New Technologies for Management of AMD Patient

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Technology and Allocation of Resources

- Clinical Decision Making
- Evaluating Need for Equipment/Instruments
  - Patient Demography and Epidemiology
  - AMD, other conditions requiring follow-up care
  - Cost and Practice Management Issues

AMD

- Complex Disease Requiring Understanding of
  - Clinical Course and Findings
  - Epidemiologic Data
  - Histopathology Investigation
  - Genetic Data
    - All of which have improved in the past decade!

AMD Causes

- Multi-Etiological Disease Risk Markers
  - Aging
  - Genetic Susceptibility
  - Environmental Factors
    - Some are modifiable
      - Dietary habits
      - Smoking
      - Others such as the aspirin debate

Epideiology

- 10,000 Baby Boomers Turn 65/Day Next 17 Years in the US
- World Population Not Much Different
- World Health Organization Causes of Blindness and Vision Impairment (WHO Priority Eye Disease-Related)
  - Cataract 47.9%
  - Glaucoma 12.3%
  - AMD 8.7% (Ranked Third)
  - Corneal Opacities 5.1%
  - Diabetic Retinopathy 4.8%

Genetics of AMD

- Genetic predisposition has been known since 1970s noted by Gass (1972) and Francois (1977) and subsequently by a number of population-based studies.
- Recent advances in genetic and genomic studies have improved understanding of AMD pathogenesis and specific genetic connection.
Genetic of AMD

- Challenges
  - Genetic Disorder Not Always Inheritable Disorder
    - Mutation, Changes to the DNA
  - Cell Reports Nov 2012: Hypermethylation of the IL17RC Promoter Associates with AMD (Environmental Modification of DNA)
  - Disease of late decades
    - Parents and siblings may be deceased
    - Offspring(s) may be too young to show any signs
  - At least 25 genetic risk markers
    - Complement Pathway Components (CTH)
    - Gene on Chromosome 10 (ARMS2)
    - Mitochondrial enzymes (Oxidative Stress)

Genetics of AMD

- Predictive Testing
  - AA Ophthalmology position
    - As of Nov 2012 (Ophthalmology 2012; 119(11) worn against genetic testing for complex eye disorders such as AMD and late onset POAG
    - Researchers’ understanding of genetic factors and its interaction with the disease factors far from complete. Knowing may not alter the course of the disease.
    - Genetic testing in the future may aid in better treatment
    - Social issues such as decision by one to not have children based on the disease.

Genetics of AMD

- Predictive Testing
  - Pros
    - Improve accuracy of diagnosis
    - Aid in prediction of prognosis
    - Genetic Counseling for Families of High Risk
    - Tailor Follow-up and Treatment Plans
      - Nashville Protocol for AMD Management (Tennessee Retina PC)

Genetic and AMD

- AAO Specific Recommendation for Genetic Testing (not a complete list)
  - Offer to patient with clinical findings suggestive of Mendelian disorders whose causative gene(s) have been identified
  - Clinical Laboratories Improvement Amendments-approved labs for all testing
  - Provide a copy of the report to the patient
  - Avoid direct-to-consumer genetic testing
  - Avoid routine genetic testing for genetically complex disease like AMD
  - Avoid testing asymptomatic minors for untreatable disorders (with some exceptions)

Genetics of AMD

- Genetic Testing
  - Cons
    - Not Definitive
      - E.g., 35% individuals carry at-risk SNP on one or both copies of factor H gene. Homozygous 7X Heterozygotes 2.5X increased risk for AMD
    - Not reimbursable
    - Growing Number of States Regulate G Testing
    - Labeling Patient with DX or Potential DX
      - Patient’s Anxieties with the Knowledge
      - Condition that has NO TREATMENT
      - Discrimination by Insurers (Disability, Life, Etc.) and Employers

Aging and AMD

- An aging population in the US and most of the industrial, western world.
- 10% 66-74 and 30% 75-85 have some degree of AMD
Smoking and AMD

- Several Studies are in the literature (Cross-sectional, prospective cohort, case-control) Not all support the linkage
  - Strong Association Between Current Smoking and AMD (as well as passive exposure)
    - Two to three folds in development
    - 300-500X increased in progression
- Exact mechanism not known
  - Oxidative Stress
  - Chemical induced (4000 chemical Substances in cigarettes)

Nutrition and AMD

- Many Fruits, vegetables, nuts, seeds, dairy products and egg are sources of these
  - Cultural, Socio-economical Issues
- Multiple Dietary Supplements
  - Ease of access and use but consumers confusion
- Smoker’s Issues with dietary supplements

Smoking and OHS (Ophthalmology Feb 2012)

- The positive effects of smoking cessation is evident both for AMD and increased longevity (Oct 2012 BMJ paper on smoking in Japan) but not immediately realized
  - Stop Smoking and Stop Early

Nutrition and AMD

- Another Complex Subject made even more fuzzy by the market battle of Nutraceutical Companies
  - Benefit of Antioxidants vitamin A, C, and E, minerals zinc (zinc oxide) and Copper (cupric oxide), beta-carotene and carotenoids Lutein and Zeaxanthin as well as Essential Fatty Acids (DHA/EPA) have been demonstrated
  - Risk associated with high fat consumption

Aspirin Use and AMD

- JAMA Dec 2012, JAMA Internal Medicine Jan 2013
  - Analysis Beaver Dam Eye Study (1)
  - Australian Study (2)
    - Odds ratio 2.46 among ASA users For Dry (2)

Aspirin and AMD

- Comment: Emily Y. Chew, MD, PhD (Deputy Director of Epidemiology and Clinical Application at the NEI)
  - “It’s a public health issue, because it’s clear that the protective effect from aspirin is high. People are going to die because of not taking aspirin for their heart disease. My patients are scared to death right now” (Medscape Medical News)
  - Consider Risk and Benefit Issues
    - Patient self-medication with ASA different that those on medical regimen
AMD other Risk Factors

- Systemic disease (Cardiovascular, Lipid Disorders)
- UV (Blue Light) exposure
- Ethnicity (Caucasian)
- Gender (Female)

AMD Natural Course

- Traditional Classification
  - Dry (Atrophic, Nonexudative)
    - 90% (10% have significant Vision Loss)
    - Drusen, RPE abnormalities and GA
  - Wet (Neovascular, Exudative)
    - Choroidal neovascularization
    - 10% (90% have significant vision loss)
  - Disciform (End-Stage)
    - Many unilateral

- AREDS Classification
  - Category 1: No Disease-No drusen or few small drusen and no RPE abnormalities, both eyes
  - Category 2: Early AMD-Several small drusen or ≥1 medium drusen or RPE abnormalities both eyes, or 1 eye + category 1 fellow eye
  - Category 3: Intermediate AMD-Numerous medium drusen or ≥1 large drusen + RPE abnormalities or noncentral GA both eyes, or 1 eye + category 1 or 2 fellow eye
  - Category 4: Advanced AMD-Unilateral GA (dry) or CNV (wet), fellow eye any stage

Drusen and AMD

- Focal deposits of extracellular debris usually form between RPE and Bruch membrane
  - Small Drusen (<63 µm) seen in many non-AMD eyes of middle-aged adults
  - Intermediate (63-125 µm) and Large (>125 µm) in the macula usually AMD

Intermediate Drusen (63-125 um)

Clinically challenging to estimate drusen size

Large Drusen (>125 um)
RPE Abnormalities – Geographic Atrophy

• Progression of AMD is evident by a potpourri of findings...

Hemorrhages- (Thing of the Past!)

Atrophic AMD/GA- Progression of vision loss

Disciform AMD

• End-Stage--No Effective Therapy
  – CNV Could have been controlled not the GA!

Neovascular AMD

• Choroidal Neovascular Membrane
  – Not Just Associated with AMD
    • Mechanical (e.g., trauma or iatrogenic)
    • Post-infectious (Histoplasmosis)
    • Myopia (Genetic component)
  – When Treated Underlying Disease is NOT Addressed

AMD-Clinical And Ancillary Examination

• Early Detection, Prevention, Timely Care and Follow-up
  – Genetic Testing
  – Clinical Findings (History and Examination)
    • Thorough Ophthalmoscopic Examination
**AMD-Ancillary Examination**

Not a single panacea!

- Ancillary
  - Macular Pigment Analysis
  - Microprimetry and PHP
  - Imaging
    - White Flash Photography
    - Wave length Specific Photography
      - RAF
      - Multispectral
    - OCT and SLO (B and C-Scans)
    - Angiography (FA/ICG)

**Macular Pigment**

- Carotenoid Xanthophylls
  - Lutein and Zeaxanthin
  - Protective properties

**Challenges AMD Care**

- Reliability on Patient Follow-up and Symptomatology...

- Availability of Necessary Technology
  - Reliability and proper use of the Available Technology

- Challenges in Treatment
  - Information overload on Modern Nutritional Care
  - **No Effective Dry AMD Treatment**
  - Paradigm Shift by Anti-VEGF for CNV but no panacea

**Measurement of Macular Pigment Optical Density in Early Detection of Dry AMD**

Proper Nutrition and Follow-up.

- Heterochromatic Flicker Photometry
  - Macuscope

- Eye Promise: QuantifEYE®

**Early Detection Of AMD**

- Genetic Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Markers</th>
<th>Sample</th>
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<tr>
<td>Macular Risk</td>
<td>CFH, ARMS2, C3, NO2, Smoking</td>
<td>Cheek Swab</td>
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<tr>
<td>RentaGene (CVN Risk)</td>
<td>CFH/CFHR region, C2, CFB, ARMS2, C3</td>
<td>Cheek Swab or Blood</td>
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<td>deCode Complete Scan</td>
<td>CFH, ARMS2/HTRA1, C2, CFB, C3, (East Asian: ARMS2/HTRA1 only)</td>
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<td>ARUP Laboratories</td>
<td>CFH, ARMS2</td>
<td>Blood</td>
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<tr>
<td>23andme</td>
<td>CFH, ARMS2, C2</td>
<td>Saliva</td>
</tr>
</tbody>
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**Nutrition and AMD**
Capturing Newly Wet AMD-Converted Patients

- Early Diagnosis of CNV have shown better treatment prognosis in both PDT and Anti-VEGF clinical trials

Imaging Technologies

- Color
- Wavelength Specific
- Scanning Devices (OCT)
- Angiography

Fundus Autofluorescence (FAF)

- Imaging of RPE using autofluorescence has become easier with the confocal scanning ophthalmoscope (SLO)
- FAF is excited at 488nm and the emitted light is detected above 500nm
- The intrinsic FAF is derived from lipofuscin accumulation in RPE (aging or disease state)
- FAF pattern can be used to detect disease or therapeutic effect such as laser

No Dry AMD Treatment

- Treatment of AMD vs Prevention of Progression vs Treatment of CNV
- www.clinicaltrials.gov Search AMD
- Smoking Cessation and Proper Nutrition + Proper care of cardiovascular and lipid disorders....
  - Vision Rehabilitation
    - Effective but Underutilized and Underserved!

Wet AMD-CNV

- Treatments
  - Chemical Models
    - Interferon, Thalidomide, Shark Cartilage, Steroids
  - Surgical
    - SMS, Retinal/Macular Translocation, RPE Transplantation
  - Laser and Radiation
    - Thermal Photocoagulation (Focal), PDT, Feeder Vessel
    - Proton Beam Radiation, TTT (Transpupillary thermotherapy)
  - Chemical Therapy
    - Steroids
    - Anti-VEGF

Anti-VEGF Five Decades of Discovery

- 1948 – Michelson: “Factor X” produced by retina
- 1971 – Folkman: “angiogenic factor”; proposes antibody as potential anti-angiogenic therapy
- 1975 – Kohler, Milstein describe antibody techniques
- 1989 – Ferrara clones/purifies VEGF
- 1989 – Queen describes humanized antibody technique
- 1990s – Development of anti-VEGF proteins
- 2005 – MARINA / ANCHOR Ph III trial results
  
  [CRI IVA Aug 2005]
Modern Definitions

- **Angiogenesis** — Formation of thin-walled endothelium-lined structures with/without muscular smooth muscle wall and pericytes (fibrocytes). This form plays an important role during the adult life span, also as “repair mechanism” of damaged tissues (response to ischemia)
- **Vasculogenesis** — Formation of vascular structures from circulating or tissue-resident endothelial stem cells (angioblasts), which proliferate into de novo endothelial cells. This form particularly relates to the embryonal development of the vascular system
- **Arteriogenesis** — Formation (or enlargement) of medium-sized blood vessels possessing tunica media plus adventitia. (response to obstruction)

Vascular endothelial growth factor (VEGF)

- sub-family of growth factors, “platelet-derived growth factor” (family of cystine-knot growth factors, cytokine)
- Important signaling proteins involved in both vasculogenesis and angiogenesis
  - **Platelet-derived growth factor (PDGF)** is one of the numerous growth factors (proteins) that regulate cell growth and division. In particular, it plays a significant role in blood vessel formation (angiogenesis), the growth of blood vessels from already existing blood vessel tissue
  - Uncontrolled angiogenesis is a characteristic of cancer
  - Vascular permeability (breakdown of blood retinal barrier)

What is in the Pipeline

- Clinical Trials (clinicaltrials.gov) >125 studies
  - Anti-VEGF
  - Combo therapies
  - Anti-Inflammatory Treatment
  - Radiation Therapy
  - Vascular Stabilization and Vascular Disruption
  - Complement Inhibition
  - Tyrosine Kinase Inhibition
  - Nicotine Cholinergic Receptor Antagonist
  - Integrin Antagonist Therapy
  - Gene Therapy

Wet AMD- CNV Treatment

- **Agent of Choice?**
  - Current Issues for compounding pharmacies
- **Treatment Intervals?**
  - Monthly vs. Treat-and-Extend vs. PRN
  - CATT q1m vs PRN not much different particularly in Lucentis patients however even PRN pts were examined q1m!
  - Most patient q6-8 weeks

Wet AMD-CNV Treatment

- **Anti-VEGF**
  - Pegaptanib (Macugen)
  - Bevacizumab (Avastin)
  - Ranibizumab (Lucentis)
    - (HARBOR) Feb 2013 (0.5 mg less freq than q1m FDA approved) (Also higher dose in FDA pipeline)
    - Aflibercept (Eyelea)

Wet AMD Treatment

- Clinical And Logistic Challenges
- Clinical Trials vs. Clinical Realities

**CASE STUDY: 6 Years of Peaks and Troughs**