BV-08  Update on Ocular and Neural Complications of Premature Birth

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Disclosure Statement:
• Nothing to disclose

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Normal gestation and birth-weight

- Normal gestation
  - 40 Wks
- Normal Birth weight
  - 7.5 lbs (boys)
  - 7 lbs (girls)
- Premature birth
  - ≤ 37 wks Gestation Age (GA)
Birthweight (BW) is more accurate predictor of “Prematurity”

- **LBW (Low)**
  - 2500 gm / 5.5 lbs
- **VLBW (Very Low)**
  - 1500 gms / 3.3 lbs
- **ELBW (Extremely Low)**
  - 1000 gms / 2.2 lbs
- **“Threshold of Viability”**
  - 21-25 wks gestation
  - 600-750 gms (23-25 wks)
Public Health Impact of Premature Birth

- 12.3% of births ≤ “37” wks in the US (2008-12)
  - Premature birth is the leading cause of infant and perinatal morbidity and mortality in the US
- 36% increase in prevalence since 1981
- ROP is increasing as more premature babies survive
  - ETROP guidelines result in treating babies born, on average, at 25.6 wks weighing 740 gms.
- IOM estimated costs of 26.5 billion in 2005
  - Not including medical care after early childhood, special education or lost productivity.
Lecture Goals:

- Understand acute and chronic health problems
- Review and Update ROP
  - Pathogenesis
  - New Treatments
  - Prevention
- CNS problems relating to low vision
- Other visual problems
## Preterm Outcomes by Gestational Age (Preterm Outcome Table)

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<thead>
<tr>
<th>Gestational Age (Wk)</th>
<th>26</th>
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<tr>
<td>% RDS</td>
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<td>85</td>
<td>80</td>
<td>70</td>
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Respiratory complications cause most morbidity and mortality

- **RDS**
  - “Baby” alveoli limit gas exchange
  - Difficult to inflate lungs
  - Must re-inflate completely each breath
  - Surfactant not produced until 32-35 weeks
Tx of respiratory complications

- Respiratory distress syndrome (RDS)
  - Endotracheal intubation; mechanical ventilation + surfactant
  - CPAP (surfactant)
  - High frequency oscillation
    - 600 times a minute at a very low lung volume (protects from too much pressure).

- Bronchopulmonary dysplasia
  - Respiratory support at 36 wks gestational age
Respiratory problems after discharge (Chronic Lung Disease)

- Defined by need for home oxygen and re-admission to hospital within first year of life
  - Damage to structurally and functionally immature lung from positive pressure ventilation

- Life long respiratory problems
  - Increased severity of colds or URI
  - Pneumonia
  - Asthma
  - Sensitivity to lung irritants like smoke, pollution
How common are RDS, CLD, and Home O2?

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<td>35</td>
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<tr>
<td>Home O2</td>
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<td>15</td>
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Patent Ductus Arteriosus

- Opening between fetal pulmonary Aa and Aorta
- RT – LT shunt
  - De-oxygenated blood to body
  - Aortic pressure is higher; back-up of fluid in lungs; can cause congestive heart failure
Necrotizing enterocolitis (NEC)

- Necrosis and perforations of the intestinal wall
  - Multifactorial (immaturity, anoxia, bacteria, blood transfusions)
- Surgical removal of dead bowel tissue
  - Colostomy (temporary)
- Caution with cycloplegics
  - 0.2% cyclopentolate + 1.0% phenylephrine (cyclomydrietil)
How common are PDA & NEC?

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<th>Wks</th>
<th>26</th>
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<td>80</td>
<td>70</td>
<td>50</td>
<td>40</td>
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<tr>
<td>% PDA Tx’d</td>
<td>45</td>
<td>40</td>
<td>25</td>
<td>15</td>
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<tr>
<td>% NEC</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>2</td>
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<tr>
<td>% Sepsis</td>
<td>40</td>
<td>40</td>
<td>25</td>
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Brain and Eye problems affecting vision

- IVH: Intraventricular Hemorrhage
- PVL: Periventricular Leukomalacia
- ROP: Retinopathy of Prematurity
Intraventricular hemorrhage

- Source of Hr is a fragile capillary network which supplies the germinal matrix surrounding the lateral ventricles
  - Involutes by term
- GM vessels can’t autoregulate
- Rapid changes in BP rupture GM vessels, which bleed around (peri) and into (intra) the ventricles
Intraventricular hemorrhage (IVH) Graded I - IV

- I germinal matrix Hx
- II blood within but not distending ventrical
- III blood filling and distending ventricular system
- IV blood spilling out to surrounding brain tissue
Intraventricular hemorrhage (IVH): Complications

- **Acute sequelae**
  - Neonatal stroke
  - Ischemic damage

- **Chronic sequelae**
  - Hydrocephalus
  - MR/DD
  - CP
  - Eye signs: CVI, Low Vision
Periventricular leukomalacia

- Hypoxic / ischemic injury of the developing white matter around the ventricles
  - With or without IVH

- Evidenced on MRI by:
  - Atrophic dilation of lateral ventricles
  - Reduced amount of PV white matter
    - Often around occipital horns
  - Thinned corpus collosum
  - Cerebellar atrophy
PVL imaged by MRI

A. Normal white matter

B. Reduced white matter
PVL Complications

- Death in ~50% (14x risk of death compared to grade III or IV IVH)
- CP (spastic diplegia)
- MR (verbal > performance IQ)
- Cortical vision impairment
What is Retinopathy of Prematurity (ROP) ?

- Abnormal vascularization of the premature retina
  - End stage is retinal detachment
- Primarily affects infants ≤1250 gms or ≤ 31 wks gestation
- Annually, 28,000 US infants at risk; ~16,000 develop ROP; 90% regress, 1100-1200 need treatment
How common are IVH, PVL, ROP?

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<tr>
<td>% IVH</td>
<td>10</td>
<td>10</td>
<td>5</td>
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<tr>
<td>% PVL</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>% ROP</td>
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"Threshold of Viability" at ~21-25 wks

<table>
<thead>
<tr>
<th>Wks</th>
<th>23*</th>
<th>24*</th>
<th>25*</th>
<th>26</th>
<th>27</th>
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<tr>
<td>BW</td>
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<td>650</td>
<td>750</td>
<td>900</td>
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<td>1100</td>
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<tr>
<td>D/Ch. alive</td>
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<td>50</td>
<td>60</td>
<td>80</td>
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<td>90</td>
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<tr>
<td>% ROP</td>
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<td>15</td>
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<tr>
<td>Mod-Sev. Disability**</td>
<td>60</td>
<td>40</td>
<td>15</td>
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## Classification of ROP

<table>
<thead>
<tr>
<th>Severity</th>
<th>Stage</th>
<th>Location</th>
<th>Extent</th>
<th>Plus Disease</th>
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<tbody>
<tr>
<td>Stage</td>
<td>Stage 1: Demarcation Line</td>
<td>Zone I: circle centered on disc with twice the disc-foveal distance</td>
<td>30-degree (clock-hours) of ROP along the circumference of the vascularized retina</td>
<td>Dilated and tortuous vessels of the posterior pole (at least 2 quadrants required)</td>
</tr>
<tr>
<td></td>
<td>Stage 2: Ridge</td>
<td>Zone II: Donut extending from edge of Zone 1 to nasal ora serrata</td>
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<td>Stage 3: Ridge with extra-retinal vascular proliferation</td>
<td>Zone III: temporal crescent outside Zone II</td>
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<td>Stage 4: Sub-total RD</td>
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<td>Stage 5: Total RD “funnel”</td>
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<tr>
<td>Location</td>
<td>Aggressive posterior ROP (AP-ROP)</td>
<td>Relatively innocuous appearance of ROP at junction of vascular and avascular retina in Zone 1 or Zone 2</td>
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<td></td>
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<tr>
<td>Extent</td>
<td>Severe dilation and tortuosity of posterior pole vasculature</td>
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<td>Plus Disease</td>
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Immature retinal vasculature

Retinal vessels grow outwards from the disc, but peripheral retina is not vascularized until 32 (nasal) or 40 (temp) wks.
Stage 1 ROP
Stage 2
Stage 3
Stage 4
Plus disease
Location

Diagram showing the location of various parts of the eye, including:
- Temporal ora serrata
- Nasal ora serrata
- Zone I
- Zone II
- Zone III
- Macular center
- Optic nerve
Development of ROP Linked to Post Menstrual Age

Stage 1, 34.1 wks
Stage 2, 35.1 wks
Stage 3, 36.6 wks
Plus, 36.0 wks
Pre-threshold, 36.1 wks
Threshold ROP, 37.3 wks
CRYO-ROP Study

- CRYO-ROP Study Group
  - International Classification of ROP
  - Randomized clinical trial (cryo Tx. Vs. no Tx)
    - Tx advised for eyes reaching “threshold” disease, at which ~50% expected to detach
  - Cryo Sx decreased retinal detachments by ~50%
    - 42.2% reduction at 15 year follow-up
  - After 15 years, acuity < 20/200 in 44.7% of treated eyes
ETROP

- Premies with “High Risk, Pre-threshold Dz” were randomized to early laser vs. conventional Tx.
  - “Pre-threshold” defined by ophthalmoscopic appearance
  - “High-Risk” defined by computer algorithm including demographic and other factors gleaned from natural history study

ETROP

- Early Tx reduced unfavorable acuity (19.8% to 14.3% (P < .005) and structural (15.6% to 9.1% (P < .001) outcomes at 9 months.

- Early Tx advised for “Type 1 ROP”
  - Zone 1, any stage, plus Dz
  - Zone 1, stage 3 without plus Dz
  - Zone 2, stage 2 or 3, with plus Dz

After the ETROP guidelines were implemented, there was a decrease from 10.3% to 1.9% of eyes developing Stage 5 retinal detachment, despite this group having a lower average EGA and lower average birth weight.

NEI Press Release
National Institutes of Health
National Eye Institute

Contact:
Jean Horrigan or Dustin Hays
National Eye Institute
(301) 496-5248
neinews@nei.nih.gov

B-roll available

Telemedicine catches blinding disease in premature babies

NIH-funded study could reduce obstacles to care for at-risk babies

June 26, 2014

Telemedicine is an effective strategy to screen for the potentially blinding disease known as retinopathy of prematurity (ROP), according to a study funded by the National Eye Institute (NEI). The investigators say that the approach, if adopted broadly, could help ease the strain on hospitals with limited access to ophthalmologists and lead to better care for infants in underserved areas of the country. NEI is a part of the National Institutes of Health.
Update on E-ROP (Telemedicine Approaches to Evaluating Acute-phase ROP)

- Designed to show whether remote interpretation of fundus images could detect “Referral Warranted” (RW) ROP
  - Zone 1 ROP; Stage 3 ROP or worse; or Plus Disease
- Streamline and improve surveillance for ROP
  - Currently hospitals need experienced ophthalmologists on site, on baby’s schedule, for multiple visits
    - 90% of examined premature babies do not need treatment
  - Telemedicine could standardize care world-wide
RetCam images taken by trained hospital staff show RW ROP
E ROP Results

- Validity (interpretation of images by trained readers vs. study certified ophthalmologist)
  - For babies needing treatment:
    - Sens 98.2%; Spec 80.2%; NPV 99.6%; PPV 44.3%
  - For both eyes at a single visit
    - Sens 90.0%; Spec 87.0%; NPV 97.3%; PPV 62.5%

- Reliability (1312 images from 200 babies (half with half without ROP)
  - RW ROP: Sens 91.4% vs. 85.9%; Spec 73.3% vs. 56.5%

- Feasibility
  - Of 27,600 individual photos, 91% were good, 6% were poor and 3% were missing.
Update on Pathogenesis: Phase I ROP

- Phase I: Vaso-obliteration (until ~ 32 weeks PMA) following relative hyper-oxia of extra-uterine environment.
  - Inability of premature infant to auto-regulate blood flow to eye
  - “hi O2” reduces vascular endothelial growth factor (VEGF).
  - Loss of placenta reduces levels of IGF-1 (necessary for VEGF) and EPO further reducing vessel growth
  - Reduced presence of anti-inflammatory factors [higher levels of factors such as tumor necrosis factor alpha (TNF-α)]
  - Increased free radicals their metabolites (many) and decreased anti-oxidents (many including Vit E)
  - (more!)

Reviews: Talkad & Bloom Neonatology 2011; Rivero et al, Neonatology 2011; Mantagos, Vanderveen & Smith, Semin Ophthalmol 2009
Phase 1: Preventive Measures

- Must be tailored for individual baby based on phase of ROP and presence of other systemic conditions

- ONLY for Phase 1:
  - Lower oxygen levels, especially during resuscitation
  - Prevent vaso-obliteration with exogenous IGF-1 ([http://clinicaltrials.gov/show/NCT01096784](http://clinicaltrials.gov/show/NCT01096784); recruiting)
  - Omega 3 supplements (DHA & EPA fortified formula) decrease free radicals and inflammation, suppression of TNF-α (NCT01908907 and others)

Phase II: Neovascular Phase: Increased retinal activity with maturation leads to progressive retinal anoxia in periphery (~≥ 32 weeks PMA)

- What happens
  - Increased levels of VEGF cause neovascularization
  - EPO and IGF-1 naturally rise exacerbating action of VEGF

- Possible treatment strategies
  - Supplemental oxygen? (see next)
  - Anti VEGF therapy? (see next)
  - Increase EPO?
  - Prevent hyperglycemia (up-regulates VEGF)
Titrating Oxygen to Prevent ROP

- Must be tailored for individual baby based on phase of ROP and presence of other systemic conditions

- Oxygen Levels:
  - Phase 1: SUPPORT study shows reduced ROP but increased death in lower oxygen group
  - Phase 2: Stop ROP: Lower ROP only in subgroup with plus Dz; but prolonged hospital stay and increased CLD in higher oxygen group
  - Phase 2: BOOST: similar ROP (lower in subgroup GA< 28 wks) but increased mortality and CLD in higher oxygen group
Update on BEAT-ROP

- Bevacizumab (anti-VEGF) injected intravitreally vs. conventional laser Tx
- Eligible pts: ≤ 1500 gm / ≤ 30 wks with Type 1 ROP and plus Dz
- Fewer recurrence necessitating re-treatment at 54 weeks for bevacizumab (6%) vs. laser (42%) for treatment of Zone 1, Stage 3+ ROP.
- Non-sig reduction of re-treatment for bevacizumab (5%) vs. laser (12%) for treatment of Zone II, posterior, Stage 3+ ROP
Cautions re anti VEGF Tx

- 13 infants with bilateral Type 1 Zone 1 ROP
- Eyes of infant randomly assigned to bevacizumab or conventional laser
- Using FA, all B. eyes had abnormalities in the vasculature at the periphery or posterior pole (hyperfluorescent lesion, absence of FAZ) which were not observed in laser treated eyes.
- Visual or structural significance of such lesions is unknown

Lepore D, Quinn GE et al, Ophthalmol 2014
CNS related eye signs in ELBW

- Strabismus
- CONH
- Optic atrophy
- Nystagmus
- Ocular motor apraxia
- Defective smooth pursuit and saccades
- Cortical vision impairment
- Visual field deficits
- Vision perception deficits
- Visual attention deficits
IVH: Sequelae

N= 1472 survivors (born 23-28 wks) assessed at age 2-3 years (all 10 NICUs in Australia)
- With GIII-IV IVH: 17.5% developmental delay; 30% Cerebral Palsy; 8.6% Deaf; 2.2% Blind
- With GI-II IVH: 7.8 / 3.4% developmental delay; 10.4 / 6.5% Cerebral Palsy; 6.0 / 2.3% Deaf compared to the no IVH group.

N = 1472 survivors (born < 27 wks) CHHDN research network (20 NICUs in US)
- With GIII-IV IVH: 15% developmental delay 28% CP, 2% Deaf, 29% language delay
- No significant increase in neurodevelopmental problems in babies with IVH G I-II

IVH: eye and vision sequelae

- N = 68 (born 28.1 wks) assessed at age 5 years
- Significant differences in severe IVH: G III-IV vs G I-II:
  - optic atrophy (32% vs. 17%) hydrocephalus (58% vs. 10%)
- No significant differences; high probability in G III-IV IVH and G I-II IVH:
  - ROP: (53% vs. 49%) Strabismus (47% vs 44%)

IVH: eye and vision sequelae

- 109 premature babies; (some with normal neuroimaging at birth and 2 years, and others with abnormal scans)
- CONH in 44% with high grade IVH vs. 9% in premature controls.

McLoone, BJO 2006; 90(4):465
PVL Grades 1-3

Fig. 1. Grade of MRI findings
A: Mild, localized white matter damage without enlarged lateral ventricle. B: moderate, white matter somewhat reduced with mildly enlarged lateral ventricle (arrows show irregular ventricular dilation that was most obvious posteriorly). C: severe, diffuse white matter is damaged with extreme enlargement of lateral ventricle (white matter adjacent to lesions from anterior horns [open arrows] to trigones [solid arrows] is lost).
PVL ➔ extensive cupping

- Other eye findings
  - Reduced VA
  - VF defects
  - Exaggerated crowding
  - Poor spatial ability
  - Poor visual perceptual skills
  - CONH
CVI updated definition

- "A neurological disorder caused by damage to the optic radiations, occipital cortex and visual associative areas in the absence of major ocular disease"
  - Fazzi, Dev. Med Child Neuro; 2009
Cortical Vision Impairment (CVI)  
(also see BV-14 on Saturday)

- Bilaterally reduced vision
- Normal retina and ERG
- Absence of prominent nystagmus

History*
- Perinatal hypoxia, prematurity, hydrocephalus, CNS abnormalities, seizures
- 69% had multiple risk factors

CVI: eye / vision signs

- Esotropia (19%)
- Exotropia (40%)
- Nystagmus (21%)
- Optic atrophy (42%)
- Significant refractive error (> +3.0; < -2.0) (20%)
- Limited prognosis to recover vision
Dutch Project on Preterm and SGA Infants at 19 years

- Infants born < 32 wks and/or BW < 1500 gm
- 74% of 959 survivors completed survey
  - 12.6% had cognitive or sensory impairment
- Compared to controls:
  - 2x as many needed special ed (24%)
  - 3X as many were neither employed or in school at age 19 (7.6%)
  - IQ negatively affected (slightly) by earlier birth and growth delay; decrease mitigated by parental education
Summary: Ocular and Neural complications of Premature Birth

Ocular
- Retina
  - Acute ROP, usually transient
  - Scarring and retinal detachment in a few
- Myopia
- Strabismus
- Optic atrophy and cortical vision impairment

Neural (additional)
- Intraventricular hemorrhage
  - Cerebral palsy, mental retardation, hearing and vision impairment
  - CVI… Visual perceptual impairment
- Periventricular leukomalacia
  - Same, more marked
  - Deep cupping from retrograde nerve cell death
Please complete your session evaluation using EyeMAP™ online at http://eyemap.cistems.net

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