Challenges and opportunities in the management of retinopathy of prematurity

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- Jayashree Kalpathy-Cramer (Harvard)
- Jim Reynolds (Buffalo), Kelly Hutcheson (Sidra), Michael Shapiro (UIC), Mike Repka (Hopkins), Phil Ferrone (LIJ), Kim Drenser (Beaumont), Maria Ana Martinez-Castellanos (APEC)
- Samir Patel (Cornell)
- Karyn Jonas, R.V. Paul Chan (UIC)
Take-home points

• Blindness from ROP is largely preventable with appropriate screening and treatment.

• There is international consensus on how and when to treat ROP based on two large prospective trials (ETROP and CRYO-ROP), however the “threshold” for treatment is subjective.

• Today, the primary burden of ROP-related blindness is in low and middle-income countries, where screening and treatment is challenging.

• Computer-based image analysis (CBIA) may improve agreement in ROP diagnosis (everywhere) and play a role in screening programs to reduce resource utilization in low resource settings.
Retinopathy of Prematurity

• The retina is not normally vascularized until near term (40 weeks gestational age, and vasculogenesis normally occurs in a relatively hypoxic environment

• Babies that are born much earlier than have immature vessels that are exposed to higher levels of oxygen than normal (sometimes artificially high levels)

• This can lead to abnormal neovascularization at the border between vascularized and avascular retina.
Classification

• Zone
• Stage
• Plus

http://www.focusrop.com/Home/Education?title=ROP%20Classification%20Update
Classification

• Zone
• Stage
• Plus

Vascular Retina

Neovascular ridge

Avascular Retina

http://www.focusrop.com/Home/Education?title=ROP%20Classification%20Update
Classification

• Zone
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• “Arterial tortuosity and venous dilation greater than standard photo”

• Critical parameter for treatment
  – CRYO-ROP, ETROP
CRYO-ROP: How common is ROP?

• Among infants with BW <1251 grams (2.75 pounds):
  - Incidence of any ROP: 66%
  - Incidence of threshold ROP: 6%

• Among infants with BW <1000 grams (2.2 pounds):
  - Incidence of any ROP: 82%
Key Point # 1:

It is largely predictable which babies will develop ROP
Figure 1. The rate of prethreshold retinopathy of prematurity (ROP) by combination of birth weight and gestational age in the Early Treatment for Retinopathy of Prematurity (ETROP) and Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) studies.
What happens to babies with ROP?

• Natural history
  – 90%: Regresses spontaneously
  – 10%: Severe disease (needs Rx)

• A leading cause of blindness in children
Key Point # 2:

It is largely predictable when babies will develop ROP
CRYO-ROP Data

ROP Examination Guidelines

• Jointly developed by AAO, AAP, AAPOS

• Initial exam at 31 weeks PMA or 4 weeks age, whichever is later

• All infants with:
  – BW <1500 g, or
  – GA ≤30 wks, or
  – BW 1500-2000 g and unstable course

• Follow-up exam at least Q1-2 wks
Key point #3:

Appropriate monitoring and timely treatment can significantly reduce incidence of blindness from ROP.

There is international consensus based on two large prospective trials (ETROP and CRYO-ROP) on when to treat ROP.
Treat plus disease!

- Any zone or stage **with plus disease**
- Or Zone 1 Stage 3 without plus – the one exception and not common
Is this plus disease?

Is this plus disease?

- 3 (14%) experts: “Plus”
- 18 (86%) experts: “Not Plus”

- 11 (52%) experts: “Plus”
- 10 (48%) experts: “Not Plus”

Key point #4:

Despite internationally accepted definitions for ROP classification, inter-observer variability is high even among experts.

There is variability in diagnosis of zone, stage, and plus, but plus disease classification is most important in terms of treatment.
Is the RSD a valid standard?

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- Agreement with RSD ranged from **79 – 99%**
- Expert consensus (mode) agreed with RSD **97%**

Campbell et al, Expert Diagnosis of Plus Disease in Retinopathy of Prematurity From Computer-Based Image Analysis JAMA Ophthalmol. Published online April 14, 2016
Experts diagnose on a continuum

- Images sorted left to right by average disease severity = continuum of severity (red arrow points towards more severe disease)
- Experts sorted top to bottom by average disease score = each has his/her own threshold

Experts diagnose on a continuum

- Images sorted left to right by average disease severity = **continuum of severity** (red arrow points towards more severe disease)
- Experts sorted top to bottom by average disease score = **each has his/her own threshold**

Same pattern in 2\textsuperscript{nd} dataset!
Conclusion: some experts consistently “under-call” and others “over-call” compared to the community average
Is it time to rethink “plus disease” as a spectrum of vascular changes rather than as a binary (plus or not), or trinary (plus, pre-plus, or normal) variable?
Which image represents more severe disease?
Experts agree on relative plus disease severity better than they agree on classification.
Key point #5:

Computer-based image analysis of images from ROP screening may increase objectivity of exam findings and standardize diagnostic agreement.

CBIA can provide both classification labels and relative disease scoring.
“i-ROP” CBIA system

- Manually segmented images
- Multiple combinations of image size, features, and vessels
- Analyzed all combinations for their ability to classify images as “normal,” “pre-plus” or “plus” compared to the RSD
- Used Gaussian mixed models and machine learning
i-ROP CBIA system

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- Agreement with RSD ranged from 79 – 99%
- Expert consensus (mode) agreed with RSD 97%
- The i-ROP system (using manually segmented images) performed better than 7/8 experts

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i-ROP score versus disease severity for 9 representative images.
Key point #6:

Today, the primary burden of ROP-related blindness is in low and middle-income countries.
ROP as a global health problem

• First Epidemic – moderately preterm babies in high-income countries
  • 1940’s-50’s.
• Second Epidemic – extremely preterm babies in high-income countries
  • 1970’s – today
• Third Epidemic – moderately preterm babies in middle-income countries
  • 1990’s – today
Figure 6. Summary of retinopathy of prematurity and associated visual impairment outcomes for survivors of 15 million preterm births worldwide in 2010.
Figure 5. Regional burden of visual impairment from retinopathy of prematurity among preterm babies born in 2010 and surviving the neonatal period.
ROP care delivery

• Care delivery challenges:
  – Time-intensive (high human resource cost)
  – Exam: difficult, imprecise, subjective
  – More infants at risk (survival)
  – Medicolegal liability (where applicable)
  – Fewer ophthalmologists willing to perform

• Educational challenges: limited access to care & training
  – Especially in rural & underserved areas
  – Very little training even in US
Key point #7:

Incorporating CBIA into telemedicine-based screening model for ROP may reduce the human resources required to perform indirect ophthalmoscopy on the babies who have normal exams and will not require treatment.
Can this system be used in automated ROP screening?

**Proof of concept:**
- A threshold of 45 would identify all babies with plus disease.
- A threshold of 38 would identify all babies with pre-plus and plus disease.
- Potentially could avoid many exams of “normal” eyes.
Coming soon: i-ROP app!
Summary

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