Neovascular Glaucoma Update

A serious secondary condition...

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• I do not have any relevant financial relationships to disclose.
• The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.

Disclosures...

• I have no disclosures to report.
• I’m not perfect...
• I can email you my reference list...
• Questions??
  • Email me: cborgman@sco.edu

NVG Background...

• First classified in 1963 by Weiss et al.
• Secondary angle closure glaucoma
• Aggressive, end-stage complication of ischemic retinal vascular disease
• TM blockage from:
  • fibrovascular membrane formation in iridocorneal angle
• Poor visual prognosis and outcomes

Advanced systemic vascular disease

• Diabetes Mellitus (~32-70% cases)
• RVO’s (CRVO>BRVO) (~20-36%)
• Idiopathic (19%)
• Carotid occlusive disease/OIS (~2-13%)
• RD (~2-6% cases)
• Trauma (4-5%)
• Chronic Uveitis (~1-2%)
• CRAO (~1-4%)
• Radiation retinopathy (<1%)
• Sickle Cell Retinopathy
• Ocular tumors (lymphoma, retinoblastoma, melanoma, etc.) (<1%)
Interesting NVG facts/stats...

- 76+% of patients are ≥60 years old
  - Avg age of onset ~53-60 YO
- 97% of confirmed cases are linked to retinal ischemia!
- 20-33% of patients with PDR will develop rubecosis iridis!
- Risk: Type 1 DM > Type 2 DM

NVG Mechanism of Action...

Mechanism of Action

- Underlying problem = retinal hypoxia and ischemia!
- Release of VEGF = retinal/iris/AC neovascularization
  - Placental growth factors = another source of neo toot
  - Müller Cells = primary source of VEGF liberation
    - Other studies show heavy VEGF in PlGF
  - Other chemical mediators possible:
    - Placental growth factors
    - Insulin-like growth factors
    - Fibroblast growth factors
    - α-TNF
    - Interleukin-6
    - Interferon-α
    - MMP3 & MMP9

3 Stages of NVG...

<table>
<thead>
<tr>
<th>STAGE 1</th>
<th>STAGE 2</th>
<th>STAGE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-glaucoma</td>
<td>Open Angle-Glaucoma</td>
<td>Closed Angle-Glaucoma</td>
</tr>
<tr>
<td>Normal IOP</td>
<td>Elevated IOP</td>
<td>High IOP</td>
</tr>
<tr>
<td>(+) NVI and/or (+) NVA present</td>
<td>(+) Fibrovascular membrane over A/C angle; (+) contraction yet</td>
<td>(+) Fibrovascular membrane over A/C angle; (+) contraction</td>
</tr>
<tr>
<td>Possible Hyphema</td>
<td>Possible Hyphema</td>
<td>(+) PAS present</td>
</tr>
<tr>
<td>Possible Hyphema</td>
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<td>Possible Hyphema</td>
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Symptoms of NVG

- Redness
- Pain
- Photophobia
- Headaches (can be severe)
- Decreased vision
- Nausea/Vomiting

**Signs of NVG**

- Variable visual acuity (typically 20/40 → NLP possible)
- NVI/NVA
- PAS
- Elevated IOP (Very high)
- A/C reaction
- Corneal Edema
- Ectropion Uveae
- Hyphema
- Optic Nerve Cupping
- Visual Field Loss
Where does NVI first start again?

- Remember:
  - VEGF released from retinal tissues
  - Ciliary body too

- NVI starts as “endothelial budding” of capillaries of the major and minor arterial circles of iris!
  - Minor > major

Can NVA occur in absence of NVI???

- YES!!!!
- 6-12% of cases can have NVA but no NVI!
- Hence gonioscopy is imperative!

NaFl Angiography of the Iris...

- Iris neo can be detected with iris Angiography in 97.2% of cases.
- Not readily available to many practitioners so not gold standard.

Treatment and Management of NVG

- **2 Main Goals!!**
  1) Eliminate underlying cause of neovascularization and control inflammation
     - Level “A”
  2) Reduce IOP
     - Level “B”

Level “A” Treatment Goals...

- PRP
- Anti-VEGF
- Medical control of Inflammation & IOP

- Goal: Eliminate Ischemia and Hypoxia
  - 1200-1600 argon laser spots = 70.4% neo regression
  - 400-650 argon laser spots = 37.5% neo regression
  - PRP performed at first sign of NVI or NVA

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“Panretinal photocoagulation remains the mainstay in controlling the neovascular drive and should be considered in all cases of NVG when retinal ischemia is present.” — Rodrigues et al. 2016.

New Horizons in NVG Tx...

- Intravitreal anti-VEGF injections
- Topical Anti-VEGF eye drops
- Pigment epithelium-derived factor

Intravitreal anti-VEGF Injections...

- Avastin, Lucentis, Eyelea
- Used as monotherapy and/or in combination therapy
- **MOA:** Bind to free-floating VEGF molecule to prevent attachment to endothelial surface receptors
  - By definition, do nothing for underlying disorder...
  - Have been shown to stimulate regression of neo within 1-2 days!
  - Short half lives (~20 days); wear off over time
  - Total duration is ~4-6 weeks
  - *"bridge the gap" until PRP effect can take hold for long term*
  - Has been accepted into mainstream NVG Tx at this time

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**Does anti-VEGF Tx alone reduce risk of needing glaucoma surgery in NVG?**

- N= 163 eyes total with NVG
  - 99 eyes = (-) Avastin
  - 64 eyes = (+) Avastin

- No → No significant difference noted
  - P=0.10
  - Only mild short term improvement noted
  - 2' short half-life of anti-VEGF agents
  - No change in need for glaucoma surgery

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**PRP vs. Anti-VEGF in combination??**

- Anti-VEGF + PRP >> anti-VEGF alone
  - PRP significantly reduced need for glc Sx
    - P < 0.001
  - 100% of NVG should get PRP!

- PRP + anti-VEGF ≥ PRP alone (maybe?)
  - Good for short term "bridging the gap"
  - Effect on long-term NVG process
    - P=0.10

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**PRP remains a mainstay Tx...**

- "Taken together, these results suggest that the role of bevacizumab in NVG is that of a temporizing rather than a definitive treatment, and eyes with NVG should uniformly receive PRP to treat ischemia, regardless of prior intravitreal bevacizumab injection(s)... Without ablation of the ischemic drive for new vessel formation, neovascularization will recur after regression with initial anti-VEGF therapy."
  --- Olmos et al. 2016

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**Final thoughts on anti-VEGF in NVG...**

- "In conclusion, there still is a debate about the real effectiveness of anti-VEGF in the management of NVG. There is evidence showing that a pre-treatment with anti-VEGF before definitive IOP lowering glaucoma surgeries can significantly lower the frequency of hyphema. But further research is still needed to evaluate the impact on long-term IOP control, visual acuity and cost-effectiveness of the anti-VEGF injections in the management of NVG."
Topical anti-VEGF therapy??

- Avastin in eye drop form!
- Has been shown to penetrate through corneal tissues into anterior chamber
- Avastin drops used QID OU x 2 weeks caused neo regression in 3 of 8 patients in one study.
- Decreases risks of VH, traumatic cataract, RD, endophthalmitis, etc.
- Still in its infancy....
- Also, for corneal neovascularization too!
- Acid/alkaline burns
- Anterior segment cancers

Topical anti-VEGF for ARMD??

- Topical Avastin & Lucentis studied in animal eyes
- Cell-penetrating peptides (CPP)= chaperone proteins that increase penetration through cornea!
- "These data show that daily topical administration of the CPP complexed with anti-VEGF was as efficacious as the standard single intravitreal injection of anti-VEGF."

Intravitreal Anti-VEGF = Topical Anti-VEGF + CPP

Other effects of PEDF...

- Neuroprotection in CNS
  - Eyes included! Glaucoma?
  - Protection from MMDA, glaucoma
- Reduces ischemia in retinal tissues
- Inhibits cancer formation/growth
  - Largest effect on metastasis!
- Reduces ROS in CNS
- Cardiovascular protection
- Enhances metabolism (for the better!)
  - DM??
Level B Goals
Surgical Control of IOP/Glaucoma

Level “B” Treatment Goals...
• Glaucoma surgery to lower IOP
  • Trabeculectomy or Tube-Shunt Procedures
  • Done when PRP and medical therapy fail...

Combination procedures???
1. Vitreous Hemorrhage?
  • PPV
  • followed by endolaser/PRP
2. Cataract and Vitreous Hemorrhage?
  • Phaco
  • Followed by PPV
  • Followed by endolaser/PRP

Medical Management
• Beta-blockers
• Alpha-agonists
• CAI’s (topical and/or oral)
  • PGA’s should be avoided; can induce inflammation
  • Pilocarpine should be avoided; can worsen PAS and inflammation
  • Corticosteroids
  • Cycloplegics (decrease pain and congestion)

High failure rate with medical Tx alone...
• Approximately 80% of patients with NVG will inevitably require surgical intervention → Wow!
• Begs the question, why not jump straight to surgery?

Surgical Management
• Biggest decision?
  • Trabeculectomy?
    • OR
    • Tube Shunt?
• Why? How do we choose which one is best?
What is definition of successful glaucoma surgery?

• Definition varies according to each study….

• IOP ≥ 6 mmHg but ≤ 21 mmHg = successful

• However, no clear definition of whether this is with or without topical medications has been decided upon.

• However, whatever means possible (topicals or not) is advisable.

Surgical Management

• Indicated when medical management fails…

• ≥ 270 degrees of synechial angle-closure

• **Gold standard = Trabeculectomy with 5-FU or MMC
  • MMC more potent → reduces scarring

• Declining effects of surgery over time with trabs are possible

• Tube-shunts have taken larger role in NVG as a result….

• Overall success rates vary widely with surgery... 22-78%.

Question?...What about the TVT study?

• Tube Versus Trabeculectomy Study (2009)

• The TVT study excluded NVG patients….

• Consequently, no direct conclusions can be drawn.

Tube Shunts...

• More favorable in NVG

• Less dependent on intraocular inflammation and do not require a bleb

• Potential drawbacks:
  • hypotony
  • drainage plate encapsulation
  • decreased IOP control over time possible
  • diplopia

• However, many studies show improved outcomes with tubes compared to trabs in NVG.

Which shunt is best for NVG???

---Ahmed vs. Baerveldt Shunts...

• **Ahmed (New World Medical)**
  • Valved
  • Lower risk of hypotony
  • Higher IOP typically

• **Baerveldt (Abbott Medical Optics)**
  • Non-valved
  • Increased risk of hypotony
  • Lower IOP typically

• Which is better?
  • No clear cut winner yet in NVG...

Final thoughts on trabs vs. tubes in NVG...

• “Success rates have improved with the adoption of intra- and postoperative use of anti-metabolites and antifibrotics. Despite these improvements, failure rates of trabeculectomy in NVG remain high... Nonetheless, there is no large randomized trial to serve as the basis for choosing trabeculectomy over a tube drainage device or vice versa. The selection of the surgery type and tube model is based primarily on the individual surgeon’s judgment and consideration of all patient variables.”

NVG Protocol Suggestion...

- n=44
- 93% patients resulted in stable or improved vision with this protocol

Laser Synechiolysis/ Goniophotocoagulation

- **MOA:** Surgically eliminate PAS and/or NVA
  - Argon Laser (YAG can worsen)
  - Surgical instrumentation
- **Pros:** can be used in early-onset NVA, effective
- **Cons:** time consuming, higher level technique/accuracy
- Has largely given way to Anti-VEGF injections which are easier to administer

Does MIGS play a role in NVG?

- **NO!**
- Need access to TM for pretty much all MIGS procedures....

End-Stage NVG....

- **Vision = NLP**
- **What’s worse than a blind eye?**
  - A blind, painful eye
- **What’s worse than a blind, painful eye?**
  - A blind, painful eye with poor cosmesis
- Most Important Goal = Patient comfort!
  - Both mental and physical
- Final surgical options include:
  - Cyclodestruction
  - Retrobulbar alcohol injection
  - Trabs/Tubes

Cyclodestructive procedures?

- Aka “transscleral cyclodestruction”
- Cryotherapy or photocoagulation
- Really reserved only for eyes with little or no useful vision.
- Treatment effects are hard to quantify
- Hard to predict level of IOP control
- May need repeat procedures
- Over-Tx can lead to:
  - Phthisis
  - Hypotony
  - Severe inflammation
- Trabs/Tubes are tried first in patients with any useful vision.
My general interpretation of the literature as of 2018...
(based on 37 articles since 2014)

1. PRP for everyone!
2. Anti-VEGF – use it!
   - Good short-term gains pros; controls neo quickly!
   - No long-term management of NVG however
3. Tubes >> Trabs → general consensus
   - If trab is chosen, mitomycin C is required...
   - Jury is still out... defer to glaucoma surgery expertise/experience at this time
4. Ahmed vs. Baerveldt?
   - Jury is still out... defer to glaucoma surgery expertise/experience at this time
5. Other surgical procedures as needed...
   - We need a RCT comparing: Trabs vs. Ahmed vs. Baerveldt in NVG!
   - Regardless, visual prognosis is poor overall and failure rates can be high, even with the best of care.

OD’s Role in Management

- Astute clinical examination
- Careful gonioscopy
- Identify underlying cause of NVI/NVA/NVG
- Order further tests
- Control elevated IOP
- Refer to retina specialist for anti-VEGF and PRP
- Followed by glaucoma specialist referral for uncontrolled IOP

NVG Pearls and Misc...

Pearls....

- In patients with NVG but no appreciable retinal ischemia, a carotid duplex ultrasound should be ordered to rule out ischemic ocular syndrome due to carotid insufficiency.

- Bottom Line?
  - If no retinal issues seen?
  - Look at carotids!

Does NVG increase risk of stroke?

- Yes!
  - p<0.001
- "Our study was the first to show that the risk of stroke is significantly higher among patients with NVG than among people without NVG. Furthermore, our study revealed that compared with those without NVG, patients with NVG were 2.24-fold more likely to develop ischemic stroke, but not hemorrhagic stroke."


Notify PCP as well...

- 15-22% mortality rate associated with NVG
- Underlying systemic condition must be found and managed with PCP
Labwork needed in unclear cases...

• CBC with differential
• ESR
• CRP
• FBG, HbA1c
• Lipid/triglyceride panel
• Carotid Duplex Ultrasound
• BP evaluation

If previous labwork is WNL or in atypical patient then need to consider other issues....

• Sickledex / Hemoglobin Electrophoresis
• ANA
• Lupus anticoagulant / Antiphospholipid Ab’s
• RPR
• FTA-ABS
• RF
• Factor V Leiden mutation
• Chest X-ray

• Protein C and S levels
• Antithrombin III mutation
• Homocysteine
• PT / PTT
• Lyme Titers
• ACE / Lysozyme
• PPD

Thank you!
Questions???

• Email: cborgman@sco.edu