

ALL WASHED UP: CORNEAL MYTHS & MISCONCEPTIONS:

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Course description: This course debunks and demystifies some of the common fears and misconceptions regarding care of the cornea and anterior segment. Included are discussions of steroid use, topical antibiotics, contact lens wear, and dry eye management.

Myth # 1: *“You can never use steroids with bacterial keratitis or other bacterial infections.”*

- **Bacterial Keratitis: Pathophysiology**
 - Breakdown of corneal defenses (dry eyes, corneal trauma, corneal hypoxia, etc.)
 - Introduction of pathogen (corneal abrasion mismanagement, contact lenses, etc.)
 - Proliferation of organisms and release of toxins and proteolytic enzymes
 - Toxic (infectious organism) and mechanical (stromal lysis) antigen-antibody reaction
 - Prostaglandin- IgE release
 - Vasodilation and vasopermeability
 - Stromal edema (splitting of stromal collagen lamellae sheets)
 - Cellular transudation and emigration
 - Infiltration
 - Phagocytosis of organisms with proteolytic enzyme release and stromal lysis
 - Antigenic neutralization (hopefully)
 - Cicatrization (fibroblastic proliferation of scar tissue)
 - Visual loss

- **Bacterial keratitis: management**
 - Broad spectrum antibiotics
 - Ciprofloxacin (Ciloxan) ii gtt Q15min X 6hrs, then ii gtt Q 30min X 18 hrs.
 - Ofloxacin (Ocuflox) Q30 minutes while awake, and then BID at night is as effective as fortified antibiotics.
 - Levofloxacin (Quixin, IQUIX)?
 - New alternatives: Vigamox (Moxafloxacin); Zymar (Gatifloxacin) hourly
 - While the new 4th generation FQ's are now the mainstay of treatment for most practitioners, they are not yet FDA approved for bacterial keratitis
 - Upon **stabilization**, the use of topical corticosteroids (e.g., Lotemax, Vexol, Pred-Forte Q1-2h while awake) is indicated.

- Reasons:
 - Antibiotics will suppress the organism.
 - Steroids will suppress the corneo-toxic inflammatory reaction.
- When is the patient considered stable?
- Negative cultures
- Non-progression of the ulcer
- Antibiotics today are extremely effective at sterilizing an eye.
- Avoidance of steroids due to fear of possible organism replication is antiquated thinking. Research (Carmichael et al, British Journal of Ophthalmology, 1990) has shown that, if an appropriate antibiotic is empirically employed, then concurrent use of a steroid will not enhance organism replication.
- Bacterial ocular infections initiate an inflammatory response as the organism and waste products are antigenic to the eye.
- Antibiotics will only remove the antigen, but will do nothing to suppress the inflammatory response.
- Anti-inflammatories must be employed in order to address inflammation. Antibiotic therapy alone is under-management.
- Concurrent use of a steroid with antibiotics is more optimal management.
- Best to use at 24-48 hours after initialization of antibiotic therapy, while the cornea is still ulcerated
 - Waiting for re-epithelialization diminishes the beneficial effects of steroids

Myth # 2: “Corneal non-healing is a sign of antibiotic failure.”

- Recognize the crucial point in the management of a case where the therapy becomes more damaging than the disease.
- In most cases of ocular infection, the invading organism is rapidly eradicated, especially in light of the great clinical efficacy of the fourth generation fluoroquinolones. However, continuation of topical medications beyond what is therapeutically necessary may result in iatrogenic disease and failure to heal.
- There are many topical medications that affect corneal healing. The issue may be:
 - the medication itself.
 - the preservatives in the medications that affects the ocular surface.
 - Preservative free-preparations are associated with significantly less ocular toxicity.
 - One study suggests that Moxifloxacin induces less damage to the corneal epithelium than other antibiotic solutions, perhaps because it is self-preserved and has no additional preservatives.
- Iatrogenic toxic ocular surface disease is an overlooked cause of treatment failure, mostly because it closely resembles other causes of surface disease.
 - One epidemiological study identified 13% of keratoconjunctivitis cases as iatrogenic. Healing was prolonged, taking 7-93 (median 28.5) days.
 - Another report described 19 patients with toxic ulcerative keratopathy, who had been referred with other diagnoses and were victims of overtreatment.
- Management of patients with iatrogenic complications involves discontinuation of the offending agent

Myth # 3: *“A good, tight pressure patch is the best treatment for corneal abrasion”*

- **Background:**
 - Historically, the treatment for corneal abrasion has consisted of three elements:
 - Broad spectrum antibiotic ointment (e.g. tobramycin)
 - Cycloplegia (e.g. 0.25% scopolamine)
 - Pressure patch
 - Proposed rationale:
 - Antibiotic provides prophylaxis against secondary bacterial infection
 - Cycloplegia stabilizes uveal response, preventing pain and inflammation
 - Pressure patch eliminates pain associated with blinking and photophobia, minimizes annoying lacrimation, and facilitates reepithelialization.
- **Question:** Have you ever had a patient that was pressure patched and just didn't get better? Why do you think that happened?
 - Disadvantages to pressure patching:
 - Persistent corneal edema – can retard epithelialization
 - Provides moist, warm, dark environment – ideal for bacterial growth
 - Generally uncomfortable – interferes with basic facial hygiene, eating, etc.
 - Prevents instillation of topical agents (e.g. lubricants, antibiotics, anti-inflammatories)
 - Negatively impacts vision by eliminating binocularity, hindering spectacle wear
 - Cosmetically unacceptable
 - Potential contact allergy to tape
- **Pivotal studies:**
 - Kaiser PK. A comparison of pressure patching versus no patching for corneal abrasions due to trauma or foreign body removal. Corneal Abrasion Patching Study Group. *Ophthalmology* 1995; 102(12):1936-42.
 - **CONCLUSIONS:** *Noninfected, noncontact lens-related traumatic corneal abrasions as well as abrasions secondary to foreign body removal can be treated with antibiotic ointment and mydriatics alone without the need for a pressure patch.*
 - Kaiser PK, Pineda R 2nd. A study of topical nonsteroidal anti-inflammatory drops and no pressure patching in the treatment of corneal abrasions. Corneal Abrasion Patching Study Group. *Ophthalmology* 1997; 104(8):1353-9.
 - **CONCLUSIONS:** *Ketorolac tromethamine 0.5% ophthalmic solution provides increased patient comfort without clinical adverse effects when used as adjunctive therapy in the treatment of noninfected, non-contact lens-related, traumatic corneal abrasions.*
 - Michael JG, Hug D, Dowd MD. Management of corneal abrasion in children: a randomized clinical trial. *Ann Emerg Med* 2002; 40(1):67-72.
 - **CONCLUSION:** *This study suggests that eye patching in children with corneal abrasions makes no difference in the rate of healing. There was no difference in discomfort and interference with [activities of daily living], other than greater difficulty walking in the patch group, and no complications in either group.*

- What about the use of bandage contact lenses?
 - Useful for several situations:
 - Traumatic abrasions in excess of 50% of the epithelial surface
 - Recurrent corneal erosions in corneal dystrophies (e.g. granular)
 - Bullous keratopathy (secondary to Fuch's dystrophy, trauma, etc.)
 - Post-operative epitheliopathy
 - Helps eliminate lid-cornea interaction, thereby diminishing discomfort (?)
 - **Advantages:** maintains binocular vision, does not hamper instillation of topical agents, allows for corneal deturgescence
 - **Disadvantages:** potential substrate for bacterial growth (?), potentially increases corneal hypoxia
 - **NOTE:** if a bandage CL is chosen, silicone hydrogel is the obvious choice!
 - Focus Night & Day is FDA approved as a therapeutic bandage lens
 - No definitive studies have been published on this specific topic to date.

Myth # 4: ***“Though annoying, dry eye is essentially a benign condition with very little risk of serious corneal compromise.”***

- Dry eye is viewed by many as simply a “nuisance” condition
 - Most patients manifest sporadic, intermittent complaints ONLY without clearly observable signs
 - Wide range of manifestations and degrees of severity
 - Numerous treatment modalities, most aimed at palliating symptoms
- Dry eye is – and must be viewed as – a DISEASE of the ocular surface of the eye.
 - Recent studies indicate that dry eye often manifests as a chronic, low-grade inflammatory state of the ocular surface.
 - Researchers have identified pro-inflammatory cytokines and activated T-cells both in the lacrimal glands and conjunctiva of Sjögren's and non-Sjögren's dry eye patients.
 - Severe complications are possible and DO EXIST
 - Most of these sequelae are inflammatory in nature; other complications may include:
 - Ocular allergy
 - Filamentary keratitis
 - Ocular infection
 - Neurotrophic damage & lacrimal gland dysfunction
- Ocular allergy
 - Tears entrap and wash away harmful particulate matter and allergens.
 - With diminished lacrimal lake, allergens achieve greater concentrations on the ocular surface, leading to potentially greater and more symptomatic responses
- Filamentary keratitis
 - Patients with moderate-severe dry eye commonly demonstrate filaments in tear film
 - Diminished aqueous allows for contamination of mucin by lipids, resulting in poor adhesion to the epithelial glycocalyx

- Inflammation stimulates prostaglandin and leukotriene synthesis, which in turn promotes mucus secretion
- Unbound mucin binds with loose, compromised epithelial cells for form filaments
- Ocular infection
 - Normal tear film provides immune protection against infection
 - Accomplished by numerous enzymes, immunoglobulins and other proteins, e.g. lactoferrin, lysozyme, and immunoglobulin A (IgA)
 - These molecules are diminished in dry eye disease
 - As the eye loses its natural protective mechanisms, normal flora can proliferate to pathological levels, resulting in microbial infection
- Neurotrophic effects and glandular dysfunction
 - Infiltration of the lacrimal gland by B- and T-cells results in the enhanced production of cytokines such as IL-1, IL-2 and TNF- α .
 - Lactoferrin normally helps to downregulate the release of pro-inflammatory mediators, but is diminished in dry eye disease
 - Inflammation in cornea and conjunctiva stimulates expression of immune activation and adhesion molecules (e.g. HLA-DR and ICAM-1)
 - Attract and retain inflammatory cells, which cause hyperstimulation of corneal nerves
 - Ultimately, these nerves may suffer “burnout”, leading to:
 - Diminished neural control
 - Acinar cell apoptosis
 - Diminished tear production
 - Neurotrophic keratitis occurs when corneal sensation is diminished or absent
 - Usually due to herpetic infection, also associated with trigeminal nerve trauma, corneal dystrophy, topical medication, toxic exposure, or systemic disease
 - Cornea suffers epitheliopathy, followed by stromal edema and stromal lysis
 - Epithelial changes in chronic dry eye are identical to Stage I neurotrophic keratitis
- **Conclusion:** *Untreated dry eye poses a long-term risk for significant and even severe ocular pathology.*

Myth # 5: ***“The prolonged use of oral antibiotics should be abandoned in female patients with Rosacea.”***

Background: A link between prolonged use of antibiotics (especially macrolides and tetracycline) and breast cancer primarily in females has caused some concern among epidemiologists and other health care practitioners. **Velicer CM et al. Antibiotic use in relation to the risk of breast cancer. JAMA. 2004 Feb 18;291(7)827-35.** Case control study shows odds 1.44 (women who used antibiotics for 1-50 days) and 2.89 (women who used antibiotics for more than 1000 days).

- **Causal Relationship**

- Important to weigh the findings with respect to the disease being treated and the alternatives to that treatment and the risk or impact associated with the treatment on another disease (in this case, breast CA). Another example is vitamin supplements for AMD and the relative risks and benefits to bleeding, lung CA, osteoporosis and AMD progression.
- Increased risk was observed in virtually all antibiotic classes studied with sub-analysis outcome of breast CA fatality.
- Risk of incident breast CA was not elevated in women with at least 50 days of tetracycline or macrolide used exclusively for acne or rosacea compared with use for respiratory infection after age and length of enrollment odds ratio adjustment.
- Study had limited power (small sample size and wide CI); antibiotic usage was determined by the number of prescriptions filled and may not accurately reflect usage over time.

- **Proposed Mechanism**

- Prolonged use of tetracycline is associated with increased production of prostaglandin E2, a remnant of inflammatory response, catalyzed by cyclooxygenase 1 and 2. Cyclooxygenase 2 is associated with mammary carcinogenesis. Inhibition of prostaglandins and other inflammatory mediators by NSAIDs associated with a 20-40% decreased risk of breast CA.
- Antibiotics work differently, yet all antibiotic prolonged usage was associated with increased risk of breast CA.
- Confounding variables: other risk factors for breast CA such as hormonal replacement therapy, familial history, and increased awareness of the disease (more mammograms),

- **Data Analysis**

- The results are inconsistent with data from animal studies that show no relationship between extended antibiotic usage or exposure and breast cancer.
- Minocycline may be more toxic (not less) than tetracycline or doxycycline. Minocycline metabolism has been associated with lupus induction and may be associated with increased risk of other adverse events.
- The condition in which the prolonged use of antibiotic is needed or patient's immune status may be in itself the risk factor for breast CA.
- The antibiotic use may be a confounding factor rather than causation for breast CA (i.e. association of macrolides and leukemia and tetracyclines and non-Hodgkin's lymphoma).
- Another aspect- matrix metalloproteinases play a vital role in tumor migration and invasion. TCNs may actually have a beneficial effect in that they inhibit MMPs.

- **Recommendations**

- The safety and efficacy data of doxycycline and tetracycline including treatment effect, optimal dose, duration of therapy, and side effects when used for ocular rosacea have not been established.
- When needed, the minimal dose and shortest duration required for a clinical effect is suggested. The over-use of any antibiotic should be avoided.
- Recommend using doxycycline monohydrate, Adoxa and Monodox, 50 mg. BID for an initial dose and then taper at 3-4 weeks to Periostat 25 mg daily. Adjunctive therapy like Restasis and omega 3 fatty acid supplements are helpful in many cases.

- Note: Wild salmon oils are tested for metals and contaminants; pressed flax seed oil may not be well metabolized in some humans to be very effective; caution with heavy usage in the elderly and others on additional blood thinners and those who have had a cholecystectomy. Additional report of omega 3 usage and increased risk of 2nd breast involvement in patients with breast CA exists.

Myth # 6: ***“Contact lenses should never be worn for swimming or other water-related activities.”***

- **Background:** It is widely held that...
 - Swimming with soft contact lenses predisposes an individual to acanthamoeba keratitis.
 - Contact lenses easily dislodge from the eye when a patient submerges in water.
- **Reality:**
 - There have been numerous published cases of acanthamoeba keratitis associated with soft contact lens wear (e.g. Kaji Y, Hu B, Kawana K, Oshika T. Swimming with soft contact lenses: danger of acanthamoeba keratitis. Lancet Infect Dis 2005; 5(6):392.)
 - HOWEVER:
 - Many individuals require contact lens correction to fully enjoy or compete in water-related activities
 - Goggles may prevent ocular exposure to water, but they limit field of view, are cumbersome and potentially dangerous if impacted
 - Acanthamoeba trophozoites are readily eradicated by several disinfection systems:
 - Renu Multiplus
 - Opti-Free Express
 - UltraCare
 - Heat
 - Discarding the contact lens immediately after swimming virtually eliminates the risk of infection – a case for daily disposables
 - Soft contact lenses generally do not displace when exposed to fresh water; rather, they tend to swell slightly and adhere to the cornea (due to the hypotonicity relative to the eye)
- **Recommendations:** Patients can confidently use contact lenses for recreational swimming if they either:
 - Remove and discard the lenses immediately upon conclusion of the activity, OR
 - Immediately remove and disinfect the lenses upon conclusion of the activity, using an approved care system with efficacy against the *Acanthamoeba* organism.

Myth # 7: ***“Corneal ring infiltrates and radial keratoneuritis are pathognomonic for Acanthamoeba keratitis.”***

• **Acanthamoeba Keratitis: Background**

- A "free living" protozoan (motile) with worldwide distribution
- Isolated from fresh water, well water, sea and brackish water, sewage, hot tubs, etc.
- Causes a relentless infection with potentially devastating consequences
- Historically, corneal ring infiltrates and radial neuritis were (erroneously) believed to be pathognomonic for Acanthamoeba.
- Clinical Features
 - Early signs are non-specific; they include:
 - patchy epithelial involvement
 - suppurative/granulomatous or non-suppurative stromal keratitis
 - pseudo-guttata and iritis
 - Recently identified early signs include:
 - ◆ a “bull’s-eye” lesion
 - ◆ randomly distributed white spots on the cornea
 - More advanced signs may include:
 - a **radial kerato-neuritis**
 - **ring infiltrate**
 - nodular episcleritis or scleritis
 - hypopyon or hyphema
- Symptomatology: usually unilateral pain disparate to ocular findings, often history to trauma +/- contact lens wear, symptoms wax and wane over time with chronicity.

• **Laboratory Confirmation**

- Corneal scrapings* with Giemsa or tri-chrome stains
- Culture with heated killed *E. coli* on non-nutrient agar or activated charcoal/yeast extract
- Cysts can sometimes be seen on soft lenses with high magnification.
- Confocal microscopy is an aid to early differential diagnosis
- Polymerase chain reaction may be more sensitive than cultures as a diagnostic test.

**biopsy with intact epithelium or graft histology*

• **Therapy and Management**

- Antibiotic/Aminoglycoside: *paromomycin* (Humatin), *neomycin*
- Antifungal: *clotrimazole*, *ketoconazole* (Nizoral), *itraconazole* (Sporanox), *miconazole* (Monistat, Micatin), *fluconazole* (Diflucon)
- Antiparasitic/Aromatic Diamidine: *propamidine isethionate* (**Brolene**), *hydroxystilbamidine* (Pentamidine), *hexamidine di-isethionate* (Desomedine)
- Biocide/Cationic Antiseptic: *polyhexamethylene biguanide* (PHMB, **Baquacil**, Cosmocil), *chlorhexidine digluconate*, *povidone-iodine* (Betadine)

**use one agent from at least two of the four categories above, plus oral ketoconazole or fluconazole, apply topicals every 30-60 minutes; for recalcitrants with significant ocular toxicity use drops in a three day cycle (hexamidine, paromomycin, and either PHMB or chlorhexidine)*

- **Additional Protozoan**
 - Similar infection may be caused by other amoeba - *Naegleria*, *Hartmannella* or *Vahlkampfiid*
 - Microsporidia
 - obligate intracellular protozoan recently found on corneal scrapings of HIV infected patients from nasopharyngeal or urinary colonization.
 - May present as a superficial punctate, multifocal keratitis in immuno-incompetent patients (genus-*Encephalitozoon*)
 - a stromal keratitis is possible following trauma especially in immunocompetent individuals (genus-*Nosema*).
- **Masquerade Syndromes**
 - Ring Infiltrates: Herpes simplex keratouveitis, bacterial keratitis, and surreptitious use of anesthetics
 - Radial Kerato-neuritis: Leprosy

Myth # 8: ***“Herpes simplex is a horrible, blinding disease that is dangerous and difficult to manage.”***

- **Herpes Simplex Dendritic Keratitis**
 - Unilateral red eye typically
 - Variable pain
 - Corneal hypoesthesia develops with repeated outbreaks
 - Photophobia and lacrimation
 - Possible ulcerative blepharitis
 - Begins as non-descript epitheliopathy
 - Coalesces into dendrite with branching
 - Terminal end bulbs
 - Stain with NaFl, rose bengal, lissamine green
 - Represents most common form of recurrent disease
 - Latent virus in terminal end bulbs
 - Trigger factors
 - Fever, stress, menstruation, solar exposure
 - Virus invades and replicates in epithelium
 - True infection
 - Stromal disease may ensue
 - More likely with recurrences
 - May occur without epitheliopathy
 - Management more difficult

Clinical Pearl: Despite what you may have heard or currently believe, herpes infections of the eye are relatively easy to manage. Herpes is not an especially virulent or aggressive microbe. It does not tend to mutate and it is susceptible to antiviral medications. Correct diagnosis is crucial in management.

- **Herpes Simplex Dendritic Keratitis: Management**
 - Self limiting
 - Simple debridement will cure most cases
 - Topical Trifluridine 1% (Viroptic) Q2H up to 9 times/day
 - Vidarabine Ung (Vira A)
 - Cycloplegia
 - Avoid steroids (at least initially)
 - Oral antivirals not proven more useful for active disease
 - Acyclovir 400 mg PO BID x 1 year proven to reduce incidence of HSK recurrence

- **Herpes Simplex Stromal Disease: Stromal Interstitial Keratitis**
 - Single or multiple patches of infiltrate
 - Largely intact epithelium
 - Acute phase will develop vascularization
 - Any layer of stroma involved
 - Indolent course over several months
 - Pain, photophobia, lacrimation
 - History of HSK common, but not required for diagnosis
 - Antigen-antibody-complement-mediated immune disease
 - Live virus not present
 - Self limiting
 - Dense corneal scarring and vascularization as end result
 - Manage as conservatively as possible
 - Cycloplegia and lubrication initially if visual axis not involved
 - Topical steroids
 - Lowest dose and concentration that will control inflammation
 - Prednisolone 1% QID
 - Topical prophylactic antivirals (Viroptic) at ½ dosage
 - Orals not helpful
 - Only used if topicals not tolerated

- **Herpes Simplex Stromal Disease: Disciform Keratitis**
 - Discrete disc shaped areas of focal stromal edema
 - Central or peripheral
 - Typically mild
 - Epithelium intact
 - Avascular
 - May be severe with corneal melting (rare)
 - Delayed hypersensitivity reaction to viral byproducts of HSV
 - No live virus present
 - Not specific to HSV
 - Self limiting
 - Manage conservatively
 - Cycloplegia and lubrication
 - topical steroids
 - Use lowest concentration that will control inflammation
 - Prophylactic topical antivirals if steroids are used
 - Orals not helpful