

**Everything You Wanted to Know About
Therapeutics, But Were Afraid to Ask-
Almost**

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AREDS 2 AND U

**Age-Related Eye Disease Study (AREDS):
Rationale and Significance**

THE RESULTS

AREDS 2 The Age Related Eye Disease Study-Part 2

- **JAMA, May 2013**
- **Lutein (+) Zeaxanthin and Omega 3 fatty acids for age related macular degeneration: AREDS 2**
- **The QUESTIONS:**
 - **1. Does adding lutein (+) zeaxanthin, the Omega 3 fatty acids DHA (+) EPA or both to the original AREDS formula decrease the risk of developing advanced AMD?**

QUESTION #2

- **Does removal of beta-carotene or reduction in the amount of zinc increase the risk of developing AMD**

QUESTION #3

- **JAMA, JULY 2013**
- **Does L/Z supplementation affect the rate of cataract surgery or cataract associated vision loss?**

The Bottom Line on ARMD/AREDS 1

- DON'T BE Northern European
- DON'T GET OLDER
- DON'T SMOKE
- DON'T GIVE SMOKERS ANTIOX
- CONTROL VASCULAR DISEASE RISK FACTORS
- SUPPLEMENTS DON'T REPLACE A BAD LIFESTYLE

Re-interpretation of results at ARVO 2013 by lead investigator, Emily Chew et al

- Adding omega 3's to AREDS: **No benefit**
- Adding L/Z to AREDS and evaluating the effect on the total cohort (study population)
 1. L/Z reduced advanced AMD by 10%
 2. Neovasc. AMD 11%
 3. Neovasc AMD 26% in low L/Z diets
 4. Cataract progression 30% in low L/Z diets
 5. Beta carotene doubles risk of lung cancer in all participants, 0.9% VS 2% W-BC
 6. **GIVE 'EM A CENTRUM SILVER**

**Ester is NOT your Jewish aunt-It's a
new approach to disease
management**

- **It's about time we had a
better anesthetic than
proparacaine**

Proparacaine-A good anesthetic for the central cornea, but not much else.

Problems:

Efficacy

**No limbal or
conjunctival
coverage**

Allergy

Name the best AMIDE anesthetic for LASIK, topical cataract surgery and lacrimal procedures.

- **1. Proparacaine**
- **2. Tetracaine**
- **3. Lidocaine**
- **4. Cocaine**
- **5. Benoxinate**

- **THINK AMIDES, NOT ESTERS**

Topical Lidocaine is a BETTER anesthetic

- **BENEFITS:**
- **NO CROSS SENSITIVITY**
- **EFFICACY ON VASCULAR TISSUE**
- **NO LOCAL METABOLISM**
- **LONGER LASTING**

Available dosage forms

- **50cc bottle 4%-can be autoclaved**
- **3.5% ophthalmic gel**
- **No preservatives**

Epithelial defects-no problemo

- **Better patching**
- **Bandage lenses**
- **Corneal micropuncture**
- **Doxycycline??**
- **Steroids??**
- **Vitamin C**

Clinical Pearl#2: Don't try to Patch Without It

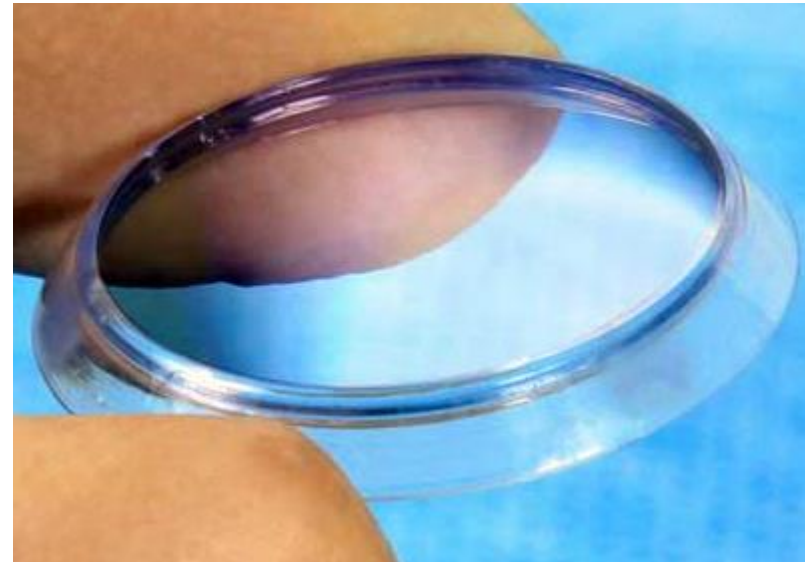
- **Proper technique requires that the patient NOT be wrapped like a mummy with tape.**
- **Do not attach tape to nose, ears or glasses**
- **One touch technique**
- **Requires adhesive-Tincture of benzoin compd.**

FIRST: HEAL IT

Bandage CL

8.4 BC

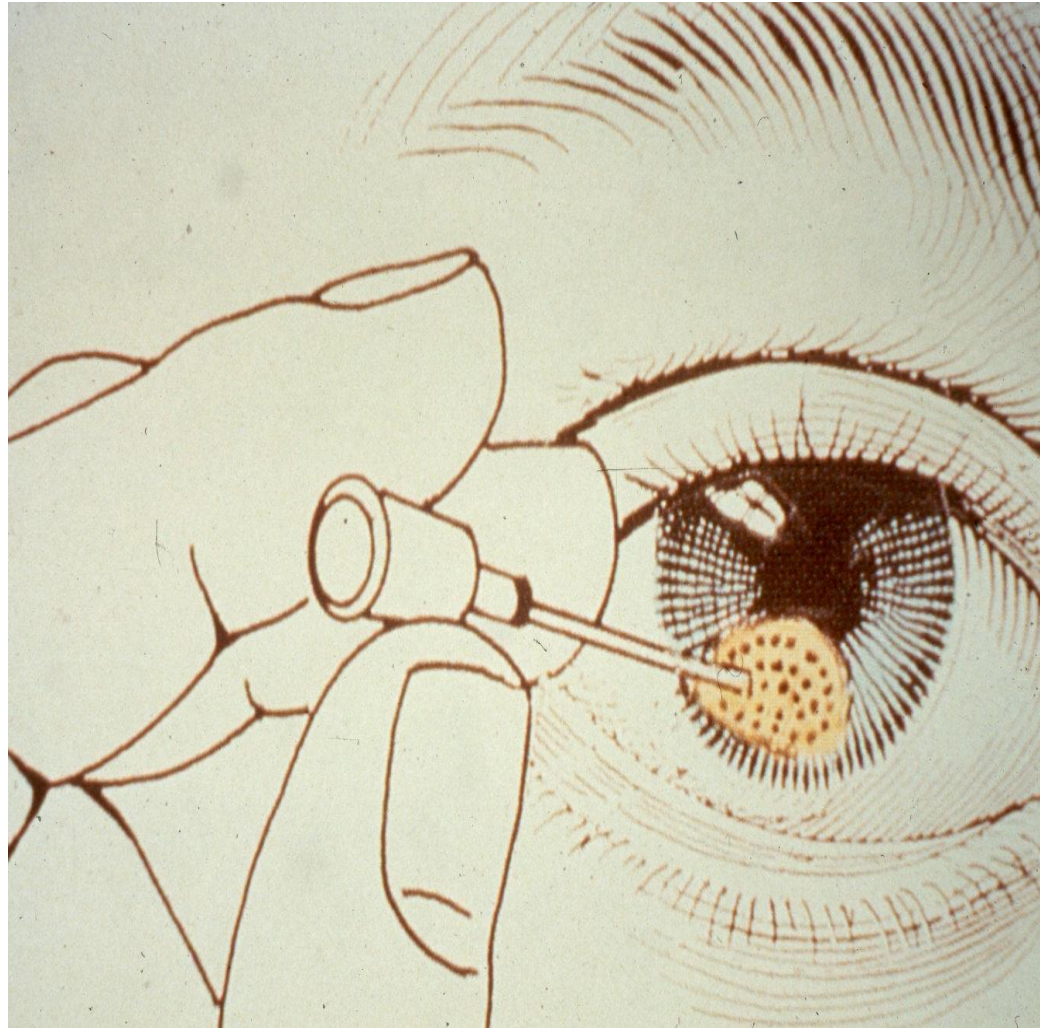
- Amniotic membrane on a scaffold ring
- Functions as a bandage lens
- Healing properties?
- COST = \$900
- REIMBURSEMENT = \$1,400



SECOND: KEEP IT HEALED

- **PEARL: Think Doxycycline (50mg BID)**
- **Watch out for smokers-Vitamin C (1-2gm/D)**
- **SALT OINT, NOT SOLUTION**

THIRD: If it don't heal-POKE IT WITH A SHARP STICK



PAIN MGT OPTIONS: Oxycodone, The “BIG GUN”

- **With ASA = Percodan**
- **With APAP = Percocett**
- **Schedule II drug = High abuse**
- **Better alternative with a
schedule III drug**

That all fine and good butttt:

- My Patients a drug abuser
- My Patient's allergic to opiates
- I CAN'T prescribe Narcotic agents
- I don't want to prescribe narcotic agents
- My patient doesn't want to use dope

Know your “ABC’s” of OSD

- **A = ALLERGY**
- **B = BLEPHARITIS**
- **C = KERATO- CONJUNCTIVITIS SICCA**

Management of Dry Eye

- **How do YOU spell D-R-Y E-Y-E**
- **Ocular surface disease is a serious business**
- **Chronic condition**
- **Multiple dry eye factors**
- **Mild to severe presentations**

Key(s) to managing dry eye?

- **1. ASK and QUANTIFY (SX's)**
- **DO YOU HAVE DRY EYE?**
- **HOW BAD IS IT?**

OCULAR SURFACE DISEASE INDEX (OSDI)

3 question sets

- First set: Symptoms
- Second set: Function
- Third set: Environment
- Scaled from (0) to (4)
- Allows us to quantify and objectify subjective data

OCULAR SURFACE DISEASE INDEX (OSDI)

Please Answer The Following Questions by Checking The Box That Best Represents Your Answer
Have you experienced any of the following during the last week:

		4)	time 3)	time 2)	time 1)	0)
1	Eyes that are sensitive to light?					
2	Eyes that feel gritty?					
3	Painful or sore eyes?					
4	Blurred vision?					
5	Poor vision?					

SX

Have problems with your eyes limited you in performing any of the following during the last week:

		All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6	Reading?						
7	Driving at night?						
8	Working with a computer or bank machine (ATM)?						
9	Watching TV?						

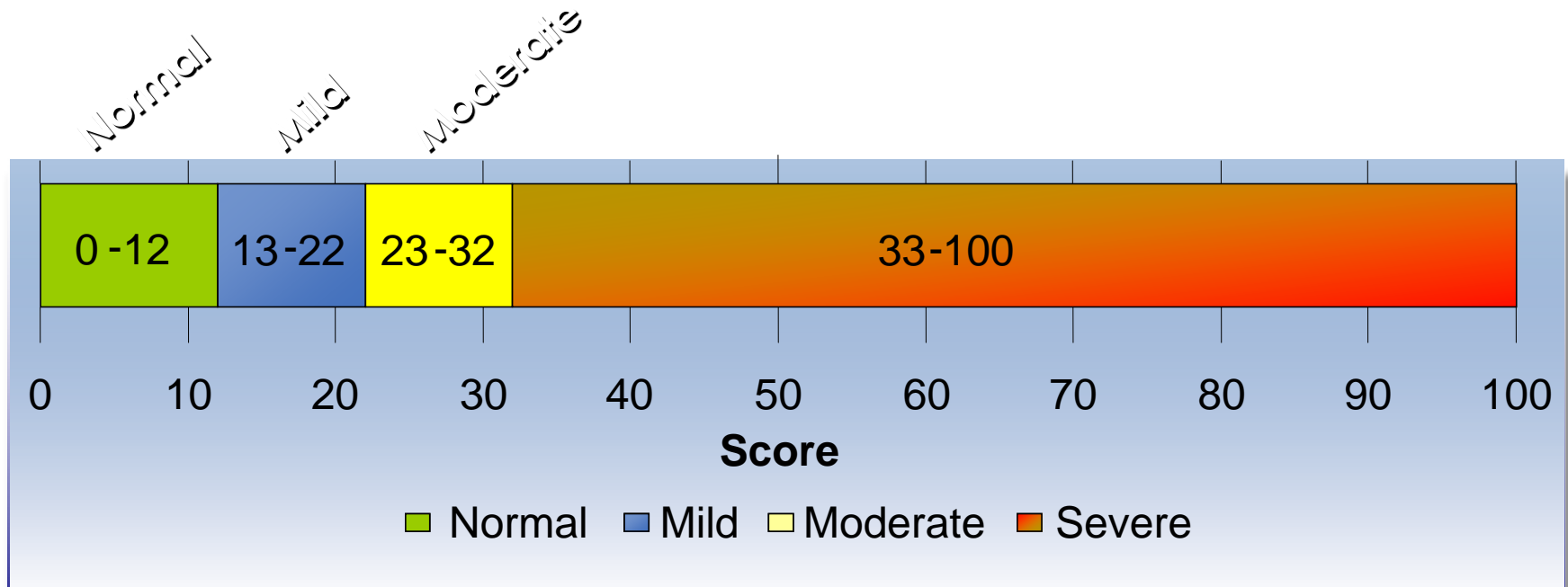
Activities

Have your eyes felt uncomfortable in any of the following situations during the last week:

		All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10	Windy conditions?						
11	Placed or areas with low humidity (very dry)?						
12	Areas that are air conditioned?						

Environment

OSDI Severity Grading



Total OSDI Score =

$$\frac{(\text{Sum of Score for All Questions Answered}) \times (25)}{(\text{Total \# of Questions Answered})}$$

Key(s) to managing dry eye?

- **2. FIND THE CAUSE:**
- **DRY EYE IS A COMPLEX DISEASE!**

Key(s) to managing dry eye?

- **2. OBJECTIVELY STAGE THE DISEASE (SIGNS)**

Key(s) to managing dry eye?

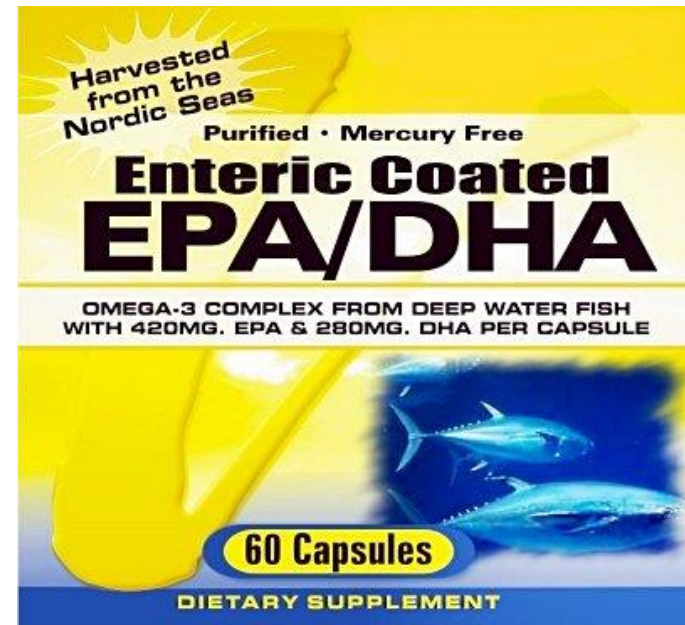
- **3. SELECT THE PROPER TX**
- **ACUTE VS CHRONIC**
- **APPROPRIATE FOR TYPE**
- **STEP THERAPY**

The Sjogrens patient

- Starts with a bad cornea and serious aqueous deficiency
- Acute and chronic disease
- TX?

DRY EYE: THE NEW WAY

- Mucomimetic drop/bandage CL?
- OMEGA 3 : DHA / EPA
- Anti-inflammatory: Steroid induction/Cyclosporin A/Xibrom?
- Punctal occlusion
- Evoxac (Sjogrens)



Evoxac: New and improved pilocarpine

- **Parasympathomimetic**
- **Better tolerated**
- **30mg TID**
- **No titration necessary-maybe**
- **NEVER in asthmatics**



Herpes simplex and dry eye: Scoper study

- Dry eye patients
- Thermal punctalplast
- Topical cyclosporin A
- 3 groups:
- Punctalplasy
- Acyclovir
- Both



Results

- **Non-treated group: 6-7 months of disease/yr**
- **TX with EITHER thermal cautery or topical cyclosporin: 1.1 months/yr of active diSease**
- **TX with both: 0.8 months/yr**

- **Learning point:**

- **OSD patients with H. simplex require aggressive management**
- **Topical cyclosporin A is safe and effective in H. simplex patients**

Prevent Evaporation

- **USE MAYONNAISE or something like it**
- **Refresh ENDURA: OLD**
- **SOOTHE XP/Systane Balance: NEW**

OLD MYTH'S

- **Blepharitis is curable**
- **Staph exotoxins produce the inflammation**
- **Ointments are the best TX**
- **SCRUB your troubles away**
- **Patient's love complex expensive treatments**
- **All tetracyclines are the same**
- **There is no substitute for tetracycline**

**Staph epidemidis DOES NOT
produce exotoxins, but it does
produce a complex organic
molecule:**

OH-POO=POO

LIPIDS (+) LIPASE = FATTY ACIDS

(STAPH POO)

RESULTS: Doxycycline significantly decreased IL-1beta bioactivity in the supernatants from LPS-treated corneal epithelial cultures. These effects were comparable to those induced by the corticosteroid,

CONCLUSIONS: Doxycycline can suppress the steady state amounts of mRNA and protein of IL-beta and decrease the bioactivity of this major inflammatory cytokine. These data may partially explain the clinically observed anti-inflammatory properties of doxycycline. The observation that doxycycline was equally potent as a corticosteroid, combined with the relative absence of adverse effects, makes it a potent drug for a wide spectrum of ocular surface inflammatory diseases.

Microbial keratitis trends following refractive surgery: Results of the ASCRS infectious keratitis survey and comparisons with prior ASCRS surveys of infectious keratitis following keratorefractive procedures

Renée Solomon, MD, Eric D. Donnenfeld, MD, Edward J. Holland, MD, Sonia H. Yoo, MD, Sheraz Daya, MD, José L. Güell, MD, Francis S. Mah, MD, Stephen V. Scoper, MD, Terry Kim, MD

In 2008, the American Society of Cataract and Refractive Surgery (ASCRS) surveyed its 9121 United States and international members to evaluate the changing trends and incidence, culture results, treatment, and visual outcomes of infectious keratitis following keratorefractive procedures worldwide. This paper presents and analyzes the results with comparisons to the data in surveys conducted in 2001 and 2004. Nineteen infections were reported by 14 surgeons who had performed an estimated 20 941 keratorefractive procedures, an incidence of 1 infection in every 1102 procedures. Sixteen cases presented in the first postoperative week, 1 case during the second week, 1 case between the second and fourth weeks, and 1 case at 1 month or later. The 16 cases that presented in the first week were diagnosed at initial presentation. The most common organism cultured was methicillin-resistant *Staphylococcus aureus* (MRSA). Microbial keratitis following refractive surgery is an increasingly recognized sight-threatening complication.

**Survey #1
2001**

**Survey #2
2004**

**Survey #3
2008**

- | | |
|---|--|
| <input type="checkbox"/> 8600 Surveys | ▪ 9129 Surveys |
| <input type="checkbox"/> | |
| <input type="checkbox"/> RESPONSE: | ▪ RESPONSE: |
| <input type="checkbox"/> 56 docs reported
116 infections | • 46 docs
reported
48 infections |
| <input type="checkbox"/> Approx 340K
procedures | ▪ 100K
procedures |
| <input type="checkbox"/> Incidence 1/3K | ▪ Incidence 1/2K |

Dominant Pathogens

- ◎ 2001: Mycobacteria 48%
- ◎ 2004 GR (+) Staph/Strep sp
- ◎ 2008 MRSA 28%

2008

EARLY INFECTIONS (2 WEEKS POST-OP)

- STAPH (MRSA AND NON-MRSA}
- STREP

LATE INFECTIONS (> 2 WEEKS)

- MYCO (NON-TB)
- NOCARDIA
- FUNGAL (NOTE, 9-19%!!)
PRK AND STEROIDS!!

Risk factors

- **SURGERY**
- **EPITHELIAL DEFECTS**
- **EXCESSIVE SURGICAL MANIPULATION**
- **INTEROPERATIVE CONTAMINATION (ICE)**
- **DELAYED RE-EPITHELIALIZATION**
- **STEROIDS**

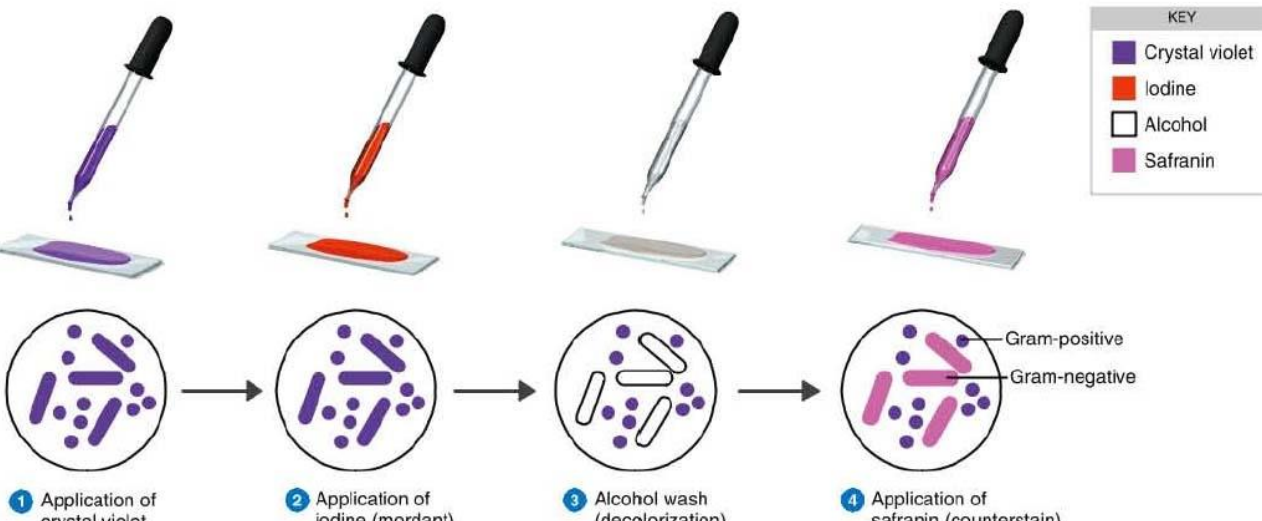
INCIDENCE BY PROCEDURE

- **% OF TOTAL PROCEDURES**
- **PRK 20%**
- **LASIK c KERATOME 50%**
- **LASIK/FEMPTOSEC. 28%**

- **2.5 X > c PRK VS KERATOME**
- **6 X > c PRK VS FEMPTOSEC**
- **2.4 X > KERATOME VS FEMPTO**

MANAGEMENT

- CULTURE CULTURE CULTURE
- SENSITIVITIES
- GRAM STAIN
- LATE INFECTIONS R/O FUNGAL



TREATMENT

ONLY AFTER LIFTING FLAP, SCRAPING AND CULTURING

EARLY

1. Irrigate flap with vancomycin 50mg/cc
2. 4th gen FQ Q 5MIN X 3 DOSES, THEN Q 30MIN ATC
3. ALT WITH VANCOMYCIN 50MG/CC Q 30MIN ATC
4. DOXY 100MG BID PO

LATE

1. IRRIGATE FLAP WITH AMIKACIN 50MG/CC OR CLARITHROMYCIN 10MG/CC OR AZITHROMYCIN 2MG/CC
2. 4TH GEN FQ Q 5MIN X 3, THEN Q 30MIN ATC
3. ALT WITH AMIKACIN 50MG/CC ATC
4. DOXY 100MGBID PO
5. MYCOPLASMA-4TH GEN FQ
6. R/O FUNGUS AND AMEBIC

For MRSA-Forget the Fluoroquinolones

Back to the OLD Drugs

- Trimethoprim (not just for kids)
- Tobramycin
- Vancomycin

Azithromycin injectable

◎ $500/X = 2\text{mg}/1\text{cc}$

◎ $2X = 500$

◎ $X = 250\text{CC solution}$

Allergy, So What? What's the big Deal??

- **Financially it IS a BIG DEAL!**
- **Billions of lost productivity**
- **Billions on treatments**
- **Lost revenue on CL fits**
- **Extra chair time**
- **Allergy is not a problem, it is an opportunity**
- **Patients doctor shop to find someone that has a strategy to control their SX**

THE TRICK TO SUCCESSFUL MANAGEMENT OF A CHRONIC ILLNESS?

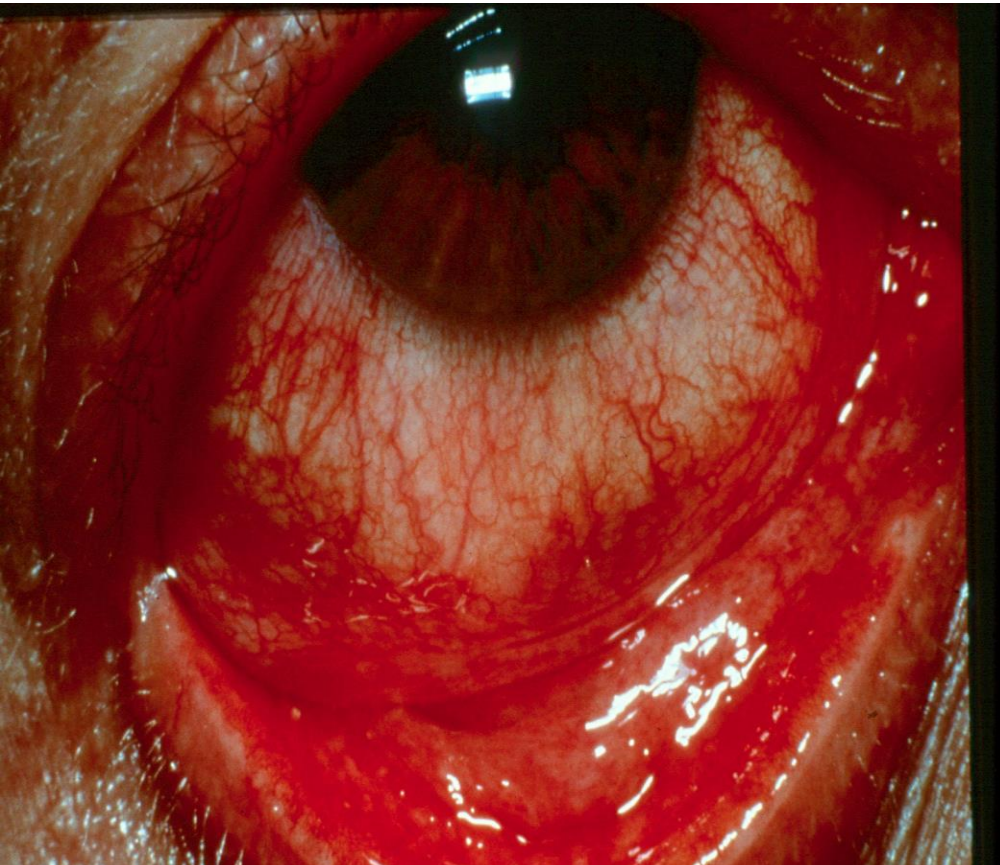
- **THE PATIENT MUST KNOW THEY CAN'T BE CURED**
- **THE DOCTOR MUST KNOW THAT THEY CANNOT CURE THE PATIENT**
- **STAGE THE DISEASE**
- **PICK A TREATMENT THAT FITS THE LEVEL OF DISEASE**
- **BE AGGRESSIVE WHEN NECESSARY**

So, What's New?

- **Better understanding of immune mechanisms**
- **User friendly, “multi-tasking drugs”**
- **Safer, more effective therapy**
- **Better understanding of disease means better patient counseling**

THE MAJOR PLAYERS

1



- **Histamine: Immediate hypersensitivity reaction; Itching, swelling and hyperemia**
- **Primarily seen in seasonal allergy**
- **No permanent tissue damage- minimal inflammation except in extreme cases**

THE MAJOR PLAYERS

2

- **Eosinophils-Nasty little WBC's full of "ACID" (Major basic protein)**
- **Attracted by release of PAF (platelet activating factor) and ECF (Eosinophilic chemotactic factor)**
- **Produce permanent tissue changes seen in VKC and GPC**

I thought Restasis was only for dry eye

- **May have value in Vernal/AKC (concentration)**
- **T cell modulating agent**
- **Equivocal results in studies**
- **Potential as a steroid sparing agent**

THE MAJOR PLAYERS

3

- **PRODUCTS OF ARACHADONIC ACID DERIVED FROM THE MAST CELL MEMBRANE**
- **PROSTAGLANDINS**
- **LEUKOTRIENES**
- **STIMULATE LATE PHASE T-CELL RESPONSE SEEN IN AKC AND GPC**

ASK YOURSELF THE FOLLOWING QUESTIONS

- **What am I treating-a histamine response or an inflammatory response?**
- **What is the severity (stage) of the disease?**
- **What do I start treatment with and what is the best maintenance therapy?**

IT DOES IT ALL -SAFELY?-

- **Extremely effective**
- **Anti-inflammatory**
- **Cures everybody**
- **Fewer side-effects-“soft steroid”**
- **How long do I use it for??**
- **Maintenance drug??**

ARE THERE TOPICALS BESIDES THE EYE DROPS YES OH HAIRY NOSED ONE

- **Do what allergists do**
- **Nasal sprays before orals**
- **Mast cell inhibitors or long acting steroids**
- **Safe**
- **Effective**
- **Synergistic with eye drops**
- **Safer than orals**

Oral antihistamines should be avoided in contact lens patient due to their _____ side-effects

- **1. Parasympathetic**
- **2. Cholinergic**
- **3. Parasympatholytic**
- **4. Anticholinergic**
- **5. Sympathetic**

Oral antihistamines should be avoided in contact

• lens patient due to their _____ side-effects

• 1. Parasympathetic

• 2. Cholinergic

• 3. Parasympatholytic @ @ @ @ @

• 4. Anticholinergic @ @ @ @ @

• 5. Sympathetic

**Never TX systemically
when topical therapy is
safer and more effective
Anticholinergic is a bad
word**

Allegra

Indications/Dosage forms

- **Indications:**
- **Seasonal allergy not responsive to topical or nasal therapy**
- **Dosage forms:**
- **60mg tablets-Adults BID**
- **Kids: 30mg tabs BID**
- **180mg SR once daily for adults**
- **Zyrtec and Claritin: Adult dose = Kids dose for 6 y/o and above@@@@**

Allegra

- **Non-sedating anti-histamine**
- **Good efficacy**
- **Minimal drug interactions**
- **No fatal interactions with erythromycin or ketaconazole (Seldane and Hismany)@@@@**
- **Dose can be titrated**

How about ocular anaphylaxis?



our lipids

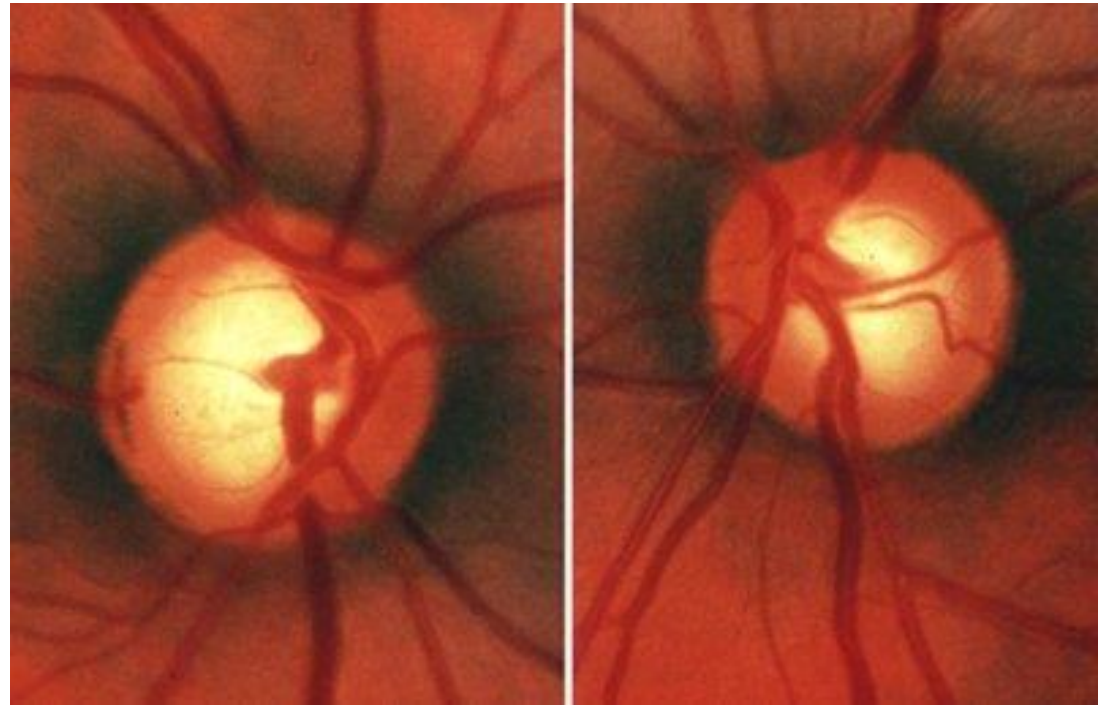


Singulair

- Leukotriene inhibitor
- No anticholinergic side-effects
- Safe in kids
- Once daily
- Lots of dosage forms:
- 4 and 5mg chewable tabs
- 4mg granules
- 10mg tablet



THE PHARMACOLOGY OF GLAUCOMA-The New Paradigm Evidence based medicine is in



The impact of clinical research on current glaucoma management

- **Who we treat and who we watch**
- **Initial drug selection/ maximizing drug combinations / max medical therapy**
- **How we (most accurately) assess disease progression**
- **The relationship between IOP and BP in GLC patients**
- **Evaluating and resolving similar studies with differing outcomes (sponsor bias?)**

Topics to be covered

Determining risk of developing glaucoma

Determining risk of glaucoma progression

**Identification and prioritization of new
glaucoma risk factors**

New drug selection criteria

Live and die by studies-both good and bad: Evidence based GLC management

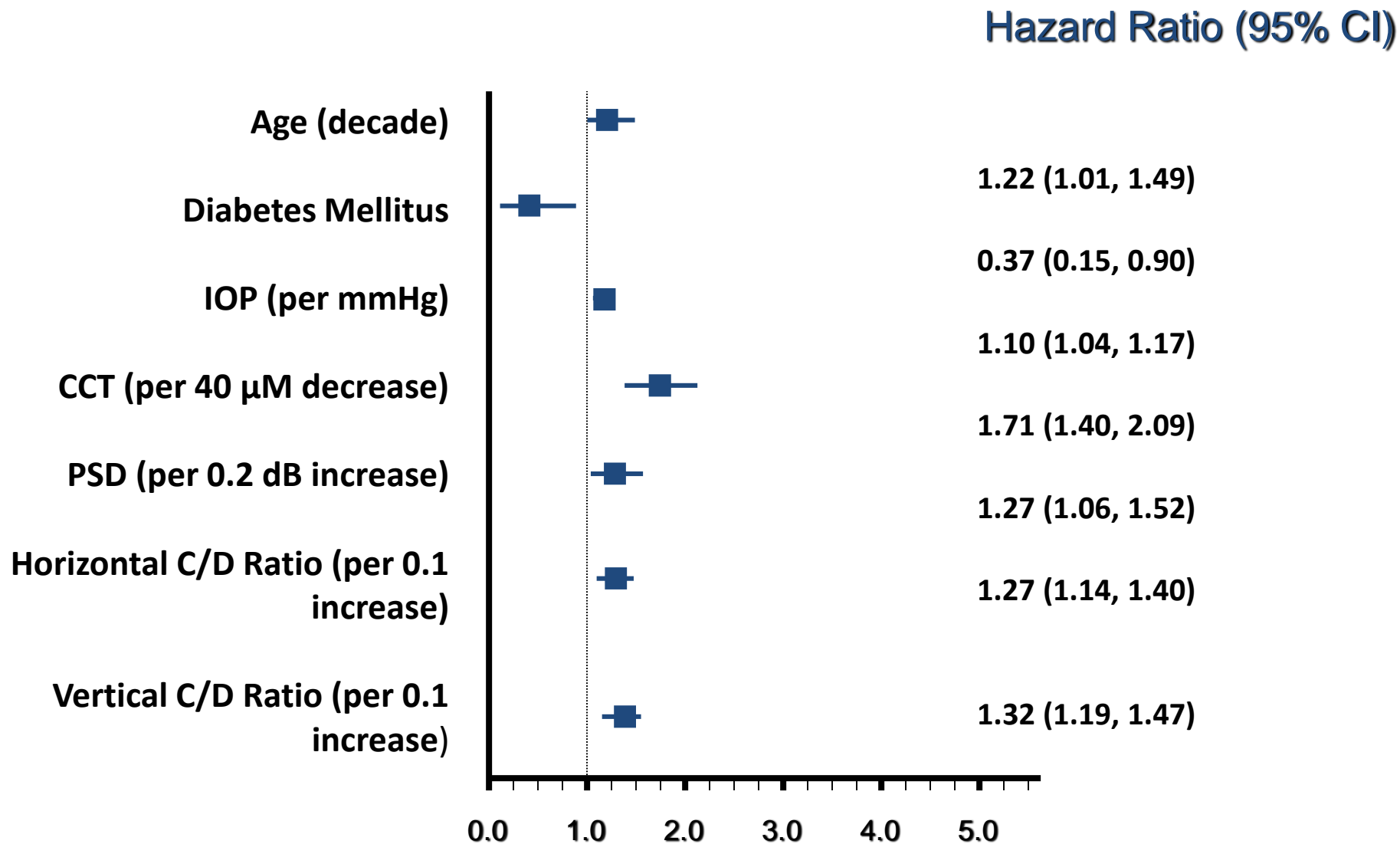
- **OHTS**
- **EMGT**
- **AGIS**
- **ASRANI**
- **NTG**
- **LALES**
- **DPP**

How have they altered our approach to glaucoma?

A NEW standard of care?

The lawyers say yes

Significant Baseline Predictive Factors from Multivariate Proportional Hazard Models



**I'm a clinician, so let's talk patients
TWO Patients (a priest and a lawyer) with the
same med HX walk into a bar**

- **54 Y/O WT M presents for general exam/DM eye evaluation**
- **FM HX DM, HTN**
- **FM EYE HX-NEG**
- **Patient Med HX:**

Type II DM X 5 Yrs-A1-C = 7

BP controlled with TX = 125/65

Lipitor for elevated lipids

- **No allergies**

Significant eye findings

- IOP's: 26/24@
9AM
- C/D: 0.5/0.5 OU
- VF: 30-2

NML VF's & Discs c elevated
IOP's.....TX??

Hold the thought

Back to our ocular hypertensive patient'- (s)

- **Guy #1: Pachymetry = 595/600**
- **Risk of conversion to GLC in 5 years = 2 - 6% monitor**

- **Guy #2 Pachymetry = 495/501**
- **Risk = 17 – 36% TREAT**
- **OHTS Individualizes risk**

EMGT-Early Manifest Glc Trial (NEI and Swedish Res. Council-Anders Hiejl 2002)

- 6 year study of TX VS non-TX of early glc patients with IOP \leq 30 and minimal VF defect N = 255 TX: Betaxolol and ALT-AVG 25% drop in IOP**
- TX lowered risk of progression by 10%/mm drop in IOP-**
- TX lowered early damage seen in control group**
- Risk increased with higher IOP, greater field defects, exfoliation and recurrent disc heme**
- First sign of progression VF-86%, Disc change 1%, Both 13% / NNT = 6**

Risk factors for progression

- **Treatment halved the risk of progression**
- **Risk lowered by 10% with each 1.0 mm of Hg reduction from baseline to the first visit at 3 months**
- **First IOP at 3 months' visit**
- **Progression occurred earlier (48 months) in untreated versus treated group (66 months)**
- **Percent of patient follow-up visits with disc hemorrhages was directly related to progression**

OK, OK-The OHT's and EMGT Study proved that lowering IOP is important in reducing the risk of:

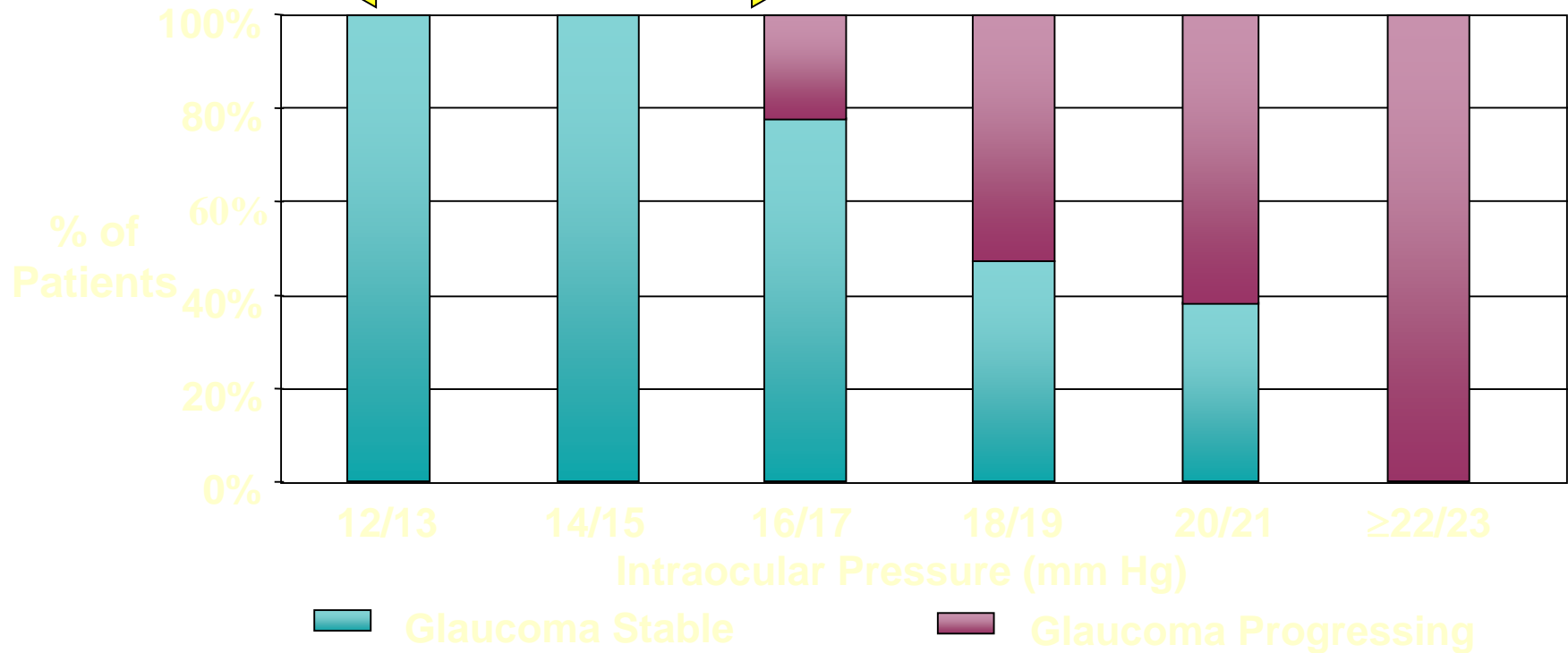
- 1. Oc. Hypertensives developing GLC**
- 2. Early GLC patients losing Vision (VF)**

How low do we go?

<18

YOU GOT A BETTER NUMBER?

Lower IOP Stabilizes Glaucoma Progression



Additional Support (AGIS):

“The AGIS data support the suggestive evidence from earlier studies that achieving low levels of intraocular pressure slows the progression of glaucomatous optic neuropathy”

Adapted from: Mao LK, et al. *Am J Ophthalmol* 1991;111:51-55.
(AGIS):7 *Amer Jrl Ophthalmol* 2000;130(4):429-440

LALES Study

C/D Ratio as screening tool

- **Los Angeles Latino Eye Study**
- **Comprehensive evaluation for predictors of eye disease in this population**
- **6,357 latinos over 40Y/O**
- **Vertical C/D > 0.6 cutoff for glc screening**
- **92.3% sensitive for glc**
- **95.3% specificity for glc**

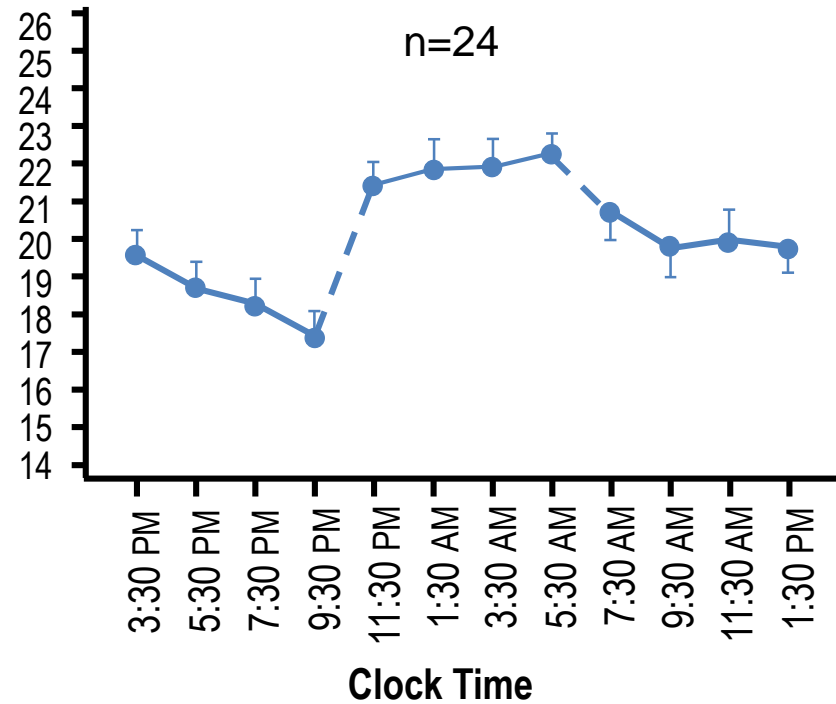
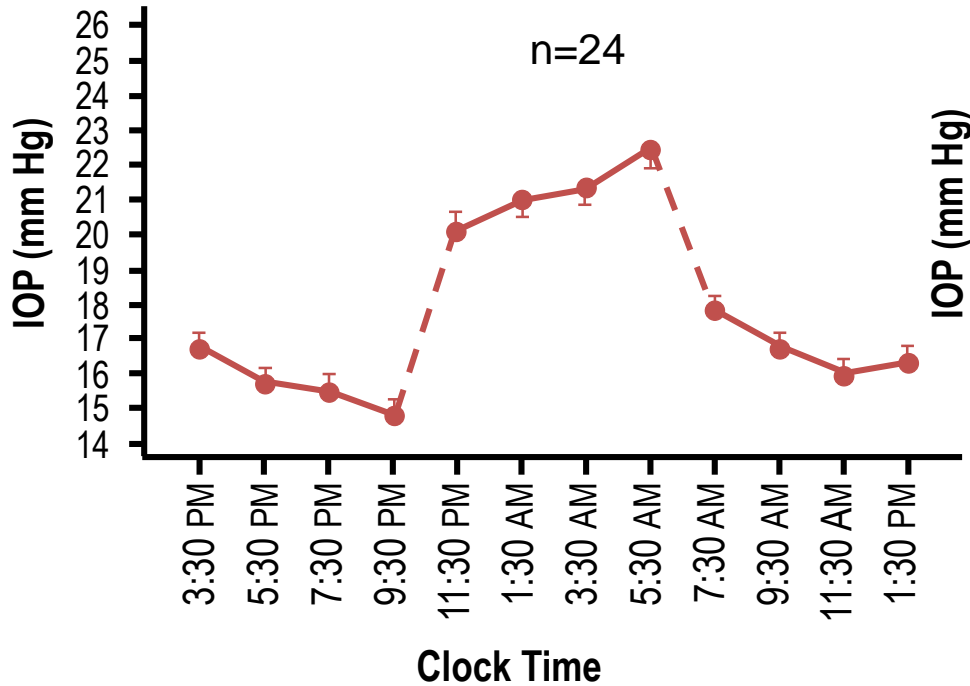
IOP Is Higher at Night (US)

● Healthy habitual IOP

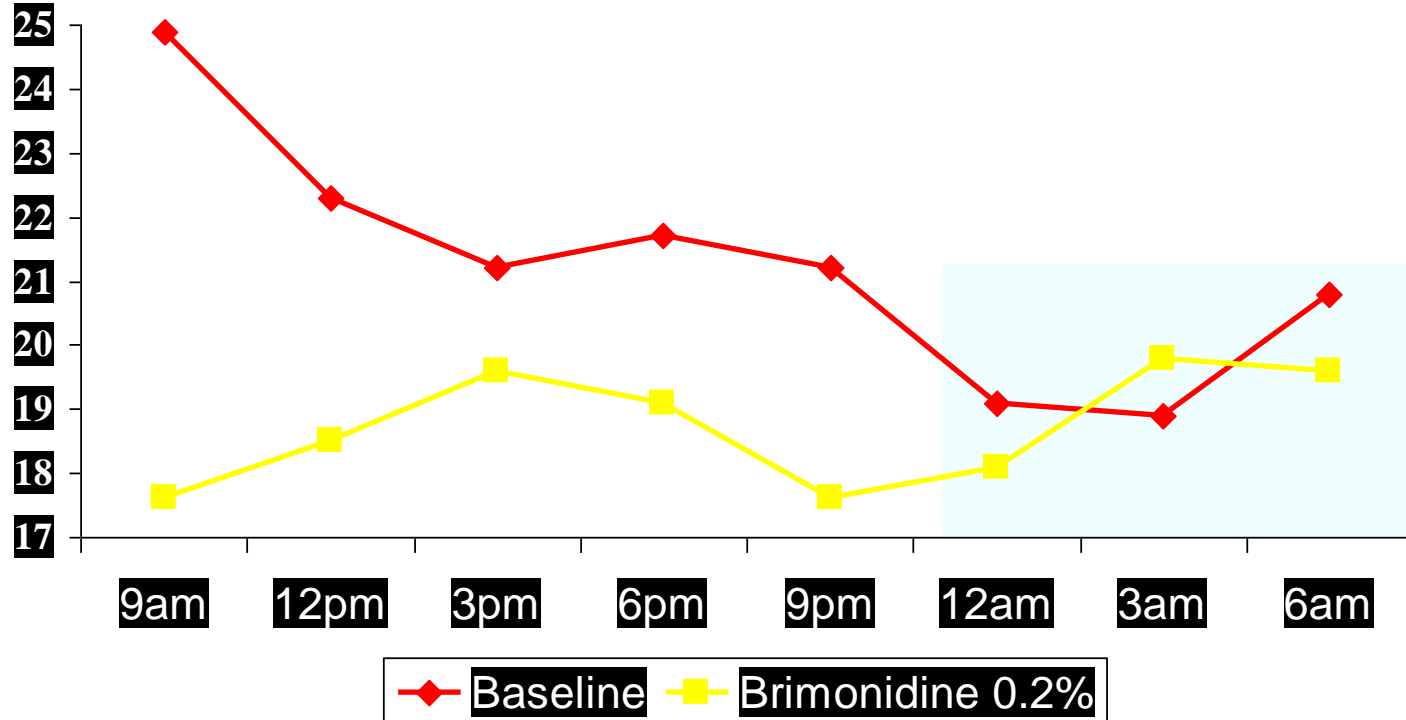
● Glaucoma habitual IOP

Diurnal Sitting Nocturnal Supine Diurnal Sitting

Diurnal Sitting Nocturnal Supine Diurnal Sitting



Brimonidine 0.2% minimally effective at night



Prostaglandins-Wonder Drug!! Yes, But.....

- **Lowers IOP up to 33%**
- **Produces red eye and darkens the iris**
- **HA, Herpes, CME, IRITIS**
- **Watch out for unpublished adverse effects**

CAI's: Azopt VS Trusopt

- **Remember your pharmacokinetics!!!!**
- **Stinging solution VS no sting suspension**
- **Equal efficacy and dosage**
- **Azopt is BID**
- **Trusopt is TID**
- **CAI's best with prostaglandins**

REASONS FOR TREATMENT FAILURE

- **Adverse drug effects/
contraindications**
- **Too many drugs**
- **Efficacy (even at night)**

THE NEW GLAUCOMA PARADIGM

- **AVOID REDUCED PERFUSION PRESSURE**
- **MUST WORK ON IOP DURING SLEEP**
- **START WITH A PROSTAGLANDIN**
- **ADD A CAI**
- **GET 3 FOR THE PRICE OF (2) COSOPT OR COMBIGAN**