



# Angiogenesis & Exudation: Retinal Vascular Disease Update

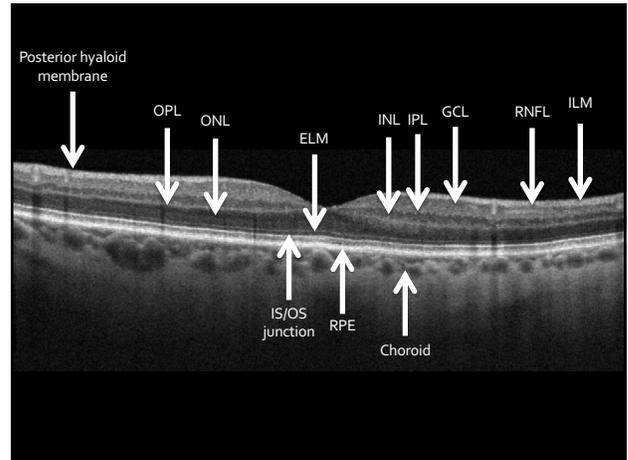
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Assistant Professor

## Financial Disclosures

- MacuLogix-speaker

## Outline

- Pathophysiology review
- The era of anti-VEGF
- Imaging strategies, treatment trends, and developments in the care of patients with:
  - 1) Diabetic retinopathy
  - 2) Exudative macular degeneration
  - 3) Retinal vein occlusion

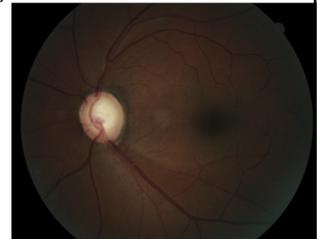


## Retinal Vasculature Review

- Highly metabolic tissue
- Oxygen is delivered by two systems
  - Retinal vasculature
    - Inner 2/3 of retina
      - Non-leaky
    - Choroidal vasculature
      - Outer 1/3 of retina (includes photoreceptors)
        - Fenestrated-allows exchange of fluid
        - Outer BRB formed by RPE

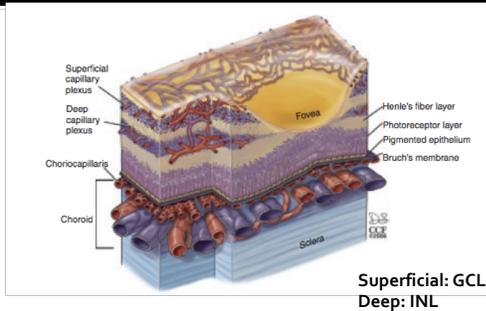
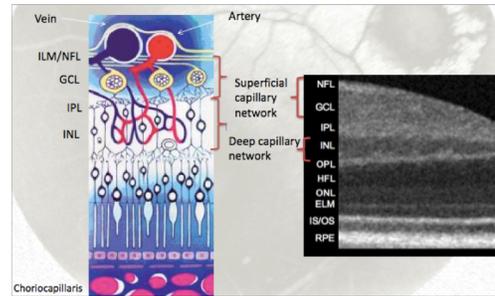
## Retinal Vasculature

- Retinal arteries
  - Supplied by CRA (branch of internal carotid artery)
- Retinal veins
  - Drains to the CRV → cavernous sinus



## Retinal Vasculature

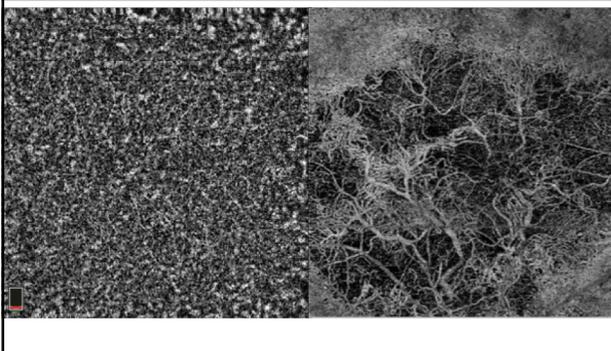
- Retinal capillaries
  - 1) Superficial capillary plexus (GCL-to-a lesser extent RNFL)
    - Most affected in artery based conditions (HTN)
  - 2) Deep capillary plexus (INL)
    - Prevenular capillary network
    - Most affected in venous congestive disease (diabetes and RVO)
    - Outer boundary is the outer plexiform layer
  - 3) Peripapillary capillary network
    - Superficial, fewer anastomoses



## Choroidal Vasculature

- RPE
  - Loose attachment to PRs
  - Strong attachment to choriocapillaris and other RPE cells
- Choriocapillaris
  - Fed by posterior ciliary artery branches
  - Window defect (RPE defect) caused by choriocapillaris infarction
    - Compartmentalized blood supply

## Choriocapillaris on OCTA



## Choroidal Vasculature

- Choroid
  - Larger blood vessels, nerves, melanocytes, immune cells
    - Presence of immunological cells represent source for inflammatory retinal disease

## OCT Angiography

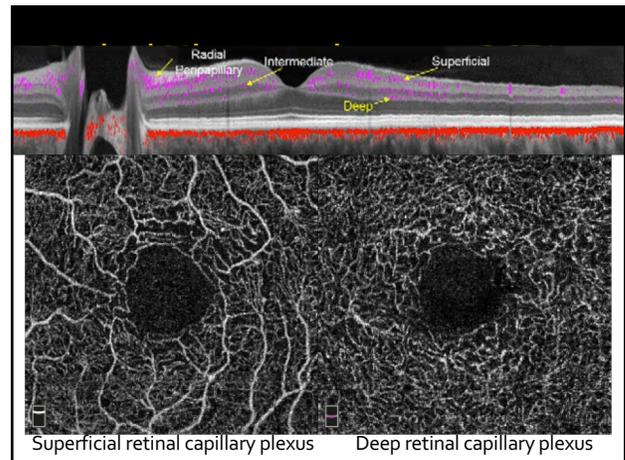
- The only thing that moves in the retina over time are red blood cells
- Take the 'difference' between multiple B scans at the same location to produce a 'decorrelation signal'

## OCT Angiography

- En face flow formation and cross sectional structural information
- Not a replacement for FA/OCT
  - Provides new information
- Important in diagnosis of NV and macular ischemia

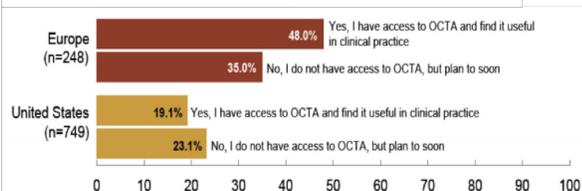
## Clinical Uses

- Choroidal neovascularization
- Diagnosis of retinal vascular disease
  - Mactel type 2
  - RVO
- Diabetic retinopathy
  - Microaneurysms, macular ischemia, NV
- AMD
  - Non-exudative lesions in eyes with intermediate AMD
- Neurodegenerative disease
- Open angle glaucoma



## OCT Angiography

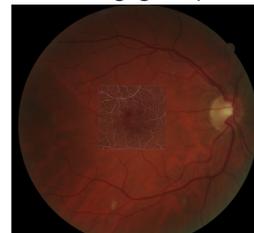
### Do you have access to OCT angiography?



Shah GK, Stone TW, eds. 2017 Global Trends in Retina. Survey. Chicago, IL. American Society of Retina Specialists; 2017.

## Challenges of OCTA

- Static blood flow information
  - No leakage, pooling or staining
- Small field of view 3x3mm; 6x6mm; 8x8mm



## Challenges in OCT Angiography

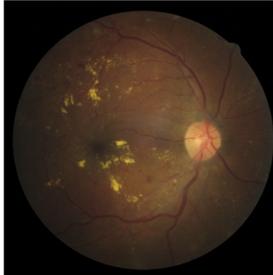
- Motion artifacts are a big deal
- Sensitivity is a challenge in eyes with pathology
- Quantification of blood flow-not yet

## Vascular Response to Disease

- 1) Exudation
  - Loss of blood retinal barrier
    - Accumulation of plasma fluid and lipid
    - Hard exudate and intraretinal edema
- 2) Ischemia
  - Capillary drop out leads to hypoxia
    - Microaneurysms, capillary drop out, collateral formation, neovascularization
- 3) Both

## Diabetic Retinopathy

- End organ response to systemic disease
- Multifactorial condition
  - Vascular component
  - Hyperglycemic component
    - Free-radical formation
  - Inflammation
  - Compromised autoregulation
- Tissue damage to metabolically active sites
  - Retina, kidney



## Diabetic Retinopathy

- Type II: High incidence of DR at the time of presentation
  - Annual exam
- Type I: No matter how poorly controlled, typically no retinopathy for 5-7 years
  - Examine 5 years after diagnosis—or at age ten, then annually
  - Insulin-dependent type II patients are considered to be of higher risk
- Gestational DM
  - Do not seem to have increased risk of DR; no eye examination during pregnancy

## Caveat

- Substratification
  - Clusters 1-5
- Diabetic retinopathy most common in cluster 2
  - “Severe insulin-deficient diabetes”
    - Shares features of classic type I diabetes
- *Better, but-treat the patient, not the disease*

## DR Severity Scale

TABLE 1 DIABETIC RETINOPATHY DISEASE SEVERITY SCALE AND INTERNATIONAL CLINICAL DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No apparent retinopathy
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	Microaneurysms and intraretinal hemorrhages in each of four quadrants
Severe NPDR	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: <ul style="list-style-type: none"> <li>• Severe intraretinal hemorrhages and microaneurysms in each of four quadrants</li> <li>• Definite venous beading in two or more quadrants</li> <li>• Moderate IRMA in one or more quadrants</li> </ul>
U.S. Definition	Any of the following and no signs of proliferative retinopathy: <ul style="list-style-type: none"> <li>• More than 20 intraretinal hemorrhages in each of four quadrants</li> <li>• Definite venous beading in two or more quadrants</li> <li>• Prominent IRMA in one or more quadrants</li> </ul>
International Definition	One or both of the following: <ul style="list-style-type: none"> <li>• Neovascularization</li> <li>• Vitreous/preretinal hemorrhage</li> </ul>
PDR	One or both of the following: <ul style="list-style-type: none"> <li>• Neovascularization</li> <li>• Vitreous/preretinal hemorrhage</li> </ul>

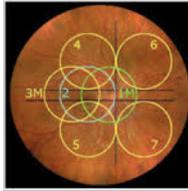
IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

NOTE:

- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.
  - PDR may be classified as high-risk and non-high-risk. See Table 6 for more information.
- Adapted with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1679.

## DR Severity Scale

- Modified Airlie House-defined by ETDRS in 1981
- Very mild NPDR
  - MA only (level 20)
- Mild NPDR
  - Hard exudate, cotton wool spots, and/or mild retinal hemorrhages (level 35)



## Diabetic Retinopathy

- Vision loss occurs secondary to:
  - 1) Diabetic macular edema
  - 2) Macular ischemia
  - 3) Proliferative diabetic retinopathy

## Diabetic Macular Edema

- Caused by microvascular occlusion or leakage
- 'CSME' defined by ETDRS
  - Hard exudate within 500 $\mu$ m of the center of the macula
  - Hard exudates at or within 500 $\mu$ m of the center of the macula with adjacent retinal thickening
  - Retinal thickening of 1DD or larger within 1DD of the center of the macula

## Hard Exudate

- Leakage of lipoproteins from permeable capillaries

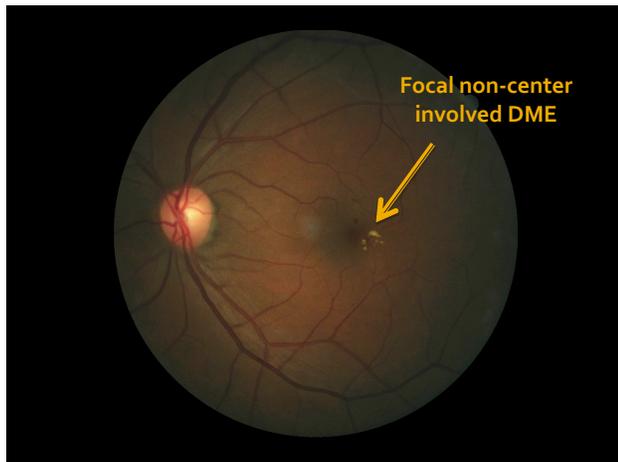
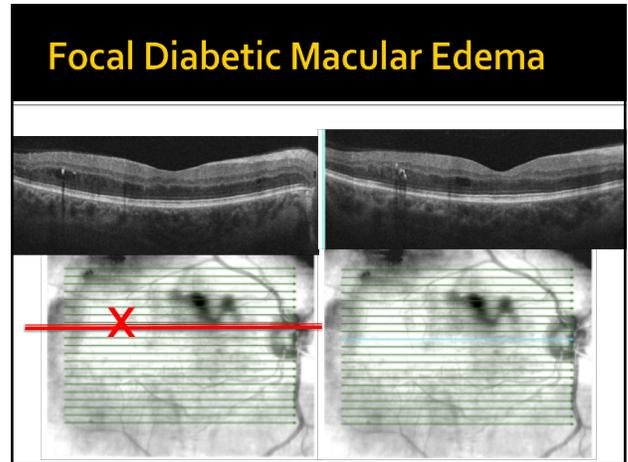
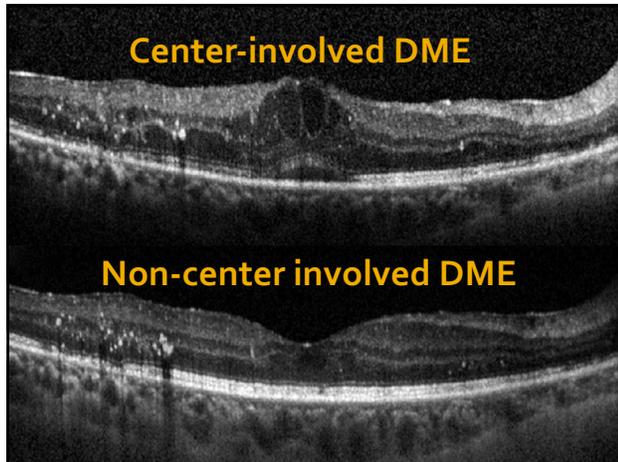


## Retinal Imaging

- Color fundus photography
  - Great for documentation
- Fundus autofluorescence
  - Few indications that alter management
- FA
  - Evolved to be a test of retinal periphery
- ICG
  - Limited availability and utility
- OCT
  - **THE** most important ancillary test in retinal disease
- OCT angiography

## Diabetic Macular Edema

- Now, trend is an OCT-based classification



### Macular Edema Grading

**TABLE 2 INTERNATIONAL CLINICAL DIABETIC MACULAR EDEMA DISEASE SEVERITY SCALE**

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy*
Diabetic macular edema present	<ul style="list-style-type: none"> <li>Mild diabetic macular edema: some retinal thickening or hard exudates in posterior pole but distant from the center of the macula</li> <li>Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center</li> <li>Severe diabetic macular edema: retinal thickening or hard exudates involving the center of the macula</li> </ul>

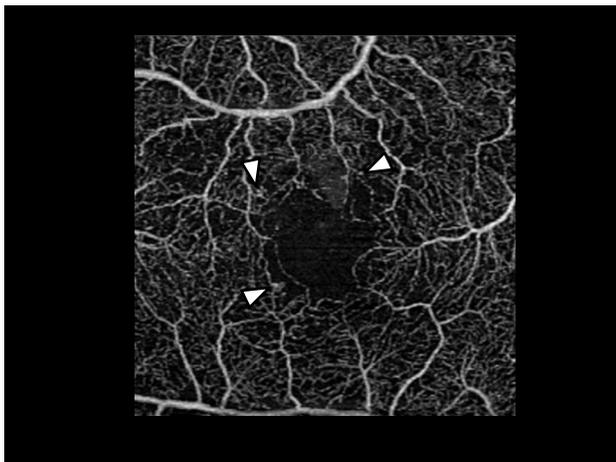
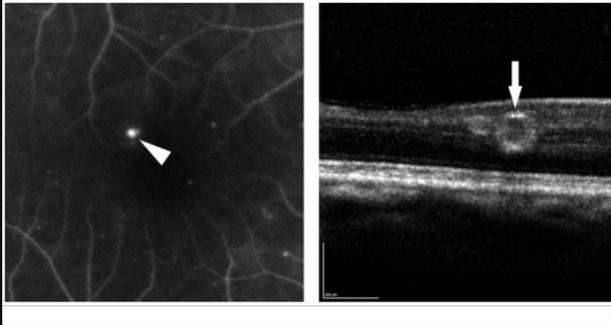
Reproduced with permission from Miller DM, Early Diabetic Macular Edema. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1680.

\* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereoscopic fundus photography. Optical coherence tomography may supplement the fundus evaluation for determining the presence of diabetic macular edema.

- ### Microaneurysms
- Early clinical feature of non-proliferative diabetic retinopathy
    - Thickening of basement membrane, pericyte loss, MAs, increased permeability
      - Leads to loss of vessel perfusion, hypoxia, increased VEGF, neovascularization
    - Most commonly found in the inner nuclear layer
      - Generally surround areas of capillary loss
        - Deep capillary plexus

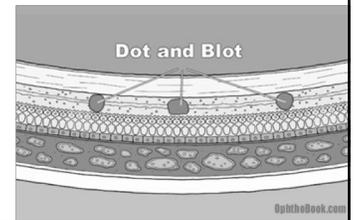
- ### Microaneurysms
- Weakening of capillary wall
  - Large MAs visible clinically
  - Leak
    - Cause intraretinal edema
-

## Microaneurysms

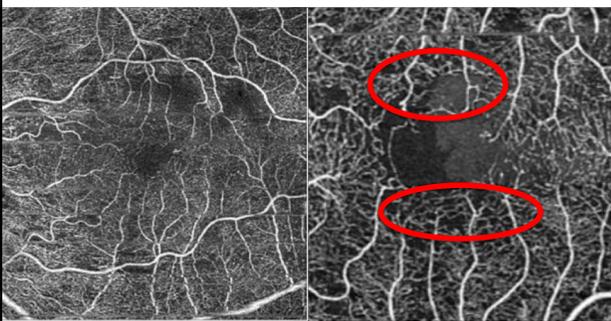


## Dot and Blot Hemorrhages

- Deep retinal hemorrhages
  - Inner nuclear layer, outer plexiform layer, outer nuclear layer
  - From pre-venular capillaries
    - DM, RVO
  - Represent ruptured microaneurysms
    - Do not leak on FA

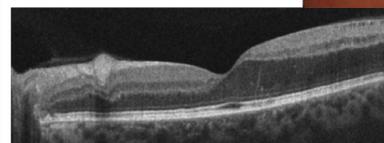


## Macular Ischemia



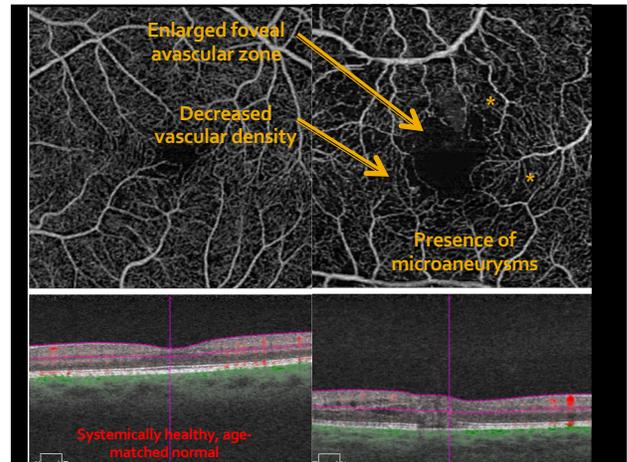
## Ischemia in Diabetic Retinopathy

- Cotton wool spot
  - Really *not* an "infarct"



## Macular Ischemia

- Vision loss either due to fluid within in the macula or a poorly perfused macula
  - **Macular ischemia** in the absence of DME/hemorrhage/exudate
- As eye care providers, we have a greater impact on disease education than other treating physicians
  - Visible changes that we can show patients due to DM

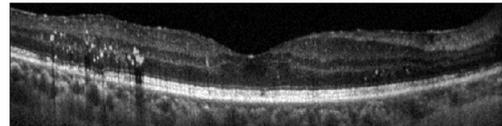


## Variation in FAZ

- Is a normative database the answer?
  - Variation with:
    - Age, sex, axial length, race/ethnicity

## Diabetic Choroidopathy

- Can we quantify choroidal changes in patients with diabetic retinopathy?
  - Increased or decreased choroidal thickness?
    - Vessel density and choroidal VOLUME seem to be reduced in advanced diabetic retinopathy
  - Deep retinal capillary plexus & PR damage



## Pharmacology in Diabetic Retinopathy

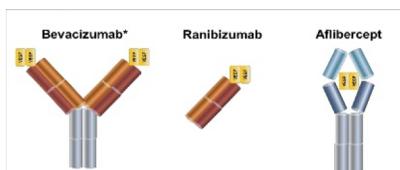
- Anti-VEGF is the typical first line treatment
  - Decreases vascular activity
  - Also decreases the amount of blood during vitrectomy

## Vascular Endothelial Growth Factor

- Signaling protein for vasculogenesis and angiogenesis
  - Secreted by RPE cells, pericytes, astrocytes and endothelial cells
- Produced in response to ischemia
  - Leads to neovascularization

## Currently Available Anti-VEGF Agents

- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Aflibercept (Eyelea)
  - VEGF trap—inhibits VEGF receptor expression



## Pharmacology in Diabetic Retinopathy

- Injectable Steroids
  - Ozurdex-dexamethasone 0.7mg
    - DRCRnet Protocol U
    - Initially indicated for RVO; now indicated for DME and non-infectious posterior uveitis
    - Causes cataract; must have an intact posterior capsule
  - Iluvien (fluocinolone 0.19mg)
  - Triescence (intravitreal triamcinolone acetonide-PF)



## Diabetic Eye Disease

- PVD is protective for DR
  - Akiba et al. Ophthalmology 1990
- So is vitrectomy
- Why?
  - Oxygen is easily transported from well-perfused areas to ischemic retinal zones to reduce ischemia and VEGF production

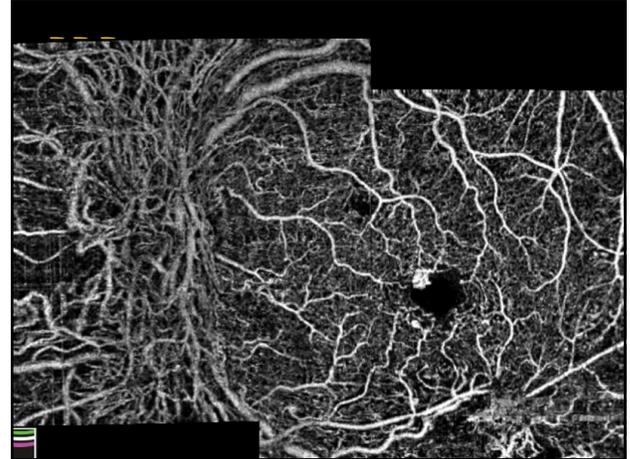
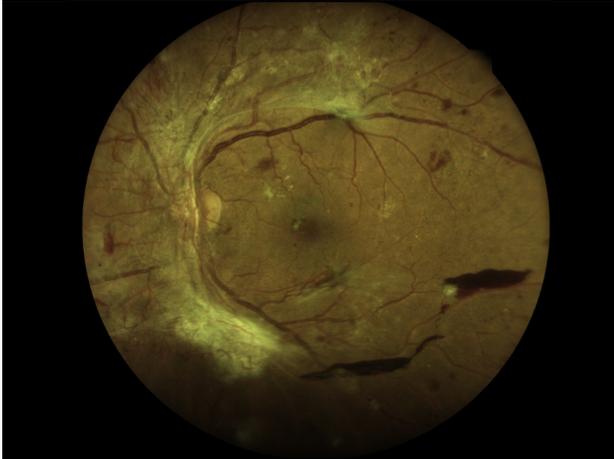
## Development of Agents Used to Induce PVD

- ALG-1001 (Luminate)
  - Anti-angiogenic agent
    - Primary effect: blocks receptors on vascular endothelial cells
      - 1) Inhibits new vessel growth (neovascularization)
      - 2) Vitreolysis
- Ocriplasmin (Jetrea)
  - Photopsia, decrease in visual acuity, outer retinal change on OCT
    - Toxic effect to photoreceptors?
      - At least 50% had acute panretinopathy, 87.5% resolved
        - Ereda, Preziosa, D'Agostino et al. Retina. 2018

## Neovascularization in DR

- PRP is considered the gold standard of DR-related neovascularization
  - Supported by ETDRS
- PRP associated with increased macular edema (initially)





## Laser in Diabetic Retinopathy

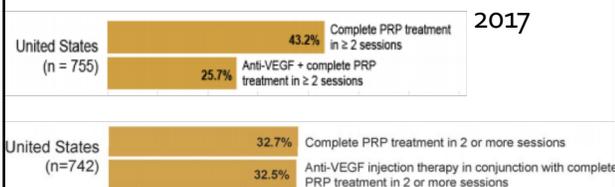
- 1987 Blankenship: PRP did not *decrease* macular edema
- DAVE-VEGF + PRP for diabetic macular edema
  - 2 year data; does VEGF demand decrease with PRP?
    - No significant difference between VA in anti-VEGF and laser vs. laser alone

## Brief Lit Review (Because it Matters)

- DRCRnet (Diabetic Retinopathy Clinical Research Network)
  - Protocol S:
    - 2 year results: Lucentis is non-inferior to PRP in PDR for maintenance of visual acuity in PDR
      - Less VF loss, fewer vitrectomies
    - Supported by CLARITY trial (RCT)
    - PRIDE: ranibizumab monotherapy = greater reduction of area of NV from baseline at 12 months vs. PRP
    - **THIS IS HUGE...**

## Impact of DRCRnet Protocol S

How would you manage a type 1 diabetic patient with high-risk PDR, no DME, and VA = 20/20?



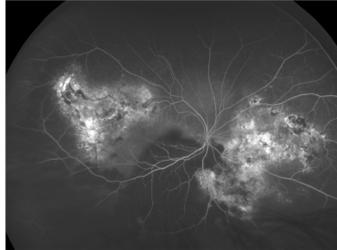
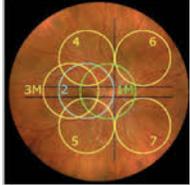
Singh RP, Stone TW, eds. 2018 Global Trends in Retina Survey. Chicago, IL: American Society of Retina Specialists; 2018.

## DRCR.net Protocol T

- Head to head (to head) anti-VEGF comparison
- Aflibercept, bevacizumab, ranibizumab
- All three agents are effective in treatment of DME
  - Bevacizumab (Avastin) had worse central thickness-but same VA
- For worse levels of VA (20/50 or worse); Eyelea is better at improving VA at one year
- *Results maintained at 2 years*

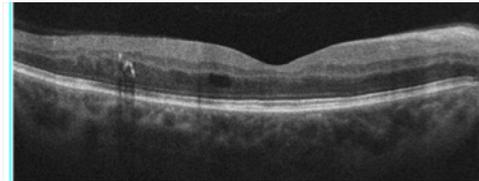
## Current Research

- Protocol AA
  - How may widefield imaging impact prognostic ability in DR?



## Current Research

- Protocol V: "Very good vision"
  - Center involved DME with good vision (20/25 or better)
    - To treat or not to treat?



## Medication Burden in DME



## Medication Burden in DME



## Cost-Effectiveness of Treatment in DME

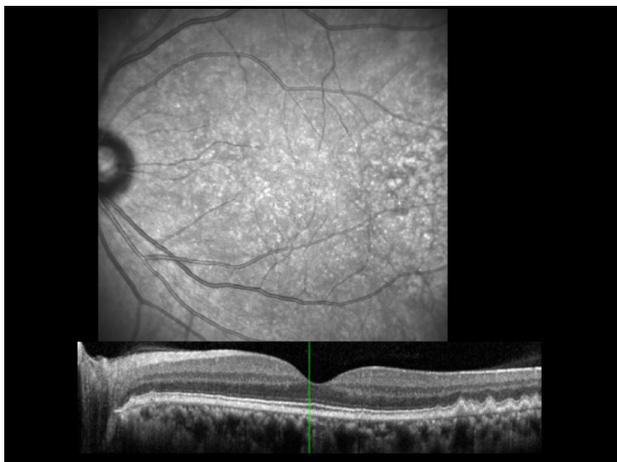
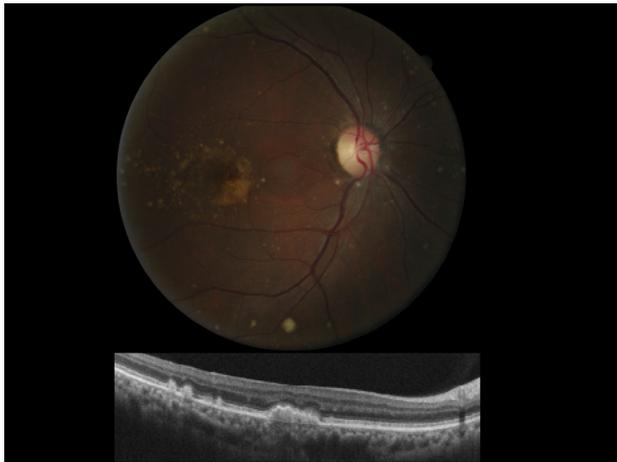
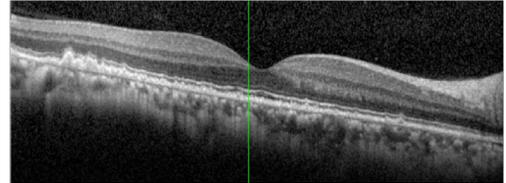
- \$1850 aflibercept (2.0mg)
- \$1170 ranibizumab (0.3mg)
- \$60 bevacizumab (1.25mg)
  
- Aflibercept and ranibizumab were not considered to be cost effective
- **Bevacizumab is a typically the first line anti-VEGF for DME in the USA**

## Macular Degeneration



## Cuticular Drusen

- Drusen subtype
  - AKA basal laminar drusen, small, hard drusen
- *Can progress to geographic atrophy and CNV*



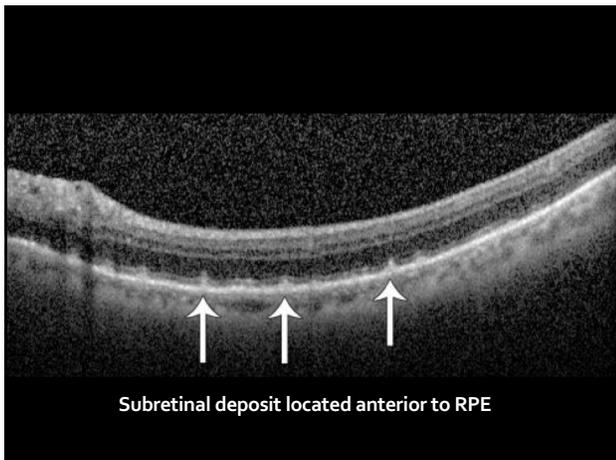
## Reticular Pseudodrusen

- Abnormal material deposited internal to RPE on OCT (including en face)
- Often common with other hallmarks of AMD
- Increased progression to late stage AMD (geographic atrophy)
  - Finger et al. 2014



## Reticular Pseudodrusen

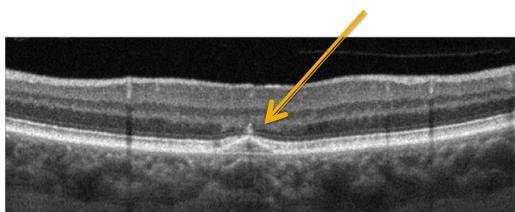
- Distinctive type of drusen
  - Subretinal space extending to the outer segments of photoreceptors
- Not *just* drusen above the RPE
  - Include immune-reactive cells (macrophages, microglia)
- Increased risk of progression to late stage AMD



## Types of Neovascularization

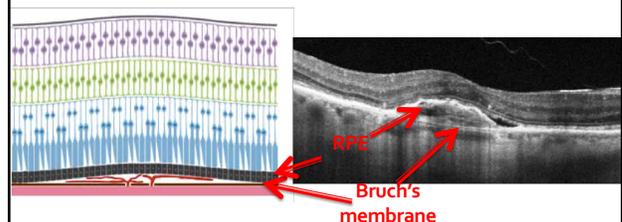
- 1: subRPE
  - Less permeable, less actively proliferating
  - Minimal late leakage on FA
  - Historically "occult"....but now we can see them on OCTA
- 2: Has penetrated the BM/RPE complex
  - Active leakage associated with dye pooling
  - "Classic"
- 3: Intraretinal complex
  - Vascular activity within the retina with choroidal anastomoses

## Early Precursor to RAP?



## Double Layer Sign

- Evidence of type 1 CNV on B-scan
  - ARMD, CSCR, "PCV"
- Arise from choriocapillaris, penetrates Bruch's membrane, lives between the RPE and Bruch's membrane



## Cilioretinal Artery and CNV

- Presence of a cilioretinal artery may be protective for development of CNV and lower AMD severity
  - No association with development of geographic atrophy
- Present in approximately 20% of the population
- May enhance oxygen perfusion to the macula

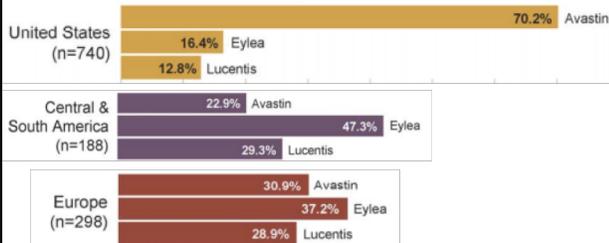
Snyder, Yazdanyar, Mahajan, et al. JAMA Ophthalmol Jul. 2018

## Exudative AMD

- PRN protocol
  - OCT and clinical examination performed once per month
    - Is dilation necessary at every visit?
    - 1/10 patients had a new retinal hemorrhage, 7% missed on OCT
    - Inject only if there is a recurrence of fluid or hemorrhage
- Treat and extend
  - Once macular fluid is cleared, extend the interval between treatments by (typically) 2 week increments
    - Patients are treated on each visit-but at longer intervals
      - Compromise approach
      - OCT-guided therapy

## Anti-VEGF Treatment

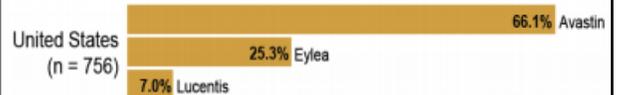
What is your first-line anti-VEGF agent for wet AMD?



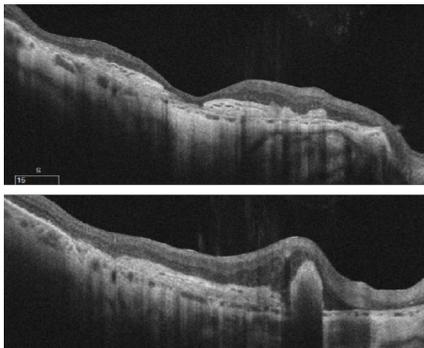
Singh RP, Stone TW, eds. 2018 Global Trends in Retina Survey; Chicago, IL. American Society of Retina Specialists, 2018.

## What Would You Do?

How would you treat *your own* wet AMD with subfoveal CNV if you had to pay out of pocket?



## Fibrovascular Scar-Inject?



## Adverse Events of Anti-VEGF

- Increased intravitreal volume
  - Increased intraocular pressure
    - Acutely—and long term
- Risk of endophthalmitis
  - Approximately 1/5000 injections
    - Role of topical antibiotic prophylaxis?
- Risk of cerebrovascular event
  - Anti-VEGF agents can raise systemic arterial blood pressure
  - Arterial thrombotic events
    - Stroke, myocardial infarction
      - Conflicting data
- Risk of retinal detachment, vitreous hemorrhage



## Geographic Atrophy

- Brimonidine
  - Intravitreal, sustained-release implant (similar to Ozurdex)
  - Phase 3 initiation Q2 2019
  - Seems to make the RPE cells and photoreceptors more resistant to injury
    - Cytoprotection and neuroprotection (RPE and Muller cells)

## New Agents in AMD

- ~~Squalamine lactate ophthalmic solution (MAKO)~~
  - For CNV due to AMD
  - Reduces signaling of VEGF, PDGF and basic FGF
  - Will a patient use a topical medication BID?
- Ziv-aflibercept
  - Variation in osmolarity
  - \$1850 USD vs. \$61 USD
- DARPin
  - "Designed ankyrin repeat protein"
    - Small proteins with a high affinity for VEGFA

## New Agents in AMD

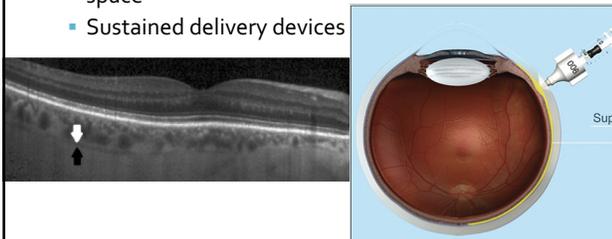
- ~~Combination anti-VEGF and anti-PDGF~~
  - Inhibition of PDGF beta results in stripping of pericytes from new vessel formation
  - Fovista
- ~~Angiopoietin 2 (Ang-2)~~
  - Vascular growth factor
  - May act with VEGF to increase vascular permeability

## New Agents in AMD

- Brolicizumab
  - Single chain antibody fragment inhibitor of VEGF
  - Molecular weight half of ranibizumab
    - Smaller molecule = better penetration, faster clearance, lower systemic exposure
  - Phase 2 data
    - Non-inferior to ranibizumab for AMD
  - Phase 3 trials-top line results
    - Improved acuity vs. aflibercept
    - Improved central thickness and fluid on OCT
  - Potential 12 week duration
    - Supported by data released April 2018

## New Agents in AMD

- Beyond intravitreal injections
  - Triamcinolone acetonide in the suprachoroidal space
  - Sustained delivery devices



## Gene Therapy

- Genes are added to a patient's cells to replace genes that don't work as they should
  - Typically involves adenovirus (type 2 or 8)
    - Retinal progenitor cells
- Typical procedure
  - PPV
  - Inject to form a bleb-subretinal
  - AF exchange
  - Subconjunctival steroid

## Gene Therapy in AMD

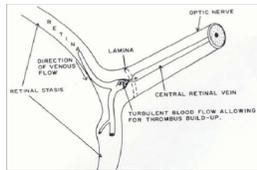
- September 2018-FDA awarded fast track designation to a gene therapy for exudative AMD
- Phase 1 study began in 2018
  - 18 patients
  - Aflibercept coding sequence + adenoviral associated vector (ADVM-022)
  - 2 year study

## Luxturna

- Biallelic RPE65 mutation
- \$850,000

## Retinal Vein Occlusion

- Central retinal vein occlusion
  - Obstruction at the level of the lamina cribrosa



## Retinal Vein Occlusion

- Arteriosclerosis
  - Loss of elasticity within the vessel wall
    - Arterioles and venules share common adventitia at crossings
    - Venular compression and turbulent blood flow
    - Thrombus formation and occlusion

## Treatment of Macular Edema Secondary to RVO

- Anti-VEGF

How would you treat a mildly symptomatic CRVO with minimal thickening on OCT, VA = 20/25?

29.6% Observation; most cases resolve spontaneously

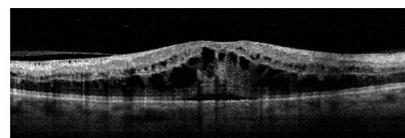
23.6% Immediate anti-VEGF, as most eyes will worsen

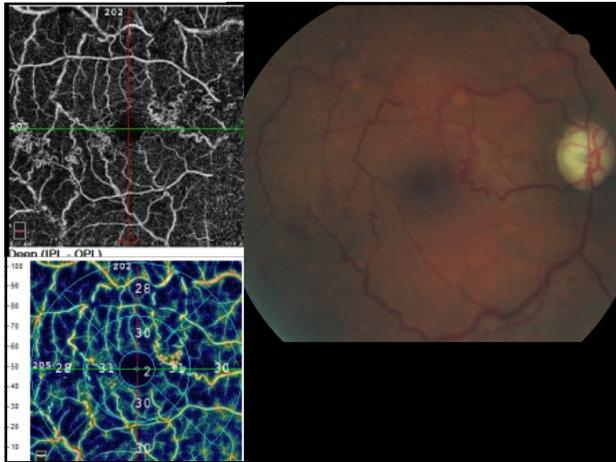
42.6% Defer treatment until the macular edema or VA worsens

Singh RP, Stone TW, eds. 2019 Global Trends in Retina Survey. Chicago, IL: American Society of Retina Specialists; 2019.

## Treatment of Macular Edema Secondary to RVO

- Intravitreal steroid
- Dorzolamide-timolol?!
  - With injections
  - Aqueous suppressant-may have an effect on RPE pump function





## Types of Retinal Vein Occlusion

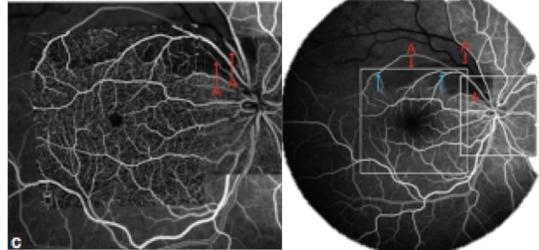
- CRVO
  - Non-ischemic (80%)
  - Ischemic (20%)
    - Classically defined as 10DD or greater nonperfusion on FA
- HRVO, BRVO

## Ischemic CRVO

- Believed that occlusion leads to increased resistance which causes stagnant blood and ischemia
  - Leads to PR death, increased cytokine production, increased VEGF
- Anterior and posterior neovascularization
  - Vitreous hemorrhage, anterior segment NV

## BRAO

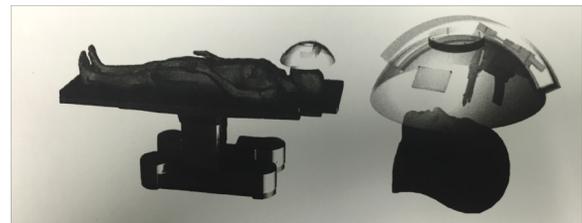
- Treatment?
  - Stroke evaluation on urgent basis



Bonnin, Kiyosic, Cognat, Tadayoni. J Ophthalmic Vis Res 2018

## Automated Anti-VEGF??

- "The difficulty is the standard of care"  
Stephan Michels CEO of Ophthorobotics



## Investigational Treatment

- Minocycline
  - Pathophysiology of retinal vein occlusion is multifactorial
    - Microvascular disease
    - Involvement of immune mediators
  - Tissue hypoxia → cytokine expression → inflammation (macrophage recruitment and microglia)
- Minocycline may down-regulate microglia to mediate inflammation

## Finally...

- Angiogenesis and exudation are significant causes of vision loss in retinal vascular disease
- Treatment targets, treatment modalities, and imaging strategies are rapidly changing
- Anti-VEGF agents are the mainstay of treatment in retinal vascular disease

## Further Developments Aim To:

- Reduce the number of injections
- Increase the time interval between treatments
- Develop alternative routes of administration of medication
- Reduce cost of treatment
- **Improve patient quality of life**

## Thank you!

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