46TH ANNUAL

L. Joseph Butterfield Perinatal Conference

September 18, 2025

AdventHealth Parker | 9395 Crown Crest Blvd, Parker, CO 80138
Conference Center | Inspiration A and B or virtually via MS Teams

Provided by

Children's Hospital Colorado

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46th Annual L. Joseph Butterfield Perinatal Conference

Hot Topics in Perinatology and Neonatology

Much progress has been made in the care of high-risk pregnant women, critically ill newborns, and families. Still, we have more work to do to ensure the best and safest care for these populations. This year the conference addresses hot topics in a changing landscape surrounding pregnancy, newborns, family, and community.

A Tribute

L. Joseph Butterfield, MD

October 5, 1926 - June 1, 1999

Dr. Butterfield, a world-renowned neonatology pioneer, visionary and master of networking, created the Newborn Center (Neonatal ICU) at Children's Hospital Colorado in 1965. He designed a regionalized system of care, "Newborn Country USA", advocated for newborns and their families in legislative and professional arenas, and endowed the L. Joseph Butterfield Chair in Pediatrics at Children's Hospital Colorado.

Target Audience and Learner Outcome

This inter-professional conference is comprised of nurses, advanced practice providers, physicians, respiratory therapists and other perinatal/child health providers practicing in a variety of roles and settings throughout the region.

At the conclusion of this event, participants will report increased knowledge and intent to change practice influencing care for pregnant women and newborns.

Agenda

Thursday, September 18, 2025

7:30 a.m.	Check-in and breakfast with exhibitors
7:50	Welcome and Opening Remarks
8:00	**Fetal MRI: How does it help?** Mariana L. Meyers, MD, FAIUM
9:00	**Group A Strep and Sepsis in Pregnancy** Jonathan Hirshberg, MD
10:00	Break with exhibitors
10:10	**Human Trafficking in the Childbearing Years** Denise C. Abdoo, PhD, CPNP
11:10	**Updates in Hypoxic-Ischemic Encephalopathy** Robert Dietz, MD, PhD
12:10 p.m.	Lunch with exhibitors
12:45	**Intrauterine Devices and Other Updates in Postpartum Hemorrhage Management** Theresa Fisher, MD
1:45	**Seeing the Bigger Picture: Retinopathy of Prematurity, Quality Improvement, and Nutrition** Lauren Beard, MD and Kendra Hendrickson, MS, RD, CSPCC
2:45	**From Protocol to Practice: The Power of a Collaborative Approach in Advancing Extreme Prematurity Care** Laura Marrs, MD
3:45	Evaluation and Wrap-Up
4:00	Adjourn

How to Participate

In-person Learners

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Virtual Learners

Click here to join the meeting via Microsoft Teams
Meeting ID: 247 381 138 174 7
Passcode: 9F8Le37w

Continuing Education Credit

Registration, marked attendance, and submission of the online evaluation, including a written response to questions related to any changes in practice that you may make as a result of learning that took place at this activity, are required for successful completion and receipt of the certificate of attendance. Claim only those hours you attend.

Attendance

Learners are required to sign-in for this NCPD activity to verify participation in the program.

Signing-in: Sign-in opens 30-minutes prior to the event. There are two sign-in options:

1. Text the attendance code below to 720-790-4423 or
2. Enter the attendance code below at ce.childrenscolorado.org/code

Attendance Code: **46BUTTER**

Evaluation

To obtain your NCPD certificate, the on-line evaluation must be completed by midnight, Thursday, October 2, 2025. After completing the evaluation, you will be prompted to claim your NCPD credits. Any questions or concerns with access should be directed to ce@childrenscolorado.org.

Credit

Nursing: Children's Hospital Colorado is approved with distinction as a provider of nursing continuing professional development by Colorado Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. This educational offering for 7.25 nursing contact hours is provided by Children's Hospital Colorado.

Other: A general certificate of attendance will be provided for all other participants.

Disclosure of Relevant Financial Relationships

Planners, faculty, and others in control of content (either individually or as a group) have no relevant financial relationships with ineligible companies.

Thank You to Newborn Hope

We extend our heartfelt thanks to Newborn Hope for their generous sponsorship of the 46th Annual L. Joseph Butterfield Perinatal Conference. Your support plays a vital role in making this event possible and in advancing our shared mission. We are deeply grateful for your commitment and partnership.

Faculty

Denise Abdoo, PhD, CPNP
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Child Protection Team
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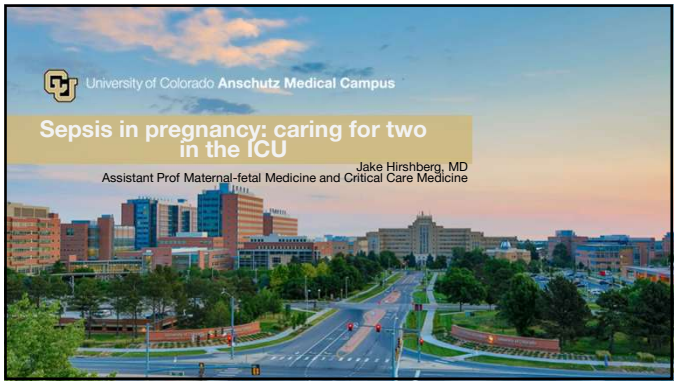
Children's Hospital Colorado

Mariana L. Meyers, MD, FAIUM
Associate Professor - Radiology
University of Colorado School of Medicine
Director of Fetal MRI
Vice Chair of Mentorship and Professional Development
Colorado Fetal Care Center
Children's Hospital Colorado



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Disclosures

- None

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Objectives

- Understand trends in maternal mortality
  - Review Colorado's newest Data
- Review physiologic changes in Pregnancy
- Apply these to the diagnosis and evaluation of sepsis in pregnancy
- Determine what alterations we need to make to sepsis care in pregnancy
- Master the care of puerperal sepsis

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Maternal Mortality

Defining the problem

- The death of a person while pregnant or within 42 days of the end of pregnancy
- Can be pregnancy "related" or not
- The US outpaces all other "industrialized" nations
- 2/3 are preventable

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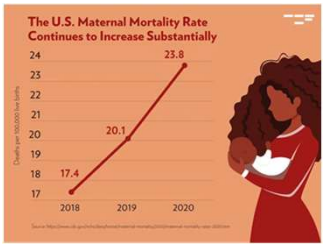
Maternal Mortality



Trends over time

- Continues to worsen
- Data from 2022 shows another 22% increase
- Historic context
  1900: 600/100,000
  1600: 1200/100,000
  Prehistoric: 1000/100,000

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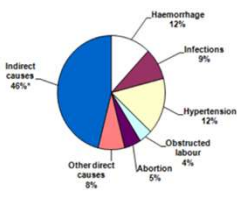
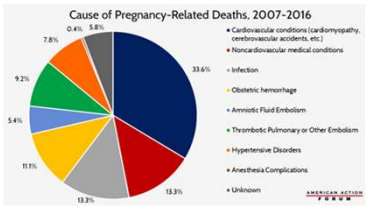
Maternal Mortality





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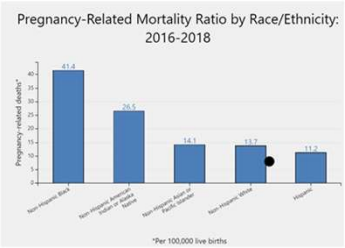
Maternal Mortality



Disparities in outcomes

- Transcends economic and educational barriers
- Access to quality care
- Implicit bias
- Preexisting conditions
- Structural racism
- Historic context

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Colorado: From 2017-2021 there were

188 pregnancy-associated deaths

59.8 pregnancy-associated deaths per 100,000 live births

87 pregnancy-related deaths

27.7 pregnancy-related deaths per 100,000 live births

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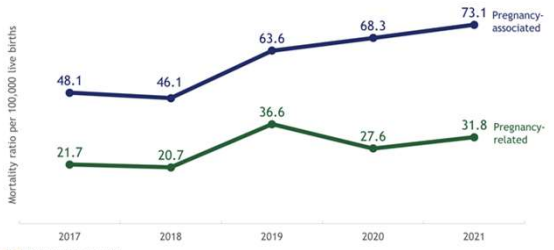
Mortality Ratios Over Time

Annual mortality ratios, 2017-2021

Pregnancy-associated mortality ratios increased in 2019 through 2021 compared to previous years.



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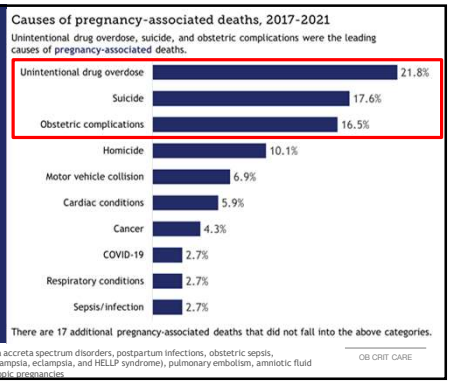
Causes of pregnancy-associated deaths, 2017-2021



Obstetric complications (e.g., uterine hemorrhage, placenta accreta spectrum disorders, postpartum infections, obstetric sepsis, hypertensive complications of pregnancy (e.g., pre-eclampsia, eclampsia, and HELLP syndrome), pulmonary embolism, amniotic fluid embolism, anesthesia complications, and ruptured ectopic pregnancies

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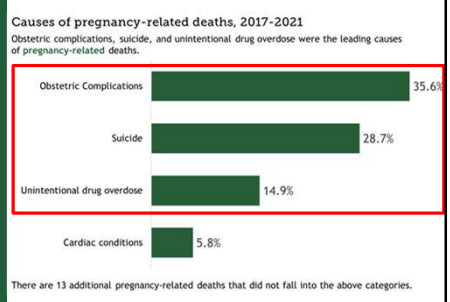
Causes of pregnancy-related deaths, 2017-2021



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Pregnancy Physiology-Cardiac

- Hemodynamic changes in pregnancy

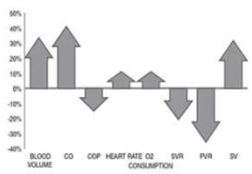

FIGURE 2. Hemodynamic alterations of pregnancy. CO indicates cardiac output; COP, colloid oncotic pressure; PVR, pulmonary vascular resistance; SV, stroke volume; SVR, stroke volume resistance.

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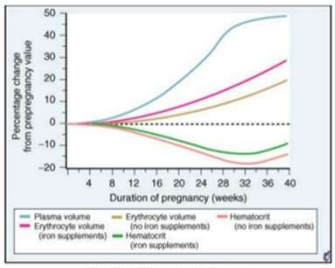
Pregnancy Physiology-heme



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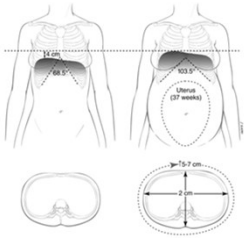
Pregnancy Physiology-pulm



Hegewald, M.J. & Crapo, R.O. (2011). Respiratory physiology in pregnancy. *Clin Chest Med*, 32, 1.

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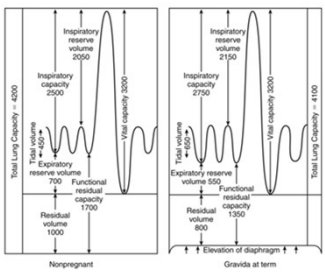
Pregnancy Physiology-pulm



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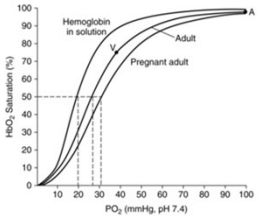
Pregnancy Physiology-pulm

Blood gas measurement	Non-pregnant adult	Third trimester
pH	7.38–7.44	7.39–7.45
Arterial partial pressure of oxygen (mmHg [kPa])	80–100 (11–13)	92–107 (12.3–14.3)
Arterial partial pressure of carbon dioxide (mmHg [kPa])	35–45 (4.7–5.9)	25–33 (3.3–4.4)
Bicarbonate (mmol/L or mEq/L)	21–30	16–22



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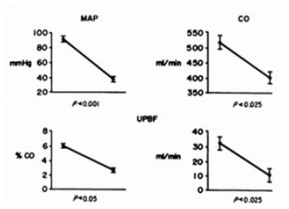
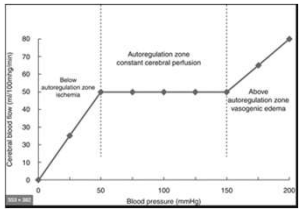
Autoregulation of placental perfusion





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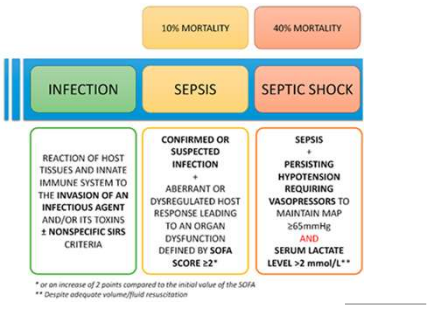
Sepsis-3



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Maternal Sepsis evaluation

Identification and escalation of care

Table 1. Characteristics of Common Maternal Early Warning Systems for Sepsis

Pregnancy Scoring System	Parameters Evaluated	Threshold	Advantages	Disadvantages
MOEWS[34]	Heart rate, respiratory rate, oxygen saturation, systolic blood pressure, temperature, and mental status changes	Varies	Simple bedside screening tool	Marked variation of thresholds and formats Validated for chorioamnionitis Overdetects severe sepsis Need for secondary testing to identify true-positives
omqSOFA[34]	Systolic blood pressure, respiratory rate, and altered mental status	2	Simple bedside screening tool Uses only clinical data, allowing for rapid diagnosis	Low specificity; low PPV Altered mental status in criteria may have nonseptic causes in obstetric patients Need for secondary testing
S.O.S.[35,*]	Temperature, heart rate, respiratory rate, oxygen saturation, systolic blood pressure, heart rate, leukocyte count, percentage of immature neutrophils, and lactic acid	6	Excellent NPV 98.6% Rapidly rules out need for ICU Does not use altered mental status in criteria	Complex scoring system with multiple variables Requires laboratory data, which can delay diagnosis

MOEWS, modified Obstetric Early Warning Signs; PPV, positive predictive value; omqSOFA, obstetric modified quick Sepsis-related Organ Failure Assessment; S.O.S, Sepsis in Obstetrics Score; NPV, negative predictive value; ICU, intensive care unit.
* Free online calculator available at https://www.perinatology.com/calculators/Sepsis%20Calculator.htm.

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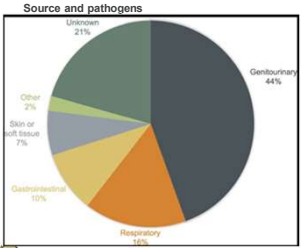
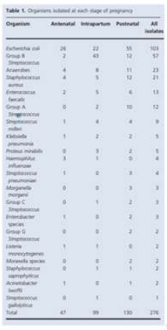
Maternal Sepsis

Source and pathogens





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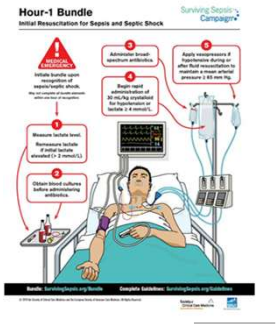
Obstetric sepsis

Treatment-2021 guidelines

	Shock is present	Shock is absent
Sepsis is definite or probable	Administer antimicrobials **immediately**, ideally within 1 hour of recognition.	Administer antimicrobials **immediately**, ideally within 1 hour of recognition.
Sepsis is possible	Administer antimicrobials **immediately**, ideally within 1 hour of recognition.	Rapid assessment* of infectious vs. noninfectious causes of acute illness. Administer antimicrobials **within 3 hours** if concern for infection persists.

*Rapid assessment includes history and clinical examination, tests for both infectious and noninfectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever



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Antibiotics

"Go big so they can go home"

Table 3. Proposed broad-spectrum empiric antibiotic regimens of peripartum sepsis.

1. **Gram-negative and anaerobic coverage**
   - Piperacillin/tazobactam 3.375 g IV q8h (extended infusion) or 4.5 g IV q6h **or**
   - Meropenem 1 g IV q8h (if recent hospitalization or concern for multi-drug resistant organisms) **or**
   - Cefepime 1–2 g IV q8h plus metronidazole 500 mg IV q8h **or**
   - Aztreonam 2 g IV q8h (for women with severe penicillin allergy) plus metronidazole 500 mg IV q8h **or**
   - Aztreonam 2g IV q8h plus clindamycin 900 mg IV q8h

   PLUS

2. **Gram-positive coverage**
   - Vancomycin 15–20 mg/kg q8h–q12h (goal trough 15–20 mcg/mL) **or**
   - Linezolid 600 mg IV/PO q12h (for women with severe vancomycin allergy)

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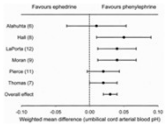
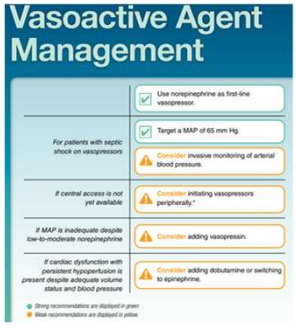
Obstetric sepsis

Treatment-2021 guidelines

- Levo is the preferred pressor in shock (and in pregnancy)
- Second line agent is controversial
  - Vasopressin may increase contractions
  - Phenylephrine improves UA blood flow
  - MAP goal is unknown





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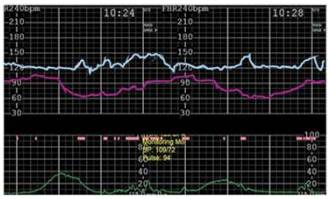
Obstetric Sepsis

Alterations in OB sepsis

- Increased rates of bacteremia for any given infection
  - Pylo=> 20-30% bacteremia
  - Transient bacteremia in labor
- Surviving sepsis guidelines
  - MAP>65?
  - Fluid tolerant
  - Often hypovolemic
- ScVO2 is lower in the 3rd trimester
- Fetal monitoring
- Don't miss GAS!
  - Surgical emergency



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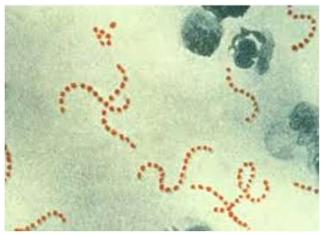
Group A Strep

1. TIME: Optimize rapid recognition and diagnosis of GAS
1. TOXIN: Understand medical management of GAS
1. TISSUE: Recognize when surgical management of GAS is indicated.
1. TRAGEDY: Review Modern outcomes from GAS



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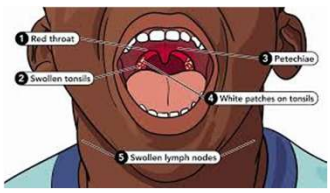
TIME

Populations at risk:

- Recently postpartum/postabortive
- Prolonged ROM
- Preterm birth
- Cesarean delivery
- Multigravida
- GAS colonization/exposure



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TIME

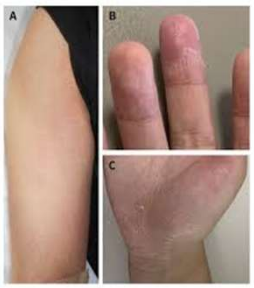
Signs and symptoms

Typical

- Pain out of proportion to exam
- Fever
- Malodorous vaginal discharge
- Tender/boggy uterus

Atypical

- Joint pain/swelling
- Nausea and vomiting
- Rash



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TIME

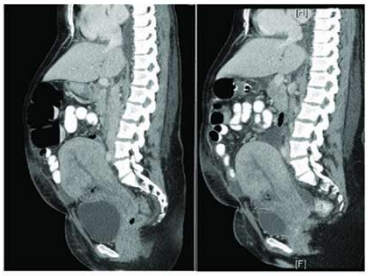
Imaging and labs

Labs:

- Bandemia (>10%)
- Renal impairment (Cr >1.1 mg/dL)
- Liver injury (AST/ALT>2x uln)
- Coagulopathy (plts <100k, DIC)
- Endometrial biopsy?
- Bacteremia (50%)

Imaging:

- Not required for diagnosis
- Can be useful if source is unknown
- MRI without contrast antepartum
- CT with contrast for deep infections
- Ultrasound for superficial infections



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Maternal Sepsis

identification

Table 1. Characteristics of Common Maternal Early Warning Systems for Sepsis

Pregnancy Scoring System	Parameters Evaluated	Threshold	Advantages	Disadvantages
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* Free online calculator available at https://www.perinatology.com/calculators/Sepsis%20Calculator.htm.

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TOXIN

Antimicrobials

Initial treatment should be broad

- Ampicillin-sulbactam is not adequate for Severe disease
- Gent/clinda is losing B fragilis activity
- Linezolid+Pip-Tazo/Carbapenem

or

- Vanc+pip-tazo/Cabbapenem+clinda

Once GAS is identified narrow coverage

- PCN+Clindamycin

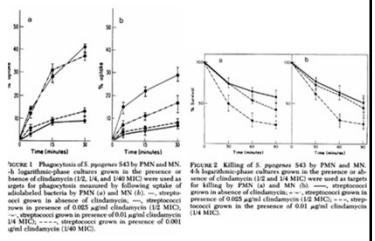


FIGURE 1 Phagocytosis of S. pyogenes S43 by PMN and MN. A h logarithmic-phase cultures grown in the presence or absence of clindamycin (1/2, 1/4, and 1/40 MIC) were used as targets for phagocytosis measured by following uptake of aldolabeled bacteria by PMN (a) and MN (b). —, streptococci grown in absence of clindamycin; —, streptococci grown in presence of 0.025 μg/ml clindamycin (1/2 MIC); – –, streptococci grown in presence of 0.01 μg/ml clindamycin (1/4 MIC); - - - -, streptococci grown in presence of 0.001 μg/ml clindamycin (1/40 MIC).

FIGURE 2 Killing of S. pyogenes S43 by PMN and MN. A h logarithmic-phase cultures grown in the presence or absence of clindamycin (1/2 and 1/4 MIC) were used as targets for killing by PMN (a) and MN (b). —, streptococci grown in absence of clindamycin; – – –, streptococci grown in presence of 0.025 μg/ml clindamycin (1/2 MIC); - - -, streptococci grown in the presence of 0.01 μg/ml clindamycin (1/4 MIC).

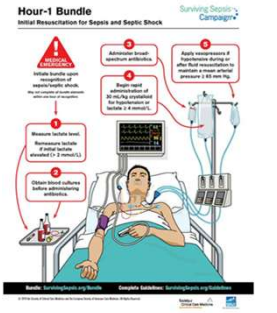
31

TOXIN

Treatment-2021 guidelines

	Shock is present	Shock is absent
Sepsis is definite or probable	Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.
Sepsis is possible	Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	Rapid assessment* of infectious vs. noninfectious causes of acute illness. Administer antimicrobials ***within 3 hours*** if concern for infection persists.

*Rapid assessment includes history and clinical examination, tests for both infectious and noninfectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever



32

TOXIN

Adjuvants

IVIG

- Theory: neutralizes Toxin/superantigen
- Data: retrospective was promising, RCT showed no improvement
- IDSA guidelines: "Additional studies of the efficacy of IVIG are necessary before a recommendation can be made supporting its use in this setting."

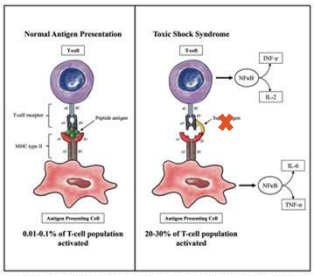


Fig. 4. Schematic of normal T-cell activation and abnormal T-cell activation induced by superantigen. Note that more inflammatory markers are secreted downstream than are shown in the figure.

Cela KB et al. PMID: 33133879

33

TISSUE

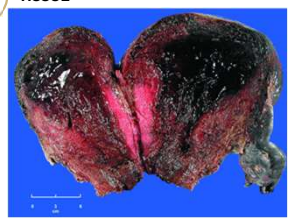
Who needs surgery?

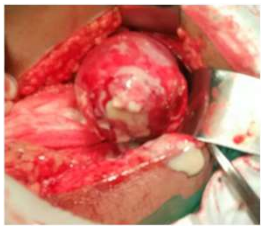
CHIPS scoring system

	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature, °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure, mm HG	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
White Blood Cell Count	≥40		20-39.9	15-19.9	3-14.9		1-2.9		≤1
Objective Concern for Capillary Leak (ARDS, Ascites, Pleural Effusion, Abdominal Distention)	Yes				No				

- From SSTI data: A 6 hr delay in surgical management leads to a 3x in mortality rates
- Calculating hysterectomy rate in puerperal sepsis score (CHIPS): The area under the ROC curve for the final model was 0.83. A score of 10 predicted a greater than 60% probability of hysterectomy, with specificity of over 90%. A score of 13 yielded specificity of 100%

TISSUE



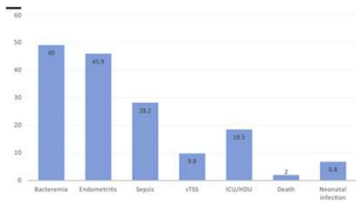


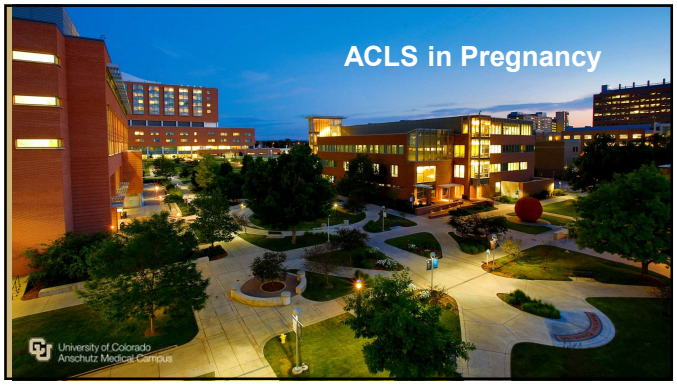
"Hysterectomy was not required in the majority of GAS cases (213/246; 86.6%), even in the context of puerperal sepsis and sTSS. In the described cases where hysterectomy was performed, there was often evidence of necrotizing fasciitis in addition to sepsis, sTSS and multiorgan failure. Most experts agree that a confirmed GAS infection in the presence of organ dysfunction should be managed surgically"

TRAGEDY

Outcomes

- Death occurs in 10–15% of all invasive cases, more than 35% of patients with streptococcal toxic shock syndrome, and approximately 25% of necrotizing fasciitis cases





37

Cardiac arrest epidemiology

In-hospital arrests

- 2-3:100,000 pregnancies
- Risks
  - Age
  - BMI
  - Mode of delivery
- Etiology: 27% anesthetic complications
- Survival: 58% (12% non preg)

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Table 4. Suspected and confirmed (at post mortem) causes for women who died and women who survived

Cause	Women who survived (n = 37)	Women who died (n = 22)
Presumed premortem causes (n = 59)		
Cardiac tamponade	1	0
Hypoxia	4	0
Hypovolaemia	5	8
Venous thromboembolism	1	7
Toxic drug cause	1	0
Anaphylaxis	1	0
Sepsis	0	1
Anaesthetic cause	17	0
Amniotic fluid embolism	5	3
Cardiac cause	5	1
Intracerebral bleed	0	3
Aortic dissection	0	2
Asthma	0	1
Pulmonary artery rupture	0	1
Postmortem causes of collapse (n = 19)		
Amniotic fluid embolism		6
Vessel bleed/rupture		5
Thromboembolic		3
Cardiomyopathy		2
Other		3

Data were available for 59 women. Some women were suspected of having more than one cause, where this is the case both causes have been recorded.

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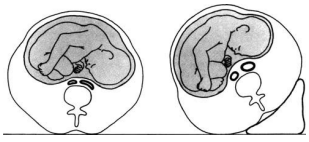
Perimortem Cesarean

- Who?
  - Any patient greater than 20 weeks gestation, or when the uterine fundus can be palpated at the umbilicus



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OB CRIT CARE

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Perimortem Cesarean

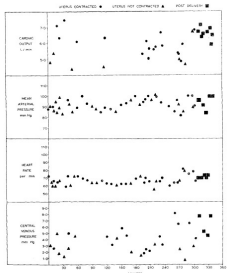

Fig. 2
Serial observations in a single case throughout 350 minutes of labour.

- Why?
  - Delivery leads to a massive maternal autotransfusion

Table 2. Time to emergency procedures in minutes, median (range), following maternal collapse

	Women who survived ($n = 38$)	Women who died ($n = 28$)	*P*-value
Collapse to BLS	0 (0–17)	0 (0–23)	0.28
Collapse to ALS	1 (0–36)	0 (0–24)	0.08
Collapse to PMCS	3 (0–39)	12 (0–67)	0.01

Mann–Whitney *U* tests for nonparametric data were applied.

40

Perimortem Cesarean

- When?
  - Initiate at 4 mins, delivery by 5 mins

Table 2. Postmortem Cesarean Deliveries With Surviving Infants With Reports of Time From Death of the Mother Until Delivery (From 1900–1985)

Cases	No. patients	Percent
0–5 min	42 (normal infants)	70
6–10 min	7 (normal infants)	13
	1 (mild neurologic sequelae)	
Subtotal	8	
11–15 min	6 (normal infants)	12
	1 (severe neurologic sequelae)	
Subtotal	7	
16–20 min	1 (severe neurologic sequelae)	1.7
21+ min	2 (severe neurologic sequelae)	
	1 (normal infant)	3.3
Subtotal	3	
Total	61	100

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Perimortem Cesarean

- Where?
  - At the site of arrest

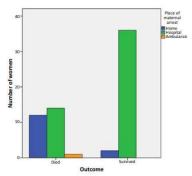


Figure 1. The place where the cardiac arrest occurred (n = 66). $P = 0.001$ chi-square test.

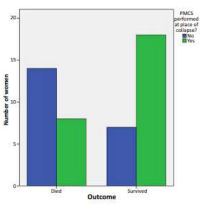
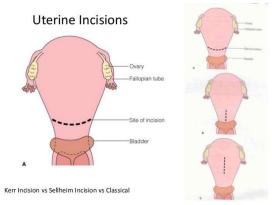


Figure 2. The site of perimortem caesarean section (n = 47, as data were missing for two cases of PMCS). $P < 0.001$ chi-square test.

42

Perimortem Cesarean

- How?
  - Midline vertical abdominal entry
  - Transverse or vertical uterine incision
  - Fetal delivery
  - Placenta can remain insitu until ROSC
  - Patient can be packed until ROSC



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HOT TOPICS IN HIE

Robert Dietz, MD, PhD
Associate Professor
Department of Pediatrics, Section of Neonatology

1

DISCLOSURES

I have no financial conflicts to disclose

2

GOALS AND OBJECTIVES

- Review pathophysiology and current treatment guidelines for HIE
- Describe latest in clinical trials for adjunctive HIE therapy
  - Sildenafil Trial at CHCO
- Evaluate latest data on HIE treatment and gestational age
  - Hypothermia for Neonatal Encephalopathy at 33-35 weeks
- Explore a new pre-clinical model for HIE

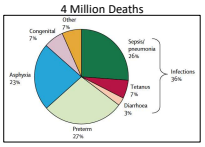
3

Hypoxic Ischemic Encephalopathy

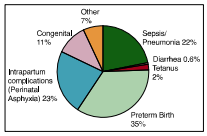
Occurs in 3-5 per 1000 live births in developed countries

But worldwide:

2005
4 Million Deaths



2015
2.7 Million Deaths

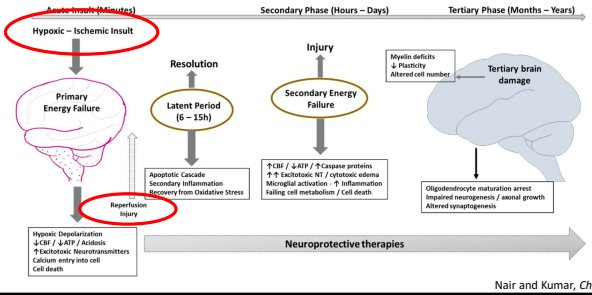


Trends in Neonatal Mortality:
- Neonatal Infections have decreased
- Prematurity is now leading cause of death
- Asphyxia remains unchanged

Lawn JE, et al, *Lancet* (2005)
Oza, Lawn JE, et al. *Bull WHO (2015)*

4

Injury Evolves over Hours and Days



Nair and Kumar, *Children* 2018

5

CRITERIA FOR THERAPEUTIC HYPOTHERMIA

Gestational Age ≥35 weeks and ≤6 hours of age AND

Acute Perinatal Event
- Apgar score ≤5 at 10 minutes after birth **OR**
- Continued need for resuscitation at 10 minute after birth **OR**
- pH <7.00 or base deficit ≥16 mmol/L or more on an umbilical cord sample or an arterial or venous blood sample obtained within 60 minutes of birth

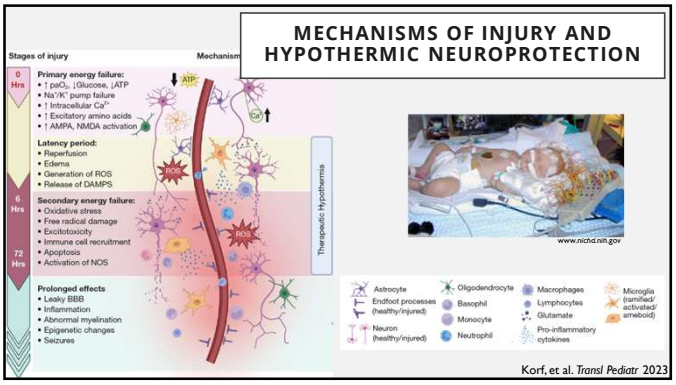
AND

Encephalopathy
- Moderate or severe encephalopathy on clinical exam **AND**
- Moderately or severely abnormal background of at least 20- or 30-minutes duration or seizure activity on aEEG after one hour of age

*Adjusted to 35 weeks in 2016

6

MECHANISMS OF INJURY AND HYPOTHERMIC NEUROPROTECTION



Korf, et al. *Transl Pediatr* 2023

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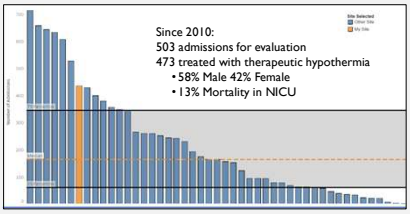
HIE AT CHCO
CHND DATA

CHNC
Children's Hospitals Neonatal Consortium

CHND was developed in 2006 to meet the data acquisition and analytics required for comparative quality and outcome measures for the unique population of medically complex neonates and infants treated in Level IV Neonatal Intensive Care Units (NICUs) at children's hospitals.



Since 2010:
503 admissions for evaluation
473 treated with therapeutic hypothermia
- 58% Male 42% Female
- 13% Mortality in NICU

Graph courtesy of Theresa Grover MD, CHND

8

HIE AND HYPOTHERMIA AT CHCO
CHND DATA SINCE 2010

ALL HIE ADMISSIONS

Summary Data			
Outcomes	My Hospital	Other Hospitals	CHND Total
Episodes of Care	503	11,948	12,451
Patients	503	11,918	12,421
NICU Mortality %	13.12	12.13	12.17
Median NICU LOS (All)	12	12	12.0
Median NICU LOS (Survivors)	13	13	13.0
Median NICU LOS (Non-Survivors)	6	6	6.0
Hospital Mortality %	13.32	12.47	12.51
Median Hospital LOS (All)	13	13	13.0
Median Hospital LOS (Survivors)	41	24	24.0
Median Hospital LOS (Non-Survivors)	6	6	6.0
Gender - Female (EOC)	212	4,949	5,161
Gender - Male (EOC)	291	6,997	7,288
Gender - Indeterminate (EOC)	0	0	0

HIE TREATED WITH TH

Summary Data			
Outcomes	My Hospital	Other Hospitals	CHND Total
Episodes of Care	473	9,992	10,465
Patients	472	9,967	10,439
NICU Mortality %	12.90	11.98	11.96
Median NICU LOS (All)	12	12	12.0
Median NICU LOS (Survivors)	13	13	13.0
Median NICU LOS (Non-Survivors)	6	5	5.0
Hospital Mortality %	13.11	11.69	11.70
Median Hospital LOS (All)	12	13	13.0
Median Hospital LOS (Survivors)	41	22	23.0
Median Hospital LOS (Non-Survivors)	6	5	5.0
Gender - Female (EOC)	195	4,139	4,334
Gender - Male (EOC)	278	5,851	6,129
Gender - Indeterminate (EOC)	0	0	0

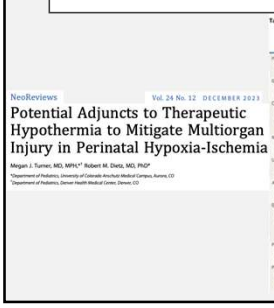
Graphs courtesy of Diane Melara, CHNC

9

CLINICAL TRIALS FOR ADJUNCTIVE THERAPY

10

LIST OF POTENTIAL ADJUNCTIVE THERAPY CONTINUES TO GROW


NeoReviews Vol. 24 No. 12 DECEMBER 2023

Potential Adjuncts to Therapeutic Hypothermia to Mitigate Multiorgan Injury in Perinatal Hypoxia-Ischemia

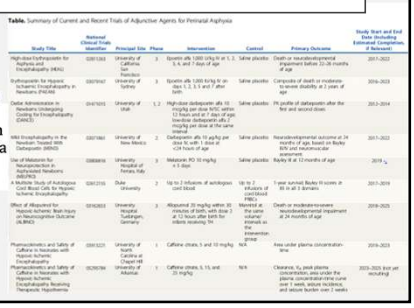


Table. Summary of Current and Recent Trials of Adjunctive Agents for Perinatal Asphyxia

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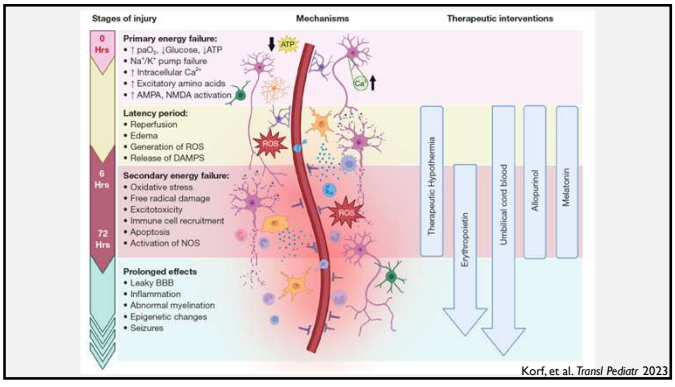

Korf, et al. *Transl Pediatr* 2023

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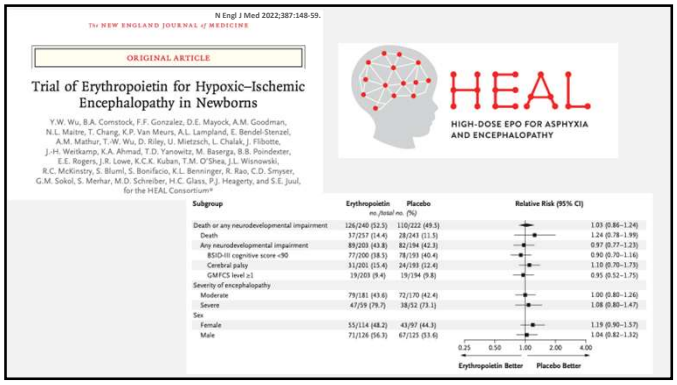

N Engl J Med 2022;387:148-59.
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Erythropoietin for Hypoxic–Ischemic Encephalopathy in Newborns

Y.W. Wu, B.A. Comstock, F.F. Gonzalez, D.E. Mayock, A.M. Goodman, N.L. Maitre, T. Chang, K.P. Van Meurs, A.L. Lampland, E. Bendel-Stenzel, A.M. Mathur, T.-W. Wu, D. Riley, U. Mietzsch, L. Chalak, J. Flibotte, J.-H. Weitkamp, K.A. Ahmad, T.D. Yanowitz, M. Basenga, B.B. Poindexter, E.E. Rogers, J.R. Lowe, K.C.K. Kuban, T.M. O'Shea, J.L. Wisnowski, R.C. McKinstry, S. Bluml, S. Bonifacio, K.L. Benninger, R. Rao, C.D. Smyser, G.M. Sokol, S. Merhar, M.D. Schreiber, H.C. Glass, P.J. Heagerty, and S.E. Juul, for the HEAL Consortium*

HEAL
HIGH-DOSE EPO FOR ASPHYXIA AND ENCEPHALOPATHY

Subgroup	Erythropoietin no./total no. (%)	Placebo no./total no. (%)	Relative Risk (95% CI)
Death or any neurodevelopmental impairment	126/240 (52.5)	110/222 (49.5)	1.03 (0.86–1.24)
Death	37/257 (14.4)	28/243 (11.5)	1.24 (0.78–1.99)
Any neurodevelopmental impairment	89/203 (43.8)	82/194 (42.3)	0.97 (0.77–1.23)
BSID-III cognitive score <90	77/200 (38.5)	78/193 (40.4)	0.90 (0.70–1.16)
Cerebral palsy	31/201 (15.4)	24/193 (12.4)	1.10 (0.70–1.73)
GMFCS level ≥1	19/203 (9.4)	19/194 (9.8)	0.95 (0.52–1.75)
Severity of encephalopathy			
Moderate	79/181 (43.6)	72/170 (42.4)	1.00 (0.80–1.26)
Severe	47/59 (79.7)	38/52 (73.1)	1.08 (0.80–1.47)
Sex			
Female	55/114 (48.2)	43/97 (44.3)	1.19 (0.90–1.57)
Male	71/126 (56.3)	67/125 (53.6)	1.04 (0.82–1.32)

0.25 0.50 1.00 2.00 4.00
Erythropoietin Better Placebo Better

13

SILDENAFIL

SILDENAFIL ADMINISTRATION TO TREAT NEONATAL ENCEPHALOPATHY (SANE TRIAL)

Led by Pia Wintermark, MD
McGill University

NeoBrainLab

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SILDENAFIL AND BRAIN INJURY

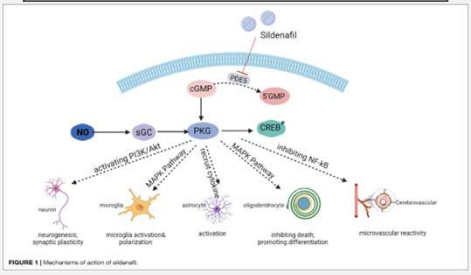


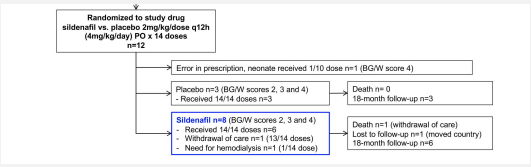
FIGURE 1 | Mechanisms of action of sildenafil.

Xiong, et al. Front cell neuroscience (2022)

15

SANE-01 (NCT02812433)

SILDENAFIL ADMINISTRATION TO TREAT NEONATAL ENCEPHALOPATHY (SANE) AND REPAIR BRAIN INJURY SECONDARY TO BIRTH ASPHYXIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED **PILOT PHASE IB STUDY**



Slide courtesy of Pia Wintermark, MD

Wintermark P, et al. *J Ped.* 2024

NeoBrainLab

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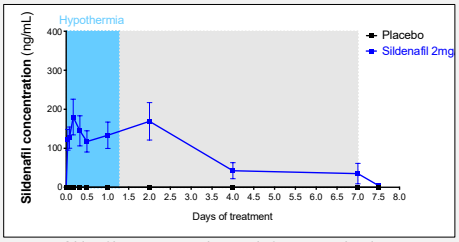
SANE-01 PK



Sildenafil concentration decreased after TH completed

Slide courtesy of Pia Wintermark, MD

Wintermark P, et al. *J Ped.* 2024

NeoBrainLab

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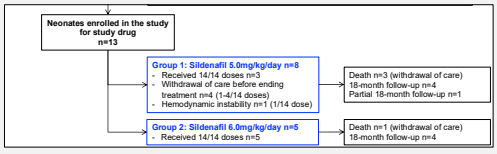
SANE-02 (NCT04169191)

TREATMENT OF NEONATAL ENCEPHALOPATHY WITH ORAL SILDENAFIL SUSPENSION
TO REPAIR BRAIN INJURY SECONDARY TO BIRTH ASPHYXIA:
AN OPEN-LABEL DOSE-FINDING CLINICAL TRIAL (**PHASE IB STUDY**)



Slide courtesy of Pia Wintermark, MD

NeoBrainLab

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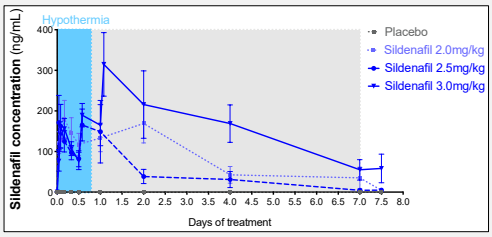
SANE-02 PK
OPEN-LABEL DOSE-FINDING CLINICAL TRIAL



Slide courtesy of Pia Wintermark, MD

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SANE-01 AND SANE-02 CHARACTERISTICS

TABLE 1: Baseline characteristics of the study population.

	TH+Placebo (n=3)	TH+S2.0 (n=8)	TH+S2.5 (n=8)	TH+S3.0 (n=5)
Gestational age, weeks (mean ± SD)	41.19 ± 0.22	39.29 ± 1.49	39.67 ± 1.20	39.97 ± 0.98
Birth weight, g (mean ± SD)	3146 ± 289	3035 ± 476	3632 ± 897	3168 ± 465
Sex, n (%)				
Male	2 (67)	6 (75)	6 (75)	3 (60)
Female	1 (33)	2 (25)	2 (25)	2 (40)
Delivery mode, n (%)				
Vaginal	2 (67)	4 (50)	3 (38)	1 (20)
Cesarean	1 (33)	4 (50)	5 (62)	4 (80)
10-min Apgar score ≤5, n (%)	2 (67)	7 (88)	4 (50)	4 (80)
Cord pH (mean ± SD)	7.05 ± 0.01	7.03 ± 0.19	7.04 ± 0.14	6.91 ± 0.18
First gas pH (mean ± SD)	7.05 ± 0.12	7.00 ± 0.24	7.15 ± 0.35	6.87 ± 0.19
Lactates on admission, mmol/L (mean ± SD)	5.73 ± 2.88	11.89 ± 7.24	10.14 ± 6.39	16.24 ± 7.76
Sarnat score on admission, n (%)				
Moderate	2 (67)	5 (62)	5 (62)	4 (80)
Severe	1 (33)	3 (38)	3 (38)	1 (20)
aEEG on admission, n (%)				
Moderate	0 (0)	3 (38)	2 (25)	3 (60)
Severe	3 (100)	5 (62)	6 (75)	2 (40)
Baseline* troponin I, mcg/L (mean ± SD)	0.03 ± 0.01	0.25 ± 0.25	0.31 ± 0.38	0.92 ± 1.88
Baseline* creatine kinase, U/L (mean ± SD)	3844 ± 2444	6246 ± 6672	3995 ± 2848	10210 ± 11922
Baseline* creatinine, mcmol/L (mean ± SD)	45.33 ± 1.53	102.60 ± 52.79	78.75 ± 37.85	139.40 ± 46.21
Baseline* AST, U/L (mean ± SD)	109.70 ± 55.14	369.80 ± 353.40	430.10 ± 402.80	654.00 ± 462.30
Baseline* ALT, U/L (mean ± SD)	52.33 ± 35.12	273.75 ± 330.00	301.10 ± 253.10	341.40 ± 222.30
Baseline* CRP, mg/L (mean ± SD)	3.93 ± 3.76	14.25 ± 14.65	16.70 ± 16.95	23.04 ± 32.94

* Baseline = on day 2 of life, before study drug administration

Slide courtesy of Pia Wintermark, MD

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SANE-01 AND SANE-02 OUTCOMES
BRAIN INJURY SCORE AND MORTALITY/NDI

* sNDI
= Bayley Scales of Infant and Toddler Development (BSID) <70, CP, GDD, and/or epilepsy

Slide courtesy of Pia Wintermark, MD

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SANE-01 AND SANE-02 OUTCOMES
DAY-30 MRI

* Reduction of brain injury
  = recovery of some injuries (basal ganglia), fewer cystic lesions, and less brain volume loss on day-30 MRI

Slide courtesy of Pia Wintermark, MD

NeoBrainLab

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SANE-01 AND SANE-02
18-MONTH FOLLOW-UP

Slide courtesy of Pia Wintermark, MD

NeoBrainLab

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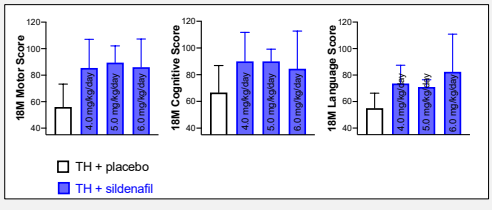
SANE-02
18-MONTH FOLLOW-UP



Slide courtesy of Pia Wintermark, MD

Wintermark P, et al. *J Ped.* 2024

NeoBrainLab

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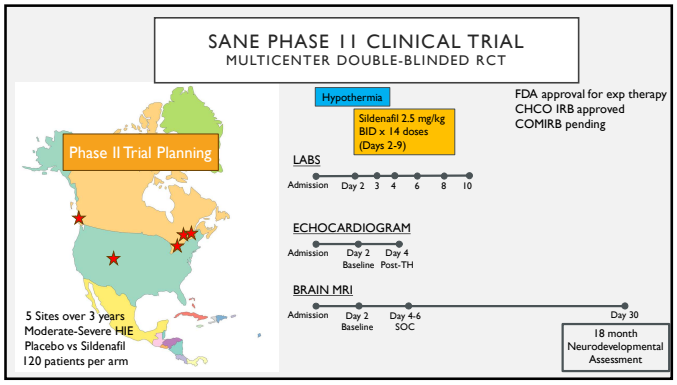

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HYPOTHERMIA AND PREMATURE GESTATIONAL AGE

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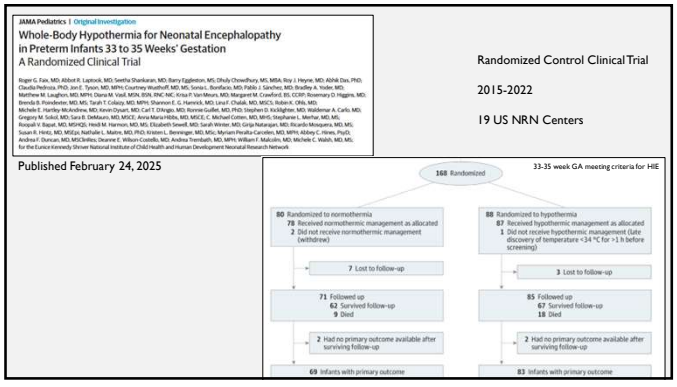

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HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY AT 33-35 WEEKS

	No./total No. (%)	
	Infant	
	Hypothermic (n = 88)	Normothermic (n = 80)
Infant		
Gestational age, mean (SD), wk	34.0 (0.8)	34.1 (0.8)
Birth weight, mean (SD), g	2464 (634)	2371 (608)
Length, mean (SD), cm	46.0 (3.2)	45.1 (2.8)
No.	86	76
Head circumference, mean (SD), cm	32.0 (1.8)	31.7 (1.8)
No.	86	77
Male	46/88 (52)	45/80 (56)
Outborn	47/88 (53)	47/80 (59)
Delivery room resuscitation		
Intubation	56/88 (64)	50/79 (63)
Chest compressions	40/88 (46)	30/79 (38)
Epinephrine	26/88 (30)	26/79 (33)
Time to spontaneous breaths, median (IQR), min	2.0 (1.0-3.0)	2.0 (1.0-3.0)
No.	80	74
Apgar score <5		
At 5 min	54/86 (63)	48/79 (61)
At 10 min	36/70 (51)	29/67 (43)
Cord blood or if unavailable, neonatal blood gas at <1 h postnatal age		
Mean (SD), pH	6.9 (0.2	6.9 (0.2)
No.	69	68
Mean (SD), base deficit	17.7 (7.0)	17.0 (7.7)
No.	60	59
Age at randomization, mean (SD), h	4.5 (1.2)	4.5 (1.3)
Level of encephalopathy		
Moderate	61/88 (69)	57/80 (71)
Severe	27/88 (31)	23/80 (29)
Clinical seizures at randomization	14/88 (16)	11/80 (14)

PRIMARY OUTCOME

Death or moderate or severe disability at 18 to 22 mo corrected age (disability defined by Bayley III cognitive score, Gross Motor Function Classification System score, active seizure disorder, blindness, or hearing loss)

Faix RG, et al. *JAMA Pediatrics* 2025

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HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY AT 33-35 WEEKS

Table 2. Comparison of Primary and Secondary Outcomes in Infants Using Neutral Prior[a]

Outcome	Group, No./total No. (%)		Bayesian effect	Median (95% CrI)[b,d]	Posterior probability of benefit, %[c]
	Hypothermia (n = 88)	Normothermia (n = 78)[b]			
Primary outcome					
Death or moderate or severe disability	29/83 (35)	20/69 (29)	aRD	0.04 (−0.08 to 0.18)	26
			aRR	1.11 (0.74 to 2.00)	26
Secondary outcomes[e]					
Any death	18/83 (22)	9/69 (13)	aRD	0.05 (−0.05 to 0.26)	13
			aRR	1.38 (0.79 to 2.85)	13
Survival with moderate or severe disability	11/83 (13)	11/69 (16)	aRD	−0.02 (−0.15 to 0.09)	68
			aRR	0.86 (0.46 to 1.63)	68
Death or severe disability	27/83 (32)	20/69 (29)	aRD	0.02 (−0.11 to 0.15)	38
			aRR	1.05 (0.67 to 1.82)	38
Death or moderate or severe disability with initial moderate NE	9/56 (16)	6/48 (12)	aRD	0.03 (−0.09 to 0.14)	32
			aRR	1.18 (0.59 to 2.41)	32
Death or moderate or severe disability with initial severe NE	20/27 (74)	14/21 (67)	aRD	0.06 (−0.14 to 0.26)	28
			aRR	1.09 (0.81 to 1.53)	28
Cause of death: asphyxial brain injury	15/18 (83)	5/9 (56)	aRD	0.10 (−0.13 to 0.36)	18
			aRR	1.17 (0.80 to 2.19)	18
Cause of death: multiorgan failure	2/18 (11)	2/9 (22)	aRD	−0.04 (−0.27 to 0.15)	69
			aRR	0.8 (0.32 to 2.04)	69
Clinical seizures after randomization	13/86 (15)	11/75 (15)	aRD	0.0 (−0.12 to 0.13)	47
			aRR	1.02 (0.55 to 1.92)	47

likelihood of a treatment being effective or beneficial

Faix RG, et al. *JAMA Pediatrics* 2025

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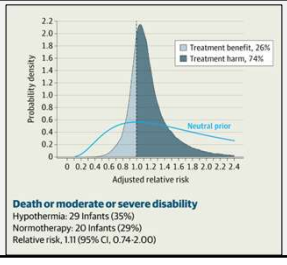
FINDINGS: WHOLE-BODY HYPOTHERMIA AT <6 H DID NOT REDUCE DEATH OR MODERATE OR SEVERE DISABILITY



Death or moderate or severe disability
Hypothermia: 29 Infants (35%)
Normotherapy: 20 Infants (29%)
Relative risk, 1.11 (95% CI, 0.74-2.00)

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HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY AT 33-35 WEEKS

Gestational Age	Death or Moderate/Severe Disability (%)		Death (%)	
	Hypothermic (N=83)	Normothermic (N=69)	Hypothermic (N=85)	Normothermic (N=71)
33-0/7 to 6/7 weeks	13/31 (42)	6/17 (35)	5/31 (16)	4/19 (21)
34-0/7 to 6/7 weeks	9/24 (38)	10/32 (31)	8/26 (31)	2/32 (6)
35-0/7 to 6/7 weeks	7/28 (25)	4/20 (20)	5/28 (18)	3/20 (15)

Faix RG, et al. *JAMA Pediatrics* 2025

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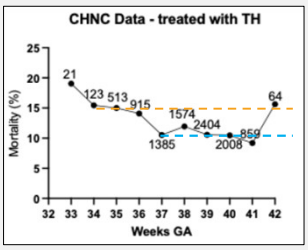
PRELIMINARY DATA FROM CHNC INDICATES CHANGE IN MORTALITY <36 WEEKS

CHNC



CHNC data, *pre-preparation*

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IMPLICATIONS

ARCH PEDIATR ADOLESC MED/VOL 165 (NO. 8), AUG 2011 WWW.ARCHPEDIATRICS.COM
ONLINE FIRST | JOURNAL CLUB

Whole-Body Hypothermia for Term and Near-Term Newborns With Hypoxic-Ischemic Encephalopathy

A Randomized Controlled Trial

Susan E. Jacobs, MD; Colin J. Morley, MD; Terrie E. Inder, MD; Michael J. Stewart, MD; Katherine R. Smith, MBInstat; Patrick J. McNamara, MD; Ian M. R. Wright, MD; Haresh M. Kirpalani, MD; Brian A. Darlow, MD; Lex W. Doyle, MD; for the Infant Cooling Evaluation Collaboration

The ICE trial was a multicenter randomized controlled trial for term and near-term infants with moderate or severe HIE

Participants were ≥ 35 weeks

The total number of 35 weeks' GA in ICE trial : 7

- *2 randomized to control (1 death, 1 normal survivor)*
- *5 to cooling (2 deaths, 2 survivors with moderate disability, 1 normal survivor).*

American Academy of Pediatrics

COMMITTEE ON FETUS AND NEWBORN

CLINICAL REPORT

Hypothermia and Neonatal Encephalopathy

This Clinical Report was reaffirmed September 2021.

Recommendation: "moderate hypothermia initiated within 6 hours of birth and continued for 72 hours is a safe and modestly effective neural rescue strategy for infants born *at greater than 35 weeks* of gestational age who have clinical evidence of moderate or severe neonatal encephalopathy."

"Cooling infants who are born *at less than 35 weeks'* gestation …should only be performed in a research setting and with informed parental consent."

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CRITERIA FOR THERAPEUTIC HYPOTHERMIA AT CHCO

Gestational Age ≥35 weeks and ≤6 hours of age AND

Acute Perinatal Event

- Apgar score ≤5 at 10 minutes after birth **OR**
- Continued need for resuscitation at 10 minute after birth **OR**
- pH <7.00 or base deficit ≥16 mmol/L or more on an umbilical cord sample or an arterial or venous blood sample obtained within 60 minutes of birth

AND

Encephalopathy

- Moderate or severe encephalopathy on clinical exam **AND**
- Moderately or severely abnormal background of at least 20- or 30-minutes duration or seizure activity on aEEG after one hour of age

HCO:
wks cooled
te

Harisa Spahic, MD

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IMPLICATIONS

JAMA Pediatrics | Original Investigation

Whole-Body Hypothermia for Neonatal Encephalopathy in Preterm Infants 33 to 35 Weeks' Gestation
A Randomized Clinical Trial

Roger G. Faix, MD; Abbot R. Laptook, MD; Seetha Shankaran, MD; Barry Eggleston, MS; Dhuly Chowdhury, MS, MBA; Roy J. Heyne, MD; Abhik Das, PhD; Claudia Pedroza, PhD; Jon E. Tyson, MD, MPH; Courtney Wusthoff, MD, MS; Sonia L. Bonifacio, MD; Pablo J. Sánchez, MD; Bradley A. Yoder, MD; Matthew M. Laughon, MD, MPH; Diana M. Vasil, MSN, BSN, RNC-NIC; Krisa P. Van Meurs, MD; Margaret M. Crawford, BS, CCRP; Rosemary D. Higgins, MD; Brenda B. Poindexter, MD, MS; Tarah T. Colaizy, MD, MPH; Shannon E. G. Hamrick, MD; Lina F. Chalak, MD, MSCS; Robin K. Ohls, MD; Michele E. Hartley-McAndrew, MD; Kevin Dysart, MD; Carl T. D'Angio, MD; Ronnie Guillet, MD, PhD; Stephen D. Kicklighter, MD; Waldemar A. Carlo, MD; Gregory M. Sokol, MD; Sara B. DeMauro, MD, MSCE; Anna Maria Hibbs, MD, MSCE; C. Michael Cotten, MD, MHS; Stephanie L. Merhar, MD, MS; Roopali V. Bapat, MD, MSHQS; Heidi M. Harmon, MD, MS; Elizabeth Sewell, MD; Sarah Winter, MD; Girija Natarajan, MD; Ricardo Mosquera, MD, MS; Susan R. Hintz, MD, MSEpi; Nathalie L. Maitre, MD, PhD; Kristen L. Benninger, MD, MSc; Myriam Peralta-Carcelen, MD, MPH; Abbey C. Hines, PsyD; Andrea F. Duncan, MD, MSCI; Nilles, Deanne E. Wilson-Costello, MD; Andrea Trembath, MD, MPH; William F. Malcolm, MD; Michele C. Walsh, MD, MS; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

"Our findings for 48 infants born at 35 weeks' GA provide no support for hypothermia at that GA."

What do we do now?

1. Stop offering TH to 35-week GA infants with HIE?
2. Provide informed consent to parents of 35-week GA infants with HIE?
3. Collect retrospective data at our center for these patients and then decide?
4. CHNC HIE sub-committee is collecting data to publish its experience

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NOVEL PRE-CLINICAL MODEL OF HIE

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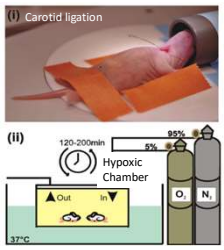
Vannucci Model of Hypoxia Ischemia has been the gold standard since 1981

- Gold standard in hypoxic injury since 1981
- Used in mice or rats
- Performed at post natal day 7-10 (p7-10), which is equivalent to full term human brain
- Has provided important data, including early studies on therapeutic hypothermia
- Has limitations, such as a lack of reperfusion



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JAMA Network Open.

Invited Commentary | Pediatrics

Taking Stock After Another Negative Erythropoietin Neuroprotection Trial

Thomas R. Wood, BM, BCh, PhD; Sandra E. Juul, MD, PhD

What can we learn from these results?

1. These results highlight the importance of adequately powered phase 3 RCTs
   - Meta-analyses of smaller phase 2 trials cannot substitute well-conducted phase 3 trials
2. Highlight the importance of preclinical trials in the development of future neuroprotective agents
   - Experiments must be adequately powered and evaluate male and female subjects separately
3. Better pre-clinical models must be developed that model the aspects of injury

JAMA Netw Open. 2022;5(12):e2247054.

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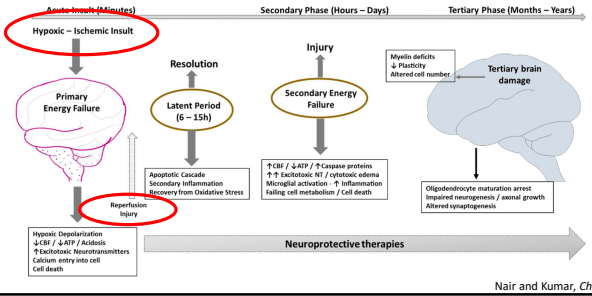
A better model would replicate the important phases of injury



Nair and Kumar, *Children* 2018

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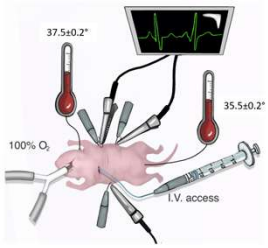
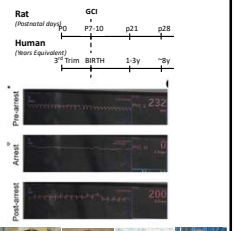
Neonatal Global Ischemia Model induced by CA/CPR





Nidia Quillinan, PhD Andra Dingman, MD Erica Tiemeier April Fineberg

Langer K, et al. *in preparation*

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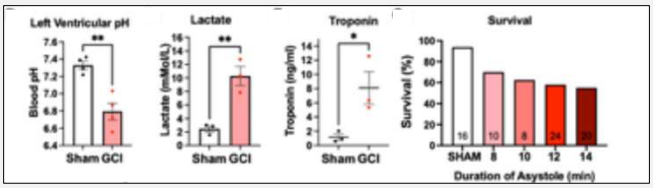
Neonatal Global Ischemia Model



Langer K, et al. *in preparation*

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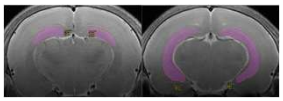
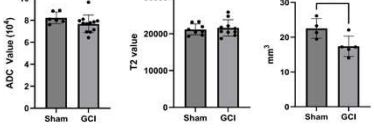
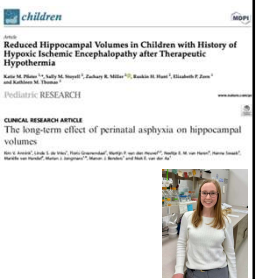
Consistent with HIE, MRI shows reduced hippocampal volume







Jamie Henry

Langer K, et al. *in preparation*

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THERAPEUTIC HYPOTHERMIA MAY NOT PROTECT THE HIPPOCAMPUS

scientific reports (2021) 11:5017 |

OPEN

Mammillary body atrophy and other MRI correlates of school-age outcome following neonatal hypoxic-ischemic encephalopathy

Kim V. Annink[1], Linda S. de Vries[2], Floris Groenendaal[2], Rian M. J. C. Eijsermans[1], Manouk Mocking[1], Monique M. J. van Schooneveld[2], Jeroen Dudink[2], Henrica L. M. van Straaten[2], Manon J. N. L. Benders[2], Maarten Lequin[3,4] & Niek E. van der Aa[3,4]

"Hippocampal volume and MB atrophy were strongly associated with neurocognitive outcome and episodic memory at 10 years of age. In non-cooled infants, the association between of hippocampal volumes and episodic memory functioning has been described previously. The present study confirmed those findings in cooled infants."

"We were able to show that memory and cognitive problems can develop at school-age even in children who were treated with therapeutic hypothermia."

"…therapeutic hypothermia does decrease neonatal death, CP, and epilepsy, but might not sufficiently protect the brain to prevent cognitive and memory problems at school-age."

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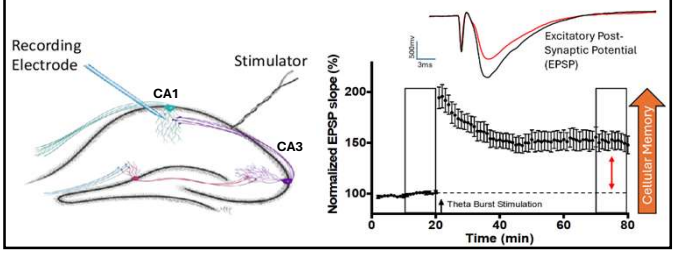
Long Term Potentiation is a tool to measure hippocampal function

- Cellular model for learning and memory



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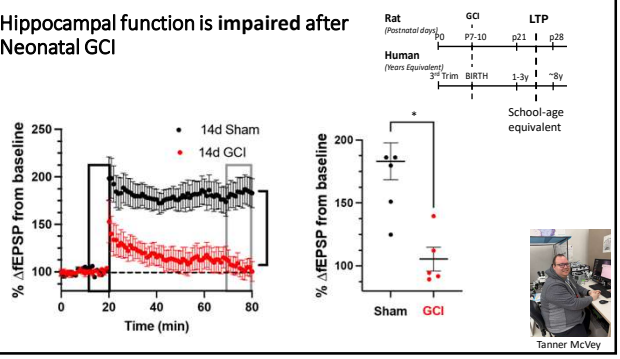
Hippocampal function is impaired after Neonatal GCI



Tanner McVey

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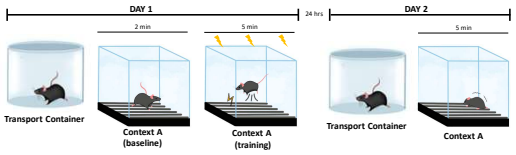
Behavior Testing: Memory and Learning

- Contextual Fear Conditioning (CFC) is a hippocampal dependent task and is considered a model of human declarative memory



A rat that freezes more indicates intact learning and memory

Jamie Henry

Figure modified from Moreno M, et al. *Neurobiol Dis.* 2022

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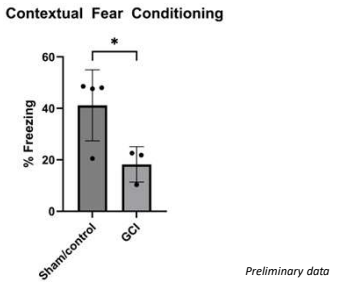
Hippocampal function is impaired in CFC



Preliminary data

Jamie Henry

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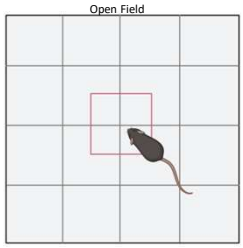
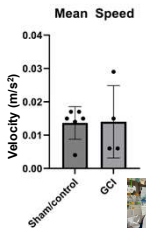
No deficit in motor function 14 days after GCI





Jamie Henry

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MECHANISTIC STUDIES:
DOES HYPEROXIA INDUCE HIPPOCAMPAL DEFICITS

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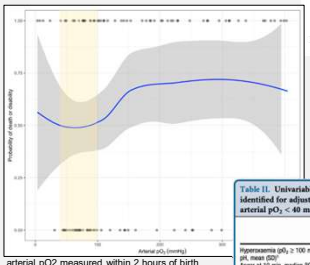

arterial pO2 measured within 2 hours of birth

THE JOURNAL OF PEDIATRICS • www.jpeds.com Volume 267 • April 2024 ORIGINAL ARTICLES

Early Hyperoxemia and 2-year Outcomes in Infants with Hypoxic-ischemic Encephalopathy: A Secondary Analysis of the Infant Cooling Evaluation Trial

Shiraz Badurdeen, MPRCPCH, PhD[1,2,3,*], Jeanie L. Y. Cheong, FRACP, PhD[1,4,5,6], Susan Donath, MA[7], Hamish Graham, FRACP, PhD[2,3], Stuart B. Hooper, PhD[8,9], Graeme R. Polglase, PhD[8,9], Sue Jacobs, FRACP, PhD[1,4,6], and Peter G. Davis, FRACP, MD[1,4,6]

"arterial hyperoxemia within 2 hours of birth increased the risk of death or disability, following adjustment for severity of perinatal hypoxic-ischemia and pCO2."

Table II. Univariable analysis of the relationship between the exposure of interest (hyperoxaemia) and the covariates identified for adjustment from the directed acyclic graph with the study outcome (death/disability). Infants with arterial pO_2 < 40 mmHg (n = 5) and extreme outliers for pO_2 (>500 mmHg, n = 5) were excluded

	Infants who died or had major disability (n = 60)	Infants who survived without major disability (n = 46)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)[a]	*P* value from adjusted model[a]
Hyperoxaemia (pO_2 ≥ 100 mmHg), mmHg	40 (67%)	18 (39%)	1.86 (1.21 – 2.00)	1.61 (1.07 – 2.00)	.03
pH, mean (SD)[a]	6.88 (0.22)	6.98 (0.20)	0.23 (0.03 – 0.87)		
Apgar at 10 min, median [IQR][a]	4 [2 – 5]	4 [3 – 5]	0.53 (0.24 – 0.90)		
Time to first breath, min, median [IQR][a]	15 [8 – 25]	7 [4 – 10]	1.31 (1.15 – 1.45)		
Adrenaline	36 (60%)	13 (28%)	1.74 (1.31 – 2.06)		
Arterial pCO_2, mmHg, median [IQR][a]	31 [23 – 44]	35 [28 – 42]	0.74 (0.40 – 1.11)		

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Does 100% oxygen contribute to neurologic impairment in following Neonatal GCI?

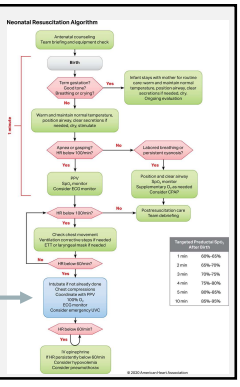
Data from Vannucci Model

Resuscitation with 100% oxygen increases injury and counteracts the neuroprotective effect of therapeutic hypothermia in the neonatal rat

Marit L. Dalen[1], Xun Liu[1], Maja Ehstad[2], Else-Marit Løberg[3], Ola D. Saugstad[1], Terje Rootwelt[4] and Marianne Thoresen[1,2]

Brief exposure to hyperoxia depletes the glial progenitor pool and impairs functional recovery after hypoxic-ischemic brain injury

Joshua D Koch[1,2], Darryl K Miles[1,2], Jennifer A Gilley[1,2], Cui-Ping Yang[1,2] and Steven G Kernie[1,2]



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Hyperoxia leads to Reactive Oxygen Species (ROS) production in Hypoxic-Ischemia and Reperfusion

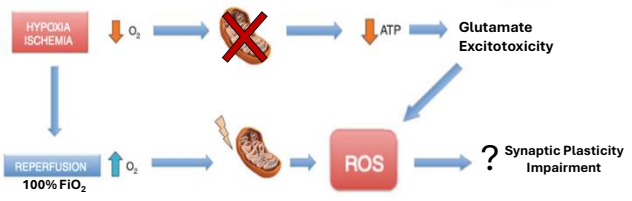

Figure modified from Martini S, et al. *Pediatric Research*. 2020

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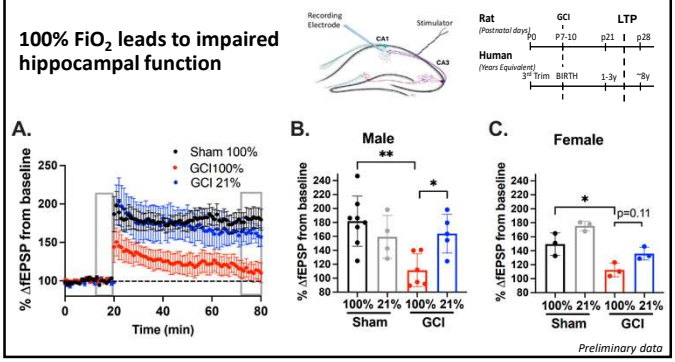
100% FiO_2 leads to impaired hippocampal function



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IMPORTANT CAVEATS

- There is some data to suggest that cardiac function improves with resuscitation using 100% FiO_2
- It is unlikely that clinical care guidelines will change based on pre-clinical models, but may lead to thoughtful hypothesis driven clinical research
- This data has driven new mechanistic hypotheses (RO1)

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CONCLUSIONS

1. HIE continues to have high morbidity and mortality worldwide
2. The search for adjuvant therapy for therapeutic hypothermia remains elusive
3. Partnership with Pia Wintermark, MD on SANE-II in coming months
4. We need to re-evaluate whether cooling 35-week GA HIE patients is best practice
5. Novel pre-clinical models are needed to further explore mechanistic interventions

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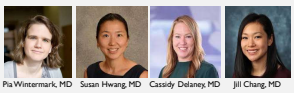
Acknowledgements and Gratitude

SANE-II



Pia Wintermark, MD Susan Hwang, MD Cassidy Delaney, MD Jill Chang, MD

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Section of Neonatology
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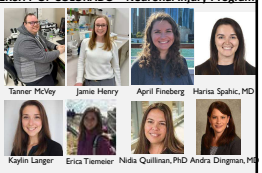
UNIVERSITY OF COLORADO – Neuronal Injury Program



Tanner McVey Jamie Henry April Fineberg Harisa Spahic, MD

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Intermountain Health

Intrauterine Devices and Other Updates in Postpartum Hemorrhage Management

46th Annual L. Joseph Butterfield Perinatal Conference
9/18/2025

Theresa Fisher, MD
OB Hospitalist
Platte Valley Hospital

1

Learning Objectives

- Understand the limits of PPH prediction and measurement
- Apply evidence based interventions for pharmacologic PPH management
- Compare intrauterine devices for PPH treatment

2

2

Historical
≥500 mL @ vaginal delivery
OR
≥1000 mL @ cesarean delivery

↓

ACOG 2017
≥1000 mL within 24 hrs of delivery
OR
signs/symptoms of hypovolemia

Postpartum Hemorrhage Definitions

- **QBL 500 - 1000 mL at vaginal delivery still needs evaluation and monitoring**
- **Low morbidity at QBL 500 - 1000 mL (Anger, 2019)**
  - Hgb drop > 2 g/dL
  - Postpartum Hgb < 10 g/dL
  - Need for transfusion
- **Minimal difference in Hgb drop after vaginal delivery vs cesarean delivery (1.4 vs 1.9) (Hamm, 2017)**

3

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Postpartum Hemorrhage Definitions

CMQCC 2022

Stage 0	Stage 1	Stage 2	Stage 3
All births	EBL ≥ 500 mL vaginal OR ≥ 1000 mL cesarean OR abnormal vital signs	Continued bleeding or VS instability AND EBL < 1500 mL	EBL > 1500 mL OR transfusion > 2u PRBC OR abnormal VS OR DIC

AWHONN 2025

Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
< 500 mL	500 ml - 999 mL	Up to 1500 mL	> 1500 mL	Cardiovascular collapse

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Stage 1	Triggers: CBL ≥ 500mL vaginal / ≥ 1000 mL cesarean with *continued bleeding* or Signs of concealed hemorrhage: VS abnormal or trending (HR ≥ 110, BP ≤ 85/45, O2 sat < 95%, shock index 0.9) or Confusion		
• Activate hemorrhage protocol • Rule out hemorrhage causes besides atony	• Activate OB hemorrhage protocol and checklist • Notify charge nurse, OB/ CNM, anesthesiologist • VS, O2 Sat q5 min • Record quantitative cumulative blood loss q5-15 min • Careful inspection with good exposure of vaginal walls, cervix, uterine cavity, placenta. If intra-op, inspect broad ligament, posterior uterus and placenta.	• **IV Access: Minimum 18 gauge** • Increase IV fluid (LR) and **oxytocin** rate • **Fundal/bimanual massage** **MOVE ON** to 2nd level uterotonic if no response (see Stage 2 meds below) • Empty bladder: Straight cath or Foley with urometer	• **Convert to High Risk and take appropriate precautions** Consider T&C 2 Units PRBCs *where clinically appropriate if not already done*

CMQCC Quality Improvement Tool Kit

Intermountain Health

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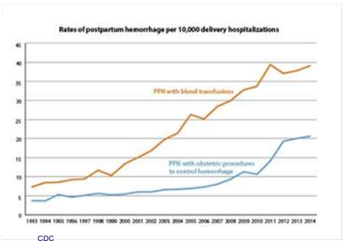
Significance



CDC

- Rate of PHH has continued to rise
  - 2.7% to 4.3%
- PPH is the 4th leading cause of maternal mortality in the US
  - 11-12% of maternal deaths
- Highly preventable
  - Nearly 2/3 of deaths
- Leading cause of severe maternal morbidity in the US

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Postpartum Hemorrhage Risk Prediction

Joint Commission requires a PPH risk assessment on admission

>30 risk prediction tools have been published in the last 10 years

None are sufficiently validated for clinical use - but better than nothing?

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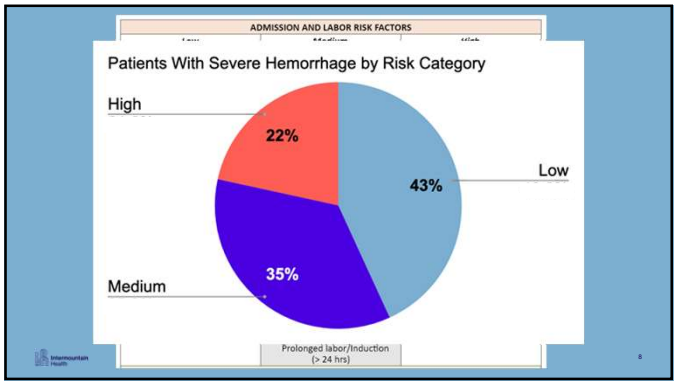

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Postpartum Hemorrhage Risk Prediction

Joint Commission requires a PPH risk assessment on admission

>30 risk prediction tools have been published in the last 10 years

None are sufficiently validated for clinical use - but better than nothing?

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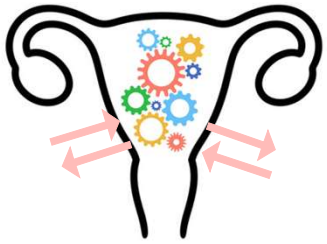
Future Advances

AI Modeling

- Flexible and dynamic
- Large number of data points
- Binary vs continuous variable
- Need large data sets
  - Affected by age and quality
  - Risk of overfitting



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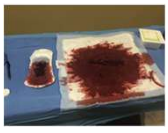
Blood Loss Calculations

Visual assessment

Gravimetric

Volumetric

Colorimetric



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Colorimetric Blood Loss

- Uses image capture and AI to quantify Hgb
  - Surgical sponges
  - Fluid canisters
- Real time QBL
- Improved diagnosis, ?? outcomes
- $$$

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Shock index

$$\frac{\text{HR}}{\text{Systolic BP}} \geq 0.9$$

- Long standing use in trauma patients
- Associated with postpartum adverse maternal outcomes
- OB SI
  - Pregnancy: 0.7 - 0.9
  - Postpartum 0.5 - 0.9
  - Intervention threshold > 1.1
  - Trend more helpful than single value

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Treatment and Prevention

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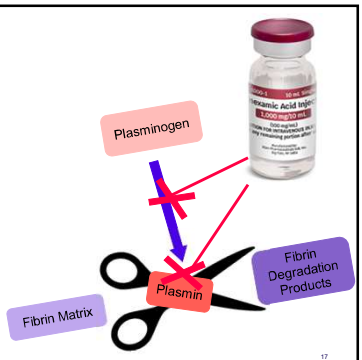
Tranexamic Acid

- Antifibrinolytic
- 1g / 10 minutes IV
  - Redose @ 30 mins if needed
- Contraindications
  - VTE in pregnancy
  - Hypercoagulable d/o
- Crosses placenta



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TXA for Postpartum Hemorrhage Treatment

Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

*WOMAN Trial Collaborators**

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TXA for Postpartum Hemorrhage ***Prevention***

Vaginal Birth

- WOMAN2 trial
  - Anemia (Hgb <10)
  - 1g TXA within 15 minutes of cord clamping
  - No difference in PPH rate
    - Timing issue??
- TRAAP
  - 4000 vaginal births
  - No difference in PPH (≥500 mL)
    - Subjective reduction in PPH & less uterotonic use

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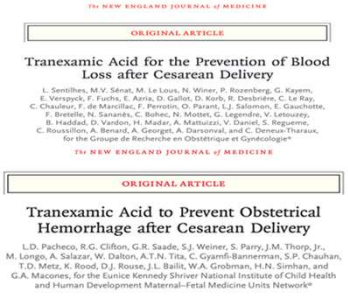
TXA for Postpartum Hemorrhage ***Prevention***

Cesarean Birth

- TRAAP2 trial
  - Reduced risk of PPH by 16%
  - BUT only 100 mL difference in CBL
- MFMU
  - No difference in death, transfusion, QBL > 1L


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid for the Prevention of Blood Loss after Cesarean Delivery

L. Sentilhes, M.V. Sénat, M. Le Lous, N. Winer, P. Rozenberg, G. Kayem, E. Verspyck, F. Fuchs, E. Azria, D. Gallot, D. Korb, R. Desbrière, C. Le Ray, C. Chauleur, F. de Marcillac, F. Perrotin, O. Parant, L.J. Salomon, E. Gauchotte, F. Bretelle, N. Sananès, C. Bohec, N. Mottet, G. Legendre, V. Letouzey, B. Haddad, D. Vardon, H. Madar, A. Mattuizzi, V. Daniel, S. Reguerre, C. Roussillon, A. Benard, A. Georget, A. Darsonval, and C. Deneux-Tharaux, for the Groupe de Recherche en Obstétrique et Gynécologie*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid to Prevent Obstetrical Hemorrhage after Cesarean Delivery

L.D. Pacheco, R.G. Clifton, G.R. Saade, S.J. Weiner, S. Parry, J.M. Thorp, Jr., M. Longo, A. Salazar, W. Dalton, A.T.N. Tita, C. Gyamfi-Bannerman, S.P. Chauhan, T.D. Metz, K. Rood, D.J. Rouse, J.L. Balli, W.A. Grobman, H.N. Simhan, and G.A. Macones, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

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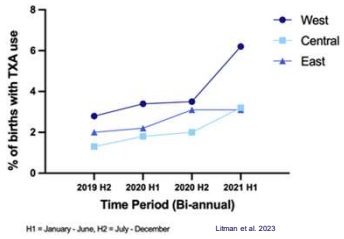
TXA for Postpartum Hemorrhage

Trends in Use

- Increased use since 2017
  - 0.5% to 2.5%
- 15% are receiving TXA pre-delivery
- Given in 10% of cases of PPH



H1 = January - June, H2 = July - December

Litman et al. 2023

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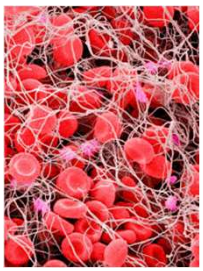
TXA for Postpartum Hemorrhage

Takeaways

- Safe
- Sooner is probably better
- TXA useful adjunct in treatment of PPH
- Unclear benefit for prevention of PPH
  - Maybe in special populations?
  - Maybe if given earlier?



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Farewell to Misoprostol??

- Benefits
  - Cheap, shelf stable, few contraindications
- Side effects
  - Shivering, fever, GI upset
- Route matters!
- CMCQC now recommend against routine use of misoprostol
  - Consider in patients with contraindications to other uterotonics

	Onset	Duration
Oral	8 min	2 hours
Sublingual	11 min	3 hours
Vaginal	20 min	4 hours
Rectal	100 min	4 hours

Gibbons et al. 2013

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Emerging Intervention

IV Calcium

- Smooth muscle requires extracellular calcium
- Benefits
  - Cheap
  - Available
  - Few contraindications, safe
- Ansari, 2024
  - Intrapartum cesarean delivery
    - Placebo controlled RCT
    - ~350 mL reduction QBL in subgroup

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Intrauterine Devices

Bakri® Postpartum Balloon, Cook Medical

JADA® System,Organon Pro

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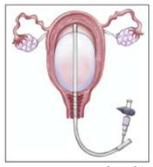
Intrauterine Tamponade Balloon

- Bakri, BT-Cath, ebb
- All apply outward pressure on the uterus
- High success (86-88%)
  - SVD, CD
  - atony, placental site
- Timing of placement?
- Antibiotics
- Timing of Removal



Suarez, Sebastian et al. 2020

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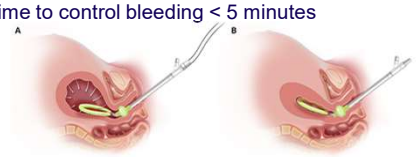
Vacuum Induced Hemorrhage Control

- JADA® system
- Intrauterine negative pressure
- RUBY study
  - 90% treatment success
  - Average time to control bleeding < 5 minutes



D'Alton et al. 2021

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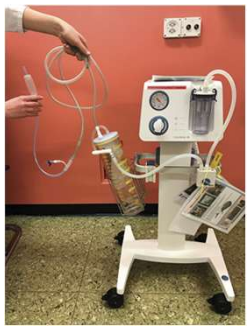
Modified Bakri

- Off-label use
- Balloon inflated with 50-100 cc
- Catheter connected to suction
  - 60-70 kPa
- Atony
  - 73 - 100% success
- Placental
  - 50 - 86% success



Haslinger et al, 2021

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Compare and Contrast

Intrauterine Tamponade Balloon		Vacuum-Induced Hemorrhage Control Device
$250-300	**Cost**	$1000
Up to 24 hrs	**Removal**	1.5 - 24 hrs
6 - 12 hrs	**Average**	2.5 hrs
Above or below	**CS Placement**	Below only
??	**Dilation**	≥ 3 cm

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Compare and Contrast

Intrauterine Tamponade Balloon		Vacuum-Induced Hemorrhage Control Device
NA	**Gestation Age**	≥ 34 wks
Atony, placental site	**Indication**	Atony
None	**Equipment**	Portable or wall suction

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Outcomes Comparisons

- Shields et al. 2024
  - Prospective, observational
  - No difference in:
    - QBL post-device placement
    - Transfusion
    - Device Failure
  - Both devices performed better @ QBL 1000 to 1499
- Chan et al. 2025 (July!)
  - VDH reduced QBL, transfusions, indwelling time

Need an RCT!

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Antibiotics

- Limited evidence, no RCTs
- Wong et al 2019
  - Retrospective
  - 59 received prophylactic antibiotics and 54 did not
  - 5 vs 26 % rate of chorioamnionitis
- Cefazolin 2 g IV every 6 hours
  - X1 dose for vacuum-induced hemorrhage control device
  - Skip 1st dose @ c-section

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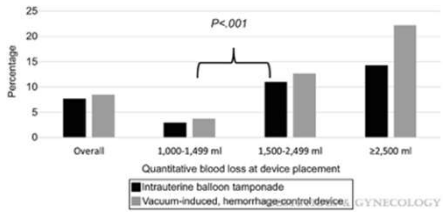
Failure Rates



Shields et al 2025

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Clinical Practice Update

ACOG
The American College of Obstetricians and Gynecologists

UPDATED CLINICAL RECOMMENDATION

The American College of Obstetricians and Gynecologists (ACOG) recommends that hospitals and other facilities that care for and transport obstetric patients have access to nonsurgical hemorrhage-control devices (ie, uterine balloon tamponade or intrauterine vacuum-induced hemorrhage-control devices) as part of a comprehensive management algorithm for postpartum hemorrhage (PPH).

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Limits to postpartum hemorrhage research

Heterogeneity in:

- Definitions
- Tools
- Management

Low resource vs high resource countries

Bundles >> Single interventions

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Takeaways

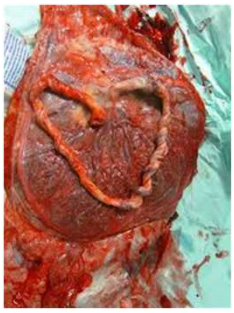
Bundles, policies and protocols increase awareness —> improved outcomes

Almost half of postpartum hemorrhages occur in low risk patients

TXA is helpful in PPH, maybe not for PPX

Stop using rectal misoprostol

Intrauterine devices successfully manage refractory PPH



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Questions?

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Seeing the bigger picture: Retinopathy of Prematurity, Quality Improvement, and Nutrition

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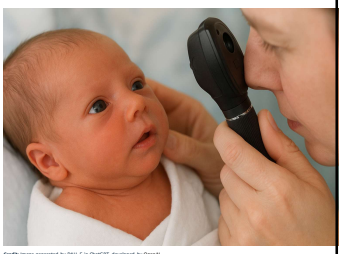
Learning Objectives

1. Summarize ROP pathophysiology and epidemiology
2. Discuss key ROP risk factors and prevention opportunities in the NICU – emphasis on nutrition
3. Describe current ROP screening & diagnostic standards
4. Identify QI strategies to reduce ROP incidence and severity



Credit: Image generated by DALL-E in ChatGPT, developed by OpenAI

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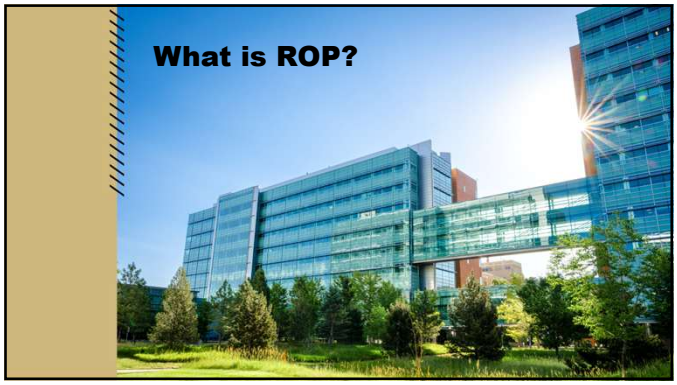

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ROP: The What & Why

Background

- ***Proliferative vascular disorder*** of the incompletely vascularized retina seen in preterm infants
- Interruption of normal retinal development due to prematurity & exposure to peri/post-natal factors impacting vascular development
  - Hyperoxia/relative hypoxia cycles → growth factor dysregulation → abnl neovascularization
- Potential progression to retinal detachment and blindness

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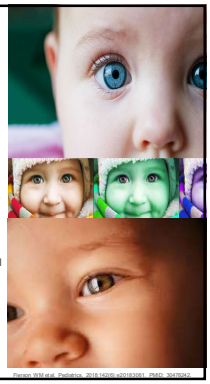

Flaxen, RW et al. Pediatrics. 2018;142(6):e20183381. PMID: 30478242

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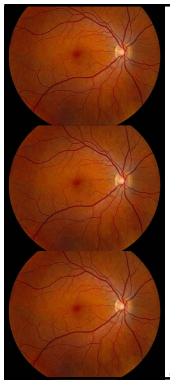

Pathophysiology

Normal retinal development

- **No vessels on retina at < ~16 weeks gestation** (external vascular supply)
  - Vasculogenesis and then angiogenesis begin to extend ***outwards from the optic disc***
- Vascular Endothelial Growth Factor (VEGF) is necessary for normal angiogenesis:
  - Developing retinal tissue has increased oxygen demand → local hypoxia → local VEGF expression → growth by following a a 'wave' of hypoxia
- Retinal vascularization completes at 36 - 40 weeks' gestation
  - Nasal @ 36 wks, temporal @40wks
  - Delayed until 48-52 weeks PMA in preterm infants

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Credit: Ophthalmic Atlas: Images by AveSeeds.org, The University of Iowa

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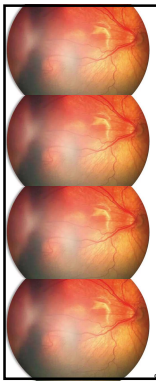

Pathophysiology

Abnormal **(disrupted) retinal development**

- ROP development is a complex interplay of factors (thought to involve two stages)
- Phase 1: ***Hyperoxia triggers vasoconstriction, down-regulation of angiogenic factors***
  - Intrauterine hypoxia → O_2-rich environment disrupts angiogenic balance
  - Immature retinal vasculature is exposed to: **Hyperoxia**, **hemodynamic shifts** (ex - hypotension), **inflammation/free radicals**
  - Immature blood-retinal barrier: ↑ susceptibility to inflammation/oxidative stress
- Phase 2: ***Hypoxia triggers up-regulation of angiogenic factors*** (notably VEGF)
  - Aberrant neovascularization (avascular retina → vitreous)
  - Fragile vessels → edema, hemorrhage, fibrovascular proliferation, and detachment

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Credit: Ophthalmic Atlas Images by EyeRounds.org, The University of Iowa

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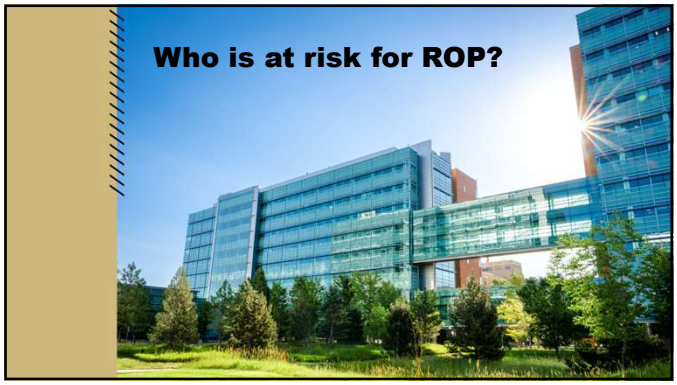

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ROP Epidemiology & Risk Factors

Factors impacting ROP include:

- **Gestational Age** & Birth Weight
- **Oxygen exposure**
- **Postnatal growth and other nutritional factors/deficiencies**
- Mechanical ventilation (> 1 week)/RDS (surfactant)
- BPD
- Sepsis/Infection (fungal)
- NEC
- Hyperglycemia
- High blood transfusion volume
- IVH/hydrocephalus
- Genetic factors

Incidence and severity vary across centers/ regions; **care practices impact risk**

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Chen ML et al. Pediatrics. 2010;125:e1483–e1491. PMCID: PMC4016714; Kim ES. Pediatr Ann. 2023. PMID:37561825.

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ROP Risk Factors

Gestational Age

- Of infants **< 31 weeks or 1500g**, ROP incidence is **25-56%** (all severities)
  - Most ROP is relatively 'mild', not requiring treatment
  - Severe ROP = 10-20% total ROP cases
- Inverse relationship of GA & ROP
  - Lower GA = ↑ risk of morbidities that ↑ ROP
- With advanced NICU care, most ***severe*** ROP occurs < 28 wks (< 25 wks = highest risk)
  - 22 to <25 WGA with *severe* ROP: 43% (90% have some severity of ROP)
  - 25 to <27 WGA with *severe* ROP: 21%
  - 27 to 30 WGA with *severe* ROP: 3%

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Todd et al. Arch Dis Child Fetal Neonatal Ed. 2007. PMID: 17251225.

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ROP Risk Factors

Oxygen exposure

- ***Hyperoxia*** and wide ***fluctuations in arterial oxygen tension*** (PaO2) are harmful
  - Increased oxidative stress and endothelial injury
  - Targeting/maintaining a goal oxygen saturation range is important (VEGF pathway; reduces severe ROP)
- Optimal oxygenation to balance the risk of ROP against improved survival is unknown
  - Studies have compared various oxygen saturation targets (not *actual* patient oxygen saturation levels) - SUPPORT, STOP-ROP, BOOST, COT, NeOProM (combines 5 studies)
  - Lower (85-89%) as compared to higher (91-95%) oxygen targets were associated with increased mortality and NEC ***BUT*** decreased ROP and BPD.

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Askie et al. *N Engl J Med.* 2003, Stenson et al. *JAMA.* 2016, Saugstad et al. *Neonatology.* 2014.

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ROP Risk Factors

Oxygen exposure

- ***Which oxygen saturation targets ↓ ROP but don't increase mortality in extremely premature infants and how do we consistently achieve them?***
- ↓ severe ROP incidence/severity without ↑ mortality by *gradually* increasing saturation targets:
  - Prevent early hyperoxia and later retinal hypoxia (compared to static oxygen saturation targets)
  - Less progression of ROP once it develops by targeting higher saturation goals
- Reduce fluctuating saturations:
  - Automated oxygen control, cerebral NIRS, and other tools warrant study

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Raghuveer et al. *Neoreviews.* 2020, Minkum et al. *BMC Ophthalmology.* 2024.

12

ROP Prevention - Protective Factors

Interventions associated with LOWER rates of ROP

- Antenatal steroids
- Delayed cord clamping
- Caffeine
- Adhering to evidence-based unit protocols
- Breastmilk feeding, optimized growth, & other dietary factors

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Raghuveer, et al. Neoreviews. 2020; Cochrane Database Syst Rev. 2018; (8):CD003248.

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Suggested Nutrition Strategies to Prevent Severe ROP

- Vitamin A
- DHA and ARA fatty acids
- Vitamin E
- Zinc
- Iron

Also:

- Human Milk/Maternal Milk
- Glucose control
- Appropriate Weight Gain
- Enhanced nutrition

Zhang, HB. 2018; Raghuveer, T. 2020; Prasad M 2023; Koc, E. 2024; Hellström, A. 2025; Rashidian, P. 2025

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Vitamin A

ROLE IN EYE HEALTH

- Supports epithelial tissue health, including the retina
- Essential for the development and differentiation of photoreceptor cells (opsins)

DEFICIENCY RISK

- Reduced transplacental transport
- Inadequate intake
- Poor absorption

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Vitamin A

- **2023 Mahmoud:** 1,500 IU/day Vit A or beta blockers or O2 therapy. n=186
  - Reduced progression from ROP grade I to II (4.6%) versus beta-blockers (59.1%) or control (36.4%) *P* < 0.001
  - Avoided new-onset ROP at four weeks and exhibited significantly higher rates of stable mild ROP
- **2020 Sun:** 1,500 IU/day, n=262
  - Raised serum vitamin A levels and resulted in lower incidence of Type 1 ROP (1.6% vs 6.9%, *P* = 0.03)

Standard NICU care provides

- 1,650-2350 IU/day with fortifier and MVI
  - Using method of estimation described by Sun
- Infants 0.5 kg: 675-810 IU/day w/o MVI
- Infants 1 kg: 1350-1625 IU/day w/o MVI

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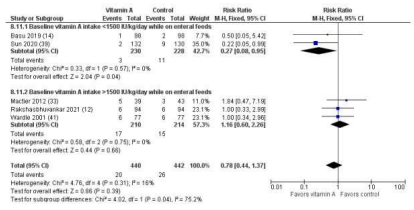
Meta Analysis of RCTs: Vitamin A supplementation in Very-preterm or VLBW infants to prevent morbidity and mortality.

Supplemental Figure 3: Effect of vitamin A supplementation on retinopathy of prematurity requiring treatment – subgroups based on baseline vitamin A intake



Local NICU practice provides (0.5-1.5kg)

- TPN MVI package: 1150 IU/kg/d
- Oral MVI: ~ 750 IU per mL
- Enteral 20-22k/oz: ~360-900 IU/kg/d
  - MVI added: 915-2500 IU/kg/d
- Enteral 24k-26k/oz: ~ 1515 IU/kg/d
  - MVI added: 2000-3100 IU/kg/d

Rakshasbhuvankar, et al. 2021

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DHA and ARA

Role in Eye Health

- Docosahexaenoic Acid (DHA) Omega 3 Fatty Acid
  - Promotes the structural development of retinal cells
  - Helps regulate inflammation and vascular development
  - Highly concentrated in retinal photoreceptors
- Arachidonic Acid (ARA) Omega 6 Fatty Acid
  - Essential for normal photoreceptor and neural and maturation
  - Supports healthy blood vessel formation in the retina
  - Regulates immune response and inflammation

Deficiency

- Placental transfer is highest in the final trimester
- Low capacity to synthesize
- Found in breast milk and added to formulas and fortifiers in small amounts to mimic breastmilk

With standard care premature infants have deficient levels compared to fetal accretion rates

Lapillone, 2010; Fu, 2022

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DHA

DHA supplementation alone has been tested for decades with inconsistent results of benefit:

- **2017 N3ro RCT**: 60 mg DHA did not lower risk of BPD, and intervention group had slightly higher rates of any BPD.
- **2020 Marc:** Halted study of maternal DHA-only supplementation (due to N3ro trial).
- **2025 Marc**: Individual Participant Meta-Analysis of previous two studies High-dose DHA (60 mg/kg/d)
  - was not significantly associated with BPD-related outcomes. (2 RCT, n=1801)

We now know:

- High DHA/ARA ratio causes blood ARA levels to decline
- Omega 6 (ARA) traditionally thought of as pro-inflammatory, but it also regulates inflammation resolution
- There is a synergistic effect with DHA and ARA

Wang, 2019 Colombo, 2015

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DHA and ARA

- **2022 Gillespie:** observational, n=56
  - Levels declined over time in all three groups
  - Type 1 ROP were more likely to be in the lowest ARAand DHA terciles than in the highest
  - A higher ARA% (≥ 17 was) associated with a 45%reduction in any ROP
- **2021-2024 Mega Donna Mega:** RCT, n=206
  - Risk of **severe** ROP was decreased by 50% in the supplemented group
  - Higher DHA levels were associated with less severe ROP with sufficient AA levels
  - Levels decline even with LC-PUFA containing IVFE
  - Every 1 % increase in ARA was associated with a reductionof BPD severity
    - Limited statistical power

Hellstrom, 2021 Pivodic, 2022 Wackernagel 2024

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DHA & ARA, continued.

- **2021-2023 Wendel ImNuT Trials:** DHA 50/ARA 100, n=121, four papers
  - Fewer days requiring respiratory support and lower FiO2 demand, but no signficant change to BPD at three months
  - Decrease markers of inflammation (IL-6)
  - Improved linear growth
- **2016 Robinson:** DHA 20/ARA 40 or DHA 60/ARA 120 or placebo, n=30
  - Doses did not affect fatty acid levels compared to placebo. Levels did not reach that of term infants.
- **2021 Frost:** Intervention: DHA 40/ARA 80 or DHA120/ARA 240 or placebo, n=30
  - Serum levels in placebo group declined, 40/80 dosing levels maintained, and 120/240 dosing levels increased but remained below levels reported for term infants

*Doses mg/kg/day

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ESPGHAN 2022 Rec & supplemental dose used in ROP RCT	Frost trial: dose to prevent declines (American)	Estimated Intake DHA/ARA 120k/kg	Gap to General Recommendations	Gap to Higher Dose
DHA 50 ARA 100	DHA 120 ARA 240	HMF+MBM DHA 29 ARA 47	DHA 21 ARA 53	DHA 91 ARA 193
(mg/kg/day)	(mg/kg/day)	Formula DHA 16 ARA 26	DHA 34 ARA 74	DHA 104 ARA 166

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Available Products

Single product available:

Mead Johnson DHA&ARA supplement

- Contains recommended 2:1 ratio. Per 0.5 mL: ARA 40 mg, DHA 20 mg
- Cost w/o formulary contract is $$$$ per case of 24 nursettes (60 mL)
- Expires 24 hours after opening

Enfamil® DHA & ARA Supplement

Liquid supplement to meet General Recs	Liquid supplement to meet Higher Dose
0.5-1.25 ml/kg/d	2-3 ml/kg/d
DHA 20-50 ARA 40-100	DHA 80-120 ARA 160-240

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Vitamin E

- Antioxidant that helps protect against free radicals and reduces oxidative stress in the retina
- Older observational data suggested high-dose vitamin E could reduce ROP severity but also increased risks of sepsis and NEC
- Routine high-dose vitamin E supplementation is not recommended due to safety concerns

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Zinc

- **2023 Mishra:** Observational, n=360
  - Low serum zinc concentrations (< 70µg/dL) were identified as an independent risk factor for the development of ROP
- Ability to check serum zinc levels in house is not common
- Current research shows zinc supplementation in preterm or LBW infants has benefits of increased weight, length, and head circumference
- Dosage 3 mg/kg/day
  - Generally safe and did not negatively affect copper levels
  - Higher amounts may be needed in very low birth weight (VLBW) infants, but evidence is less well established

Sinha, 2022

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Iron

- Deficiency is associated with ROP risk due to impaired oxygen delivery and retinal development.
- Iron overload is associated with ROP risk due to oxidative stress.
- Iron deficieny anemia occurs at high rates in premature infants.

No consensus guidelines

- Ferritin
  - Reflects iron stores and can be monitored for iron overload (> 400 ng/ml)
    - Elevated in the setting of inflammation
  - limited as a marker of sufficiency
- Hemoglobin and hematocrit are late indicators of deficiency
- Reticulocyte Hemoglobin Equivalent (RET-He)
  - Sensitive to acute changes in iron supply to the bone marrow
  - Not significantly affected by inflammation
  - Measured with the reticulocyte panel
  - Deficiency ≤29 pg

Moreno-Fernandez, 2019 Trevino-Baez, 2017 Amin, 2012 Pomrop, 2022

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ROP Screening

The who and when

- Screen all < 31 weeks or < 1500g (or 1500-2000g or > 30 weeks with high-risk course)
  - UK/Canadian guidelines: ≤1250g or < 31 weeks
- First exam is 31 weeks PMA or 4 weeks, whichever is **LATER**
  - Infants ≥ 27 wks at 4 wks, < 27 wks at 31 wks PMA
- Exam is done typically with Cyclomydril = phenylephrine and cyclopentolate, 30 mins or more before an exam
  - Side effects of meds + exam = bradycardia, arrhythmia, apnea, desaturation, emesis

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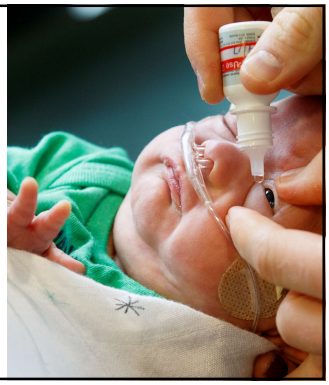

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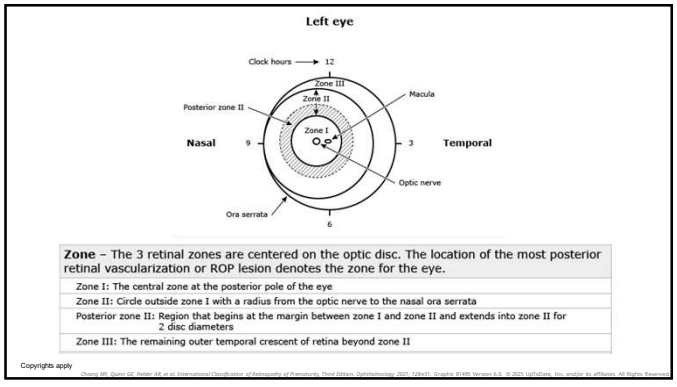

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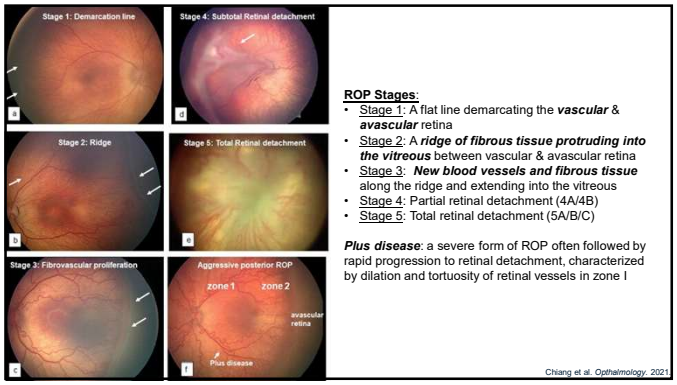

ROP Stages:
- Stage 1: A flat line demarcating the ***vascular*** & ***avascular*** retina
- Stage 2: A ***ridge of fibrous tissue protruding into the vitreous*** between vascular & avascular retina
- Stage 3: ***New blood vessels and fibrous tissue*** along the ridge and extending into the vitreous
- Stage 4: Partial retinal detachment (4A/4B)
- Stage 5: Total retinal detachment (5A/B/C)

Plus disease: a severe form of ROP often followed by rapid progression to retinal detachment, characterized by dilation and tortuosity of retinal vessels in zone I

Chiang et al. *Opthalmology*. 2021

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ROP "Types" and Treatment

ROP Type	Definition (ETROP/ICROP criteria)	Management
Type I ROP	- Zone I: Any stage with **plus disease** - Zone I: Stage 3 with or without plus disease - Zone II: Stage 2 or 3 with **plus disease**	- **Treatment indicated** (within 72 hrs) - Preferred: **Intravitreal anti-VEGF** or **laser photocoagulation** - Close ophthalmology follow-up post-treatment
Type II ROP	- Zone I: Stage 1 or 2 **without plus disease** - Zone II: Stage 3 **without plus disease**	- **Observation** with careful, frequent follow-up - Treat if progression to **Type I**

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Remote ROP Screening

Telemedicine

- Identify infants with potentially severe ROP using ***wide-angle ocular digital fundus photography*** → digital retinal images
- AAP/AAO/AAPOS/AACO:
  - Same exam schedule
  - Infants should undergo indirect ophthalmoscopy *at least once* before initiating treatment/terminating screening
- Digital retinal photography - **high accuracy to detect clinically significant ROP**
  - Telemedicine Approaches to Evaluating Acute-phase ROP (e-ROP) study: 1257 infants VLBW infants underwent ophthalmologist exam and nonphysician staff wide-field digital imaging
  - High sensitivity (90%) and specificity (87%) for detecting referral-warranted ROP

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Daniel et al. *JAMA Opthalmology*. 2015.

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