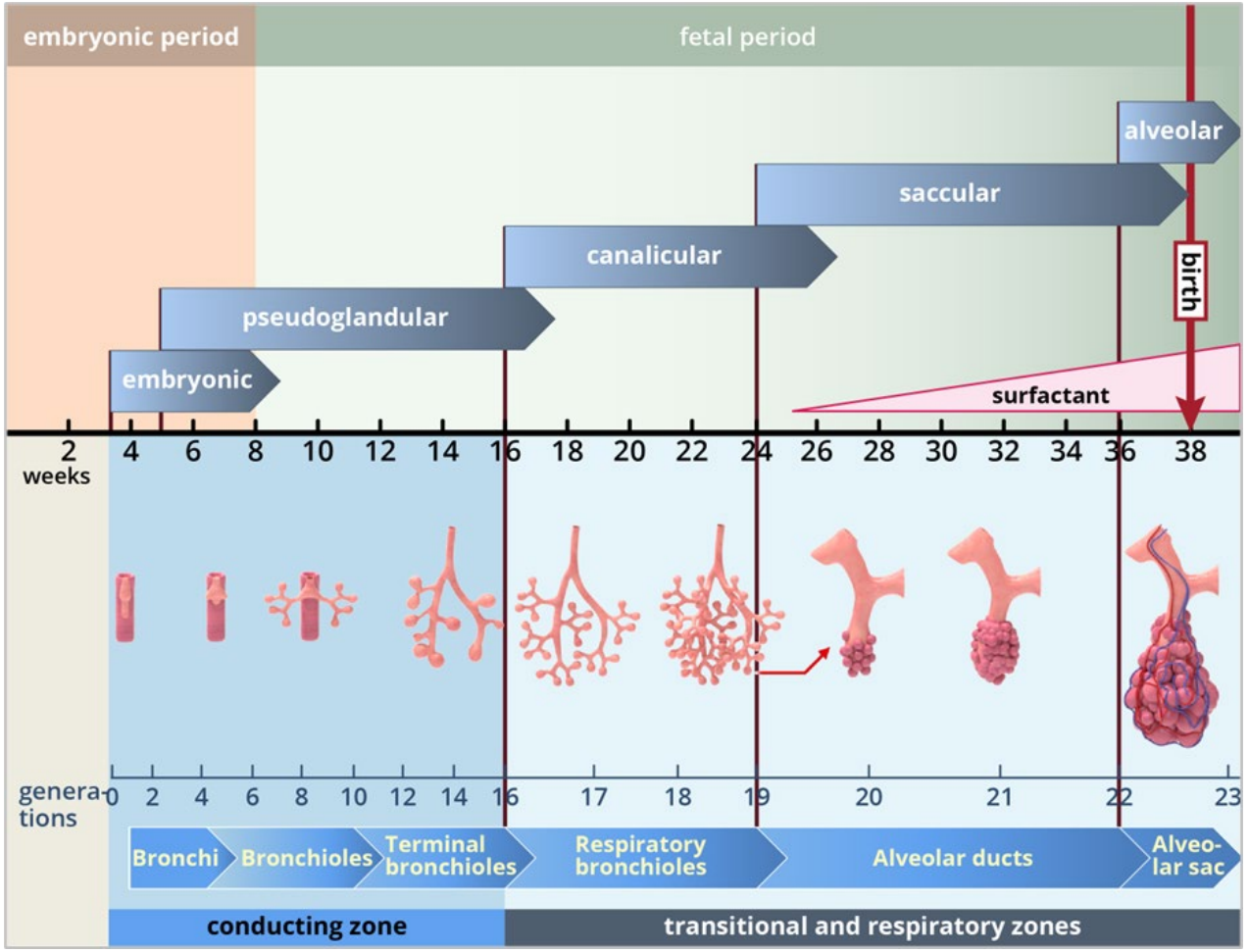
Write orders day before surgery
NPO at 24:00; Check platelet count by 06:00 on day of surgery, transfuse platelets if < 100K
Hydrocortisone 1 mg/kg IV Q 6h (wean over 48 to 72 h) – start at 0600 on day of surgery
Peri-operative antibiotic coverage: **Gentamicin, Zosyn, and Vancomycin**
To have at bedside for surgery:
Vecuronium 0.1 mg/kg IV x 4 doses
Fentanyl 5- 10 mcg/kg IV x 4 doses
Ativan 0.1 mg/kg IV x 4 doses
Morphine drip to start at 10 mcg/kg/h in preop
Dopamine drip at 2 mcg/kg/min to be in line prior to surgery
pRBCs 1 unit that is typed and crossed, in cooler @ bedside
To avoid fire, stop O2 flow in resus bag when draping
Pre- and post- oximeters during surgery

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

- **Terminal bronchioles branch to Respiratory bronchioles which branch to Alveolar ducts which terminate at the tip into an Alveolar Sac** (thin wall + vascularized) beginning at 24-27 weeks, importantly cranial segments mature faster than caudal segments so you can have areas of the lung mature enough for gas exchange even at 22 weeks gestation if you 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 !



Standardization of Care - Ventilator Issues
Developmental Pathophysiology Framework

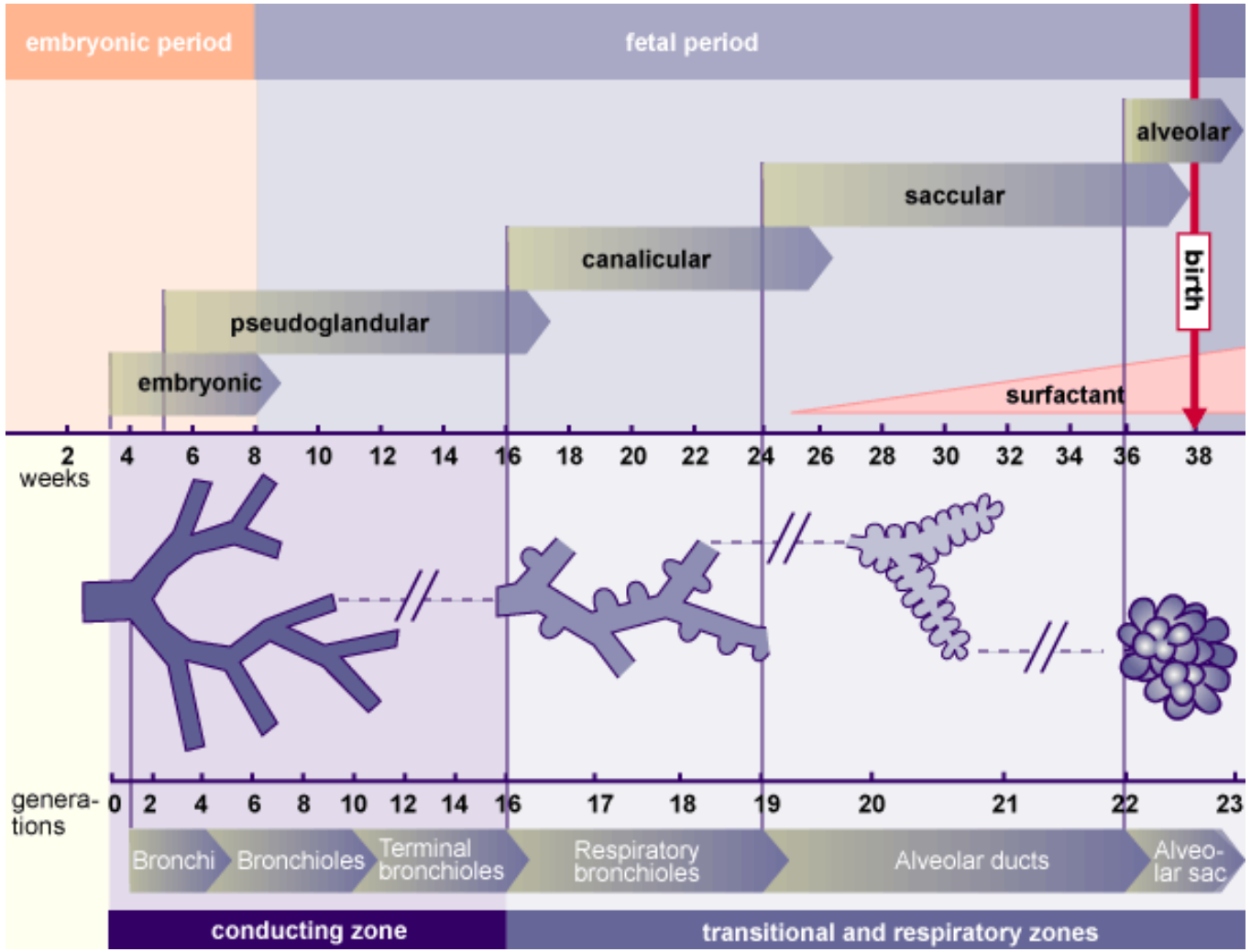
University of Iowa Stead Family Children's Hospital

Prime Directive: Focus on a **Lung Protective Strategy** to reduce the risk of **PIE** and **Pneumothorax** at the canalicular stage of lung development with HFV

1) At the **canalicular stage** of lung development (< 24-26 weeks gestation) it is critically important to avoid shear force injury, primarily PIE (volutrauma)

2) Iowa is a **1st Intention HFV** Center - NICU Difference

✓ **First Intention High Frequency Jet Ventilation** is used for all infants < 27 weeks GA 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.

Importance of PIE Prevention for the < 24-week GA

- Pulmonary Interstitial Emphysema (PIE) is a collection of gases outside the conducting and gas exchanging airways which obstructs both pulmonary blood flow and ventilation and often develops with 48 hours of life.
- PIE has high mortality and morbidity associated with earlier chronological age, lower birth weight and lower GA [1].
- In the pre-surfactant era, mortality was > 60% if conventional PIP reached > 25 cm H_2O at any time during the first 2 weeks of life for VLBW infants [1].

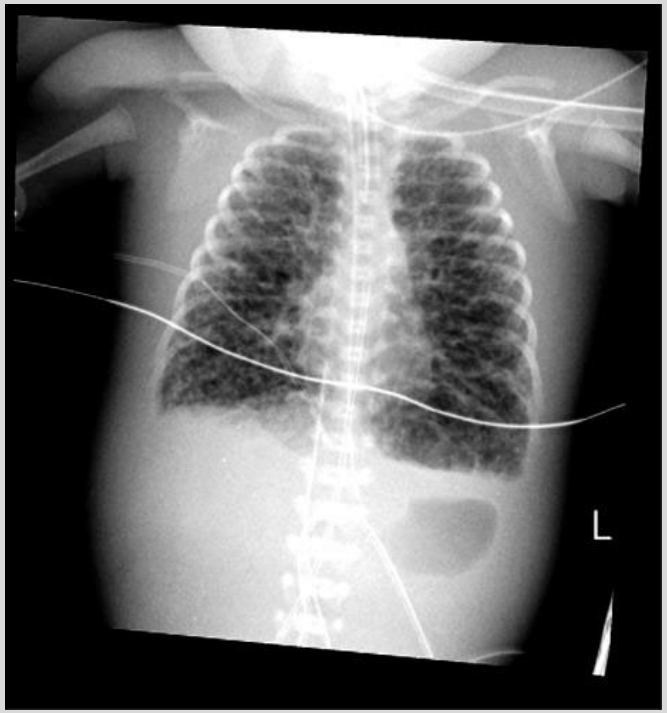


TABLE 3. Outcome for 55 Infants with Birth Weight Less Than 1,500 Grams*

	Died [N = 35 (64%)]	Survived [N = 20 (36%)]	*P*
Birth weight (g)†	971 ± 240	1,162 ± 191	<.004
Gestational age (wk)†	27.6 ± 1.8	29.0 ± 1.8	<.003
Day pulmonary interstitial emphysema (PIE) developed‡	1.4 ± 0.8	2.0 ± 1.1	<.030
PIE day 1§	27 (77%)	9 (45%)	<.050

* Values are means ± SD.
† Student's *t* test.
‡ Mann-Whitney test.
§ χ^2 analysis.

1) Gaylord MS et al, Predicting Mortality in Low-Birth-Infants with Pulmonary Interstitial Emphysema. Pediatrics 1985;76:219-224

Global Ventilator Approach for Infants born < 24 weeks gestation

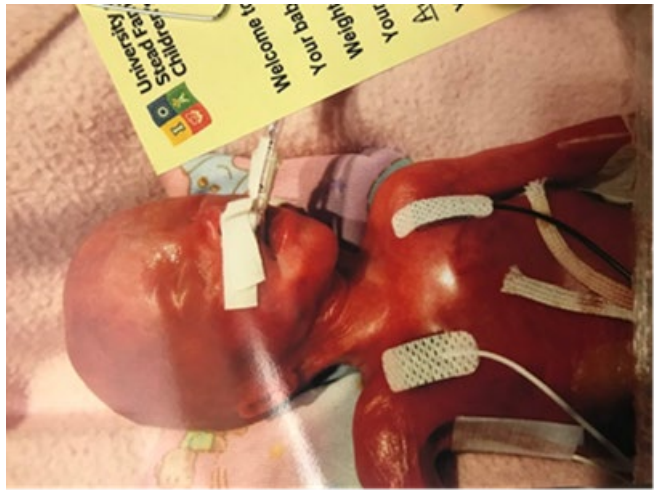
- ✓ Follow pCO_2 levels closely with **rigid adherence** to goals to avoid fluctuations in Cerebral Blood Flow – **neuroprotective** focus
- ✓ Proactive use of **First Intention Low Tidal Volume strategies (lung protective focus)** whether HFJV, HFOV or low tidal volume targeted conventional devices with early rescue with HFV being available [1]
- ✓ Use of 2.0 ETT electively at 22 weeks gestation [1]
- ✓ Avoidance of overdistention (**neuroprotective focus)** with oversight from experienced faculty [1]
  - Focus on prevention of pulmonary interstitial emphysema (PIE) due to high mortality with PIE [2]
- ✓ Extubate when ready for success not failure.
- ✓ Consistent ventilator and respiratory strategy for all 22-week gestation infants, there should not be random variation in respiratory management styles depending on the whim of the Neonatologist.
- ✓ Oxygen Saturation targets based on PMA to minimize ROP and use alarms for emergencies to avoid alarm fatigue; not for targeting [3]

1) Sindelar R, Nakanishi H, Stanford AH, Colaizy TT, *Klein JM*. Respiratory management for extremely premature infants born at 22 to 23 weeks of gestation in proactive centers in Sweden, Japan, and USA. *Semin Perinatol* 2022; 46:151540. doi: 10.1016/j.semperi.2021.151540.
2) Gaylord MS et al, Predicting Mortality in Low-Birth-Infants with Pulmonary Interstitial Emphysema. Pediatrics 1985;76:219-224
3) Colaizy TT, Longmuir S, Abramoff MD, Klein JM. Use of a supplemental oxygen protocol to suppress progression of retinopathy of prematurity. Invest Ophthalmol Vis Sci 58:887-891, 2017.

Respiratory management for extremely premature infants born at 22 to 23 weeks of gestation in proactive centers in Sweden, Japan, and USA

Semin Perinatol 2022; 46:151540. doi: 10.1016/j.semperi.2021.151540.

Richard Sindelar[a,], Hidehiko Nakanishi[b], Amy H. Stanford[c], Tarah T. Colaizy[c], and Jonathan M. Klein[c]*



22 1/7 Weeks Gestation

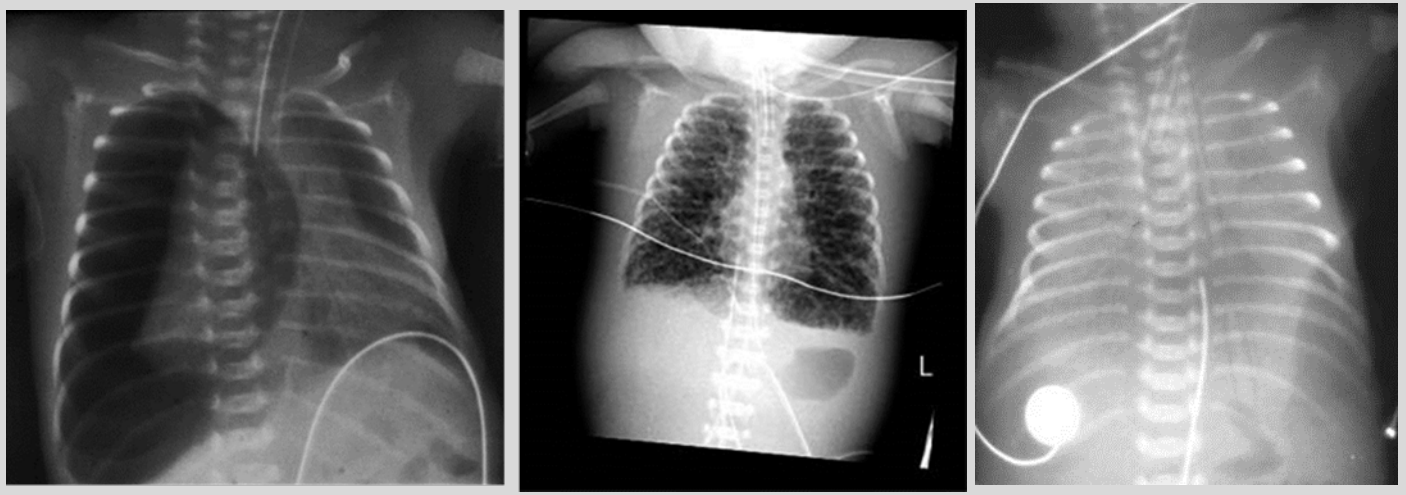
Table 2 – Ventilatory Strategies for Infants Born at 22-24 weeks Gestation Across 3 International Centers

Center	Uppsala University, Uppsala, Sweden	University of Iowa, Iowa City, United States	Kitasato University, Kanagawa, Japan
Prenatal management	Antenatal Steroids	Antenatal Steroids	Antenatal Steroids
Delivery room management	Intubate immediately with 2.0 ETT and place on ventilator. Transfer to NICU on ventilator. ETT depth 5.5 cm at lip.	Bag mask ventilation trial for <30 seconds, then intubate with 2.0 ETT. Transfer to NICU with bagging via ETT. ETT depth 5.5-6.0 cm at lip.	Intubate with 2.0 ETT and placed on conventional ventilation. ETT depth 5.5-6.0 cm at lip.
Initial mode of ventilation	Synchronized intermittent ventilation with volume guarantee (VG), then switched to assist control with pressure support ventilation with VG.	First intention high frequency jet ventilation on admission, sigh breaths (4 per minute) added later if needed for atelectasis or desaturation spells.	Converted to high frequency oscillator ventilation with volume guarantee depending on cardiac function, sustained inflation (sigh breaths 3 per minute) regularly used.
Strategic Goals	Minimize volutrauma and overdistention with oversight from experienced faculty	Minimize volutrauma and overdistention with oversight from experienced faculty	Minimize volutrauma and overdistention with oversight from experienced faculty
Initial Target Saturation Limits	85-90%	84-93%	90-95%
Initial pCO_2 Goals	37-52 mmHg (5-7 kPa)	45-60 mmHg (6-8 kPa)	50-60 mmHg (6.7-8 kPa)
Surfactant Administration	Instilled immediately in delivery room	Instilled within the first hour of life in the NICU after radiographic confirmation of ETT position	Instilled in the NICU within six hours of life with radiographic confirmation of ETT position

Anti-Volutrauma Approach with High Frequency Jet Ventilation (HFJV) to Prevent and Treat Pulmonary Air Leaks

HFJV

1) Increases healing of PIE [1]
2) Reduces incidence of air-leaks [2]
3) Improves survival of neonates with pneumothorax or PIE [3]
4) Reduced the incidence of BPD in half for infants with RDS treated with surfactant [4]
5) For neonates ≤26 weeks GA with OI >5, HFJV vs VTV significantly reduced the incidence of Grade 3 BPD (OR 0.21, 95% CI 0.05–0.92) adjusted for GA, BW, A-a grad [5]



1) Gonzalez F, et al. Decreased gas flow through pneumothoraces in neonates receiving high-frequency jet versus conventional ventilation. J Pediatr 1987;110:464-466
2) Spitzer AR, et al. Ventilatory response to combined high frequency jet ventilation and conventional mechanical ventilation for the rescue treatment of severe neonatal lung disease. Pediatr Pulmonol 1989;7:244-250
3) Keszler M, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr 1991;119:85-93.
4) Keszler M, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics 1997;100 (4):593-599*
5) Rallis D, et al. Single center experience with first-intention high-frequency jet ventilation vs. volume-targeted ventilation in extremely preterm neonates. Front. Pediatr. 11:1326668. 2024. doi: 10.3389/fped.2023.1326668

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HIGH FREQUENCY VENTILATION REMAINS CONTROVERSIAL

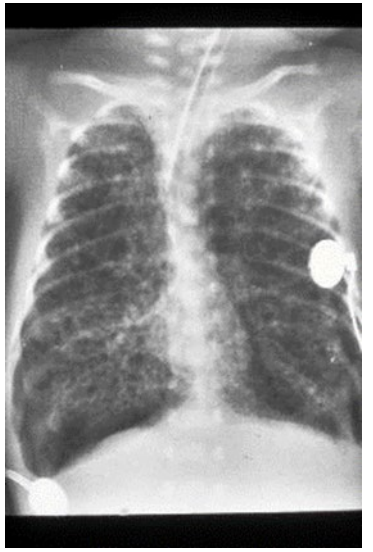
Just remember, *it's the **carpenter**, not the **hammer***

- *"Although the tools we use to support gas exchange are important, so are the **expertise** and **training** of the **"carpenters"** that use them."*
- *"Without evidence-based, physiologically targeted **strategies**, our tools for supporting gas exchange can promote injury instead of improving the quality of the lives we save ." (Reese Clark)[1]*

(1) Both the tool and the carpenter are important. Clark RH, J Pediatr. 1997 Dec;131(6):796-8.

High Frequency Jet Settings for 1st Intention Use for RDS [1,2]

- **Initial Jet Rate**:
  - **< 24 weeks GA: Start at 300 BPM (I:E of 1:9)**
  - At a lower rate, more time is spent in exhalation with a fixed IT which decreases air trapping from passive elastic recoil
  - Rate can be increased as needed after a few weeks as lung develops to improve oxygenation and ventilation
- Inspiratory Time - 0.02 seconds (20 milliseconds) for 1st Intention to reduce volutrauma
- Goal is to avoid air trapping leading to **PIE**, hyperinflation, overdistention, and minimize hypocarbia
- Lower rates decrease alveolar ventilation minimizing hypocarbia.
- No sigh breaths initially
- **Initial PIP** for 1st Intention Use
  - Start at @ 22-24 cm H_2O *Good Chest Wall Shake*, adjust based on pCO_2
  - **Tidal Volume** is proportional to Delta P (PIP-PEEP)
- **Initial PEEP** for **First Intention Use** for RDS:
  - Start at **5 cm** H_2O in the Antenatal Steroid and improved Surfactant era
  - ➢ To avoid mechanical injury to the extremely immature lung from hyperinflation – **Lung Protective Strategy**
  - ➢ To avoid impeding venous return – **Neuroprotective Strategy**

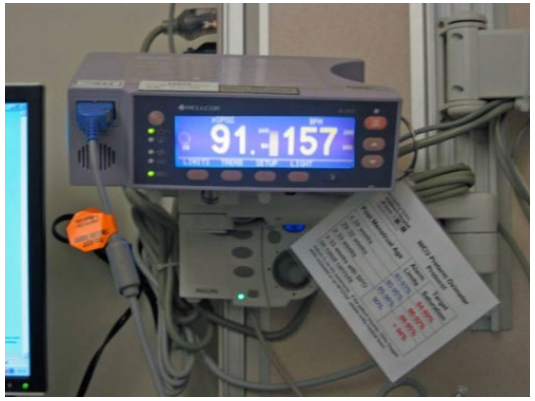


1) Elgin TG, Stanford AH, Klein JM, First intention high-frequency jet ventilation for periviable infants. *Curr Opin Pediatr* 2022 Apr 1;34(2):165-169.
2) Sindelar R, Nakanishi H, Stanford AH, Colaizy TT, *Klein JM*. Respiratory management for extremely premature infants born at 22 to 23 weeks of gestation in proactive centers in Sweden, Japan, and USA. *Semin Perinatol* 2022; 46:151540. doi: 10.1016/j.semperi.2021.151540.

Standardized and Balanced Ventilator Goals

1st Intention HFJV for all infants 22-24 weeks GA

1. Follow pCO_2 levels closely with **rigid adherence** to goals to avoid fluctuations in Cerebral Blood Flow – neuroprotective focus **outweighs** lung protection avoid both hypocarbia as well as hypercarbia
   a) Target 45 - 55 first 3 days
   b) Target 45 - 60 next 4 days
   c) Gases Q3-6 hours in the first few days
   d) After ventilator change, repeat in 20 minutes



2. Oxygen Saturation Issues
   a) Standardized Targets, Alarms and Responses
   b) Based on Post Menstrual Age [1]
   c) Transparency - Card attached at every bedside

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NICU Preterm Oximeter Protocol

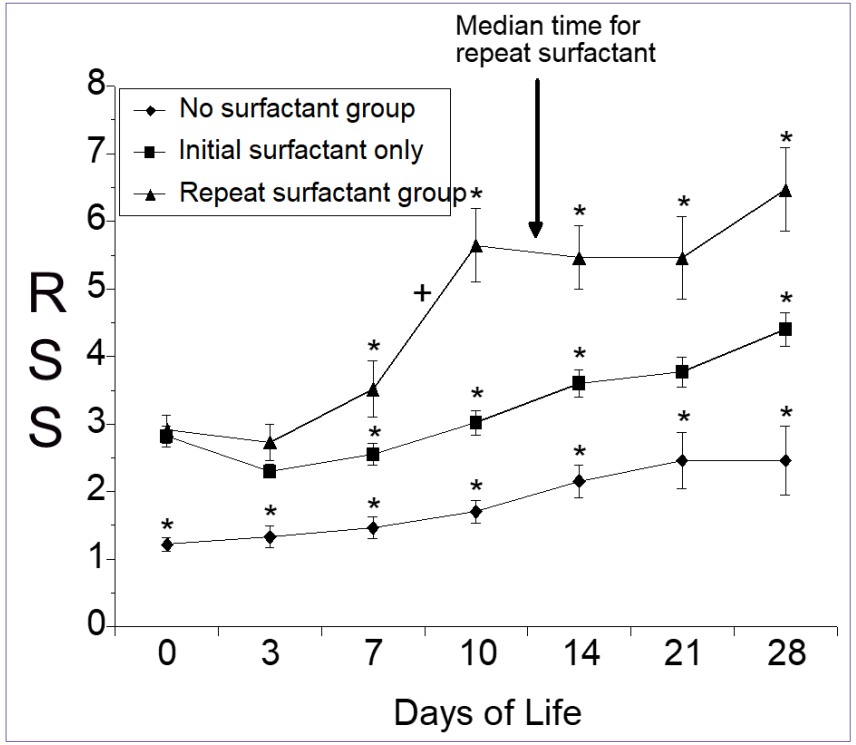
Post Menstrual Age	Alarm Limits	Target Saturation
≤ 26 weeks	80 - 93%	84 - 93%
27 - 31 weeks	80 - 95%	86 - 94%
≥ 32 weeks	85 - 98%	90 - 95%
≥ 32 wks on RA or on nasal cannula ≤ 1 LPM	90%	> 94%

Adjust O_2 by 5% increments. If the patient requires > 70% O_2 on Nasal CPAP or while intubated, please notify medical team. If high alarming on 21% O_2 may change upper alarm limit with order. 4/06, 11/08, 5/13.

1. Colaizy TT, Longmuir S, Abramoff MD, *Klein JM*. Use of a supplemental oxygen protocol to suppress progression of retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 58:887-891, 2017.

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

- PSS is the lack of endogenous surfactant production
- 20% of Infants <1000 g with RDS develop post-surfactant slump after DOL 6
- 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[2] as well as sepsis/pneumonia and atelectatrauma leading to surfactant dysfunction and inactivation



RSS (respiratory severity score):
FiO2 x MAP (mean airway pressure).

1. Katz LA, Klein JM. Repeat Surfactant Therapy for Post-Surfactant Slump *J Perinatol.* 2006;26(7):414-22.
2. Beauchene MS et al. Patent Ductus Arteriosus (PDA) and Response to Late Surfactant Treatment in Premature Infants, *J Perinatol.* 2023;43(10):1245-1251

Failing Extubation in the first 2 weeks of life for premature infants 24 0/7 to 27 6/7 weeks gestation increases all the following except for?

Chawla S et al. J Pediatr. 2017;189:113-9

1) Severe IVH (III/IV)
2) Death
3) BPD
4) PDA
5) Late Onset Sepsis

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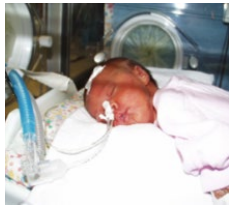
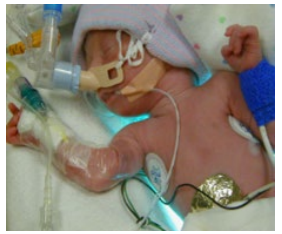


NICU Difference: Standardized Balanced Approach to Extubation for Infants Born at 22-23 weeks' Gestation



1) Minimize the risks of atelectatrauma and apnea leading to failure
   - Failed extubation even for the more mature 24-26 weeks' gestation premature infant is associated with poor outcomes
     - Failure in first 2 weeks of life at < 28 weeks GA (mean 25.8 weeks) is significantly associated with increased death before discharge **28% vs 6%** as well as an increased incidence of BPD, late onset sepsis and severe IVH even after adjustment for multiple variables (GA, SGA, 5-minute Apgar score, …) [1]
     - Failed extubation in the first 12 days of life for infants with a median GA of 25.5 weeks led to a significant setback in respiratory status with ventilator parameters and blood gas values significantly worse compared to pre-extubation, even 72 hours after reintubation [2]
     - Apex cohort (n=250 infants < 1250 g). Early failure infants (< 8 days of life) had a significantly greater risk of death (median 26.3 weeks). 22-week GA excluded and 100% extubation failure rate at 23 weeks gestation [3]
   - Minimize multiple failure attempts
   - Extubate "**when ready**" to have a sustainable respiratory drive, ***"don't push them off!"***
2) Optimize Post-Extubation Respiratory Support
   - Compared to nasal CPAP, noninvasive ventilation decreases rates of extubation failure and BPD [4]
   - One approach is to extubate directly to NAVA for noninvasive ventilation (> 850-900 grams) [5]

1) *Chawla S et al. Markers of Successful Extubation in Extremely Preterm Infants and Morbidity After Failed Extubation. J Pediatr 2017;189:113-9*
2) *Gupta D et al. Pediatric Pulmonology 2021; E pub DOI: 10.1002/ppul.25387*
3) *Shalish W, et al. Age at First Extubation Attempt and Death or Respiratory Morbidities in Extremely Preterm Infants. J Pediatr 2022 Aug 24:S0022-3476(22)00760-0.*
4) *Ramanathan R et al. J Perinatology 2012;32:336-343*
5) *Colaizy et al. Am J Perinatol 2017;34:593-598*

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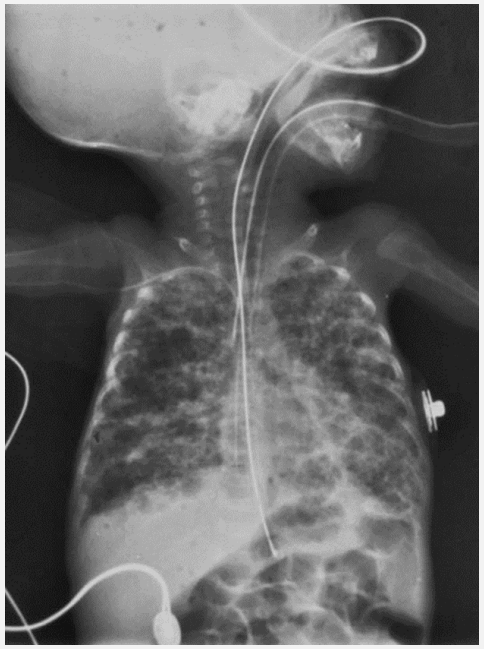
Goal of 1st Intention HFJV Is to Avoid Lethal BPD [Grade III(A)][1] and Minimize Grade 3 BPD - Invasive Respiratory Support at 36 weeks PMA[2]



- **Diagnosis of Grade 3 BPD [2]**
  - "twofold higher rate of late death, serious respiratory morbidity, and moderate to severe neurodevelopmental impairment … strongly supports the distinct classification of these infants… "
  - Serious respiratory morbidity: tracheostomy, supplemental oxygen for >2 years, …
  - Infants with Grade 3 BPD, 2018 VON data: 18% required tracheostomy vs 0.8 % with Grade 1-2 [3]

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

Thus, 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

1) Bronchopulmonary dysplasia: executive summary of a workshop. Higgins R, Jobe A, Koso-Thomas M, et al. *J Pediatr*. 2018;197:300-308
2) Jensen EA, Dysart K, Gantz MG, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. *Am J Respir Crit Care Med*. 2019;200(6):751-759.
3) Jensen EA, Edwards EM, Greenberg LT, et al. Severity of Bronchopulmonary Dysplasia Among Very Preterm Infants in the United States. *Pediatrics.* 2021; 148(1): e2020030007.

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)

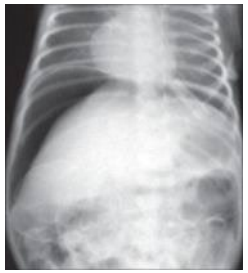
Supplemental Oxygen at 18-22 months corrected age-17% [1]

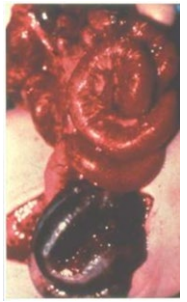
517 grams twin
22 6/7 weeks
AGA 29%

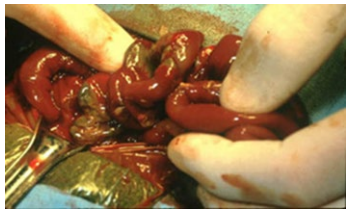
*31 weeks PMA age at extubation was the same as the APEX cohort PMA 31.3 weeks (IQR 29.8-32.1) for infants extubated at > 35 days of life and 22-week GA infants were excluded from the APEX cohort. Median GA 24.1 (IQR 23.8-24.9) [3]

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.

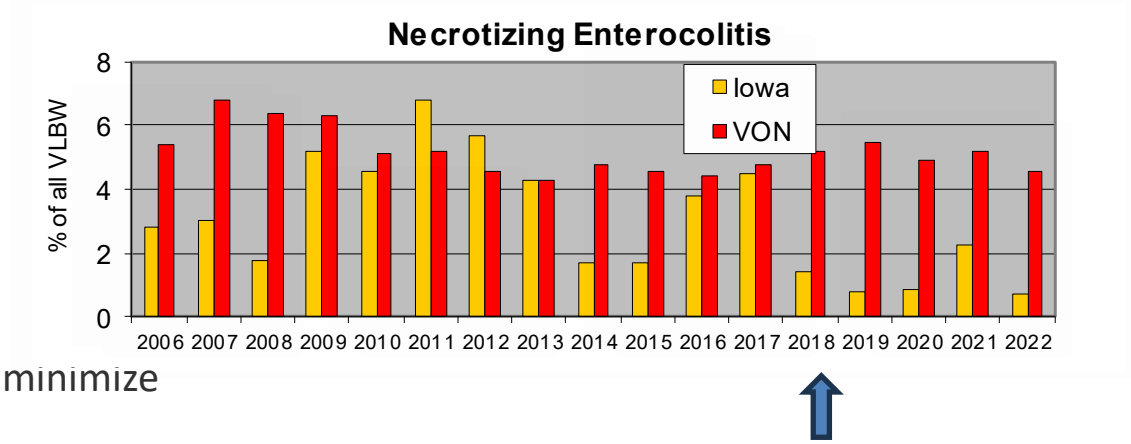
Gut Protective Strategies: Minimize the Incidence of Spontaneous/Focal Intestinal Perforation (SIP/FIP) and Necrotizing Enterocolitis (NEC)





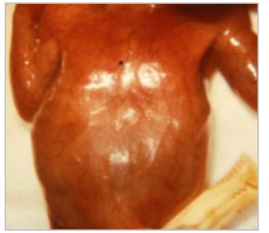


1. Avoid Prophylactic Indomethacin:
   - 5% incidence of SIP with early Indomethacin alone
   - 19% incidence of SIP with the combination of Indomethacin plus Dexamethasone in ELBW patients (Stark AR et al, *NEJM* 2001 Jan 11; 344(2):95)
   - Hydrocortisone alone was not associated with an increase in 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)
   - Abdi HH, et al. "Our investigation [22-28 weeks] detected no protective benefit of PI treatment …The risks of treating all eligible infants with PI may exceed potential benefits…there remains no clear evidence that PI … improves the long-term outcomes of most extremely preterm infants " J Perinatology. 2021;41:749-755.
   - **Avoid the combination of indomethacin and steroids**
   - Address the PDA using a Targeted Neonatal Echocardiographic Hemodynamics Approach[1]
2. Minimize NEC and focal intestinal perforation:
   - Early trophic feeds (10 ml/kg/day) within 24–36 hours
   - Maternal breast milk or donor
   - Advance very slowly 10–12 ml/kg/day only if tolerating
   - Give bolus feeds by pump over 1 hour when > 4 ml
   - Probiotics (not supported by the FDA)
   - Early detection of meconium obstruction of prematurity [2] to avoid or minimize meconium related ileus/intestinal injury



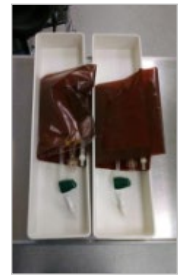
1. Giesinger RE et al, Seminars in Perinatology. Mar;47(2):1517212023.
2. Siddiqui MMF, et al. Arch Dis Child Fetal Neonatal Ed. 2012;97:F147-F150.

Standardized TPN Strategies
Priority to Minimize Hyperglycemia and Hyperlipidemia



1. 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 but with acetate, TPN at 80-100 ml per kg/day for optimal protein, calcium, phosphorus and D2.5 W carrier fluid
   - Ambient or minimal humidification to **accelerate keratinization** [1]
   - Strict regulation of fluids
   - 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

2. 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 TPN cholestasis
   - **Mortality rate** (pulmonary hemorrhage) increased significantly in 600 to 800 gm infants receiving Intralipid at <12 hours of life vs controls (24% to 48%, p = 0.032) [2]

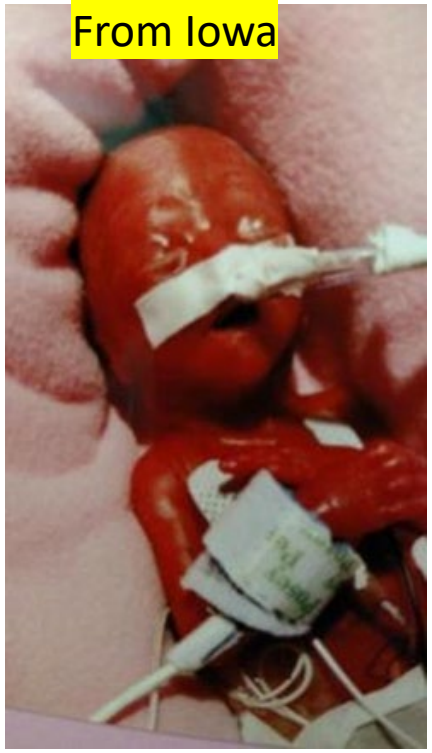


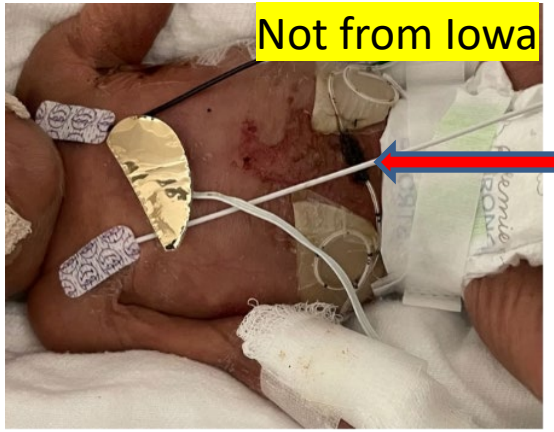
3. Goal NVN protein 3.5 - 4.0 gm/kg/day, starter TPN at birth (1.5 gm/kg)
4. Photoprotection of TPN [3]
   - Shielding Parenteral Nutrition from Light Improves Survival Rate in Premature Infants
   - Premature Infants - minimal antioxidant defenses. TPN when light exposed generates hydrogen peroxide and other oxidants leading to free radical cellular damage associated with increased mortality

1. Ågren J et al. Ambient humidity influences the rate of skin barrier maturation in extremely preterm infants. *J Pediatr. 2006;148:613-7*
2. Sosenko IR et al. Effect of early initiation of intravenous lipid administration on the incidence and severity of chronic lung disease in premature infants. *J Pediatr.* 1993;123:975
3. Chessex P, et al. Shielding parenteral nutrition from light improves survival rate in premature infants, *JPEN J Parenter Enteral Nutr.* 2017;41:378-383.

Skin Care for Periviable Infants (< 24 weeks GA)

Skin Care for 22- and 23-week Gestation Infants





- **Brief Highlights – Iowa Approach**

1. May take weeks for the stratum corneum to provide effective protection.
2. **Reposition Q3-4 hours** with use of approved supportive positioning aids.
3. Use **silicone polymer** lotion **once daily** for skin surfaces. Cover wounds and cracks with a flexible porous soft silicone wound dressing and then cover with the silicone polymer lotion.
4. Minimize adhesive use and use adhesive remover if needed.
5. Use **micro-ECG** leads. Cut out small ECG sized flexible wound dressings to use under the ECG leads to prevent skin breakdown.
6. Change oximeter probe site **q8**, use *non-adhesive Velcro wrap* for all infants <26 weeks gestation. Change Temp probe **q8** and secure with *Blue Silicone Tape*
7. Do not bathe until > 2 weeks of age. **Use only water** until 32 weeks PMA
8. **Do not use Chlorhexidine on the skin of ELBW babies (risk of severe skin injury: chemical burns, blisters, etc. and neurotoxicity)**[1,2]. Only use on lines and wires once daily.
9. Change linen and stocking/cover on the PICC lines daily

1) Chapman AK, et al, Safety of chlorhexidine used for skin antisepsis in the preterm infant. Journal of Perinatology, 2012;32; 4-9.
2) Vanzi V and Pitaro R, Skin injuries and chlorhexidine gluconate-based antisepsis in early premature infants. Journal of Perinatal & Neonatal Nursing 2018; 32:341-350.

Blood Pressure Management - Differences

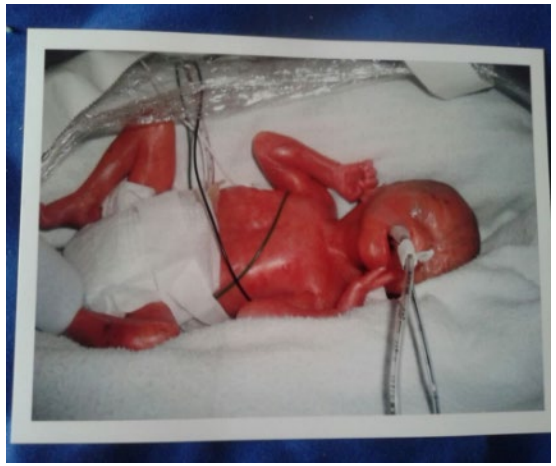
- Aim for MABP ≥ 22-24 or Systolic ≥ 10-12 above the MABP within a few hours of birth

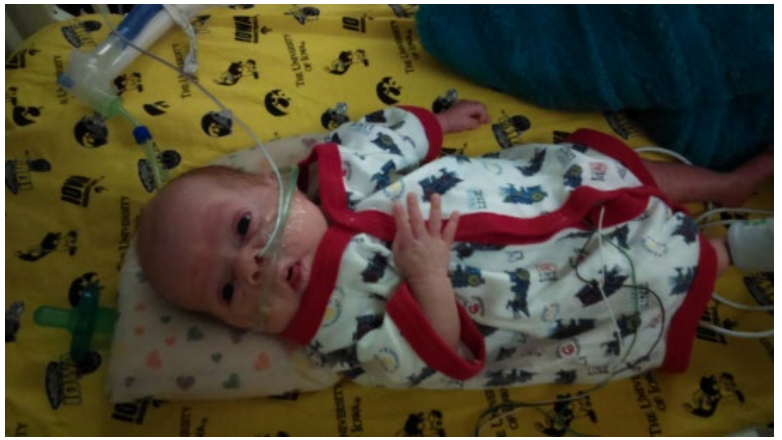
  Durrmeyer X, et al. *Arch Dis Child Fetal Neonatal Ed. 2017 Mar 16.* Abstention or intervention for isolated hypotension in the first 3 days of life in extremely preterm infants: association with short-term outcomes in the EPIPAGE 2 cohort study

  - Treated infants had a significantly higher survival rate without major morbidities including less severe IVH

  1) Consider stress dose Hydrocortisone
  2) Slow fluid boluses only (10cc/kg) over 1 hour
     - UAC flushes - very slowly over at least 30 seconds
  3) Dobutamine if BP still low despite hydrocortisone especially if lactates rising
  4) Septic shock will need additional vasopressors: dopamine, norepinephrine, etc.

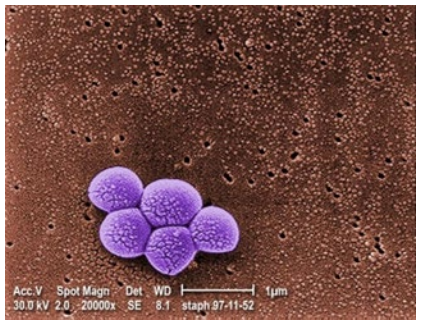
450 gm
23 6/7 weeks
SGA 3%





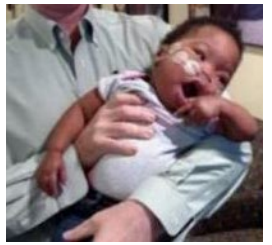
Infectious Disease Management - Differences

- Prophylactic Nystatin to prevent fungal infection
  - Given to all patients on antibiotics and continued for 24 hours post therapy
  - RCT of prophylactic fluconazole versus nystatin for the prevention of fungal colonization and invasive fungal infection in very low birth weight infants. *Aydemir C et al, Arch Dis Child Fetal Neonatal Ed (2010)*
- Additionally, prophylactic fluconazole is given for at least 2 weeks and the skin has keratinized
  - RCT of prophylactic fluconazole versus placebo for 6 weeks reduced invasive candidiasis. Benjamin et al, JAMA 2014;311(17):1742
- IgG screening for 6 weeks
  - Give IVIG if < 200 (RCT of prophylactic IVIG for the prevention of nosocomial infection in LBW Neonates. Reduced infections (500-750 gm group), Baker et al, NEJM 1992;327:213
- Central line removal protocol
  - Antibiotics Before Removal of Percutaneously Inserted Central Venous Catheters Reduces Clinical Sepsis in Premature Infants. *Reynolds G et al, J Pediatr Pharmacol Ther 2015;20(3):203*



Controversial Differences in Management Strategies

22 1/7-week, twin, 394 gm



1) Endocrine

- ✓ Repeat thyroid screening at 1 month of age (Kaluarachchi DC, et al. *J Perinatol* 37:277-282, 2017)
- ✓ Depending on TSH and free T4 values will be placed on thyroid replacement
- ✓ Use stress dose and physiological hydrocortisone replacement for days to weeks to occasionally months depending on BP stability

2) Cardiopulmonary Failure

- ✓ Rescue with inhaled NO if O2 requirement > 60-70% with appropriate mean airway pressure, usually patients with PPROM (< 22 weeks), pulmonary hypoplasia and/or acute or chronic pulmonary hypertension
  - ✓ iNO use: 22 weeks-55%, 23 weeks-46%, 24 weeks-37% (2018-2022); Positive response 63% of infants at 22-26 weeks; 78% (22-23 weeks) [1]

3) Management changes since 2014

- ✓ Probiotics (on hold for FDA concern since 9/29/23)
- ✓ Delayed Cord Clamping (48% at 22-23 weeks)

4) Use of Aggressive Phototherapy (Neuroprotective Strategy, significantly reduces overall NDI as well as profound impairment): Morris BH et al. *New Engl J Med 2008; 359:1885*

BW (g)	1d	2d	3d	4d	5d	6d	7-14d
<1000	5	5	5	5	5	5	7

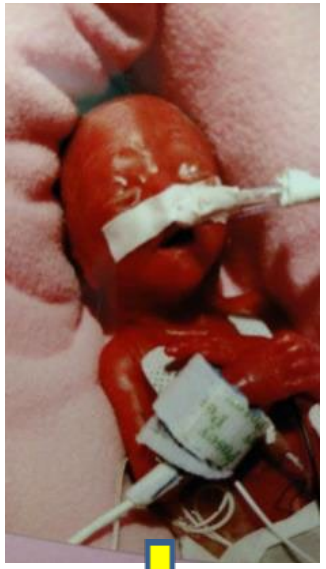
5) Targeted Neonatal Echocardiography since 2018

- ✓ During the first 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 (50% efficacy at reducing the shunt) then if it reoccurs on the 2nd week of life, Indomethacin (up to 2 courses), if still significant shunting, mechanical device closure/ligation [2]

1) Boly TJ et al, Response categorization and outcomes in extremely premature infants born at 22-26 weeks gestation that received inhaled nitric oxide for hypoxic respiratory failure. J Perinatol, 2023;43; 324-331
2) Giesinger RE et al, Seminars in Perinatology. Mar;47(2):1517212023.

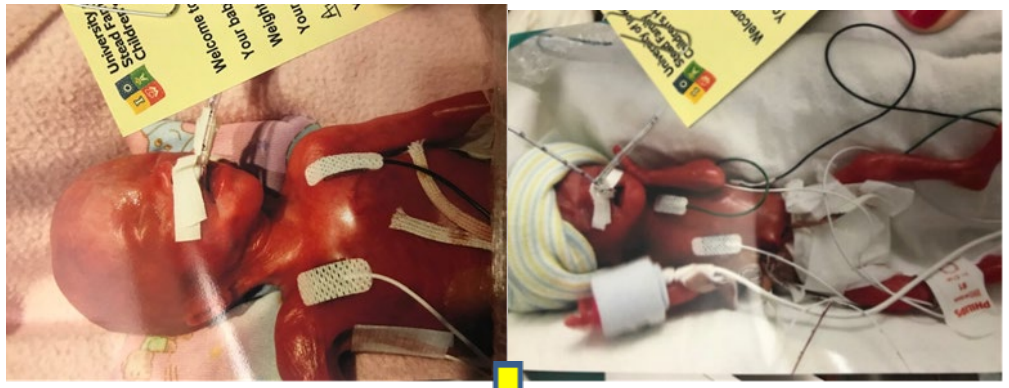
Conclusion: Survival at 22 weeks Gestation is Extremely Difficult but not Impossible

22 2/7 weeks, 335 g

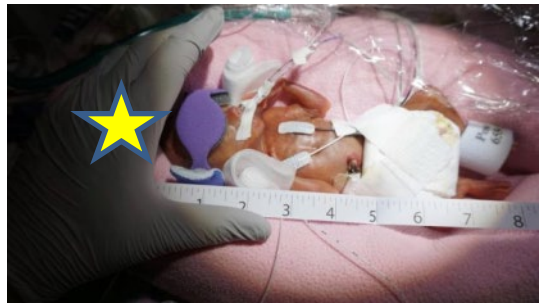


14 months old

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



22 6/7 weeks twins,
465 & 395 g



22 1/7-week twins, 2-year birthday

13 months old, Normal at age 2

Age 4

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