

DISCLOSURE STATEMENT

Ron Melton and Randall Thomas are consultants to, on the speakers bureau of, on the advisory committee of, or involved in research for the following companies: ICARE, Valeant.

Course Title: **Melton – Thomas
Clinical Rounds**

Lecturer: Ron Melton, OD
Randall Thomas, OD, MPH

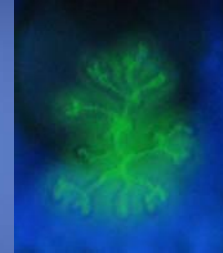
Anti-Viral Medicines

Topical

Trifluridine Viroptic
Ganciclovir Zirgan

Oral

Acyclovir Zovirax
Valacyclovir Valtrex
Famciclovir Famvir



- These are anti-herpetic drugs and are ineffective against the various adenoviral serotypes -

Finer Points to Antiviral Prescribing

- For lactose intolerant patients: valacyclovir
- For children, use the oral suspension: acyclovir
- For patients over 65, famciclovir is recommended

Reference: AAO Guideline: Herpes Simplex Viral Keratitis: A Treatment Guideline- 2014 Appendix IV. Am. Acad. Ophthal.

Herpes Simplex Keratitis

- Epithelium is primarily infected
- Also acute unilateral follicular conjunctivitis
- Affected cornea has decreased sensitivity
- Factors predisposing to prolonged healing:
 - » delay in seeking care
 - » pre-treatment with steroids
 - » infectious foci near limbus
 - » stromal inflammation
- Tx: topical or systemic antivirals

Zostavax

- Vaccine for prevention of shingles in 50 and older
- Marketed by Merck as Zostavax and is given as a single dose by injection
- Anyone who has been infected by chicken pox (more than 90% of adults in US) is at risk for developing shingles
- Contraindicated if Hx of allergy to gelatin, neomycin; Hx of acquired immunodeficiency states; pregnancy
- In landmark Shingles Prevention Study, Zostavax reduced risk of developing shingles by 51% (4 yrs of follow-up)



References: www.cdc.gov/vaccine/vpd-vac/shingles; FDA News Release, March 24, 2011 "FDA approves Zostavax vaccine to prevent shingles in individuals 50 to 59 years of age."

Zostavax Efficacy: How Long?

- "After 10 years, vaccination lost most of its power"
- "Efficacy against HZ incidence fell from 46% in year 7 to 14% in year 10 and was negligible among 1470 participants who were followed for the 11th year."
- "Vaccination at age 60 is unlikely to confer protection for the duration of a person's life."
- We foresee new public health recommendations advising re-vaccination after about 8 years. This certainly sounds prudent to us.

Reference: *Clinical Infectious Disease*. March 15, 2015.

Shingrix May Replace Zostavax®

- Shingrix is the 2nd vaccine to be FDA approved to help prevent shingles.
- Approved for people aged 50 and older
- A non-live vaccine (Zostavax is live, attenuated)
- Administered in 2 - I.M. doses (initially then 2-6 months later)
- About 90% effective and maintained over four years
- If the last Zostavax vaccine was at least 5 years ago, can have Shingrix
- Marketed by GlaxoSmithKline



Herpes Zoster Ophthalmicus

- Acute vesicular eruption of ophthalmic division of 5th cranial nerve
- Etiology: varicella-zoster virus; more common after 50 or in the immuno-compromised
- Symptoms: skin pain most common
- Ocular involvement in 50%
 - » more common - zoster epithelial lesions, anterior uveitis, stromal keratitis, episcleritis
 - » Tx: valacyclovir 1000mg tid for 1 wk; famciclovir 500 mg tid for 1 wk; acyclovir 800mg 5x d for 1 wk
 - » If ocular involvement, treat with topical steroids

IMPORTANT DRUG WARNING

- Fluoroquinolones, including AVELOX®/ CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Reference: HCNN (electronic health alerts) 10-22-08

- Fluoroquinolone therapy has been associated with possible tendinitis of the EOM's, resulting in diplopia.

Reference: Fraunfelder FW, Fraunfelder FT. Diplopia and fluoroquinolones. Ophthalmology 2009; Jul 28 [Epub ahead of print]

Fluoroquinolones (Oral)

- Broad spectrum; especially effective for organisms (not effective against chlamydia)
- Resistant bacteria continue to emerge
- Side effects: mild GI, mild HA, dizziness
- Use conservatively in pregnancy and children when benefits outweigh risks; photosensitivity warning
- Avoid Ofloxacin and Levofloxacin with theophylline
- Avoid fluoroquinolones with Coumadin
- Cipro also available once daily; available generically
- Levofloxacin (Levaquin) has replaced Cipro as "gold standard" in oral fluoroquinolone therapy

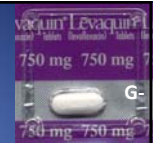


Table 1. Systemic Fluoroquinolones Available in the US

Ciprofloxacin (Cipro)	Moxifloxacin (Avelox)
Gemifloxacin (Factive)	Ofloxacin (Floxin)
Levofloxacin (Levaquin)	

1. Only available generically.

The Medical Letter, June 6, 2016

Table 2. Alternatives to Fluoroquinolones

Drug	Usual Adult Dosage ¹	Cost ²
Acute Sinusitis and AECB³		
Amoxicillin - generic	500 mg PO tid x 5-7 days ⁴	\$3.20
Amoxicillin/clavulanate - generic Augmentin	875 mg/125 mg PO bid x 5-7 days ^{4,5}	23.50
Doxycycline ⁶ - generic	100 mg PO bid ⁷ x 5-7 days	32.20
Acute Uncomplicated Cystitis		
Trimethoprim/sulfamethoxazole - generic Bactrim DS, Septra DS	160/800 mg PO bid x 3 days	1.00
Nitrofurantoin monohydrate/macrocrystals - generic Macrobid	100 mg PO bid x 5 days	25.60
Fosfomycin tromethamine - Monurol	3 g PO once	66.50

The Numbers Behind Antibiotic Use

- "More than 8 in 10 Americans received antibiotic prescriptions in 2011
- "A total of 262.5 million courses of outpatient antibiotics were prescribed in 2011
- Rate of 842 prescriptions per 1000 persons
 - » For infants (age < 2 years), children (age 3-9) and older adults (age > 65) rates actually exceeded 1000 prescriptions per 1000 persons
 - » Amoxicillin was the most commonly prescribed antibiotic among children and teenagers
 - » Azithromycin was the antibiotic most commonly prescribed among young adults
 - » Women were almost twice as likely as men to receive antibiotics
- Antibiotic prescribing rates were considerably higher in the South
- Per-physician prescribing rates were highest among dermatologists, family practitioners and pediatricians"

Abigail Zuger, MD. Clin Infectious Diseases; Open Forum Infectious Diseases. May 2015.

Antibiotic Resistance Monitoring in Ocular microorganisms (ARMOR) Study

- Prospective, multicenter, longitudinal survey of antibiotic susceptibility trends
- Participating sites in the US include community hospitals, university hospitals, and ocular centers
- ARMOR isolates:
 - » *Staphylococcus aureus*
 - » Coagulase-negative staphylococci (CoNS)
 - » *Streptococcus pneumoniae*
 - » *Haemophilus influenzae*
 - » *Pseudomonas aeruginosa*

Asbell PA et al. JAMA Ophthalmol. 2015;1-10

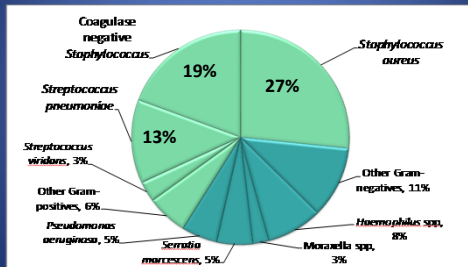
MIC₉₀ Comparisons for ARMOR Surveillance Study Isolates

	<i>S aureus</i> (n=1169)	MRSA (n=493)		CoNS (n=992)	MRCoNS (n=493)
Besifloxacin	0.25	2	Besifloxacin	0.25	4
Vancomycin	1	1	Vancomycin	2	2
Trimethoprim	2	2	Clindamycin	1	>2
Clindamycin	0.12	>2	Oxacillin	>2	>2
Oxacillin	>2	>2	Gatifloxacin	2	32
Moxifloxacin	1	16	Tobramycin	4	16
Gatifloxacin	2	16	Chlormaphenicol	4	8
Chlormaphenicol	8	16	Ofloxacin	8	>8
Ofloxacin	8	>8	Moxifloxacin	1	32
Levofloxacin	4	128	Ciprofloxacin	8	64
Ciprofloxacin	8	256	Levofloxacin	4	128
Tobramycin	1	>256	Trimethoprim	32	>128
Azithromycin	>512	>512	Azithromycin	>512	>512

Asbell PA et al. JAMA Ophthalmol. 2015;1-10

Background

- *Staphylococcus aureus*, CoNS, *S. pneumoniae*, *P. aeruginosa*, *H. influenzae* are significant causes of ocular bacterial infections¹



¹ Kowalski RP, Dhaliwal DP. Expert Rev. Anti. Infect. Ther 2005;3(1):131-9. Figure adapted from Kowalski RP, Dhaliwal DP. Expert Rev. Anti. Infect. Ther 2005;3(1):131-9.

ARMOR Data - 2017

“This latest data demonstrate that while decreases in resistance are being observed, resistance to several commonly used antibiotics continues to be a challenge.” “Understanding these resistance trends can help eye care professionals ensure that their patients are matched with effective treatments and potentially avoid sight-threatening ocular infections.”

ARMOR, now in its tenth year, is the only nationwide study that monitors antimicrobial resistance in ocular infections.

Penny Asbell, MD, lead ARMOR study author, professor of Ophthalmology at Icahn School of Medicine at Mount Sinai, and director of the Cornea Service and Refractive Surgery Center at The Mount Sinai Hospital

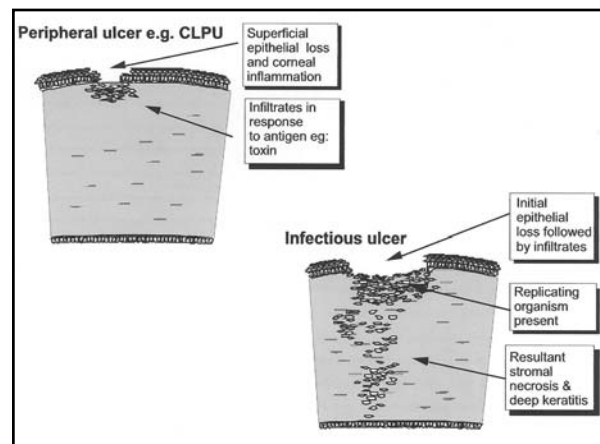
Fluoroquinolone Non-susceptibility to Staphylococcal Epidermidis

- This Bascom Palmer study was done between 1995 and 2016

Ciprofloxacin	28% - 56%
Levofloxacin	17% - 56%
Moxifloxacin	22% - 57%

- Over half of *Staphylococcus epidermidis* pathogens were resistant, in vitro, to fluoroquinolones in 2016
- Conclusion: Prescribe based on science, not habit

Stringham JD, et al. JAMA Ophthalmol 2017;135(7):814-15



Differential Diagnosis of Corneal Ulcers vs. Infiltrates

Ulcer (UK)

- ♦ Rare
- ♦ Usually painful
- ♦ Tend to be central
- ♦ 1 to 1 staining defect to lesion ratio
- ♦ Cells in anterior chamber
- ♦ Generalized conjunctival injection
- ♦ Usually solitary lesion
- ♦ Possible tear lake debris

Infiltrate

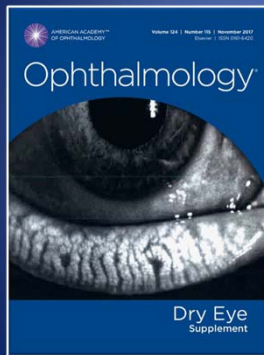
- ♦ Common
- ♦ Mild pain
- ♦ Tend to be peripheral
- ♦ Staining defect size relatively small
- ♦ Rare cells in anterior chamber
- ♦ Sector skewed injection pattern
- ♦ Can be multiple lesions
- ♦ Clear tear lake

Expert Perspective on Infiltrates

“Left untreated, marginal infiltrates generally disappear within a week or two. Ocular steroids have been shown to be the best and only recognized drug therapy for sterile marginal infiltrates, and their application will shorten the course of inflammation, regardless of causative origin. For many patients, a quicker recovery from symptoms such as redness, tearing, and discomfort is important for improving their quality of life. Steroids are often prescribed in conjunction with an antibiotic in order to decrease the chance of developing a secondary infection or corneal ulcer and to protect against misdiagnosis.”

Reference: M Abelson. Review of Ophthalmology. January 2005

Global “Ophthalmology” Perspective on Dry Eye Disease



From a Comprehensive Supplement in Ophthalmology, November, 2017.

Dry Eye Disease

- “Dry eye disease is a heterogeneous disorder of the ocular surface in which the common denominator is inflammation.”
- “Topical corticosteroids also play an important role in breaking the inflammatory cycle.” “Repeated short-term pulse therapy has produced a disease-free state for more than 1 year in a study of patients with Sjögren’s syndrome.”
- “When meibomian glands function correctly, the lipids secreted reduce ocular surface water evaporation and prevent dry eye. When these glands are reduced, absent or dysfunctional, the impact on the ocular surface can be immense.”
- “Treatment of DED is based on minimizing inflammation and optimizing various components of the tear film.”

Dry Eye Disease

- “Inflammation is one of the major targets in treating DED, and breaking the cycle of inflammation is crucial in improving symptoms. All patients DED deserve a trial of anti-inflammatory therapy at some point during their treatment.” “Corticosteroids are one of the most effective and rapid therapies available for suppressing inflammation on the ocular surface.”
- “Omega-3 supplementation is a well-tolerated therapy to improve ocular surface health in nearly all forms of DED and is generally recommended to be used for all patients with no other medical contraindications.”

Discordance Between Symptoms and Signs

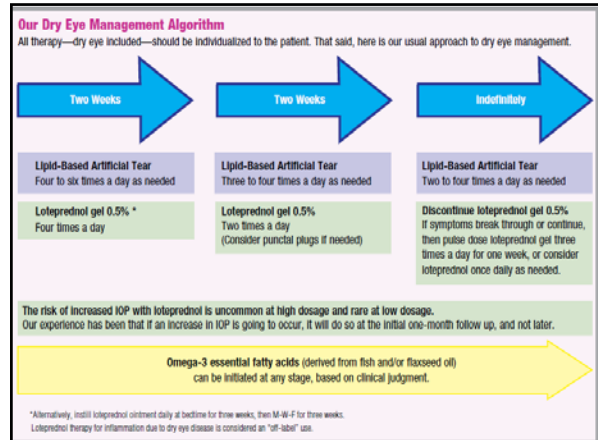
- Patients with chronic pain syndromes (CPSs) had 30% greater symptoms than signs.
- Important CPSs are irritable bowel syndrome, fibromyalgia, chronic pelvic pain and osteoarthritis.
- There is “growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, indicating neuropathic ocular pain.”
- It is thought that “patients with atopy or allergy have a sensitized ocular surface because of inflammatory processes influencing corneal nerves, which can lead to symptoms of dry eye even when the homeostasis of the ocular surface is minimally compromised.”

Ophthalmology, March 2017

Expert Perspective on DED Inflammation

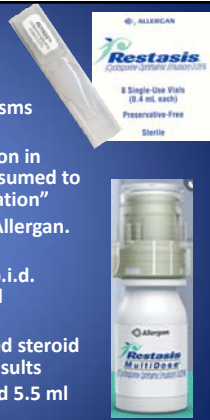
“It is now well understood that inflammation is one of the most important aspects of DED pathogenesis, and no matter the trigger, untreated or undertreated, established disease can lead to severe refractory disease. At this time, there are three topical prescription therapies available to treat inflammation in DED: corticosteroids, topical cyclosporine A and lifitegrast. Oral essential fatty acid supplementation and tetracycline-class antibiotics are also commonly prescribed for inflammatory ocular conditions, including DED.”

Sheppard J. Advanced Ocular Care, April 2017



Cyclosporine 0.05% Ophthalmic Emulsion

- Topical immunomodulator with anti-inflammatory effects – exact mechanisms unknown
- Indication: “to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation”
- Available in 0.4 ml unit dose vials by Allergan. Supplied in 30-vial tray.
- Dosage: one drop to affected eye(s) b.i.d. Usually takes 4-6 months to reach full therapeutic effect
- Concurrent treatment with ester-based steroid for the first 1-2 months may hasten results
- Available in multi-dose, non-preserved 5.5 ml bottle and unit-dose PF vials



Xiidra (lifitegrast 5%)

- Only FDA-approved drug to treat both signs and symptoms of DED
- A lymphocyte function-associated antigen antagonist
- 5%, unit-dose (0.2ml), PF, foil-pouched solution
- Dosage is approximately every 12 hours for many months or years
- Takes 2-4 weeks to achieve clinical results
- Stored at room temperature – protect from light
- Side effects seen in 5-25% of patients include instillation site irritation, taste perversion (dysgeusia), and transient blurred vision
- Marketed as Xiidra by Shire (1 carton contains 12 foil packs holding 5 unit-dose containers)



Alternative Supplementation

- Orally administered omega-3 essential fatty acids
- May take 4-6 months to obtain a significant clinical effect
- Liquid formulations are available for those patients who have difficulty swallowing large capsules.



Role of Omega 3 EFA's in DED

- 30% reduction in the risk of DED for each gram consumed per day
- Recommend: about 1000mg of EPA and about 500mg of DHA per day
- Tear film BUT highly sensitive and specific
- Onset of benefits, including hyperemia; 30-60 days
- Loteprednol .5% QID x 2 weeks reduces ocular surface inflammation
- Krill oil appears to be slightly more effective than fish oil.

Reference: Oph. January 2017

Melton-Thomas Recommendations for Dry Eye Treatment

Artificial Tears

- We recommend **Soothe XP** artificial tears. These tears contain mineral oil, which makes them more soothing for your eyes. Another good option is **Systane Balance** tears.
- Use these artificial tears 2-4 times a day (morning and evening are critical).

Warm Compresses

- Wet a washcloth with warm water and place it over your closed eyelids. Leave it there for 5-10 minutes; do this once per day.
- This will help stimulate the glands in your eyelids to produce more oil, helping to make better quality tears.

Blinking Exercises

- Close your eyes, squeeze them using your eyelid muscles, and release. Repeat these motions every 5 seconds for 1 minute. Do this one-minute exercise 4 times a day (breakfast, lunch, dinner, and bed times).
- These exercises will help your oil glands work better and will keep your eyes from drying out as much.

Fish Oil Supplements

- Take 2000 mg fish oil supplements every day.

Intranasal Neurostimulation

- FDA approved in April 2017
- Novel approach in dry eye treatment
- MOA: intranasal stimulation of tear production
- Triggers goblet cell degranulation
- Unknown: length, frequency of Tx sessions, efficacy, and duration of effect
- Marketed as TrueTear by Allergan



Neurostimulation and the Goblet Cell

- It is recognized that neural stimulation of the nasal mucosa plays a crucial role in stimulating homeostable aqueous tear production.
- Questions remaining:
 - » How long the increased aqueous or mucous tear volume lasts after a single application?
 - » How many treatment sessions per day are optimal?
- Numerous studies have found evidence of ocular surface inflammation.
- Such nasal neurostimulation might stimulate conjunctival goblet cell degranulation.
- Such an approach may be a unique feature of this therapy compared to other currently available treatments.

Gumas K, et al. Am J Ophthalmol 2017; 177:159-168

Summary

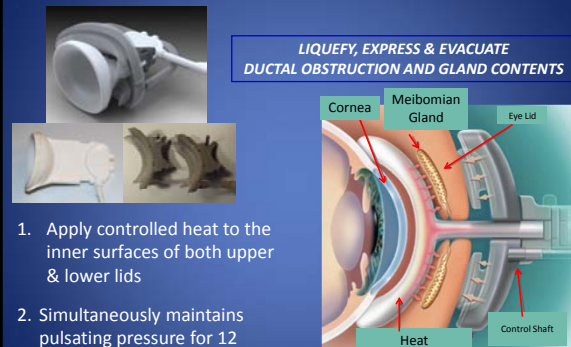
- Global consensus – MGD is the leading cause of Dry Eye
 - Chronic and progressive
 - The sequelae can be catastrophic
- Function and structure
 - A turning point for understanding MGD and dry eye and to practice both restorative treatment and prevention
- Consider MGD first – the root cause of the vast majority of all dry eye
 - DE is complex due to the infinite sequelae of MGD
 - Understanding and treating MGD is now straightforward

Progressive MGD

	Normal Function	Nonobvious MGD	Obvious MGD	Obvious MGD
Function				
Structure				

Thermal Pulsation

LIQUEFY, EXPRESS & EVACUATE DUCTAL OBSTRUCTION AND GLAND CONTENTS



- Apply controlled heat to the inner surfaces of both upper & lower lids
- Simultaneously maintains pulsating pressure for 12 minutes

Lipiflow Treatment for Contact Lens Wearers

- After a single Lipiflow treatment, contact lens wearing time was extended by 4 hours, and this benefit held for about three months, on average.
- This could be a major benefit to thousands of patients struggling with contact lens wearing comfort.

Clinical Ophthalmology, January 2018

Pediatric DED and Risk Factors: Things to Ponder

- “Multi-screen” lifestyle – major risk factor
- Vegetarian and vegan lifestyle – insufficient consumption of Omega 3 EFA’s
- Meibography revealed that about 10% of grade school children had compromised meibomian glands.
- This compromise was directly correlated to the amount of time looking at screens
- “Evaporative DED associated with smartphone use is a lifestyle disease.”

Reference: OSN, January 25, 2016

MG Scraping in Treating DES

- “In the future, the health and maintenance of the MCJ and keratinized lid margin may be considered integral to routine eye care. This shift in our culture will involve improvements in our observation skills and also the willingness to incorporate novel techniques such as debridement-scaling of the MCJ and keratinized lid margin in our clinical practice.”

Korb/Blackie. Cornea. December 2013



Lid and Lash Hygiene

- Eye care products containing hypochlorous acid .01% / .02%
- Fast-acting cleanser for lids, lashes, periorbital skin with low toxicity
- Used for blepharitis and other conditions of eyelids or eyelashes which often cause inflammation and discomfort
- Effective against broad range of pathogens usually found on the lids and lashes
- Available in variety of formulations (solution, gel, spray)



Eyelid Cleansing Treatments for Blepharitis

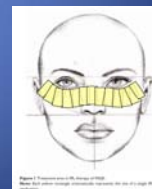
- Study compared “dedicated eyelid cleanser to diluted baby shampoo”
- Cleaning was done bid for four weeks
- Conclusion: improvements occurred with both treatments. “However only the dedicated eyelid cleanser proved effective in reducing inflammation and was the preferred therapy.”

The Ocular Surface, October, 2017

Intense Pulsed Light (IPL) Therapy

- IPL is a tx option for skin rosacea
- Studies show IPL reduces signs and symptoms of DED in patients with MGD
- Mechanism of action of IPL for DED not well understood; localized destruction of superficial blood vessels reduces inflammation associated with DED

Clinical Ophthalmology 2017:11



Doxycycline versus Azithromycin for MGD

- Patients (110) with MGD received oral azithromycin (500 mg day one, then 250 mg/d 4 days) vs one month oral doxycycline (200 mg/day) x 1 month
- After 2 months both groups significant improvement; percentage of clinical improvement better for azithromycin; less GI SE with azithromycin (4% vs 26%); azithromycin less expensive.

(Kahului MB et al. "Oral azithromycin versus doxycycline in meibomian gland dysfunction. Br J Ophthalmol. Feb 2015)

Dermatologists Prescribing for Acne

- Minocycline 44.4%
- Doxycycline 40.5%
- Azithromycin 3.2%

Reference: J Am Acad of Dermatology, October 2015

Alternative Oral Anticoagulants to Coumadin

- Direct thrombin inhibitor
 - » Pradaxa (dabigatran)
- Oral factor Xa inhibitor
 - » Xarelto (rivaroxaban)
 - » Eliquis (apixaban)
 - » Savaysa (edoxaban)

Intraocular Bleeding with Novel Anticoagulants

- Dabigatran (Pradaxa[®]), rivaroxaban (Xarelto[®]), apixaban (Eliquis[®]), edoxaban (Lixiana[®])
- Reduce the risk of intraocular bleeding by ~1/5 compared with warfarin (Coumadin[®])
- Consider for patients at risk for proliferative diabetic retinopathy, the wet forms of ARMD, etc.

Sun MT, et al. JAMA Ophthalmol, 2017;135(8):864-70

Efficacy of New Oral Anticoagulants Compared to Warfarin

- 50% fewer hemorrhagic strokes
- 25% more GI bleeds
- 10% lower all cause mortality

Lancet, December, 2013

Reversal Agents for Anticoagulants

- Vitamin K quickly reverses warfarin, a vitamin K antagonist
- Newer anticoagulants: Pradaxa, Xarelto, Eliquis, and Savaysa
- Praxbind reverses Pradaxa
- The Xa-inhibitors; Xarelto, Eliquis, and Savaysa are inhibited by Andexanet within minutes
- Andexanet is a major enhancement to the clinical usefulness of these newer anticoagulants!

Reference: NEJM. November 2015

INR: International Normalized Ratio

- A universally accepted measure of “coagulability”(clotting) behavior of blood in patients taking Coumadin® (warfarin).
- An INR of 1 is a normal, physiological clotting behavior.
- Target anticoaguable profile is an INR generally between 2 and 3.
- The higher the INR > 3, the thinner the blood thus increasing the risk of bleeding and hemorrhagic stroke.

A New App for Calculating Plaquenil Dosing

- About half of patients are overdosed
- Two somewhat competing approaches
 - » Calculating “Ideal Body Weight”
 - » Using “Actual Body Weight”
- This app known as “dose checker” blends the two approaches
- Put in the patient’s height and weight and the proper weekly dose appears
- Proper dosing is the critical step in minimizing risk of Plaquenil maculopathy

JAMA Ophthalmology, February, 2018

Perspective on Poor Plaquenil Practice

- Based on “ideal body weight calculations”, 50% of patients were overdosed (at 400 mg/day)
- At initial screening visits about 5% of patients received a 10-2 plus one objective test (usually a HD-OCT)
- Undertesting - - only a 10-2, or only an objective test (OCT, FAF, or mfERG) in about 30% of patients
- No testing occurred in 25% of Plaquenil patients!
- Amsler grid is of no value in HCQ testing, yet was done on 40% of patients.

AJO, September 2015

Perspective on Poor Plaquenil Practice

- “Retina and comprehensive ophthalmologists see a majority of the patients for HCQ screening but are appropriately screening patients less than half the time.”
- “The import of all the recent literature and our current study indicates that we are failing to provide patients proper HCQ screening, which is of particular concern given the rising detection rate of toxicity.”
- This study was done at a highly prestigious ophthalmology clinic in the midwest, and these results are nothing short of pitiful. Optometry can and should provide a much higher level of care!

AJO, September 2015

Rheumatologic Dosing of HCQ

- “Slightly more than ½ of all patients currently on treatment continue to receive excess doses.”
- Toxicity can be up to 20% in patients taking HCQ after 20 years.
- “Our findings are particularly concerning given that choosing a proper starting dose is the single safest, simplest, and most cost-effective measure available.”
- M+T: this is why it is vitally important for optometric physicians to know the science, then gently and authoritatively communicate with rheumatologists.
- “The calculation of a safe dose should be based on lean body mass, best estimated by the lesser of actual or ideal body weight.”

Braslow RA, et al. Ophthalmology 2017;124(5): 604-8.