Childhood blindness due to ROP
Number of blind children/10 million pop, by cause and level of development

Unavoidable causes: CNS lesions; congenital abnormalities; retinal dystrophies

Treatable: cataract and glaucoma

Preventable: corneal scarring - measles, ON, VADD, HTEM

ROP

High income  Middle income  Low income  Very low income
Proportion of blindness due to ROP, by World Bank region

<table>
<thead>
<tr>
<th>Region</th>
<th>% Blindness due to ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSE</td>
<td>26</td>
</tr>
<tr>
<td>LAC</td>
<td>24</td>
</tr>
<tr>
<td>EME</td>
<td>10</td>
</tr>
<tr>
<td>OAI</td>
<td>5</td>
</tr>
<tr>
<td>China</td>
<td>2</td>
</tr>
<tr>
<td>India</td>
<td>0.5</td>
</tr>
<tr>
<td>MEC</td>
<td>0.5</td>
</tr>
<tr>
<td>SSA</td>
<td></td>
</tr>
</tbody>
</table>
Estimates of numbers blind from ROP, by World Bank region. Being revised...

Total >50,000

- LAC: 24,000
- OAI: 12,000
- FSE: 10,000
- EME: 5,000
- China: 4,000
- India: 1,500
- MEC: 1,000
- SSA: 200
Proportion of blindness due to ROP, by infant mortality rates
ROP blindness – likely risk using IMR as a proxy 2010

- **≤8/1000**: Low risk of ROP blindness - good neonatal care and screening
- **9-60/1000**: High risk of ROP blindness - inadequate neonatal care and screening
- **≥61/1000**: Low risk of ROP blindness - neonatal care not well developed
Retinal vascularisation during development

16 weeks GA

26 weeks GA

36 weeks GA

40 weeks GA
Pathogenesis of ROP

Relative hypoxia

A: Premature birth
B: Vessel growth stops
C: Retinal neovascularization

Early Treatment:
Supplement to normal levels
- IGF-1
- VEGF
- EPO
- ω-3 PUFA

Late Treatment:
Suppress to normal levels
- VEGF
- EPO
- [IGF-1]

Resolution of retinopathy

in utero
Normal vessel growth

Increasing metabolism
Hypoxia
Peripheral retinal hypoxia drives the new blood vessel growth
Classification of ROP

- Site (zones and clock hours)
- Severity (Stages)
- Signs of BRB breakdown ("plus disease")
- Scarring
Classification of ROP - by zone (site)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Demarcation line</td>
</tr>
<tr>
<td>II</td>
<td>Ridge</td>
</tr>
<tr>
<td>III</td>
<td>Fibrovascular ridge</td>
</tr>
<tr>
<td>IV</td>
<td>Subtotal retinal detachment</td>
</tr>
<tr>
<td>V</td>
<td>Total retinal detachment</td>
</tr>
</tbody>
</table>
Stage 1 demarcation line
Stage 1 demarcation line
Stage II ROP - ridge
Stage II ROP
Stage III - early
Stage III
Stage III ROP
Stage III ROP
Stage III ROP
Courtesy Ells
Stage 4 – subtotal retinal detachment

Courtesy Azad
Stage 4 – subtotal retinal detachment
Stage V - total retinal detachment with open funnel
Stage V - total retinal detachment with closed funnel
Stage V - inoperable retinal detachment
End stage eye blind from ROP
Child blind from ROP
Cicatricial disease with dragged vessels
Natural history of ROP

- Disease starts 4-7 weeks after birth, and progresses over the following few weeks
- Stage I and II disease
  - spontaneous regression common
- Stage III “plus” disease (threshold disease)
  - 50% progression to retinal detachment
- Stage IV and V disease
  - blinding
Classification of ROP - other

- “Plus” disease:
  denotes breakdown of blood-ocular barriers, with pupil rigidity, dilated tortuous retinal vessels, vitreous haze

- Threshold disease:
  5 + continuous clock hours of Stage III “plus” disease
  or 8 hours in total of Stage III “plus” disease
“Plus” disease in posterior pole
Changes to classification (2005)

- Pre-plus disease
- Clarification of how to assess if disease is in zone 1
- Aggressive, posterior ROP (AP-ROP)
“Pre-plus” disease
New stage: Aggressive posterior ROP (AP-ROP)

Courtesy Ells
New stage: Aggressive posterior ROP (AP-ROP)
Indications for treatment - old

Threshold disease:
A total of 8 discontinuous clock hours of stage III “plus” disease, or 5 or more continuous clock hours.
Indications for treatment – new (earlier in the course of the disease)

Type 1 pre-threshold disease:
- Zone 1, any ROP with plus disease ($\geq 6$ hours)
- Zone 1, Stage 3 ROP +/- plus
- Zone 2, Stages 2 or 3 with plus disease ($\geq 6$ hours)
Rates of threshold disease

- Vary, depending on
  - Case mix
  - Neonatal care and survival of most at risk
  - Screening criteria
- <1% in some UK units (<1,500g and/or <32 weeks)
- 15% in middle income countries (same criteria)
Treatment of threshold disease

Aim: confluent treatment of avascular retinal periphery with cryo or laser, avoiding long ciliary vessels and ridge
Indirect laser treatment
Baby receiving cryotherapy
Peripheral retinal cryo with laser
Disease regression after treatment
Plus disease resolves with treatment

Before treatment                At 2 weeks                  At 4 weeks

[Images of eye scans at different stages: before treatment, at 2 weeks, and at 4 weeks]
Schematic representation of blindness due to ROP in the West since 1940

Oxygen restriction

Survival LBW babies

“first epidemic”

“second epidemic”

Blindness due to ROP


BW: 1,000-1,500 gms

600-900 gms

International Centre for Eye Health
Risk factors during the “first epidemic of ROP” in the West (1940s and 1950s)

- Supplemental oxygen
- No monitoring of blood gases
- Birth weight: mean 1,300 (800 – 3,400 gs)
Risk factors during the “second epidemic of ROP” in the West (1970s onwards)

- Extremely low birth weight (<1,000 gms, av 750 gms)
- Extreme prematurity (<30 weeks GA: av 25 weeks)
- Small for gestational age (SGA)
- Poor post natal weight gain
- Fluctuating blood gases - hyperoxia/hypoxia
- Factors predisposing to the “oxygen radical disease of neonatology”

[Ocular factors]
Characteristics of babies with “severe” ROP in UK, USA and Canada

Full term

Gilbert et al. Paediatrics 2005 115  518-525
Characteristics of babies with “severe” ROP in low/middle income countries

Gilbert et al. Paediatrics 2005 115 518-525
Varying neonatal care in India - variation in exposure to risk factors for ROP
...variation in risk

Courtesy Ells
Risk factors during the “third epidemic of ROP” in middle income countries

<table>
<thead>
<tr>
<th>Historical perspective of ROP</th>
<th>1940-50s</th>
<th>1960-70s</th>
<th>1980s-present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st epidemic</td>
<td>2nd epidemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors for ROP:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- prematurity</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>- low birth weight</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>- high oxygen</td>
<td>+++++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>- illness factors</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>&lt;1,000 gms</td>
<td>High mortality</td>
<td>Mod mortality</td>
<td>Low mortality</td>
</tr>
<tr>
<td></td>
<td>No ROP</td>
<td>ROP +</td>
<td>ROP +++</td>
</tr>
<tr>
<td>1,000-1,500 gms</td>
<td>Improved Survival</td>
<td>Low mortality</td>
<td>Very low mortality</td>
</tr>
<tr>
<td></td>
<td>ROP +++</td>
<td>ROP ++</td>
<td>No ROP</td>
</tr>
<tr>
<td>Level of neonatal care provided</td>
<td>Poor</td>
<td>Moderate</td>
<td>Excellent</td>
</tr>
<tr>
<td>3rd epidemic encompasses babies represented</td>
<td>in all three columns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**International Centre for Eye Health**
Risk factors during the “third epidemic of ROP” in middle income countries

- Mixture of the first and second epidemic
- Different risk factors probably important in different clinical settings
- May be varying susceptibility in different racial groups - blacks less susceptible
Summary of risk factors, and babies at risk of ROP

- Varies, depending on neonatal outcomes:
  - **good neonatal outcomes**: risk factors and babies at risk similar to the West (i.e. extremely low birth weight; extreme prematurity; fluctuating oxygen levels etc)
  - **poor neonatal outcomes**: risk factors similar to first epidemic (i.e. poorly controlled oxygen levels in more mature babies)
Prevention of blindness in children due to ROP

- Primary prevention: prevention of the disease from occurring in the first place
- Secondary prevention: early identification and treatment, to prevent the consequences of the disease
- Tertiary prevention: Interventions to restore function
Primary prevention of ROP - 1

- Prevent preterm birth:
  - avoid unnecessary Caesarian sections
  - good antenatal care
  - prevent teenage pregnancies (26% mothers <20 years old in a recent screening prog study in Ecuador)
  - prevent multiple birth (e.g. from IVF)
  - good obstetric care
Primary prevention of ROP - 2

Excellent neonatal care

- Proven effectiveness:
  - monitoring blood gases
  - systemic steroids prior to preterm delivery

- Unproven effectiveness:
  - surfactants
  - vitamin E

- Ineffective:
  - Light restriction
  - Vitamin A supplementation
Secondary prevention:

- Screening to identify babies with threshold, or pre-threshold disease
- Treatment by peripheral retinal ablation by cryotherapy or laser
- Increasing oxygen saturation in babies with threshold disease gave essentially negative findings (STOP-ROP trial)
Screening for threshold ROP

- Is a screening programme needed?
  - Only if there is intensive neonatal care
- Which units should be included?
  - Start in larger units where at risk babies are surviving
- Which babies?
  - <2,000 gms and/or <32 weeks + “sickness”
- When?
  - First examination 4 weeks after birth
- How?
  - Indirect ophthalmoscopy with dilated pupil
  - +/- lid speculum, with depressor to rotate the eye
Indirect ophthalmoscopy in the neonatal unit
Screening for ROP

- Who?
  - Skilled ophthalmologist (VR, or paediatric)

- How often:
  - Every 1 or 2 weeks, depending on degree of prematurity, and findings at each examination

- For how long?
  - Until regression / vascularisation

- How should this be organised?
  - Neonatologist is responsible for identifying babies to be examined
  - Diary system useful
  - Nurse dilates the pupils
  - Regular visits, on a pre-determined day and time (for discharged babies to be brought back)
New developments in screening: digital imaging

Courtesy Ells
RetCam

• RetCam can be used
• 1. As an adjunct to indirect ophthalmoscope
  – advantage: can record image
• 2. For telemedicine screening with a) a technician who takes and grades images there and then, or b) uploaded images onto the internet. Images have to be interpreted by remote experts within 48 hours. For each baby have to decide: a) discharge b) follow up (& when) c) needs treatment
• Telemedicine screening: still experimental
New concepts in screening: WINROP

- Weight gain during first few weeks of life predicts subsequent ROP risk
- Mediated via IGF-1
- WINROP: a computer model developed in Sweden. It needs to be validated in settings where bigger babies are also developing severe ROP
Treatment of ROP

- **Indications:**
  - Prethreshold disease in one or both eyes

- **How:**
  - Laser (or cryotherapy if laser not available)

- **Aim of treatment:**
  - Complete ablation of avascular retinal periphery

- **Anaesthesia:**
  - Sedation + analgesia or GA

- **Post op:**
  - Mydriatics and topical steroids
Follow up

- All babies who have been treated, to ensure regression
  - If not regressed, retreat
- Premature babies with or without ROP have a markedly increased risk of the following:
  - significant refractive errors
  - strabismus
  - cortical visual impairment
  - disorders of higher visual pathways
  - optic atrophy and hypoplasia
Tertiary prevention of ROP

- Vitreoretinal surgery for Stage IV and Stage V:
  - no randomised clinical trials have been done
  - some surgeons believe in retinal detachment surgery for Stage IV
  - most surgeons do not now operate on Stage V, as the surgery is so difficult, and the functional results are poor
- Rehabilitation, special education, support services
Potential new treatment for ROP

- Anti-VEGF preparations by intravitreal injection
- Effective as a “salvage” treatment
- Some advocate it as first line treatment
- Safety not yet known
  - is absorbed systemically
  - not known what effect it might have on developing vasculature elsewhere, glomeruli and alveoli
- Clinical trial on-going in US BUT not investigating long term complications
Programmes for ROP

- Need good coverage
- Need good management information systems e.g. online data recording for each baby
- Need to be co-ordinated and monitored
- Need financial support, ideally from Ministries of Health
- Need to involve parents
- May need
  - training
  - equipment