ROP 2013
Failure is Not an Option
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ROP Background
- ROP first described in 1942 by Terry as retrolental fibroplasia
- Association with high oxygen tension and low birth weight

ROP Pathogenesis
- Normal vascularization - 39-42 weeks
- Mesenchymal cells --> retinal capillary endothelial cells
- Excessive O2 concentration at 4-5 months of gestation
- Intercurrent illness (infection, lung disease)
- Nutrition
- Role of VEGF

ROP Epidemiology
- Increased survival of neonates
- Increased incidence of ROP
- In the U.S. alone, 4 million babies are delivered annually with 15% of those being premature
- Of those, 59% are born weighing less than 2 lbs., of which 75% survive
- Approximately 300 children / million live births have at least one blind eye from ROP
- Worldwide prevalence of blindness due to ROP is 50,000
- Economics

ROP Initial Screening
- < 1500 G or gestational age of 32 weeks or less
- Selected infants with a birth weight between 1500-2000 G or gestational age of more than 32 weeks with an unstable clinical course (high risk)*
- Experienced Ophthalmologist*

Scheme of Retina in ROP and Terminology
ARA Screening Form

ROP Follow up Examinations
1 week or less follow up
- Stage 1 or 2 ROP : Zone I
- Stage 3 ROP : Zone II
1-2 week follow up
- Immature Vascularization : Zone I – no ROP
- Stage 2 ROP : Zone II
- Regressing ROP : Zone I
2 week follow up
- Stage 1 or 2 ROP : Zone II
- Regressing ROP – Zone II
2-3 week follow up
- Stage 1 or 2 ROP : Zone I
- Stage 3 ROP : Zone II

Severity of Disease (stages)
- Stage 0   Immature Retina
- Stage I    Flat demarcation line
- Stage II   Elevated Ridge
- Stage III  Neovascularized Ridge
- Stage IV   Partial RD
- Stage V    Total RD

“Plus Disease”
- Engorgement/tortuosity of vessels in posterior pole
- Marker of aggressive disease

Examining the Premature Infant
- Pupil
- Iris
- Lens
**Examining the Premature Infant**

- Pupil
- Iris
- Lens

**Examining the Premature Infant**

**Funduscopy**
- Dilation
  - Cyclomydril (0.2% cyclopentolate/1% phenylephrine)
  - Lid speculum, 28D lens
- Examine posterior pole 1st
- Examine periphery with scleral depression

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The fundamental process leading to ROP is **INCOMPLETE VASCULARIZATION** of the retina.

The clinical appearance of ROP is related to the location of the vascular-avascular junction.

**Stage I**

**Type I ROP**
- Zone I ROP: Any stage with plus disease
- Zone I ROP: Stage 3 – no plus disease
- Zone II: Stage 2 or 3 with plus disease

When to wait: The concept of “Threshold Disease” – 2013 ETROP

**Type II ROP**
- Zone I ROP: Stage I and II without plus disease
- Zone II ROP: Stage III without plus disease
Conclusion of Acute Retinal Screening
- Zone III retinal vascularization attained without previous Zone I or II ROP
- Full Retinal vascularization
- 45 weeks
- Regression of ROP / concept of Individuality

Options for ROP Treatment
- Cryotherapy
- Diode Laser
- Intravitreal ANTI-VEGF

Cryotherapy for ROP
- Landmark study 1990
- Unfavorable outcome reduced by ~ 50%
- No longer the treatment of choice
- High rate of progression in treated eyes

Diode Indirect Photocoagulation
- Treat avascular retina
- Rate of progression in dense laser pattern
  - 3.6% overall
  - 0% zone I eyes
  - 3.8% zone II eyes

Diode Indirect Photocoagulation

<table>
<thead>
<tr>
<th>SERIES</th>
<th>REGRESSION</th>
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<tbody>
<tr>
<td>CRYO-ROP</td>
<td>74%</td>
</tr>
<tr>
<td>McNamer 92</td>
<td>25/28 eyes (89%)</td>
</tr>
<tr>
<td>Hunter 93</td>
<td>16/17 eyes (94%)</td>
</tr>
<tr>
<td>Benner 93</td>
<td>9/9 eyes (100%)</td>
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<tr>
<td>Goggin 93</td>
<td>16/21 eyes (76%)</td>
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<tr>
<td>Tsitsis 97</td>
<td>27/31 eyes (87%)</td>
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<tr>
<td>Selber 97</td>
<td>25/25 eyes (100%)</td>
</tr>
<tr>
<td>Dense</td>
<td>54/56 eyes (96%)</td>
</tr>
<tr>
<td>Less Dense</td>
<td>36/51 eyes (71%)</td>
</tr>
</tbody>
</table>

Threshold ROP (type 1) before Laser

Threshold ROP (type 1) immediately post laser

Threshold ROP (type 1) 1 week post Laser

Threshold ROP (type 1) 2 weeks post Laser

Threshold ROP (type 1) 3 weeks post Laser

Laser Issues
- Time consuming
- Difficult
- Mentored training
- Decreased peripheral vision
- Decreased night vision
ANTI-VEGF Therapy for ROP

- Theory
- Original work by Quiroz-Mercado M.D.
- Bevacizumab (Avastin)
- Ranibizumab (Lucentis)
- Aflibercept (Eylea)

BEAT-ROP Trial: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity

BEAT-ROP - 2011

Background:
- Prospective, multicenter, randomized, unmasked, phase II trial of intravitreal Bevacizumab (0.625mg in 0.025ml) vs. conventional diode laser photocoagulation
- Eligible patients were 1500g or less and 30 weeks G.A. or less with stage 3+ ROP in Zone I or Zone II or Zone II posterior disease in both eyes
- Primary outcome of the trial was modified from an absence of recurrence of stage 3+ ROP in Zone I or Zone II posterior by 54 weeks to recurrence of retinal neovascularization requiring retreatment by 54 weeks

Authors conclusions:
- Bevacizumab is superior to laser for treatment of Zone I, Stage 3+ ROP
- Peripheral retinal neovascularization continued as normal in the Bevacizumab group, but not the laser group
- "Bevacizumab is an inexpensive drug that can be rapidly administered at the bedside by any Ophthalmologist"

BEAT-ROP - 2011

Issues:
- Safety- not demonstrated in the Beat-ROP trial
  - Sample size not large enough
  - Systemic risks include Thromboembolic events as well as failure of pulmonary maturation
  - 71% of all mortality occurs in the Bevacizumab group, although not statistically significant
  - Injections were performed 2.5mm to the limbus- the pars plana is not fully developed in a premature infant until approximately 6 months of age, and injecting greater than 1.5-2.0mm posterior to the limbus potentially passes through full thickness retina
  - Laser failure rate high
BEAT-ROP - 2011

Results:

- **Zone I Stage 3+**
  - Bevacizumab Group: 6% recurrence
  - Laser Group: 42% recurrence
- **Zone II Stage 3+**
  - Bevacizumab Group: 5% recurrence
  - Laser Group: 12% recurrence

Time of recurrence – “NOT ONE AND DONE”

- 19.2 8.6 weeks vs. 6.4 6.7 weeks for Bevacizumab and laser for Zone I eyes
- Continuity may continue 80 WEEKS post gestational age

Serum Concentrations of Bevacizumab (Avastin) and VEGF in infants with ROP

- 11 infants with ROP
- Received 0.25 mg or 0.5 mg of intravitreal Avastin to either one eye or both eyes with vascularity active ROP
- Serum concentrations of Avastin and VEGF were measured by Elisa and correlation between the two was determined

Results

- **Serum levels of Avastin**
  - 0.5 mg Avastin
    - Before: 0 mg/ml
    - 1 day: 195 ± 351 ng/ml
    - 1 week: 946 ± 680 ng/ml
    - 2 weeks: 1214 ± 351 ng/ml
- **Serum levels of VEGF before and after 0.5mg Avastin**
  - Before: 1628 ± 929 pg/ml
  - 1 day: 427 ± 140 pg/ml
  - 1 week: 246 ± 110 pg/ml
  - 2 weeks: 269 ± 157 pg/ml
• New Neonates seen in 2013 = 406
• Neonates treated in 2013 = 31 (7.6%)
  • INJECTION = 16 (3.9% of total babies seen, 51.6% treated babies)
  • LASER = 15 (3.6% of total babies seen, 48.4% treated babies)

SUMMARY ROP 2013 ARA
• UHS Neonates treated in 2013 = 13 (11.6%)

BRACK = 16  NAMC = 122  SDMC = 109
DELL = 45  UHS = 112  SETON = 2
LASER for ROP 2013 ARA
- Average Birth Weight = 787.5 gms (600 - 1465)
- Average Gestational Age = 25 wks (24 - 28)
- Average Age at Treatment = 37 wks (33 - 43)
- Average Age of Maturity = 42 wks (40 - 52)
- Average Follow-up Post Treatment = 7 wks
BRACK = 2   NAMC = 1   SDMC = 3
DELL = 3   UHS = 4   SETON = 2
MALES = 7   FEMALES = 8

Anti-VEGF INJECTION for ROP 2013 ARA
- Average Birth Weight = 717 gms (450 - 1130)
- Average Gestational Age = 25 wks (22 - 30)
- Average Age at Treatment = 35 wks (31 - 41)
- Average Age of Maturity = 52 wks (49 - 56)
- Average Follow-up Post Treatment = 18 wks
BRACK = 0   NAMC = 3   SDMC = 3
DELL = 1   UHS = 9   SETON = 0
MALES = 6   FEMALES = 1
IVA = 10   IVL = 06

Treatment results ROP 2013 ARA
- Anti VEGF Group – 0% recurrence
- Laser Group – 0% recurrence
* All zone II

Conclusions
- ROP regresses spontaneously in the majority of infants in whom it occurs.
- Birth weight and birth age are major risk factors for severity of disease.
- Supplemental oxygen in late stages is not harmful, and may be helpful, in most cases.
- Bevacizumab / Ranibizumab play a role in ROP
- Myopia and strabismus occur with greater frequency in ex-preemies, especially in the first year of age.

Vigilance is Critical!
Conclusions

Failure is not an Option