Clinical Research in Pediatric Ophthalmology

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Magnitude and causes of blindness worldwide

- 37 million blind people
- 161 million with visual impairment
- 80%+ is avoidable
- 90%+ live in developing countries
- 2/3 are women

Courtesy W Anninger
WHO/PBL Eye Examination definitions for children with blindness or low vision

- **Childhood**: 0-15 years of age
- **Visual Impairment**: <6/18 (20/60) better eye
- **Severe Impairment**: <6/60 (20/200) better eye
- **Blindness**: <3/60 (20/400) better eye
Change in a 10 year period

• Estimate of 1.4 million blind children in 1999
• Estimate of 1.26 million in 2010 (10% decrease)

• Likely due to:
  – Improved socio-economic development
  – Increased coverage of specific programs aimed at decreasing childhood mortality rates
    • Measles immunization
    • Vitamin A supplementation
Challenges in obtaining reliable population based data on blindness in children

- Large sample sizes
- Dispersed in population
- Associated handicaps
- Difficult to measure level of impairment

- High mortality rate - prevalence underestimates the magnitude of the problem
Number of blind children/million population, by cause and level of development

- Corneal scarring
- Cataract, glaucoma
- ROP

Courtesy C. Gilbert
Epidemiology and health system research essential

- Surveys of blind schools and national surveys
- Botswana – W Anninger, MD and S Nallasamy, MD
  - CHOP collaboration with University of Botswana
  - Identified 250 visually handicapped or blind children
  - Useful in defining needs for allocation of resources
Bilateral Visual impairment in Botswana:

63% Avoidable

- Preventable: 5%
  - ON injury: 2%
  - congenital rubella: 1%
  - Corneal Scar: 1%

- Treatable: 58%
  - Refractive Error: 19%
  - Lens Related: 19%
  - Glaucoma: 7%
  - Ref Amblyopia: 6%
  - Vernal: 4%

Unavoidable: 37%

- ON Atrophy: 7%
- Albinism: 6%
- Ret dystr: 4%
- Disorganized: 4%
- Microophth: 3%
- Aniridia

Nallasamy et al, BJO 2011
15 million premature babies per year

Born too soon, WHO, 2012
IC-ROP

ROP Stage 3
Stage 5: total RD
Who gets ROP in the US?
CRYO-ROP
Cryotherapy for ROP (mid-80’s)

• Largest study detailing natural history:
  – 23 nurseries
  – 4000 babies <1251g BW enrolled (Jan 86-Nov 87)
  – 246 infants randomized to one eye treated and fellow eye observation

• More than 15 year of follow-up

• Marks the point at which the treatment of ROP became data-driven

Arch Ophthalmol 1993; 111:339-344
Arch Ophthalmol 2001; 119:1110-1118
Arch Ophthalmol 2007;125: 1276-1281
CRYO-ROP

- Defined “threshold” disease (50% of eyes expected to progress to RD or macular fold)

Proves the effectiveness of peripheral retinal ablation:

- ↓ Unfavorable anatomical outcome by 40%
- ↓ Unfavorable visual outcome by 20%
- Trial was stopped: unethical to not offer treatment
Visual acuity results

**Recognition Visual Acuity**

Unfavorable - 20/200 or worse

**Grating Visual Acuity**

Unfavorable - >1 octave below normal
VISUAL ACUITY RESULTS AT 1, 3½, 5½, 10 & 15 YRS*

*Denominators vary due to ability to perform test
Effects of ROP and Cryotherapy on Visual Field Extent

Threshold ROP, post CRYO

Recovered without CRYO

Never ROP

Cartoon courtesy, Dale Phelps, MD
ETROP Study

- Does earlier treatment with retinal ablation in high-risk prethreshold ROP lead to:
  - improved visual function?
  - improved retinal structure outcomes?
- 26 sites in US
- 401 had high-risk prethreshold (>15% risk of unfav)
  - Randomized to:
    - “Earlier treatment”
    - Conventional management
- Laser photocoagulation

Arch Ophthalmol 2003;121:1684-96
ETROP

- Final 6-year examinations completed
- Visual acuity – reported June 2010
- Visual fields – Arch Opth Feb 2011
- Grating acuity – accepted
- Contrast sensitivity submitted
ETROP – 6 year outcome

- Visual acuity
  - Type 1 eyes
    - 25.1% ET unfavorable vs 32.8% CM unfavorable
      \((p = 0.02)\)
  - Type 2 eyes
    - 23.6% ET unfavorable vs 19.4% CM unfavorable
      \((p = 0.37)\)
- 52% CM eyes regressed without treatment

Arch Ophthalmol
2010;128:663-671
ETROP – 6 year outcome

- Visual field measured with white-sphere double arc perimeter
  - All eyes
    - Field extent 0.1 to 3.7 deg larger in ET than CM eyes
  - Bilaterally sighted subjects
    - Type 1 eyes – no difference ET vs CM
    - Type 2 eyes – ET significantly smaller than CM (3.6 to 8.7 deg)

Arch Ophthalmol, Feb 2011
Current treatment – 2003
ETROP based

• Type 1 → laser
  – any plus in zone I,
  – stage 3 in zone I w/o plus
  – stage 2-3 in zone II with plus

• Type 2 → careful observation
  – stage 2, zone 1 w/o plus,
  – stage 2-3 in zone 2 w/o plus
BEAT-ROP Study
(Bevacizumab Eliminates the Angiogenic Threat of Retinopathy Of Prematurity)

• Prospective, randomized, non-blinded multicenter with 150 infants randomized to laser or bevacizumab
• Recurrence requiring retreatment
  – Bevacizumab (Bev)-4/70 infants (6%)
  – Laser – 19/73 infants (26%)
• Recurrence requiring retreatment by zone of ROP
  – Zone I
    • Bev 6% (2/31) vs Laser 22% (14/33), \( p = 0.002 \)
  – Zone II
    • Bev 5% (2/39) vs Laser 12% (5/40), \( p = 0.27 \)
BEAT ROP

- Underpowered to assess safety for mortality or systemic morbidity
  - 5 bevacizumab infants and 2 laser infants died
- Dosage concerns
- Longer follow-up needed for assessing bevacizumab response
Current status of treatment for severe ROP

• Current treatment should be peripheral retinal ablation
  – Local

• Anti-VEGF therapy may be indicated in selected severe cases
  – Compassionate use
  – In clinical trials
What are the manpower demands for detection of serious ROP?

8200 babies ~20K exams

363 infants treated

A Fielder et al; 2002

UK cohort study 1997/8
Options available beyond BW and GA for identifying at risk babies

- Illness indicators (NEC, sepsis)
- Digital imaging with remote evaluation
- Rate of weight gain
  - Lofqvist et al – cumulative deviation
  - Binenbaum et al – logistic regression
- Genetic markers
- Antioxidant deficiencies
Shift from diagnostic examination to ROP screening

Referral-warranted ROP (Ells et al, 2003)

1) Any ROP in zone 1
2) Any stage 3
3) Presence of plus disease (2 or more quadrants)

RW-ROP indicates need for a diagnostic examination to determine whether treatment is indicated
ROP as a cause of blindness in children

- Data on almost 20,000 blind children in published and unpublished studies
- 40 countries, grouped by UNDP development indices

Courtesy C. Gilbert
Epidemiology and health system research essential (early 2000s)

- ROP as a cause of blindness
- C Gilbert – 40 countries, nearly 20,000 children

% blindness due to ROP

USA 13
Ireland 11
Nordic 10
Sweden 4
UK (new cases) 3

Guatemala 4.1
Nigeria 0.5
India 0.2
Uzbekistan 0
Mongolia 0
Cambodia 0
Pakistan 0
ROP as a cause of blindness in middle income countries

- Argentina: 60%
- Czech Rep: 41.4%
- Cuba: 39.6%
- Paraguay: 33.3%
- Colombia: 23.9%
- Bulgaria: 22.9%
- Chile: 17.6%
- Thailand: 16.9%
- Peru: 16%
- Brazil: 14.2%

Courtesy C. Gilbert
Characteristics of infants with severe ROP (1999-2004)

- BW and GA on the following babies:
  - “Severe ROP”:
    - treated for pre/threshold ROP
    - surgery for Stage V
    - attending low vision clinics
- From
  - 3 high income countries
  - 11 middle income countries
  - 3 low income countries

Gilbert et al Pediatrics 2005 115: e518-525
Characteristics of babies with “severe” ROP in UK, USA and Canada
Characteristics of babies with “severe” ROP in low / middle income countries

![Graph showing gestational age vs. birth weight for babies with severe ROP in different countries.](image-url)
Visual impairment due to ROP in premature babies (2010 data)

- Low ROP blindness
- High ROP blindness
- Variable ROP blindness
- No ROP blindness

Blencowe et al, Peds Res Dec 2013
Telemedicine and ROP

What are the steps needed to maximize the opportunity to detect serious ROP in at risk premature babies using a telemedicine system?
Digital imaging and ROP detection

7 Level I studies (458 infants)

- **Sensitivity:**
  - 76-100% for ≥Type-2 ROP
  - 87-100% for ≥Type-1 ROP
  - (one 57% for stage 3)

- **Specificity:** 37-98%

3 Level III studies (1462 infants)

- **Sensitivity:** 100% (one N/A)
- **Specificity:** 99-100%
<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Outcome</th>
<th>% Sensi</th>
<th>% Spec</th>
<th>% NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2000</td>
<td>10</td>
<td>Plus</td>
<td>100</td>
<td>0</td>
<td>-</td>
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<tr>
<td>Yen et al, 2000</td>
<td>23</td>
<td>Predict prethresh at 32-34 wks PMA imaging</td>
<td>33</td>
<td>100</td>
<td>90</td>
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<tr>
<td>Ells et al, 2003</td>
<td>44</td>
<td>RW-ROP</td>
<td>100</td>
<td>96</td>
<td>100</td>
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<tr>
<td>Chiang et al, 2006</td>
<td>64</td>
<td>Type 2 or worse</td>
<td>77</td>
<td>96</td>
<td>94</td>
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<tr>
<td>Wu et al, 2006</td>
<td>43</td>
<td>Type 2 or worse</td>
<td>100</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Chiang et al, 2007</td>
<td>67</td>
<td>Type 2 at 31-33 wks</td>
<td>76</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>PHOTO-ROP</td>
<td>51</td>
<td>Clinically significant ROP</td>
<td>92</td>
<td>37</td>
<td>76</td>
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<tr>
<td>Dhaliwal et al, 2009</td>
<td>81</td>
<td>Stage 3</td>
<td>57</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Lorenz et al, 2009</td>
<td>1222</td>
<td>Suspect treatment requiring</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Silva et al, 2011</td>
<td>230</td>
<td>Type 2 or worse</td>
<td>100</td>
<td>99.6</td>
<td>100</td>
</tr>
<tr>
<td>Dai et al, 2011</td>
<td>108</td>
<td>Treatment requiring</td>
<td>100</td>
<td>98</td>
<td>100</td>
</tr>
</tbody>
</table>

*table concept adapted from Chiang et al, 2012*
Where is telemedicine in ROP most likely useful?

- Underserved areas with:
  - Few ophthalmologists
  - Sparse ROP expertise
- Countries with rapidly developing NICU systems
- Cost effectiveness of use in the US health system to be established
Principles to consider when adopting telemedicine in ROP

• Define purpose
  – Case detection of serious ROP

• Ensure performance is sufficient compared to “appropriate criterion standard”
  – Diagnostic exam by ophthalmologist

Adapted from P Lee on diabetic retinopathy in Arch Ophthalmol 1999;117:1639-40
Digital retinal cameras used at CHOP for at risk babies

<table>
<thead>
<tr>
<th>Camera:</th>
<th>Retcam Shuttle</th>
<th>NIDEK NM200-D</th>
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</thead>
<tbody>
<tr>
<td>Field of view:</td>
<td>130 degrees</td>
<td>30 degrees</td>
</tr>
<tr>
<td>Price:</td>
<td>$90,000</td>
<td>$17,000 (no longer available)</td>
</tr>
<tr>
<td>Contact:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Portability:</td>
<td>Fair within institution</td>
<td>High</td>
</tr>
</tbody>
</table>
Not RW-ROP

RW-ROP
Multicenter observational study

Evaluate validity, reliability, feasibility, safety, and cost-effectiveness of a telemedicine system to detect eyes of at-risk babies in need of a diagnostic examination by an ophthalmologist experienced in ROP.

Funded by NEI/NIH July 2010
Study design

• Need 250 “cases” – i.e. babies BW <1251g with RW-ROP
  – 11 centers in US
  – 1 center in Canada
• Study certified investigators
• Study Headquarters, Data Coordinating Center and Reading Center in Philadelphia
• Imaging Data Center -
Sessions at Clinical Centers

- **Ophthalmologist**
  - Diagnostic eye examination

- **Non-physician Retinal Imager**
  - Digital retinal imaging – wide field, using RetCam Shuttle

- **Study Center Coordinator**
  - Consents, scheduling procedures
  - Completion of data forms and uploading data

All using standard protocols
e-ROP Image Reading Center

- Images graded by masked non-physician trained readers to determine presence of:
  - Zone I ROP
  - Stage 3 ROP or worse
  - Plus disease

- Sample also graded by masked ROP experts
e-ROP Study team
Outcome measure

• Comparison of results of diagnostic examination by Study certified ophthalmologist with grading of image by Trained non-physician Readers

• Sufficiently large study to address:
  • Validity (sensitivity, specificity, NPV, PPV)
  • Reliability
  • Feasibility
  • Safety
  • Cost-effectiveness
Requirements of a telemedicine system

- High sensitivity and specificity
- Standardized and generalizable protocols
- Low morbidity
- Effective and efficient feedback
Challenges of implementing telemedicine for ROP

- High cost of false negatives and how to handle them
- Determining “criterion standard”
  - Diagnostic examination - “imperfect” standard
- Obtaining good quality retinal images
- Grading of images and timely feedback
  - non-physician readers vs ophthalmologist readers
Where do these efforts lead?

- In US and countries with well developed NICU systems
  - May allow physicians to examine only the most at-risk babies
  - Will likely decrease early transfers for treatment
  - Allow ROP screening in underserved areas
  - May be most useful in level II nurseries
- Other regions of the world
  - Very useful in NICUs with no current coverage or limited ROP expertise
  - Countries with widely dispersed population (Canada, Russia)
ROP challenges in MHDCs and LHDCs

- Raising awareness
  - Basic epidemiologic and health systems research
- Capacity building
  - Personnel/equipment/funds
- Partnerships between institutions
  - NGOs and governmental agencies
14 NICUs in a major city in a MHDC

<table>
<thead>
<tr>
<th></th>
<th>Babies/nurse in NICU</th>
<th>Pt on oxygen/O$_2$ analyzer</th>
<th>Lab test availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>3</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>4</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>only macro</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>6</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>7</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>only macro</td>
</tr>
<tr>
<td>8</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>9</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>only macro</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>11</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>only macro</td>
</tr>
<tr>
<td>12</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
<tr>
<td>13</td>
<td>&gt;3</td>
<td>&gt;4</td>
<td>intermittent</td>
</tr>
</tbody>
</table>

standard | deficient | critical

Courtesy A Villanueva, L Gordillo
Rates of ROP requiring treatment by nursing capacity

A Zin, M Moreira, C Gilbert – PAS 2007

* compared with lowest rate
Meetings: National/Regional ROP Workshops (supported by IAPB-LA, CBM, ORBIS and PAHO)

- 2001: Mexico
- 2002: Argentina, Brazil
- 2003: Colombia, Brazil
- 2004: Ecuador, Brazil, Cuba
- 2005: Colombia, Brazil, Ecuador, and Latin American meeting in Peru
- 2006: Argentina, Ecuador, Brazil, Venezuela, LA ROP group during the WCO in Brazil
<table>
<thead>
<tr>
<th>Country</th>
<th>Pop (millions)</th>
<th># VLBW</th>
<th>% Survive</th>
<th># Thres</th>
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<tbody>
<tr>
<td>Argentina</td>
<td>39</td>
<td>7052</td>
<td>60%</td>
<td>444</td>
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<tr>
<td>Bolivia</td>
<td>8</td>
<td>2356</td>
<td>30%</td>
<td>49</td>
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<tr>
<td>Brazil</td>
<td>188</td>
<td>31055</td>
<td>60%</td>
<td>1304</td>
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<tr>
<td>Chile</td>
<td>16</td>
<td>2602</td>
<td>70%</td>
<td>82</td>
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<tr>
<td>Costa Rica</td>
<td>4</td>
<td>704</td>
<td>70%</td>
<td>59</td>
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<td>Colombia</td>
<td>44</td>
<td>9258</td>
<td>60%</td>
<td>389</td>
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<tr>
<td>Cuba</td>
<td>11</td>
<td>1311</td>
<td>60%</td>
<td>55</td>
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<tr>
<td><strong>Dominican Republic</strong>*</td>
<td>9</td>
<td>2028</td>
<td>60%</td>
<td>85</td>
</tr>
<tr>
<td>Ecuador</td>
<td>13</td>
<td>2896</td>
<td>60%</td>
<td>122</td>
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<tr>
<td>El Salvador</td>
<td>7</td>
<td>1800</td>
<td>60%</td>
<td>76</td>
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<tr>
<td><strong>Guatemala</strong>*</td>
<td>12</td>
<td>4190</td>
<td>60%</td>
<td>176</td>
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<td>7</td>
<td>2180</td>
<td>60%</td>
<td>92</td>
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<tr>
<td>Mexico</td>
<td>107</td>
<td>23415</td>
<td>60%</td>
<td>983</td>
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<td><strong>Nicaragua</strong>*</td>
<td>6</td>
<td>1386</td>
<td>60%</td>
<td>58</td>
</tr>
<tr>
<td><strong>Panama</strong>*</td>
<td>3</td>
<td>613</td>
<td>60%</td>
<td>26</td>
</tr>
<tr>
<td>Paraguay</td>
<td>6</td>
<td>1930</td>
<td>60%</td>
<td>81</td>
</tr>
<tr>
<td>Peru</td>
<td>28</td>
<td>6546</td>
<td>60%</td>
<td>275</td>
</tr>
<tr>
<td>Uruguay</td>
<td>3</td>
<td>655</td>
<td>60%</td>
<td>31</td>
</tr>
<tr>
<td>Venezuela</td>
<td>26</td>
<td>5113</td>
<td>60%</td>
<td>215</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>539</strong></td>
<td><strong>106,434</strong></td>
<td><strong>4,571</strong></td>
<td></td>
</tr>
</tbody>
</table>
Meetings: National/Regional ROP Workshops:

- 2007: Ecuador, Dominican Republic, Venezuela, Mexico, Peru, Brazil, Cancun, Mexico during PAAO, Vietnam, Serbia
- 2008: Panama, Honduras, Colombia, Dominican Republic, Mexico, Venezuela, Brazil, Argentina (SIBEN), Vietnam
- 2009: Indonesia, India, Central America Regional workshop, Brazil
- 2010: Peru, Indonesia, Nicaragua
- 2011: El Salvador, Brazil, Russia
- 2012: Peru, Brazil, Russia
- 2013: Indonesia, 3rd Latin America (Cartagena), Russia, Brazil, Bulgaria
- 2014: India, Poland, Russia, Mexico
Aprueban Norma Técnica de Salud de Atención del Recien Nacido pre término con riesgo de Retinopatía del Prematuro

RESOLUCIÓN MINISTERIAL
N° 707-2010/MINSA

Lima, 13 de setiembre de 2010

Visto el expediente N° 10-065290-001, que contiene el Memorandum N° 3619-2010-DGSP/MINSA, de la Dirección General de Salud de las Personas, e Informe N° 624-2010-OGAJ/MINSA, de la Oficina General de Asesoría Jurídica;

CONSIDERANDO:

Que, el artículo 2° de la Ley N° 27657, Ley del Ministerio de Salud, establece que el Ministerio de Salud es el ente
Retinopathy of Prematurity

Neonatal/perinatal care

DANGER

ROP screening and treatment

Courtesy B Darlow