Presentation: ROP: Retinopathy of Prematurity: *What We Are Seeing More Clearly Now*

Presenter: Terry S. Johnson, APN, NNP-BC, ASPPS, CLEC, MS

Outline:

- **I. Overview of Development**
  - **a. Brain**
  - **b. Eye**
  - **c. Vision**
- **II. "Burdens of Prematurity"**
  - **a. ROP, BPD, NEC, LOS**
  - **b. Impact on long-term outcomes**
  - **c. Increase in cost of care**
- **III. Risk Factors for ROP**
  - **a. Prematurity**
  - **b. Oxygen toxicity**
  - **c. Inflammation**
  - **d. Poor growth**
  - **e. Changing epidemiology of ROP**
- **IV. Overview of Neonatal Ophthalmologic Exam**
  - **a. Procedural overview**
  - **b. Classification- Location, stage, severity, plus disease, extent**
  - **c. Zones- location**
  - **d. Severity of disease**
  - **e. Plus disease**
  - **f. Extent of disease**
  - **g. Techniques – OCT**
- **V. Treatment Options**
  - **a. Cryotherapy**
  - **b. Laser therapy**
  - **c. Anti-VEGF**
- **VI. Role of Nutrition**
  - **a. Human milk and EHMD**
  - **b. Vitamin A, vitamin, and omega-3 fatty acids**
- **VII. Summary**

ROP: Retinopathy of Prematurity
What We Are Seeing More Clearly Now

Terry S Johnson, APN, NNP-BC, ASPPS, MN
Director, Education and Professional Development
Prolacta Bioscience

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Disclosures

- **Director of Education and Professional Development at Prolacta Bioscience**
  - I personally prepared this slide deck; it is without commercial bias or influence
  - I have received financial reimbursement for non-marketed, non-branded, non-promotional educational presentations through the Abbott Nutrition Health Institute (ANHI)

Terry S Johnson
APN, NNP-BC, ASPPS

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Objectives

- Identify three risk factors for the development of ROP
- Describe what is meant by the "Third Wave" of ROP
- Discuss the current evidence regarding oxygen saturation targets
- List the benefits of human milk in reducing the incidence/severity of ROP

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Poll Time

The first thing I want to do when the COVID-19 restrictions are finally able to be lifted is:

A. Travel anywhere and do something
B. Go out to dinner (no box, bag, Styrofoam, plastic utensils, Uber Eats, or Grubhub involved)
C. Plant a big ol' kiss and a huge bear hug on the first stranger I see
D. Have friends and/or family in my home for a visit

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"What's Going On In There?"

Eye Development and Vision

- The eye is an extension of brain tissue
- Embryologic development begins on day 17
- Retinal layers grow from neural ectoderm
- Macula needs 4 to 5 months just to begin development, and matures 6 months after birth

"The brain devotes more of its territory to vision than all the other senses combined."

Human embryo eye lid formation at 8 weeks gestation

Eliot L. *What's Going on in there? How the brain and mind develop in the first five years of life.* New York, NY;Bantam Books:1999.
Jnah AJ, Trembath AN, eds. *Fetal and neonatal physiology for the advanced practice nurse.* New York, NY;Singer Publishing Company:2019.

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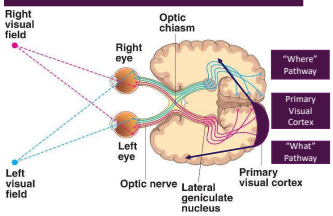
Vision as We Understand It

How Vision Works



How Vision Works

- **Segregation of left and right**
  - Left side of brain gets input from right half of the visual field
  - Right side of brain gets input from the left half of the visual field
- **"What" vs "where"**
  - Further "parses" input to a distinct region for specialized different perceptions
  - 32 distinct visual areas in each hemisphere
  - Detects shape, color, detail, motion, location, depth perception

Eliot L. *What's Going on in there? How the brain and mind develop in the first five years of life*. New York, NY;Bantam Books:1999.

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A Very Short History of Prematurity

- 1896 World's Fair in Berlin; Dr Budin had a display
- Attended by a "Dr" Martin Couney
- 1903 New York World's Fair; *"Preemies at Coney Island"*
- 1943 US hospitals began the use of "incubators"
- 1950 Surfactant identified in sheep/calf lungs
- 1950s "Neonatal Care" emerging as concept
- 1963 Huge leap forward after death of Patrick Kennedy
- 1970s to 1980s ↑ Oxygen therapy; beginning of ventilation
- 1984 ICROP refines RLF definition/staging to retinopathy of prematurity (ROP)
- 1990s Surfactant available for use with oxygen/ventilation; POX monitoring
- 2008 Saugstad publication on resuscitation with/without oxygen; changes in NRP, cryotherapy
- 2010 Targeted oxygen saturations, aggressive ROP screening, laser, and Avastin therapies
- 2021 Novel new thoughts on reducing this ***"burden of prematurity"***

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"The Burden of Prematurity"

Bronchopulmonary Dysplasia

Retinopathy of Prematurity

Short Bowel Syndrome

"These infants have immediate and persistent physical, psychological, social, and financial consequences."

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"Dual Burden" of Severe Maternal Morbidity and Preterm Birth

"Dual burden births"

- Occur in one in every 270 births
- Strongest predictors are hypertensive disorders with preeclampsia and multiparous primary cesarean
- Twice as likely to affect Black mothers
- Risk is increased more than sixfold with multiple gestation

Lyndon A, Baer RJ, Gay CL, El Ayadi AM, Lee HC, Jelliffe-Pawlowski L. A population-based study to identify the prevalence and correlates of the dual burden of severe maternal morbidity and preterm birth in California. *J Matern Fetal Neonatal Med*. 2021;34(8):1198-1206. doi:10.1080/14767058.2019

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ROP: An Overview

"ROP is a rapidly changing disease condition in the newborns. It can regress completely in some, regress with some sequelae in others while progress to severe retinal detachment and vision loss in a few babies".

"This complex and variably progressive nature of ROP warrants a robust description of the disease and its classification into various severities, which helps clinicians to properly document, prognosticate and treat the disease."

Agarwal K, Jalali S. Classification of retinopathy of prematurity: from then till now. *Community Eye Health*. 2018;31(101):54-57. Accessed March 10, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6157799/

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Risk Factors for ROP

Risk Factors for ROP

- Prematurity
- Supplemental use of oxygen
- Low birth weight
- Hyperglycemia and insulin use
- Apnea
- Sepsis
- Blood transfusions
- Antioxidant deficiency
- Bronchopulmonary dysplasia
- Patent ductus arteriosus
- Inflammation

Jnah AJ, Trembath AN, eds. *Fetal and neonatal physiology for the advanced practice nurse*. New York, NY:Singer Publishing Company:2019.

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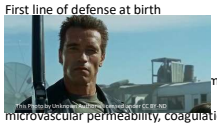
The Role of Neonatal Immune Responses

Innate Immunity

- First line of defense at birth
- [illegible]
- [illegible]
- [illegible]ns
- [illegible]
- microvascular permeability, coagulation
- Secondary collateral damage



Adaptive Immunity

- Later d[illegible]ponse
- Require[illegible]ns
- Amplifi[illegible]osure
- Highly [illegible]
- Relies [illegible]emory"
- Elabora[illegible]ses
- More b[illegible]

Cacho NT, Lawrence RM. Innate immunity and breast milk. *Front Immunol.* 2017;8:584. doi:10.3389/fimmu.2017.00584
Jakaitis BM, Denning PW. Human breast milk and the gastrointestinal innate immune system. *Clin Perinatol.* 2014;41(2):423-435. doi 10.1016/j.clp.2014.02.011

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Inflammation and the "Oxygen Radical Diseases of Neonatology"

Inflammation and oxidative stress

Inflammation
Infection
Ischemia
Reperfusion

Increased ROS production

Deficient antioxidant defenses

Human milk
Anti-inflammatory
Anti-oxidant

Cell/Tissue/Organ Injury
Retinopathy of Prematurity
Chronic Lung Disease/BPD
Periventricular Leukomalacia
Intraventricular Hemorrhage
Necrotizing Enterocolitis
Patent Ductus Arteriosus
Cerebral Palsy

INFLAMMATION

Trindade CEP, Rugolo LMSS. Free radicals and neonatal diseases. *NeoReviews.* 2007;8(12):e522-e532. doi:10.1542/neo.8-12-e522

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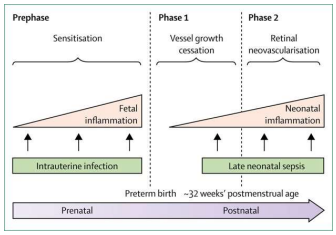
ROP and Inflammation

- **Sources of inflammation**
  - Perinatal inflammation
    - >80% on infants <30 weeks have positive *in situ* bacteria
    - Chorioamnionitis most common factor associated with PTB
  - Neonatal immune responses
    - Innate and Adaptive responsivity
    - ↑ Inflammation, oxidative stress
  - Systemic inflammatory response
    - Sepsis and reperfusion injuries
  - Neonatal comorbidities
    - NEC, BPD, ROP



Hellström A, Smith L, Dammann O. Retinopathy of prematurity. *Lancet.* 1991;337(8733):83-84. Accessed March 10, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020289/
Vento M, Aguar M, Brugada M. Extremely premature infant: overcoming inflammation and oxidative stress. *Pediatric Health.* 2008;2(4):397-400. doi:10.2217/17455111.2.4.397

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Poll Time

The "Third Wave of ROP" refers to:

A. ROP diagnosed in the late preterm infant population
B. ROP in preterm infants weighing less than 1000 g
C. ROP seen in term infants with neonatal abstinence syndrome
D. All of the above

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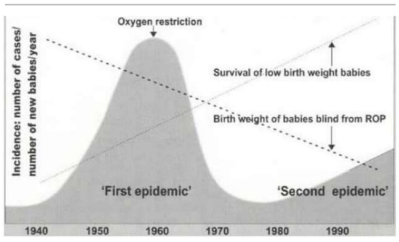
ROP: "The Third Epidemic or Wave"



"The third epidemic of ROP"

- ↑ numbers and with ↓ GA
- 65% of infants with BW <1250 g
- 80% of those with BW <1000 g
- Will develop some degree of ROP

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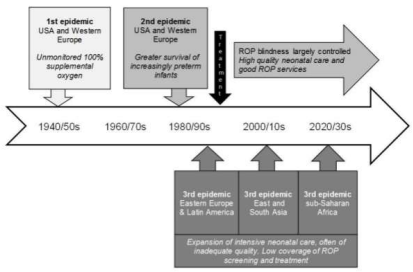
Epidemiology of ROP – "Third Wave"



Gilbert C, Malik ANJ, Nahar N, Das SK, Visser L, Sitati S, Ademola-Popoola DS. Epidemiology of ROP update - Africa is the new frontier. *Semin Perinatol*. 2019;43(6):317-322. doi: 10.1053/j.semperi.2019.05.002

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Poll Time

Potential side effects of ROP treatment with Avastin (Bevacizumab) include which of the following:

A. An increased risk of motor impairment at 18 months of age
B. Vascular and macular abnormalities
C. Improper lung development and developmental disabilities
D. All of the above

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ROP Examination

- **How it's done**
  - Dilating the pupil
  - Topical anesthesia
  - Placement of an eyelid speculum
  - Use of scleral depressor
  - Baby NPO
  - Baby is "Gently Held"
  - Special lens and bright light
  - Moving the eye in different directions
  - Total time: 30 to 60 minutes

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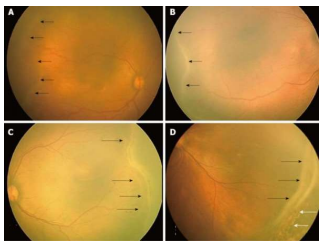
ROP Examination



- **Findings**
  - **A**: Fundus image of the right eye showing stage 1 ROP with demarcation line (black arrows)
  - **B:** Fundus image of right eye showing stage 2 ROP with ridge (black arrows)
  - **C:** Fundus image of left eye showing stage 3 extra retinal fibrovascular proliferation (black arrows)
  - **D:** Fundus picture of left eye showing a stage 4 partial retinal detachment (black arrows); Laser scars are shown (white arrows)

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Classification of ROP

- **How ROP is classified**
  - ***Zone***
    - Location
  - ***Stage***
    - Severity
  - ***Plus disease***
    - Blood vessel characterization
  - ***Extent***
    - Amount of retina involved

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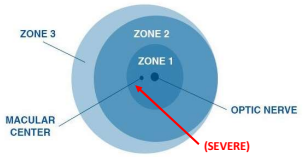
Zones of ROP

- **Three locations (or zones) on retina**
  Retina divided into three zones centered on the optic disc



Zone 1: Optic Nerve Head—most immature vasculature; ↑ severity
Zone 2: Extends to ora serrata nasally; ↓ severity
Zone 3: Extends to the temporal side; ↓ severity

Jnah AJ, Trembath AN, eds. *Fetal and neonatal physiology for the advanced practice nurse*. New York, NY:Singer Publishing Company:2019.

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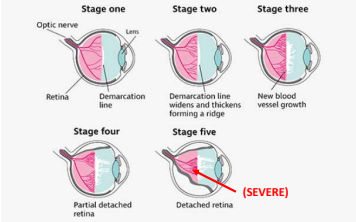
Staging of ROP

- **Severity of disease in five stages**



The disease can exist in more than one stage in the eye at a time. For staging, the worse stage is noted, however, for proper documentation.

Jnah AJ, Trembath AN, eds. *Fetal and neonatal physiology for the advanced practice nurse*. New York, NY:Singer Publishing Company:2019.

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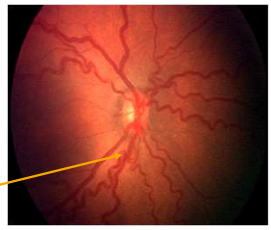
Plus Disease ROP

- **Appearance of the retinal vessels**
  - Dilatation (venous)
  - Arterial tortuosity (arterial)
  - Usually in all four quadrants
  - Secondary to increased blood flow
  - Iris engorged → pupillary rigidity
  - Vitreous haze appears
  - Arises gradually or readily
  - Indicator of severity of disease
  - ***It is the main factor determining the need for treatment at stage 3 disease***

(SEVERE)



Jnah AJ, Trembath AN, eds. *Fetal and neonatal physiology for the advanced practice nurse*. New York, NY;Singer Publishing Company:2019.

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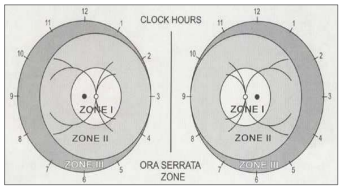
Extent of ROP

- **Clocking the extent of ROP**
  - Amount of disease
  - Retina is divided into three zones centered on the optic disc
  - Separated into 30-degree segments
  - Involvement of disease is expressed in the number of "clock hours" that are affected



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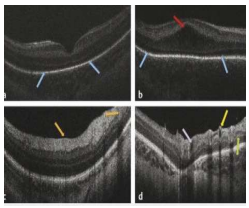
ROP Examination



Spectral Domain Optical Coherence Tomography (SD-OCT)

- **SD-OCT**
  - Noninvasive imaging technology
  - High resolution cross-sectional images
  - Determination of retinal thickness
  - Uses rays of light – no radiation
  - Allows for 50- to 100-fold less time needed to capture an image
  - Can identify and measure retinal and macular edema, holes, and detachments
  - Actual imaging not painful (the exam – ***yes***)

Erol MK, Ozdemir O, Coban DT, Bilgin AB, Dogan B, Sari ES, Toslak D. Macular findings obtained by spectral domain optical coherence tomography in retinopathy of prematurity. *J Ophthalmol.* 2014;2014. doi:10.1155/2014/468653

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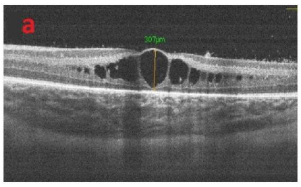
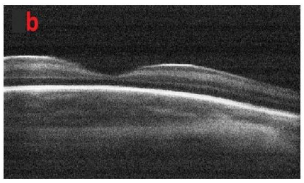
Avastin Treatment

Pre-Avastin



OCT image of a premature infant with type 1 ROP (zone 2 stage 3 with plus disease)

Post-Avastin



Same infant wo months after intravitreal ranibizumab (Lucentis) treatment

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Diagnosis and Plan for ROP

"Ophthalmology speak"

"OK … but what do I tell the family and what's our plan?"

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Diagnosis and Plan for ROP

"Ophthalmology speak"

"Yeah OK … but what do I tell the family and what's our plan?"

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ROP Treatment Options

Cryoplexy

- ***Cryotherapy***
  - Formerly the procedure of choice
  - Uses cold temperatures to freeze parts of the affected retina via the outer wall of the eye
  - Largely replaced by laser therapy
  - Still useful when the retina can't be fully seen (hemorrhage)

Photocoagulation

- ***Laser therapy***
  - First line of defense in ROP
  - Much like a retinal exam
  - Local or general anesthesia
  - Diode laser ophthalmoscope
  - Multiple, tiny burns in/along the periphery of the retina

Both photocoagulation and cryoplexy destroy part of the retina's periphery and result in loss of vision.

Boston Children's Hospital. Retinopathy of prematurity (ROP): treatments. Accessed March 10, 2021. https://www.childrenshospital.org/conditions-and-treatments/conditions/r/retinopathy-of-prematurity-rop/treatments

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ROP Treatment Options

VEGF & Anti- Endothelial Growth Factor

- **Vascular endothelial growth factor (VEGF)** is a signal protein that induces growth of blood vessels → supply
- **Anti-VEGF**
  - Works by ↓ VEGF production
  - Injected directly into the eye
  - Avastin most researched in NICU
    - Benefits in most severe cases of ROP
    - Risk ↓ growth of other organs
    - ? Dosage (0.004 mg)
  - Shorter duration of anesthesia, NPO

Anti-Vascular Endothelial Growth Factor

- **Anti-VEGF costs**
  - Cost of drug < OR, anesthesia, etc
  - Not every NICU (step down) offers it
  - ? Transport – away from family
  - May require anesthesia
  - Use of intubation/ventilation
  - Baby with a history of:
    - RDS, surfactant, steroids
    - Oxygen, ventilation, BPD
    - Potential ↑ length of stay
- **Additional anti-VEGFs**
  - Eylea, Lucentis, Macugen

NIH/National Eye Institute. Very low-dose Avastin effective for preventing blindness in preterm infants: very low doses effective for treating retinopathy of prematurity. *ScienceDaily*. Accessed April 23, 2020. www.sciencedaily.com/releases/2020/04/200423130503.htm | Wallace DK, Kraker ME, Yang MB, et al. Short-term outcomes after very low-dose intravitreous Bevacizumab for retinopathy of prematurity. *JAMA Ophthalmol*. 2020;138(6):698-701. doi:10.1001/jamaophthalmol.2020.0934

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ROP and Nutrition

"Evidence is accumulating that one of the strongest predictors of ROP, in addition to low gestational age, is poor weight gain during the first weeks of life."

- **Beneficial role of nutrition**
  - Strong association SGA &↑ risk of ROP
  - Role of IGF-1 and VEGF
    - Hormone similar to insulin
    - Stimulates overall somatic growth
    - ↑ Retinal vasculature/brain growth
    - ↓ Results in halt of angiogenesis
    - ↑ IGF-1 improves retina vessel survival
    - Prompts the onset of ROP
  - IGF-1 associated with weight gain
    - Early aggressive nutrition, TPN, enteral
    - ↑ Use of MOM and HM (species specific)
    - Early fortification strategies

Lenhartova N, Matasova K, Lasabova Z, Javorka K, Calkovska A. Impact of early aggressive nutrition on retinal development in premature infants. *Physiol Res*. 2017;66(Suppl 2):S215-S226. doi:10.33549/physiolres.933677
Hellström A, Smith L, Dammann O. Retinopathy of prematurity. *Lancet*. 1991;337(8733):83-84. Accessed March 10, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020289/

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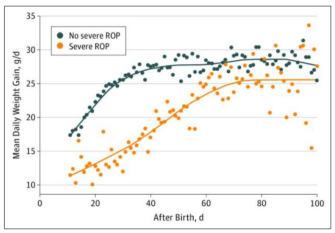
ROP and Nutrition

Mean daily weight gain by chronological age of 7483 infants in the postnatal growth and retinopathy of prematurity study



Is this baby having …

- Feeding Intolerance?
- Slow to advance feedings?
- Slow to fortify feedings?
- Not maximizing fortification?
- Start/stop feedings?

Binenbaum G, Bell EF, Donohue P, Quinn G, Shaffer J, Tomlinson LA, Ying GS; G-ROP Study Group. Development of modified screening criteria for retinopathy of prematurity: primary results from the postnatal growth and retinopathy of prematurity study. *JAMA Ophthalmol*. 2018;136(9):1034-1040. doi:10.1001/jamaophthalmol.2018.2753

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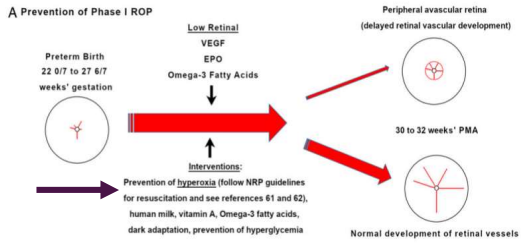
Prevention of ROP

- **Phase I ROP**



Raghuveer TS, Zackula R. Strategies to prevent severe retinopathy of prematurity: a 2020 update and meta-analysis. *NeoReviews*. 2020;21(4):e249. doi:10.1542/neo.21-4-e249

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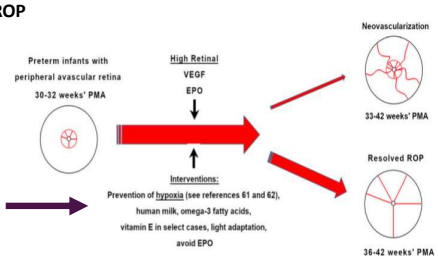
Prevention of ROP

- **Phase II ROP**



Raghuveer TS, Zackula R. Strategies to prevent severe retinopathy of prematurity: a 2020 update and meta-analysis. *NeoReviews*. 2020;21(4):e249. doi:10.1542/neo.21-4-e249

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Prevention and Reduction of ROP

"There is evidence that human milk, vitamin A, omega-3 fatty acids, and vitamin E can decrease the risk of ROP and are recommended in addition to adequate oxygen saturation monitoring."

Raghuveer TS, Zackula R. Strategies to prevent severe retinopathy of prematurity: a 2020 update and meta-analysis. *NeoReviews*. 2020;21(4):e249. doi:10.1542/neo.21-4-e249

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Human Milk: A "Biological Product"

- **AAP Policy: 2017** ***"Human milk is a biological product"***
- **FDA: "What is a biological product?"**
  - Biological products, or biologics, are medical products
  - Many biologics are made from a variety of natural sources (human cells, tissue, animal, microorganism)
  - Like drugs, some biologics are intended to treat diseases and medical conditions
  - ***Biologics are used to prevent and treat diseases***

U.S. Food and Drug Administration. FDA Basics; What is a biological product? U.S. Department of Health and Human Services. Accessed March 10, 2021. http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194516.htm. Page Last Updated May 31, 2016.

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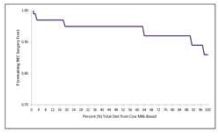
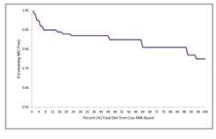
Human Milk: A "Dose Response"

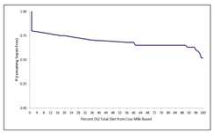
"Dose response" **of an EHMD and why it matters**



For every 10% increase in CMBD a 12% INCREASE in NEC



For every 10% increase in CMBD a 21% INCREASE in surgical NEC



For every 10% increase in CMBD 17.9% INCREASE in sepsis

Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeed Med*. 2014;9(6):281-285. doi:10.1089/bfm.2014.0024

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Interventions To Prevent ROP: A Meta-analysis

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OBJECTIVE: To estimate the effectiveness of nutritional interventions, oxygen saturation targeting, blood transfusion management, and infection prevention on the incidence of retinopathy of prematurity (ROP).

- **Summary of the evidence**
  - Meta-analysis of two cohort studies on the effect of ***breastmilk versus formula feeds found a 60% reduction in the risk of severe ROP***
  - Favorable finding was complicated by the need to categorize intervention and control groups as only or mainly breastmilk fed compared with only or mainly infant formula fed
  - ***Two RCTs of exclusive human milk feedings that used a human milk–based fortifier demonstrated a significant overall reduced relative risk of mortality***

Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2016;137(4):e20153387. doi:10.1542/peds.2015-3387

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EHMD and Reduction of Neonatal Comorbidities

EHMD

- **Multicenter retrospective cohort study**
- 1587 extremely preterm infants <1250 g
- Institutional change to an EHMD
- Four geographically disparate hospitals
- California, Florida, Illinois, Texas

Role of similar pathophysiology of disease? Similar protective benefits of an EHMD?

EHMD Group Findings

	CMD	EHMD	*P* Value
NEC	16.7%	6.9%	*P* < 0.00001
Mortality	17.2%	13.6%	*P* = 0.04
BPD	56.3%	47.7%	*P* = 0.0015
ROP	9.0%	5.2%	*P* = 0.003
PDA	64.7%	55.1%	*P* = 0.0001
Late-Onset Sepsis	30.3%	19.0%	*P* < 0.00001

Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet [published correction appears in *Breastfeed Med*. 2017;12(10):663]. *Breastfeed Med*. 2016;11(2):70-74. doi:10.1089/bfm.2015.0134

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Prevention of ROP: Role of Human Milk

- *"It is tempting to speculate that differences in the nutrient composition of the fortifiers used herein could account for the reduction in severe ROP in the HMBF group. A recent systematic review concluded that supplemental vitamin A, vitamin E, or inositol showed evidence, at least in observational studies, of being associated with a reduction in all stages of, or severe, ROP.* ***However, BMBF contributed more vitamin A and E than HMBF, and whereas there is a small amount of inositol in BMBF, there is none in HMBF.***" (O'Connor et al, 2018)
- *"The present meta-analysis showed that* ***inositol supplementation may have no effect in prevention of severe ROP but a trend toward an increase on mortality in preterm infants less than 32 weeks. Routine inositol supplementation to preterm infants should not be recommended based on current evidence.***" (Du et al, 2019)

[1] O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial [published corrections appear in *Am J Clin Nutr*. 2019;110(2):529 and *Am J Clin Nutr*. 2020;111(5):1112]. *Am J Clin Nutr*. 2018;108(1):108-116. doi:10.1093/ajcn/nqy067
[2] Du Y, He Y, Wang YL, Zhou JG, Chen C. The efficacy and safety of inositol supplementation in preterm infants to prevent retinopathy of prematurity: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):135. doi:10.1186/s12886-019-1140-z

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EHMD and Reduction of Neonatal Comorbidities

Retinopathy of Prematurity (ROP)

- **Relative reduction of ROP with EHMD**
  - ***The relative reduction (RR) tells you by how much the treatment reduced the risk of bad outcomes relative to the control group who did not have the treatment.***

Implementation of an EHMD (2019)

- **RR of ROP with EHMD**
  - ***22% ROP RR***
  - Cohort 205 infants ≤1250 g
  - Both groups fed human milk
  - n = 101 CM–based fortifier
  - n = 104 HM–based fortifier
  - ***The risk for CMB 62% vs risk for EHMD 48.5%; P = 0.054***

Delaney Manthe E, Perks PH, Swanson JR. Team-based implementation of an exclusive human milk diet. *Adv Neonatal Care*. 2019;19(6):460-467. doi:10.1097/ANC.0000000000000676

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EHMD and Reduction of Neonatal Comorbidities

ROP

- **RR of ROP with EHMD**
  - ***The RR tells you by how much the treatment reduced the risk of bad outcomes relative to the control group who did not have the treatment.***

Nutrient Enrichment Using Fortifiers (2018)

- **RR of ROP with EHMD**
  - ***84% ROP RR***
  - RCT 125 infants ≤1250 g
  - Both groups fed human milk
  - n = 61 CM–based fortifier
  - n = 64 HM–based fortifier
  - Primary outcome: feeding intolerance
  - Secondary outcome: length of stay
  - ***The risk for CMB 10.2% vs risk for EHMD 1.6%; P = 0.04***

O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial [published corrections appear in *Am J Clin Nutr*. 2019;110(2):529 and *Am J Clin Nutr*. 2020;111(5):1112]. *Am J Clin Nutr*. 2018;108(1):108-116. doi:10.1093/ajcn/nqy067

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EHMD and Reduction of Neonatal Comorbidities

ROP

- **RR of ROP with EHMD**
  - ***The RR tells you by how much the treatment reduced the risk of bad outcomes relative to the control group who did not have the treatment.***

Nutrient Enrichment Using Fortifiers (2018)

- **RR of ROP with EHMD**
  - ***42% ROP RR***
  - Retrospective study 1587 infants ≤1250 g
  - Both groups fed human milk
  - n = 768 CM–based fortifier and/or formula
  - n = 819 HM–based fortifier
  - Reduction of neonatal comorbidities
  - ***The risk for CMB 9% vs risk for EHMD 5.2%; P = 0.003***

Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet [published correction appears in *Breastfeed Med*. 2017;12(10):663]. *Breastfeed Med*. 2016;11(2):70-74. doi:10.1089/bfm.2015.0134

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EHMD and Reduction of Neonatal Comorbidities

ROP

- **RR of ROP with EHMD**
  - ***The RR tells you by how much the treatment reduced the risk of bad outcomes relative to the control group who did not have the treatment.***

Nutrient Enrichment Using Fortifiers (2018)

- **RR of ROP with EHMD**
  - ***55% ROP RR***
  - Retrospective study 293 infants ≤1500 g
    - Group H EHMD (n = 87)
    - Group B HMF with MOM (n = 127)
    - Group M MOM, HMF, preterm formula (n = 49)
    - Group F preterm formula fed (n = 30)
  - ***The risk for CMB 31.0% vs risk for EHMD 4.2%; P = 0.001***

Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016;36(3):216-220. doi:10.1038/jp.2015.168

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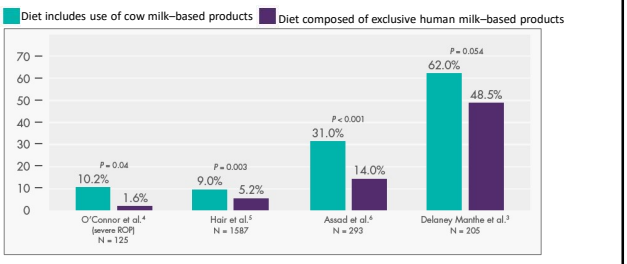
Role of Diet in ROP



Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016;36(3):216-220. doi:10.1038/jp.2015.168 | Delaney Manthe E, Perks PH, Swanson JR. Team-based implementation of an exclusive human milk diet. *Adv Neonatal Care*. 2019;19(6):460-467. doi:10.1097/ANC.0000000000000676 | Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet [published correction appears in *Breastfeed Med*. 2017;12(10):663]. *Breastfeed Med*. 2016;11(2):70-74. doi:10.1089/bfm.2015.0134 | O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing<1250 g: a randomized clinical trial [published corrections appear in *Am J Clin Nutr*. 2019;110(2):529 and *Am J Clin Nutr*. 2020;111(5):1112]. *Am J Clin Nutr*. 2018;108(1):108-116. doi:10.1093/ajcn/nqy067

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Co-occurrence and Burden of Complications of Prematurity

Resource utilization and costs among extremely preterm infants (≤28 weeks GA) with PMA ≥36 weeks at discharge or death, by complications cohorts, during index hospitalization, and one-year readmission after index hospitalization

	No complications n=2,456	1 complication n=4,188	≥2 complications n=5,406
In-hospital mortality after 36 wk PMA, n (%)	8 (0.3)	32 (0.8)	97 (1.8)
Mean (SD) length of stay (d)			
Full hospitalization*	77 (20)	85 (25)	102 (33)
NICU†	60 (28)	68 (32)	85 (38)
Mean (SD) charges and costs (2015 USD)‡			
Total charges§	$508,560 ($314,893)	$606,596 ($383,621)	$804,317 ($529,433)
Total costs#	$151,173 ($83,403)	$176,956 ($95,262)	$223,648 ($121,498)
1-year readmission, n (%)#	226 (9.2)	474 (11.3)	811 (15.0)

Mowitz ME, Ayyagari R, Gao W, Zhao J, Mangili A, Sarda SP. Health Care Burden of Bronchopulmonary Dysplasia Among Extremely Preterm Infants. *Front Pediatr*. 2019;7:510. doi:10.3389/fped.2019.00510

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Prevention of Severe ROP: A 2020 Update and Meta-analysis

- **Summary**
  - Incidence of ROP in US shows ↑ing trend with ↓ BW and GA
  - Severe ROP ↑ risk of visual and ND deficits in premature infants
  - Laser therapy and intravitreal injection of VEGF inhibitors are effective in most infants
    - Both laser surgery and VEGF inhibitors have many side effects
  - In the NeOProM trials
    - Mortality was ↑ in infants with a ↓ oxygen saturation range (85% to 89%)
    - Incidence of ROP was ↑ in infants with a ↑ oxygen saturation range (91% to 95%)
  - Recent studies have used ↑ oxygen saturation targets as premature infants mature
    - Mirroring the pathogenesis of ROP and have not found an increase in mortality
  - There is evidence that human milk, vitamin A, omega-3 fatty acids, and vitamin E can decrease the risk of ROP and are recommended in addition to adequate oxygen saturation monitoring

Raghuveer TS, Zackula R. Strategies to prevent severe retinopathy of prematurity: a 2020 update and meta-analysis. *NeoReviews*. 2020;21(4):e249. doi:10.1542/neo.21-4-e249

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Stevland Hardaway Judkins Morris

- **Born 6 weeks prematurely in 1950**
- **Incubator with flowing oxygen**
- **Diagnosed RLF/ROP at 6 weeks of age**
- **Singer, songwriter, musician, producer**
- **Sold over 100 million records worldwide**
- **He has won 22 Grammy Awards**

"Isn't he lovely …"

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NICU Dietitian Support
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