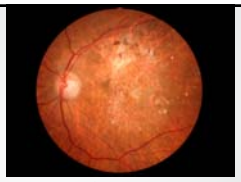

ImmunOptometry:

Update On Immunology As It Relates To Primary Care Optometry

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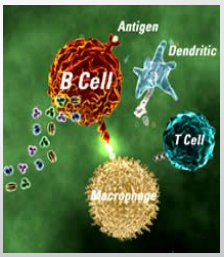
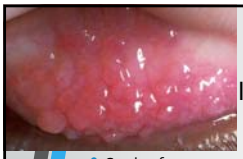
Overview

- Resources: Basic Immunology, 5th edition, Abbas Lichtman Pillai
  - Review of Optometry including Guides
  - Shhh…It's a secret: Medscape
  - Robbins Basic Pathology text
- How did I get here? I need to KMMS (just joking)
- What are we covering?
  - Basic Immunology Concepts
  - Relavent to Optometry: some updates and cases, terminology helps with literature
- COI: Shire Advisory Board: 2017
- **Bold and Underline**
- *what does it mean?





Immunology Defined

- Study of:
  - Immunity: protection against infections
  - Immune system: collection of cells and molecules needed to protect us from them (environmental microbes)
    - Immune Response: mechanisms to distinguish Self vs. Non-self
      - Non-self = "foreign" antigen
  - Deficient and excessive responses cause big problems
    - AIDS and Hypersensitivity

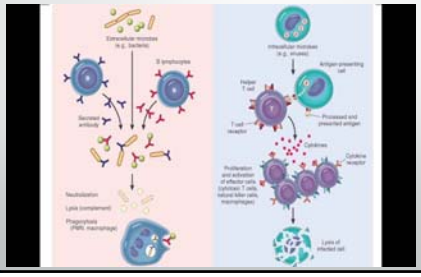
Innate and Acquired Immunity

- Two main types of defense against microbes
  - 1. Innate (natural or native) Immunity
    - Non-specific
    - Quick to respond and protect
    - Barriers (skin, phagocytes, natural killer cells, complement)
    - *www.biologyexams4u.com
  - 2. Acquired (adaptive or specific) Immunity
    - Responds by becoming active
    - Lymphocytes and their products
    - Specificity, diversity, and memory
- Both can cause and be associated with inflammation

Acquired Immunity Types

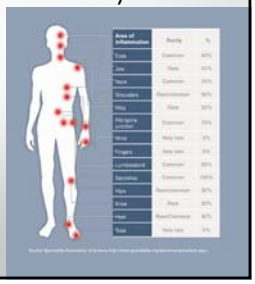
- Two types
  - 1. Humoral: antibodies
    - Soluble proteins, produced by B lymphocytes (B Cells)
    - Protect against extracellular microbes in blood, tissues, and mucosal secretions
  - 2. Cell-mediated: T lymphocytes (T Cells)
    - Protect against intracellular microbes
    - Cytotoxic and Helper T Cells
    - CMI = Cell-Mediated Immunity
    - **No antibodies / Immunoglobulins (IgA, IgD, IgE, Ig G, IgM)**

Acquired Immunity Types *Elsevier Science



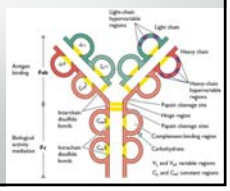
The "Players" / Cells of the Immune System

- Major Histocompatibility Complex (MHC) Molecules
  - The peptide display system of Acquired Immunity
  - HLA: Human Leukocyte Antigen
- Lymphocytes
  - Recognize antigens and provide the acquired immune response
  - Include NK (Natural Killer) Cells *courses.lumenlearning.net
- Antigen-Presenting Cells
  - In the acquired immune response, capture and display the antigens to the lymphocytes
- "Other" Effector Cells
  - Phagocytes: macrophages, neutrophils, and eosinophils for example
- **Cytokines**: messenger molecules of the immune (and inflammatory) systems
  - Innate and acquired immunity, stimulation of hematopoiesis

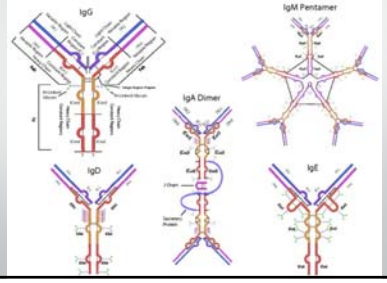


B Lymphocytes

- Bone Marrow-derived
- Produce Effector cells of Humoral Immunity: Plasma Cells
- 10-20% of circulating peripheral lymphocytes
- Membrane bound IgM on B cells recognize antigen
  - After recognition→plasma cells→antibody
  - Antibody types: IgA, IgD, IgE, IgG, IgM
  - Ig = Immunoglobulin
  - *microbiologyinfo.com

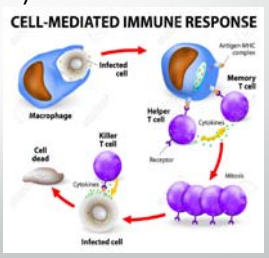


Antibody Structure & Classes *www.sigmaaldrich.com

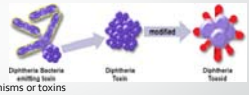


T Lymphocytes

- Thymus-derived
- Effector cells of CMI
  - *www.123rf.com
- CD designation: cluster of differentiation receptor
- 60-70% of circulating peripheral lymphocytes
- Recognize MHC bound proteins on antigen cell surfaces
- Helper cells for antibody responses against protein antigens
  - $CD4_+$ T cells
- Cytotoxic cells directly kill virus-infected or tumor cells
  - $CD8_+$ T cells
- There are other types of T cells besides $CD4_+$ and $CD8_+$



Acquired Immunity: Cross-Reactivity



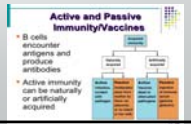
- Basis of immunization
  - "Trick the immune system"*www2.cdc.gov
  - Destroy the biologic activity of highly pathogenic microorganisms or toxins
    - Without destroying their antigenicity
  - Toxoid
    - Modified toxin that is no longer toxic but still maintains its antigenicity
    - Cross-reactivity between toxoid and toxin
    - Immunize with a toxoid, thereby inducing an immune response to some of the shared epitopes between the toxoid and toxin
    - In other words, they share enough epitopes allow the immune response to the toxoid to mount an effective defense against the toxin

Acquired Immunity: Cross-Reaction

- Immunological Reaction in which the immune components (cells or antibodies)
  - React with two molecules that share epitopes
  - But are otherwise dissimilar
- Edward Jenner: late 1700's
  - Experimentally induced immunity to smallpox
  - Inoculated a young boy with cowpox from a lesion of a dairy maid with cowpox
    - Smallpox (toxin) and cowpox (toxoid) are related
  - Deliberately exposed the boy to "smallpox" and he did not get sick
  - **Vaccination** (from the latin word vacca, meaning cow)
    - Induced acquired immunity from protective effect of the inoculation with cowpox
    - *vaxtruth.org

Acquired Immunity: Achieving Immunization

- **Active immunization: via administration of an antigen**
- Passive immunization: via the transfer of specific antibody from an immunized individual to a non-immunized individual
- Adoptive immunization: via transfer of immunity via transfer of immune cells
- *www.slideshare.net



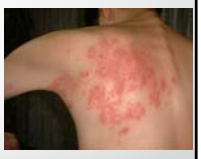
Acquired Immunity: Adjuvant

- Defined: a helper
  - Substance that when mixed with an antigen, enhances the immune response against the antigen
  - Used with vaccines to enhance immune response
    - Adjuvants containing microbial components→increased function of APC's (macrophages and dendritic cells)
    - *www.nature.com
  - Examples:
    - In use: aluminum hydroxide or aluminum phosphate (alum)
    - Experimental: Freund's complete adjuvant
      - Killed Mycobacterium tuberculosis

Acquired Immunity

- Vaccination and Herpes Zoster
  - Options : Shingrix and Zostavax
  - Zostavax
    - 2006: first licensed and recommended in 2006
    - Live, weakened form of the chickenpox (varicella) virus
    - 14 x the dose of the varicella vaccine (Varivax)
    - Efficacy against rash about 51% and against post-herpetic neuralgia (phn) about 67%
    - Duration: after about 4 years, protective effect for phn down to about 30%

Acquired Immunity

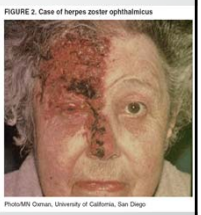


- Vaccination and Herpes Zoster
  - Shingrix
    - 2017: another vaccine licensed and recommended
    - Not a whole weakened form of the virus; instead, just a surface-sitting protein (glycoprotein E) and 2 adjuvants (one is from a Chilean soap tree)
    - Efficacy against rash mid to high 90% range for all age groups and against phn upper 80's to low/mid 90's % range
    - Duration: after 4 years, the protective effect is still about 85%

Acquired Immunity

- Vaccination and Herpes Zoster
  - Shingrix: recommendations for use
    - Can be given starting at 50 years of age
    - 2-dose vaccine, with second dose given 2-6 months after the first
    - Preferred vaccine
    - **Even if already had Zostavax, you should receive the two doses of Shingrix**
    - *ResearchGate

Acquired Immunity



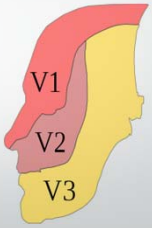
- Vaccination and Herpes Zoster
  - Shingrix: side effects
    - Fever, myalgia, chills: somewhat worse vs. Zostavax
      - Fewer than 5-10% said it interfered in any sense with their daily lives
    - More than 75% reported pain at injection site
    - Do not engage in strenuous activities for a few days post-injection
    - OTC NSAIDS help with side effects
    - A reaction to the first dose did not predict a reaction to the second dose

A Case To Think About

- My Worst? Case Ever Of Herpes Zoster Ophthalmicus
- S:
  - 36 yo African-American male
  - Augmentin, neurontin, "pain med with codeine", acyclovir
  - Blur, dryness, discharge, redness, grittiness, itching, burning, tearing, light sensitivity, pain, tiredness, fever
  - 2006

A Case…

- My Worst? Case Ever
- S continued:
  - H/O HZO , OD red with "matting" and burning
  - Right facial skin lesions involving nose
  - Onset 6 days ago
  - Began Acyclovir 800 mg 5x/day 1 day ago
  - *tomaselloneurochirurgo.unime.it



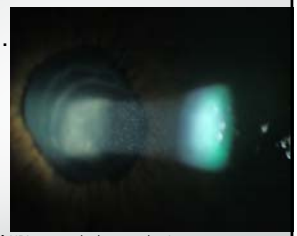
A Case…

- My Worst? Case Ever
- O:
  - VA: 20/200 (ph 20/30), 20/20
  - SLE: diffuse SPK with pseudodendrites, endothelial KP's, at least 3+ cells, 3+ conjunctival injection OD
  - IOP: 15 OU

A Case…

- My Worst? Case Ever
- A/P
  - HZO with severe uveitis and pseudodendrites OD
  - Prednisolone Acetate 1% q2h OD, Homatropine 5% bid OD, Tobramycin qid OD, Bacitracin ung bid to lesions
  - CPM per PCP (Continue Present Meds per Primary Care Physician)

A Case…



- My Worst? Case Ever
- Second visit (2 days later)
  - Improvement in signs symptoms?
  - "tested for HIV…no results yet"
  - VA 20/400 (ph 20/200)
  - Diffuse SPK with pseudodendrites, ALL 3+ →KP's, corneal edema and striae, conjunctival chemosis and injection, GD 2-3 cells
  - *Symphony Slit Lamp by Keeler

A Case…

- My Worst? Case Ever
- Second visit
  - Unable to assess retina
  - IOP: 16
  - A/P: HZO with slight improvement in AC reaction, decreased VA secondary to corneal edema, CPM

A Case…

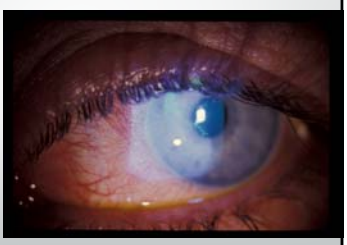
- My Worst? Case Ever
- Third visit (3 days later)
  - "skin lesions better"
  - "vision not good and eye discomfort"
  - VA 20/400 (phni)
  - SLE the same but corneal edema worse and ptosis present

A Case…

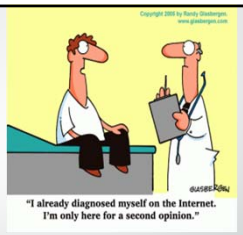
- My Worst? Case Ever
- Third visit
  - IOP: 19
  - A/P: same assessment except worse overall
  - change Pred Acetate 1% to QID, Add Viroptic 9x/day x 1 week, otherwise CPM

Dendrites or Pseudodendrites?

- Dendrites: Arborization and terminal end bulbs (rose Bengal)
  - History helps too: prior HSK (decreased corneal sensitivity, iris atrophy, corneal staining)
    - Vs HZO, trauma / abrasion, DED, CL complications
- Pseudodendrites stain lightly with NaFl
  - Lack of central staining
  - Elevated without central ulceration

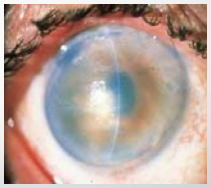


A Case…



- My Worst? Case Ever
- Third visit
- A/P: HELP…refer to corneal specialist for second opinion
- Colleague worried about the patient…

A Case…



- My Worst? Case Ever
- 4th visit / prior to consult
  - 3+ eye pain, decreased VA
  - Corneal bullae and increased IOP (29)
  - Decreased pseudodendrites
  - Added Medrol dose pack, NaCl drops, Pred 6x/day, D/C Tobramycin
  - Lots of patient education

A Case…

- My Worst? Case Ever
- 5th visit / visit prior to consult
- Finally, some definite improvement
  - Decreased eye pain
  - Pinhole 20/80, no microbullae, IOP normal
  - CPM

A Case…

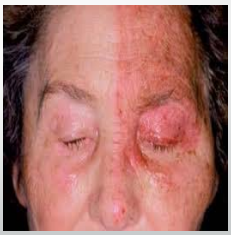
- My Worst? Case Ever
- Consult
- Agreed with management
- Gave taper schedule

A Case…

- My Worst? Case Ever
- Make a long story short
- About 2 months after initial visit
  - No eye pain, mild photophobia, tearing, mattering in AM
  - Still on Pred 6x/day
  - Skin lesions resolved
  - Ptosis, trace cells, mild SPK and injection, tonometry 19, retina fine
  - VA 20/25

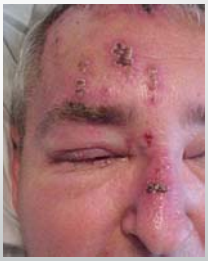
A Case…

- What did I learn
  - HZO oral meds may include more than Acyclovir
    - Prednisone
    - Narcotic
    - Neurontin
      - Analgesic to treat the pain associated with PHN
    - Antibiotic
    - *youtube MEDICO THEORY



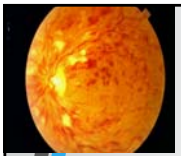
A Case…

- Keep in Mind with HZO: Zovirax (Acyclovir)
  - 800 mg 5x/day for 7 days
  - **Within 72 hours**
  - Generic available
  - Remarkably safe
  - Alternatives
    - Valtrex (valacyclovir) 1 gram tid x 7d
    - Famvir (famciclovir) 500 mg tid x 7d
  - *Medscape Image courtesy of JS Huff



Antibodies: Tissue repair

- Regeneration (and scar formation)
  - Cell proliferation
    - Occurs with injured tissue, vascular endothelial cells, fibroblasts
      - Fibroblasts supply fibrous tissue for scar
      - Cell cycle
  - Growth factors
  - ECM (Extracellular Matrix)

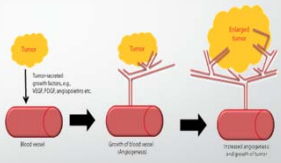


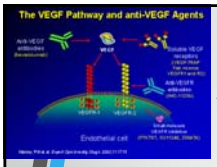
Antibodies: Tissue Repair

- Regeneration and Growth Factors
  - VEGF (Vascular endothelial growth factor)
    - Source: mesenchymal cells
    - Functions: stimulates proliferation of endothelial cells, increases vascular permeability
    - Anti-VEGF intravitreal injections
      - Avastin, Lucentis, Eylea
      - To treat many neovascular and edematous ocular retinal conditions: **wet AMD**, diabetic macular edema, proliferative diabetic retinopathy for example
        - Other disorders associated with choroidal neovascularization and macular edema
  - *www.imperialhealth.org

Antibodies: Tissue Repair

- Angiogenesis & Growth Factors
  - The VEGF Family
    - ABCD and E
      - VEGF-A responds to injury, and in tumors
    - Expressed in most adult tissues
    - Hypoxia is an important inducer of VEGF activity
    - Stimulates
      - Migration and proliferation of endothelial cells ☞capillary sprouting
      - Vasodilation
    - **Antibodies against**
      - **Approved for the treatment of some tumors**
      - **Used for the treatment of many ocular neovascular and edematous disorders**
      - **Mansdoug**
  - *www.biopharminternational.com





Antibodies: Tissue Repair

- Angiogenesis & Growth Factors
  - Newly formed vessels in the ECM
    - Leaky: incomplete interendothelial cell junctions and VEGF-induced increased vascular permeability
    - Associated with **edema** in adjacent tissues

Case 2007: The Importance of Anti-VEGF

- S:
  - 89 yo Caucasian female
  - Aricept, Lexapro, HCTZ, Ocuvite
  - Cataract sx OU 12 years prior
  - Family hx: cataract, glaucoma, arthritis, cancer, leukemia
  - Non-smoker
  - F/U on ARMD dry OD, wet OS and dry eye syndrome OU

Case 2007

- S: About the ARMD
  - 11 years
  - Constant duration
  - No changes in vision
  - Uses Home Amsler daily with compliance

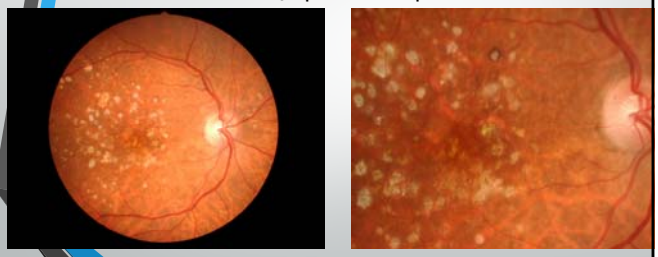
Case 2007

- O:
  - BVA OD: 20/40, OS HM@ 3 ft
  - PERRL without APD, FROM, FTFC OU
  - Amsler: negative scotoma, metamorphopsia OD, positive metamorphopsia OS
  - SLX: dermatochalasis, collarettes, arcus, PCIOL, syneresis
  - T(a): 16, 15 at 3:12 pm
  - Trial frame refraction: no change OU

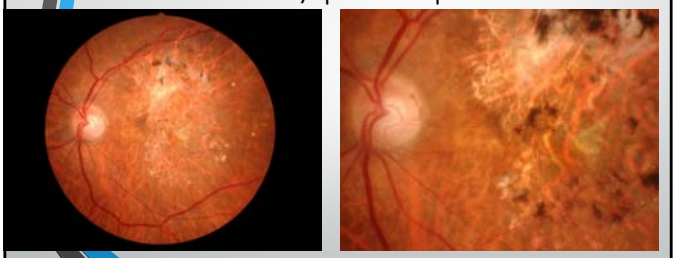
Case 2007

- O: DFE with 20; and 90 D lenses
  - ONH normal, .4 rd OU
  - Macula / posterior pole: drusen OD, scarring, fibrosis, and pigmentary changes OS
  - Normal periphery OU

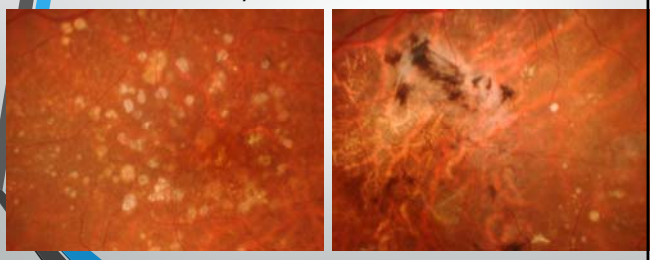
Case 2007: posterior pole OD



Case 2007: posterior pole OS



Case 2007: macula OD / fibrosis OS



Case 2007

- A:
  - ARMD OU stable, OD dry, OS wet
  - Pseudophakia OU
  - Dry Eye Syndrome OU

Case 2007

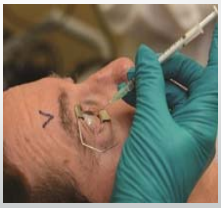
- P:
  - To monitor, fundus photos today, RTC 6 months
  - To monitor
  - Continue artificial tear regimen

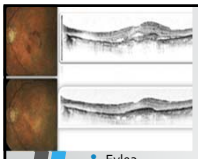
Case 2007

- Considerations: etiology and diagnosis
  - Risk factors?
  - Why no OCT?
  - Fundus Autofluorescence?
  - Foresee PHP or QuantifEYE/MPOD?
  - Fluorescein angiography?
    - OCT-A
  - Home amsler?
  - Nutritional modifications?
  - Referral to retinal specialist
  - **AMD is inflammation, angiogenesis and leakage**

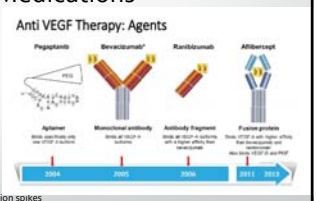
Anti-VEGF Medications:

- Alone or with other treatment modalities
  - Macugen (Pegaptanib)
    - Antiangiogenesis
    - 2004
  - **Lucentis / Novavtis (Ranibizumab / Genentech)**
    - **Monoclonal antibody binds to VEGF-A**
    - **2006**
  - **Avastin (Bevacizumab)**
    - **Monoclonal antibody binds to VEGF-A**
    - **Off-label / cancer drug / cheapest $50 vs. $2000**
  - **Eylea (Aflibercept, Regeneron)**
    - **Receptor-antibody fusion protein**
  - *Retina Specialist





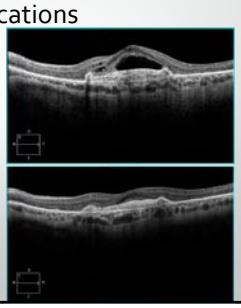
Anti-VEGF Medications



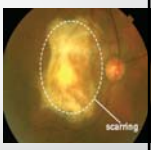
- Eylea
  - Vs Lucentis and Avastin
    - Longer lasting
      - After 3 months, not needed every month
    - Binds to both VEGF-A and VEGF-B
      - More efficacious
  - FDA-approved
  - 1 injection of Anti-VEGF→
  - Recently associated with intraocular inflammation spikes
  - *Health & Medicine

Anti-VEGF Medications

- Lucentis and Avastin
  - Can allow for improvements in vision (70%)
    - 30-40% significant visual recovery
    - Disease control (80%)
  - Can reduce the signs and symptoms of **wet AMD**
  - Increased frequency improves outcomes



Anti-VEGF Limitations: Reality vs. Clinical Trials



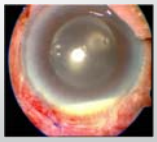
- VEGF Indications
  - Cases of active wet AMD where vision loss is not due to scarring
- Best predictor of visual outcome(MOLINA Study):
  - Baseline VA: patient with better baseline achieved less positive results
- Largest sized baseline neovascular lesions
  - Older neovascular nets develop a relative immunity to VEGF suppression

Anti-VEGF Limitations: Reality vs. Clinical Trials

- Some cases of wet AMD
  - Recalcitrant and continue to progress even with therapy
  - Regression of CNV is not complete
    - Vessel remnants become less dependent on VEGF for continuous growth
    - pericytes and PDGF (platelet-derived growth factor) → abnormal maturation of vessels

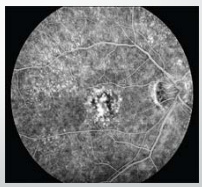
Anti-VEGF Side Effects: Reality vs. Clinical Trials

- Increased risk of stroke among elderly patients receiving Avastin vs. Lucentis?
- Slow increase in IOP long-term
- Endophthalmitis (1/5000)
- Drying out the retina too much?
  - 10%-20% patients → decreased VA due to atrophic changes
  - VEGF supports the health of choriocapillaris



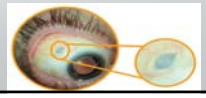
Lucentis vs Avastin

- Lucentis not significantly better
- Retinal specialists: evenly matched
- Lucentis is FDA-approved for wet AMD
- CATT: Comparison of AMD Treatment Trials
  - Long term, Lucentis better via anatomical findings



Anti-VEGF and Optometry

- Preparation of patients:
  - "A needle in the eye?"
  - Making all the appointments
  - 20% will be non-responders or under-responders
  - Risk of endophthalmitis
    - Blepharitis prior
- Early Detection
  - OCT and FLAN
  - Foresee PHP and PreView PHP
  - QuantiFEYE and MacuScope
  - Genetic testing
- Refractive solutions and observation
- Management Discussion

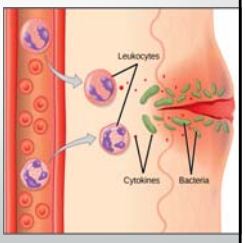


Recent Considerations and Updates: Implant Port Delivery System: Ranibizumab

- Phase 2 LADDER Trial
- Hoping to achieve:
  - Outcomes achieved with monthly injections
  - Device that eliminates need for monthly injections
  - Port about the length of rice grain
    - Surgically implanted in pars plana
    - Refilled with customized needle…thinking every 6 months
    - Continuously diffuse ranibizumab into vitreous cavity
  - Phase 3 Clinical Trial coming: Archway
  - *www.reviewofoptometry.com/article/breaking-the-burden-a-new-way-to-deliver-antivegf
  - "Take A Break"

Cytokines

- Cell-Derived Mediators
  - Cytokines: "Immune and inflammatory messengers"
    - Polypeptides
      - **Interleukins** (IL-#) are molecularly named
        - Generally between leukocytes
        - IL-1 and IL-6
      - **Tumor Necrosis Factor** (TNF)
      - **Interferons**
      - Chemokines

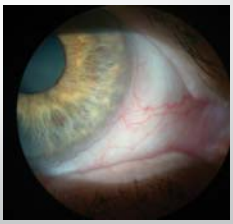


Cytokines

- Cell-Derived Mediators
  - TNF and IL-1
    - Origin: macrophages, mast cells, endothelial cells +
    - Roles: endothelial cell activation in immunity and inflammation
      - Chemotaxis, leukocyte adhesion
      - Activation of tissue fibroblasts
      - Systemic acute-phase reaction (fever)
  - Chemokines
    - Family of small, structurally related proteins
    - Recruit leukocytes to inflamed areas
    - Organizers of cells in lymphoid tissues

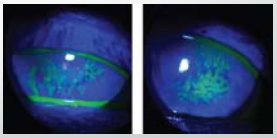
Cytokines: Dry Eye Disease (DED) and Inflammation

- Corticosteroids
  - Broad-spectrum in terms of anti-inflammation
  - Includes acting on cytokines / chemokines / MMP's (matrix metalloproteinases)
- Cyclosporine 0.05%
  - Immunomodulator
    - Calcineurin inhibitor that prevents IL-2 formulation
    - Halts propagation on additional T cells
  - At least 4-6 weeks to take effect
  - Restasis > 2 billion annual sales in US
    - Evidence of efficacy?
  - Unit-dose regimen and multi-dose (5.5 ml) bottle
  - DED associated with autoimmunity
  - *www.reviewofoptometry.com/article/sizing-up-antiinflammatories-in-dry-eye-disease



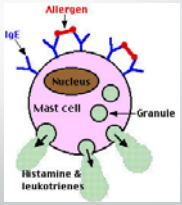
Cytokines: Dry Eye Disease and Inflammation

- Lifitegrast 5%
  - Xiidra: targets integrin signaling
    - LFA-1 (lymphocyte function-associated antigen-1 found on surface of T cells
    - Blocks coupling of LFA-1 to ICAM-1 (intacellular adhesion molecule 1)→
    - Prevention of inflammatory cycle
  - Also, decrease in cytokine release at inflammation sites
  - Improves symptoms in as little as two weeks
  - Side effects: irritation, dysgeusia (metallic aftertaste), blur
  - Single-use vial bid
- Issues with all: cost & pre-authorization ("Step-Up Strategy")
- Both Restasis and Xiidra inhibit T cell medicated inflammatory pathways
- *www.reviewofoptometry.com/article/sizing-up-antiinflammatories-in-dry-eye-disease

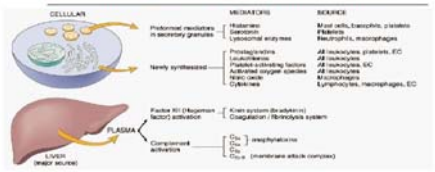


Complement: Inflammation

- Chemical Mediators and Regulators
  - Cell-Derived
    - Produced locally by cells at site of inflammation
      - In intracellular granules until activation and secretion
      - Synthesized in response to stimulus
    - Vasoactive Amines, Arachidonic Acid Metabolites, Platelet-Activating Factor, Cytokines,
    - Reactive Oxygen Species, Nitric Oxide, Lysosomal Enzymes of Leukocytes, Neuropeptides
  - Plasma Protein-Derived
    - Come from circulating, inactive precursors
      - Manufactured in the liver
      - Proteolytic cleavage to activate
    - Complement, Coagulation and Kinin Systems



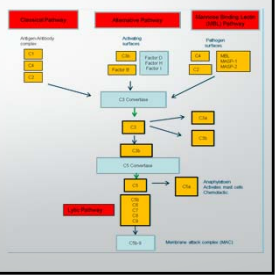
Chemical mediators of inflammation



- Perform biological activity by binding to specific receptors on target cells
- Some have direct enzymatic activity (lysosomal proteases) or mediate oxidative damage (oxygen metabolites).
- Once activated and released from cell, most of these are short lived- quickly decay, inactivated or inhibited.

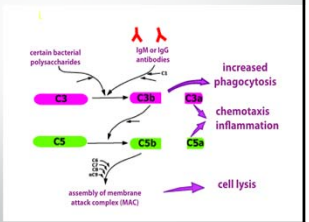
Complement: Inflammation

- Plasma Protein-Derived Mediators
  - Complement
    - $C_1 \rightarrow C_9$: inactive in plasma
      - Activation (proteolysis)→enzymatic cascade
    - Activation of C_3
      - Cleavage via three pathways
      - 1. classical: antigen-antibody complex + C_1
      - 2. alternative: microbial cell wall components + properdin + Factors B and D
      - 3. lectin: lectin in plasma binds to microbes(mannose components)
    - C_3 convertase cleaves $C_3 \rightarrow C_{3a}$ and C_{3b}
      - C_{3b} + microbe surface→ C_5 convertase cleaves $C_5 \rightarrow C_{5a}$ and C_{5b}
      - C_6-C_9 assembly
      - MAC- Membrane Attack Complex generated



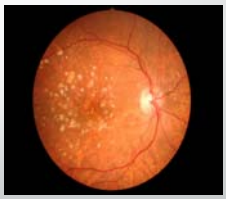
Complement: Inflammation

- Plasma Protein-Derived Mediators
  - Complement: Bottom Lines
    - More mediators of inflammation
    - Generation of Anaphylatoxins (C_{3a} and C_{5a})
      - Cause release of histamine from mast cells
      - Leukocyte activation (especially C_{5a}):
        - adhesion and chemotaxis
    - Phagocytosis and C_{3b}
      - Augmented when C_{3b} attached to microbe surface
    - MAC and C_9
      - Creates "hole" in bacterial cell membranes



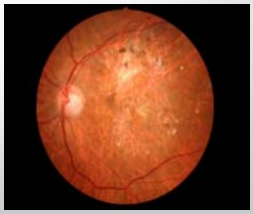
Complement and Dry AMD

- Getting Started
  - **AMD** vs ARM vs ARMD
  - Non-neovascular vs dry vs non-exudative vs atrophic
    - Everyone with AMD has
    - Geographic is advanced dry AMD: 20% of all AMD?
  - Neovascular vs wet vs exudative
    - Complication of the disease



Complement and Dry AMD

- Not really dry versus wet
- Really dry has the potential to become wet
  - Drusen, pigmentary abnormalities, atrophy
  - Neovascularization, heme, fluid, exudate, fibrosis

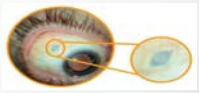


Complement and Dry AMD

- Geographic Atrophy (GA)
  - Circumscribed areas of RPE atrophy
    - May enlarge with disappearance of drusen
    - Significant vision impairment possible
  - Retina and choriocapillaris loss
- Dry is the new wet in terms of treatments
  - Complement inhibitors to halt AMD progression
  - Lampalizumab
  - No treatments currently
    - Besides AREDS supplements
    - Reduction of modifiable risk factors

AMD Treatment

- Forever Changing / Emerging Treatments
  - Next Slides: a few examples
    - Subretinal, intravenous and intravitreal injections, topical drops, intravitreal implants, oral agents
    - Dry>Wet (drug ports)
  - **We Need To Keep Up**
- Speaking of Keeping Up…
  - Your satisfaction and ultimate happiness



Recent Considerations and Updates: Dry AMD

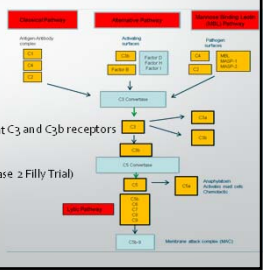
- Topical AMD Therapy
  - Why? Injections unpleasant, inconvenient and expensive
  - Squalamine lactate 0.2% (Ohr Pharmaceuticals)
    - Topical anti-VEGF agent
      - Derived from internal organs (liver) of dogfish shark
      - Inhibits VEGF, PDGF, bFGF
    - Phase 3 Clinical Trial
      - Failed 1/2018

Recent Considerations and Updates: Dry AMD

- Lampalizumab (Roche pharmaceuticals)
  - Treatment for geographic AMD
  - Antigen binding fragment of humanized monoclonal antibody
    - Targets complement factor D
    - Part of cascade implicated in geographic AMD
  - 10 mg intravitreal injections
  - Two Phase 3 Clinical Trials
    - Failed 2017 regarding reduction of GA
    - Fundus AutoFluorescence (FAF)
      - Enhanced signal at lesion boundaries
      - Lesion progression
  - *www.reviewofoptometry.com/article/a-clinical-guide-to-fundus-autofluorescence

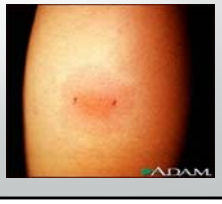
Recent Considerations and Updates: Dry AMD

- 2018: Promising new GA Treatment
  - Intravitreal Complement Inhibitor (APL-2)
    - Synthetic cyclic peptide that binds to complement C_3 and C_{3b} receptors
    - Blocks all three complement pathways
    - Intravitreal injections slowed GA progression (Phase 2 Filly Trial)

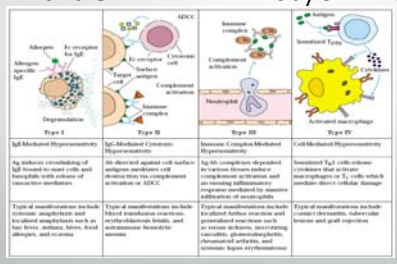


Hypersensitivities

- Inappropriate and vigorous innate and/or adaptive responses to antigens that pose little or no threat
  - Overreaction of the immune system
- Anaphylaxis (greek) meaning = against protection
- Multiple types
  - Immediate: antigen-antibody reactions
  - Delayed: t cell reactions



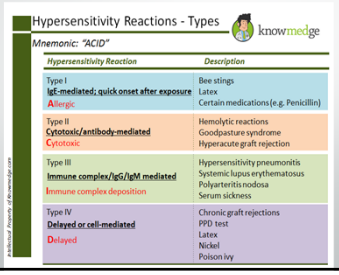
BOLD and UNDERLINE *Kuby's Immunology



Hypersensitivity Reactions

- **Type 1: Immediate, Ig-E, Allergy, Anaphylaxis, Seasonal Allergic Conjunctivitis**
- **Type 2: antibody-mediated. Antibodies bind to fixed tissue or cell surface antigens. Autoimmune Hemolytic Anemia, Graves' Disease**
- **Type 3: immune complex-mediated, antigen-antibody complexes circulate, deposit in vascular beds, and cause inflammation, Systemic Lupus Erythematosus**
- **Type 4: Delayed, T-cell mediated, Contact Sensitivity**
- **Types 1 & 4: GPC, VKC, AKC, Contact Dermatitis**
  - *facultyofmedicines.blogspot.com

Hypersensitivity "Wrap-Up"



Hypersensitivity Reactions - Types

knowmedge

Mnemonic: "ACID"

Hypersensitivity Reaction	*Description*
Type I **IgE-mediated; quick onset after exposure** **A**llergic	Bee stings Latex Certain medications (e.g. Penicillin)
Type II **Cytotoxic/antibody-mediated** **C**ytotoxic	Hemolytic reactions Goodpasture syndrome Hyperacute graft rejection
Type III **Immune complex/IgG/IgM mediated** **I**mmune complex deposition	Hypersensitivity pneumonitis Systemic lupus erythematosus Polyarteritis nodosa Serum sickness
Type IV **Delayed or cell-mediated** **D**elayed	Chronic graft rejections PPD test Latex Nickel Poison ivy

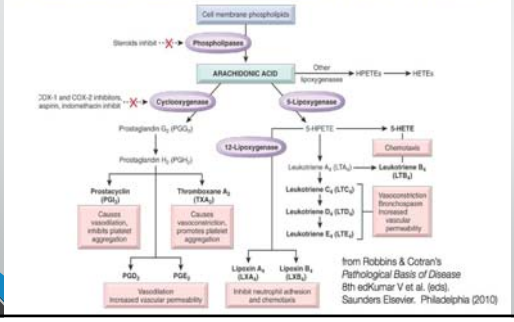
Hypersensitivity and Inflammation

- Cell-Derived Mediators: from tissue macrophages, mast cells, endothelial cells, leukocytes
  - Vasoactive Amines: preformed in mast cells +
    - **Histamine**
      - Produced by many cell types, including mast cells, basophils, and platelets
      - Stimuli / sources include injury, immune reactions (IgE + mast cells), anaphylatoxins, leukocyte-derived, neuropeptides, cytokines
      - Actions: vasodilation, increased vascular permeability
    - Serotonin
      - Found in platelet granules, vasoconstriction during clotting

New Ocular Antihistamine

- **Zerviate** (Cefirizine Ophthalmic Solution 0.24%)
  - Eyevance / Nicox
  - US FDA Approval: May 30, 2017
    - Ocular itching associated with Allergic Conjunctivitis
  - Active Ingredient: Cetivizine
    - Like Zyrtec, a 2nd generation **antihistamine** / "topical Zyrtec"
  - Clinically
    - 1 drop affected eye bid
    - Adverse reactions: ocular hyperemia, pain upon instillation, decreased VA
  - But, what do most OD's use for ocular allergic conditions?
    - Nary a mention in CG2OD's 2018

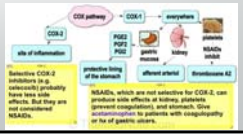
Arachidonic acid metabolites and inflammation



from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)

Hypersensitivity and Acute Inflammation

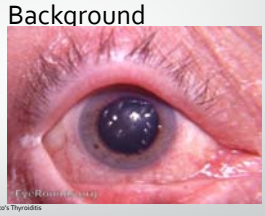
- Cell-Derived Mediators: AA Metabolites
  - **Principle Inflammatory + Actions**:
    - Vasodilation: Prostaglandins, including Prostacyclin
    - Increased vascular permeability: Prostaglandins, Leukotrienes
    - Chemotaxis, leukocyte adhesion: Leukotrienes, HETE (Hydroxyeicosatetraenoic acid)
    - Pain and fever: Prostaglandins
    - Vasoconstriction: Thromboxane A2, leukotrienes
    - Inhibit neutrophil adhesion and chemotaxis: Lipoxins
    - Platelet aggregation: Thromboxane A2



A CASE

- 55 yo Caucasian male
- Ccx: cannot tolerate CL's and itchy red eyes
- NKDA or significant medical history
- Pertinent findings: subconjunctival heme OS, large papillae OU with UEL eversion, bulbar conjunctival edema and injection OU
- Management Options?

Autoimmunity: Background



- Humoral or T cell-mediated response against self antigens
  - Failure of host to distinguish self from non-self
  - Preventive control mechanisms: tolerance or self-tolerance
- Conditions
  - 5-8% of human population
  - Typically, chronic, inflammatory, debilitating diseases
  - Non-Organ specific (Systemic) Conditions
    - Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis
  - Organ specific Conditions
    - Type I Diabetes Mellitus,, Myasthenia Gravis, Graves' Disease, and Hashimoto's Thyroiditis
  - Optometrically: associations and treatment side effects
    - Filamentary Keratitis

Autoimmununе Disease

- Self antigens and primary immune mediators
  - Rheumatoid Arthritis (RA):
    - IgG and connective tissue
    - Autoantibodies, immune complexes
  - Systemic Lupus Erythematosus (SLE):
    - DNA, nuclear protein, RBC and platelet membranes
    - Autoantibodies, immune complexes
  - Multiple Sclerosis:
    - Brain or white matter
    - T helper and cytotoxic cells, auto-antibodies
  - *www.studyblue.com

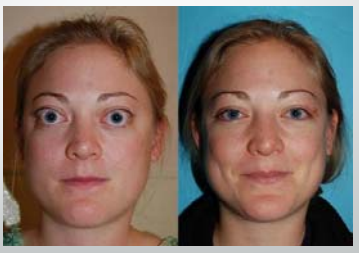
Classification of Autoimmune diseases

Antibody vs. T cell-mediated autoimmunity

Disease	T cells	B cells	Antibody
Systemic lupus erythematosus	Pathogenic Help for antibody	Present antigen to T cells	Pathogenic
Type 1 diabetes	Pathogenic	Present antigen to T cells	Present, but role unclear
Myasthenia gravis	Help for antibody	Antibody secretion	Pathogenic
Multiple sclerosis	Pathogenic	Present antigen to T cells	Present, but role unclear

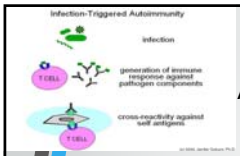
Autoimmune Disease

- Self antigens and primary immune mediators
  - **Type I diabetes mellitus:**
    - Pancreatic beta cells
    - T helper cells, auto-antibodies
  - Myasthenia Gravis
    - Acetylcholine receptors
    - Blocking auto-antibodies
  - Graves' disease
    - Thyroid-stimulating hormone receptor
    - Stimulating auto-antibodies
  - Hashimoto's thyroiditis
    - Thyroid proteins and cells
    - T helper cells, auto-antibodies
  - *greatesthangovers.tumblr.com



Autoimmune Disease

- Risk Factors: "It's all about the patients"
  - Women account for nearly 80% of 50 million living with autoimmune disease in U.S.
    - Especially SLE, also Hashimoto's, Sjogren's syndrome, Graves' disease, RA, and Scleroderma
    - Estrogens associated with enhanced immunity
    - Pregnancy and pre-disposed risk: fetal cells in circulation of women following birth

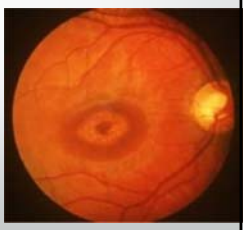


Autoimmune Disease

- Risk Factors: "Its all about the patients"
  - Multifactorial development
    - Environmental and genetic roles→autoimmune disease
      - Diet and geographic locations
      - Exposure to infections
        - Potential for DNA damage and polyclonal activation
        - Molecular mimicry: some pathogens express protein epitopes resembling self components
        - Rheumatic Fever: autoimmune destruction of heart muscle cells after Group A Streptococcus infection, antibodies to streptococcal antigens cross-react with heart muscle proteins
      - Links between HLA alleles and autoimmunity
        - Ankylosing Spondylitis and HLA-B27
    - In general, autoimmune diseases are familial
    - In general, a patient with one autoimmune disease is at increased risk of having another autoimmune disease.

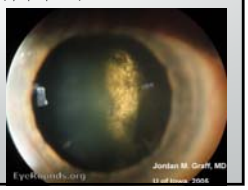
Autoimmune Disease

- Management
  - Optometry:
    - Recognition and assist diagnosis of disease
    - Management of ocular associations
      - **DED most common associated ocular condition**
        - **Lupus and Rheumatoid Arthritis**
    - Management of ocular side effects from treatment
      - **Plaquenil : besides Bull's Eye, don't forget about:**
        - **much more common Vortex Keratopathy**
    - *www.studyblue.com: Bulls-eye maculopathy



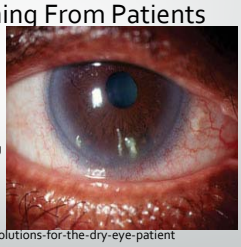
Autoimmune Disease

- Management
  - Systemic: ideally, reduce immune response and leave rest of immune system intact
    - Broad-spectrum immunosuppressive agents: corticosteroids, azathioprine, cyclophosphamide, anti-malarials
      - Hydroxychloroquine (Plaquenil) and Chloroquine (Aralen)
        - **Most common Rxed condition: Lupus**
      - Posterior subcapsular cataract (PSC)
    - Removal or organ or set of toxic compounds
      - Thyroidectomy: Graves' Disease
      - Thymectomy: Myasthenia Gravis
      - Plasmapheresis: removal of plasma antibodies
    - Mechanism or cell-type specific strategies
      - For example, monoclonal antibodies against B cells or T cells



Autoimmune Disease: Learning From Patients

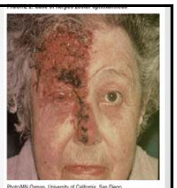
- Older African-American female with OAG
  - Severe DED and dry mouth too
  - DED treatment regimens never helped enough
  - Finally went in for systemic autoimmune disease W/U
  - Diagnosed with Lupus
    - Treated with Prednisone 5 mg/day
  - DED much more amenable to treatment
  - *www.reviewofoptometry.com/article/customized-solutions-for-the-dry-eye-patient



Immunodeficiency (ID)

- Introduction
  - Defined: failure of immune system to protect host from disease-causing agents
  - Primary ID
    - ID resulting form inherited or genetic effect in the immune system
    - Defect present from birth
  - Secondary (Acquired) ID
    - Loss of immune function that results from exposure to external agent (infection)
    - AIDS = Acquired Immunodeficiency Syndrome
      - Due to HIV (Human Immunodeficiency Virus)
    - Also associated with drug treatment, metabolic disease, and malnutrition *selfchec.org

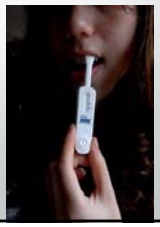
Secondary ID's



- Other Causes and Conditions besides AIDS
  - Hypogammaglobulinemia: young adults, no genetic transmission, recurrent infection
  - Agent-Induced ID
    - Immunosuppressive and corticosteroid drugs: after transplantation, for treatment of autoimmune disease
    - Cytotoxic drugs or radiation treatment for cancer
  - Extremes of age
    - Premature babies: increased susceptibility to infection
    - Elderly age as a risk factor for certain viruses, bacteria, and cancers
  - Single most common cause of Acquired Immunodeficiency worldwide
    - Malnutrition: hypoproteinemia; deficiency in dietary zinc, ascorbic acid, vitamin D
  - Metabolic Disease: Diabetes Mellitus

HIV/AIDS

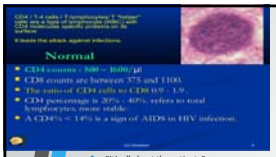
- Diagnosis
  - HIV EIA (Enzyme-Linked Immunosorbent Assay)
    - Presence of antibodies against HIV-1 proteins
    - Present within 6-12 weeks post-exposure (up to 6 months)
    - Western Blot confirms
  - HIV Rapid Antibody test
  - OraQuick



HIV/AIDS

- Treatment
  - Reverse transcriptase inhibitors
    - Nucleoside: AZT (Zidovudine)
    - Non-nucleoside
  - Protease Inhibitors
    - Onset of HAART (Highly Active Anti-Retroviral Treatment)
    - ART now
  - Fusion/Attachment Inhibitors
  - Integrase Inhibitors
  - Chemokine coreceptor antagonists
  - Integrase inhibitors
  - PREP: Pre-Exposure Prophylaxis: Truvada *www.truvada.com/hcp/[illegible]
    - STI's may be on the rise among users
  - Broadly Neutralizing Antibody / Vaccine

HIV/AIDS



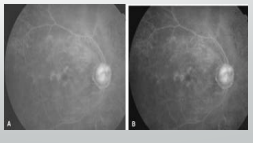
- "It's all about the patients"
  - History
    - CD4 count? Risks increase if < 200, 500: threshold for initiating ART?
    - Viral load? Amount of actively replicating HIV
      - < 500 is low / "good", Reported as "negligible"
      - Undetectable = untransmittable
      - >30,000/microliter: 18 x more likely to die of AIDS than those with undetectable viral loads
    - Treatment / Management
      - Combination agents *one pill daily constitutes a complete regimen
        - Atripla®:Tenofovir + Emtricitabine + Efavirenz
        - Trimeq®: Dolutegravir + Abacavir + Lamivudine
        - Epsicom, Trizivir, Stribild®, Complera®,Genvoya®, Odefsey®, Symfi®, Biktarvy®, Symtuza®
    - PREP
    - "Normal" life span

HIV/AIDS Optometric Considerations

- CMV Retinitis
- Non-infectious retinopathy
  - Cotton wool spots and hemes
- Herpes Zoster Ophthalmicus
- Kaposi Sarcoma
- Dry eye, conjunctival microvasculopathy, uveitis, herpes simplex ocular disease, orbital lymphoma, molluscum contagiosum, toxoplasmosis, progressive outer retinal necrosis, syphilis, TB
- Visual Fields
- How Often To See / Monitor
- 1994 vs 2018

HIV/AIDS Optometric Considerations

- Immune Recovery Uveitis
  - Without active CMVR and on potent HAART
  - Decrease vision with 2/3 of the following
    - Vitreal cells
    - ERM (Epiretinal Membrane)
    - CME (Cystoid Macular Edema)



HIV/AIDS Optometric Considerations


Case: Long Term Survivor

- 45-year-old Caucasian male
  - HIV+ for at least 20 years
  - H/O CMV Retinitis OU, treated RD OD, cataract removal OU, peripheral LP OS
  - Uses telescope OS
  - "Sketchy" hx regarding viral load, CD_4+, and meds
    - Atripla as of 2017, Valtrex currently
  - NLP OD, 20/70+ OS (-2.75-125 x 180) consistent with retinal findings
  - Band keratopathy OD
  - Sees retinal specialist annually

Tumor and Transplantation Immunology

- Cytotoxic T lymphocytes
  - Major mediators of mechanisms by which immune system kills both tumor cells and cells of tissue transplants
- Tumor Immunology
  - Immunotherapy for Cancer
    - Vaccination with tumor antigens +
    - Treatment with antibodies that block T cell inhibitory receptors
- Transplantation Immunology
  - Types of Grafts
    - **Allografts: donor and recipient same species but different from each other / corneal transplant**
    - Xenografts: different species
    - Syngrafts: same species and not different from each other
  - Major antigen targets of graft rejection are MHC molecules: allografts and xenografts

Thank You