Viral and bacterial keratitis…An applied overview

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Corneal viral infections

- **HSV 1 and 2**
- **Varicella Zoster.**
- CMV: Endotheliitis and corneal edema.
- **Adenovirus.**
- Epstein Barr: corneal infiltrates and uveitis.
- Human herpes virus 6.

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12 Tips in 12 minutes

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Tip 1
HSV vs HZV

OCULAR HEREPS SIMPLEX	VS	HERPES ZOSTER OPHTHALMICUS
• Recurrent most common • Dendrites w terminal bulbs • Tx: Topical antivirals		• Hutchinson's sign • Pseudodendrites • Tx: Systemic Antivirals

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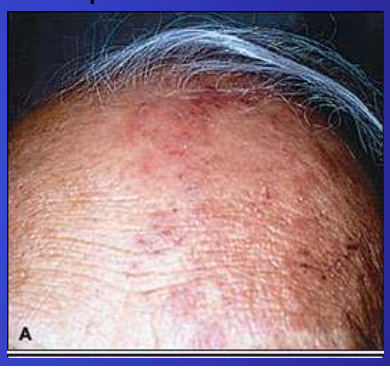
- Blisters /vesicles

- Papulomacular rash - vesicles-pustules-crusts: dermatomal distribution and respects the midline



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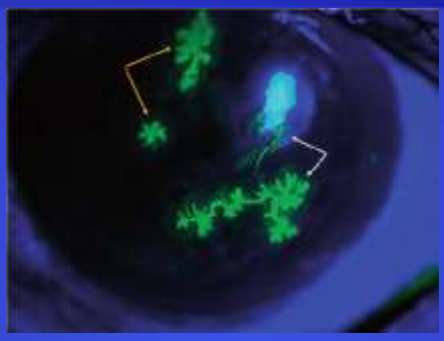
HSV **HZV**



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Medusa-like HZV

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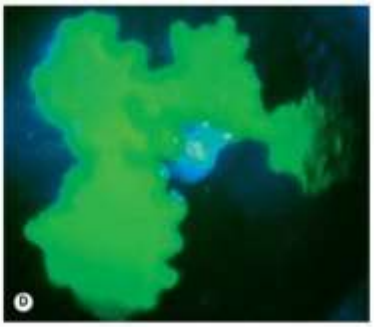
Double stain only in HSV



C) margins of a dendritic ulcer stained with rose Bengal; (D) geographic ulcer;

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HSV stromal keratitis

HZV nummular keratitis

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Keratouveitis

Patchy in HSV

Sectoral in HZV

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Tip 2

- Mutations affecting the production or specificity of viral **thymidine kinase(TK)** essential for phosphorylation resistance to acyclovir and Valaciclovir.
- Prevalence 1% in immunocompetent and 5% in Immunocompromized patients; Management should involve improving the immune status of infected patient.

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Anti-HSV mechanism

Viral-TK dependent	Inhibit DNA Polymerase-independent of viral TK
Acyclovir	Cidofovir 1%
Valaciclovir	**Foscarnet** (IV &topical 3%)

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Prevalence of HSV

- 90% of adults are seropositive for the herpes simplex virus (HSV) antigen.
- Approximately 500 000 cases of active ocular herpes simplex infection are seen per annum in the USA.

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Tip 3
HSV in children

- Measles virus suppresses cell mediated immunity by interfering with T cell function.
- Children with **acute Measles** are at risk for secondary infection ,including HSV.

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Compared to adults, children tend to have:

more severe disease,
more recurrences,
incidence of bilaterality ,
more secondary corneal scarring and astigmatism,
and **amblyopia**.

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Tip 4

- Reported recurrence rates of herpetic keratitis in donor corneas following PKP=27% in the first year.

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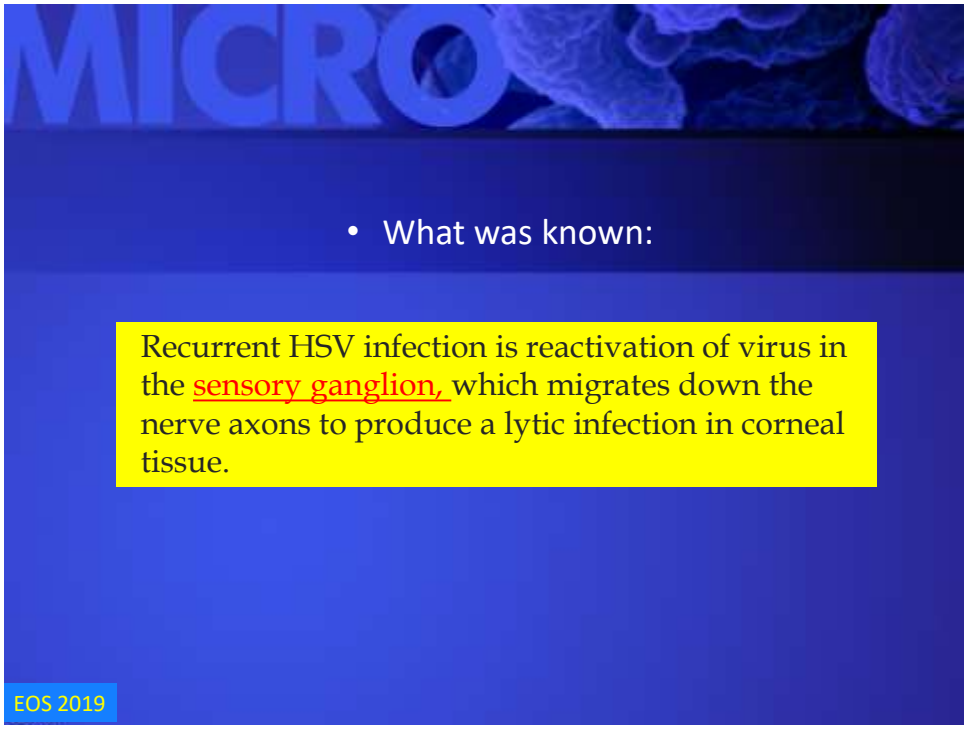
MICRO
• What was known:
Recurrent HSV infection is reactivation of virus in the sensory ganglion, which migrates down the nerve axons to produce a lytic infection in corneal tissue.
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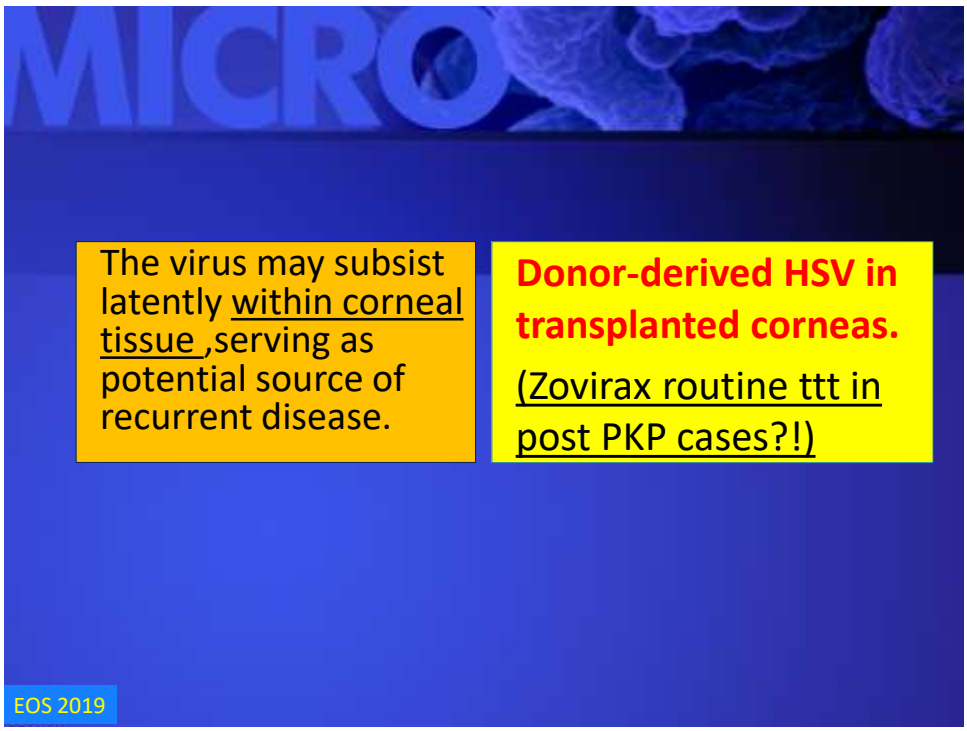
MICRO
The virus may subsist latently within corneal tissue ,serving as potential source of recurrent disease.
Donor-derived HSV in transplanted corneas.
(Zovirax routine ttt in post PKP cases?!)
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Donor-derived HSV in transplanted corneas.

The incidence of newly acquired HSV keratitis is **14-fold higher** in transplant (PKP patients or any transplant patients, e.g. renal)patients compared with the normal population.

(Zovirax routine ttt in post PKP cases?!)

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Detection of Herpes Simplex Virus in Corneal Buttons with Clinical Diagnosis of Corneal Scarring

Fahimeh Asadi-Amoli, MD[1] • Mehrnaz Alaie-Gohar, MD[1] • Reza Shahriari, MD[1,2]

Abstract

Purpose: The evaluation of the presence of Herpes Simplex Virus (HSV) in corneal scars by real-time polymerase chain reaction (PCR) and comparison of the results with histopathologic findings and clinical diagnoses

Methods: Eighty-seven corneal scar samples obtained after penetrating keratoplasty (PK), were selected after reviewing the records from 2006 to 2010. Nucleic acid was extracted from paraffin embedded corneal samples and PCR-amplified for HSV DNA.

Results: Among 87 samples, four samples were excluded because internal controls were negative. HSV infection was established in 9.6% (8/83) of all patients. The prevalence of HSV infection in patients with no clinical suspicion of herpetic keratitis was 7.3%. Histopathologic evaluation revealed that among samples with positive PCR results, 100% had evidence of inflammation, 62.5% had giant cells, 37% had necrosis, 62.5% had vascularization, 62.5 % had ulcer and all of them had inclusion bodies.

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- The use of (topical or/and systemic) antivirals following penetrating keratoplasty is supported by several studies and is recommended for at least the first year postoperatively…..

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When to decide antiviral therapy?

- Definite history of HSV.
- **Decreased corneal sensation preop.**
- Faint scars with areas of **thinning away from scar**.
- Failed previous graft due to **PED(Neurotrophic ulcer).**

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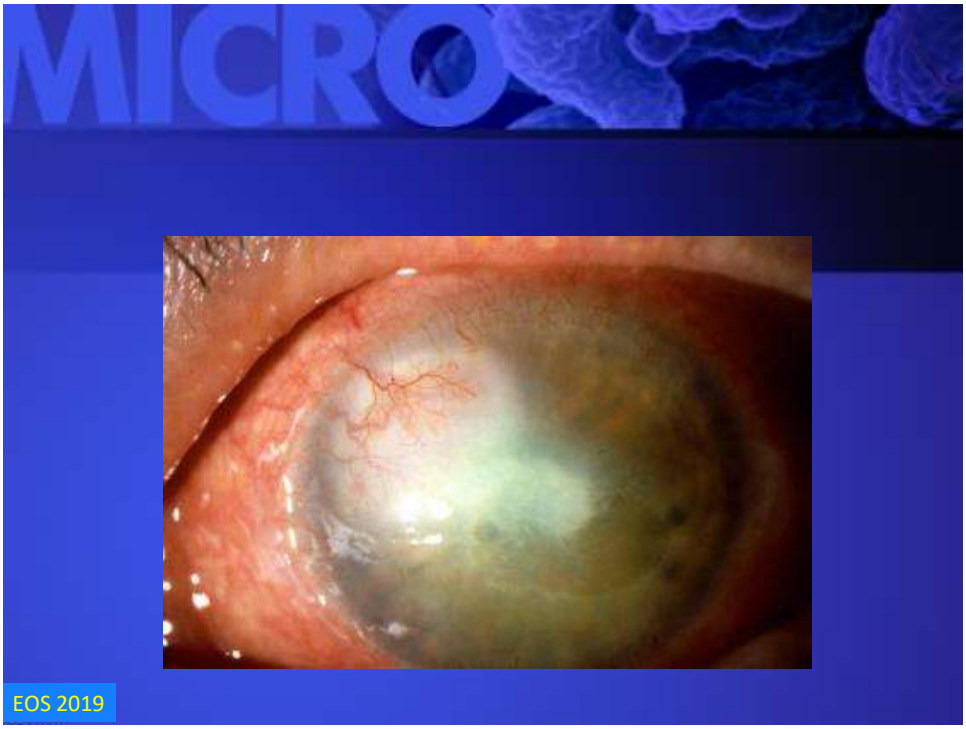

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Clinical science

Comparison of oral antiviral therapy with valacyclovir or acyclovir after penetrating keratoplasty for herpetic keratitis

D Goldblum,[1,2] C Bachmann,[1] C Tappeiner,[1] J Garweg,[3] B E Frueh[1]

ABSTRACT

Aims: To compare the outcome of prophylactic oral valacyclovir (VAL) or oral acyclovir treatment (ACV) in patients having undergone penetrating keratoplasty for herpetic keratitis (HK).

Methods: All patients having received a penetrating keratoplasty for HK and being treated postoperatively with either oral VAL or oral ACV (inclusion period from 12/97 to 3/06 and 5/92 to 9/96, respectively) were retrospectively evaluated. Records were analysed for postoperative reactivation of recurrent HK, graft rejection, endothelial cell loss, central corneal thickness and visual acuity after a follow-up of up to 5 years.

Results: Twenty patients received VAL and were compared with 19 patients being treated with ACV. Two patients developed clinical signs of recurrent herpetic disease in the VAL group compared with three patients in

prophylactic oral VAL on the survival of corneal grafts performed for herpetic keratitis.

We therefore retrospectively evaluated the long-term outcomes of oral VAL prophylaxis in a consecutive series of patients after penetrating keratoplasty (PKP) for herpetic keratitis and compared the results with controls having received the ACV treatment regimen (before VAL was available) for the same indication.

PATIENTS AND METHODS

We identified 43 patients having undergone penetrating keratoplasty for inactive or active HK. Thirty-nine patient records (four records were missing) with a documented follow-up of at least 1 year were retrospectively/historically reviewed. Two surgeons performed all PKPs for herpetic

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400 mg Acyclovir twice daily vs
500 mg Valacyclovir once .

Conclusion: Prophylactic oral VAL treatment is at least as effective as ACV in preventing recurrence in patients who underwent corneal transplantation for HK. The tolerability of the two drugs is similar, but the dosing for VAL might be more comfortable for patients.

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Acyclovir Therapy in Prevention of Recurrent Herpetic Keratitis Following Penetrating Keratoplasty

SUDIPTA GHOSH, VISHAL JHANJI, ECOSSE LAMOUREUX, HUGH R. TAYLOR, AND RASIK B. VAJPAYEE

• PURPOSE: To compare systemic vs topical acyclovir therapy for the prevention of recurrence of herpetic keratitis following penetrating keratoplasty (PK).
• DESIGN: A retrospective observational study.
• METHODS: Patients who underwent PK for herpetic eye disease (HED) and prophylactically received acyclovir therapy postoperatively, either systemically (26 eyes) or topically (29 eyes), were analyzed. The main parameters evaluated were recurrence of herpetic keratitis, graft rejection, visual acuity, and graft survival rate.
• RESULTS: Mean average follow-up period was 24.7 ± 3.6 months and 23.5 ± 2.3 months in the systemic and topical group, respectively (P = 0.73). The average duration of prophylactic antiviral therapy in systemic group was 16.1 ± 4.8 months and in topical group was 15.1 ± 3.5 months (P = .59). Recurrence of herpetic keratitis was seen in 12% in the systemic group compared to 55% in the topical group (P < .001). More eyes in topical group 15 (52%) had rejection episodes than in the systemic group 5 (19%) (P < .001). A best-corrected visual acuity of ≥ 20/40 was achieved in 31% and 7% eyes in the systemic and topical group, respectively, at the end of two years (P = .002). The clear graft

ing PK for herpetic eye disease is mainly attributed to the recurrence of herpes simplex virus (HSV) infection after corneal transplantation.[1,5–7] Prophylactic antiviral therapy has been used to prevent the recurrence and relapse of herpetic keratitis after corneal transplantation. The efficacy of systemic and topical acyclovir therapy in the reduction of such episodes has been well documented in the literature.[5,8–11]

In the present study, we retrospectively evaluated and compared the efficacy of systemic and topical acyclovir therapy in the prevention of recurrence of herpetic keratitis and in the improvement of overall graft survival rate in cases of PK performed for HSV related corneal diseases.

METHODS

CASE RECORDS OF 55 CONSECUTIVE PATIENTS WHO HAD undergone PK for herpetic eye disease between June 1995 and June 2005 at our hospital and had received prophylactic antiviral therapy for at least one year postoperatively were analyzed retrospectively. The preoperative diagnosis of her-

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Tip 5

15.1 ± 3.5 months ($P = .59$). Recurrence of herpetic keratitis was seen in 12% in the systemic group compared to 55% in the topical group ($P < .001$). More eyes in topical group 15 (52%) had rejection episodes than in the systemic group 5 (19%) ($P < .001$). A best-

Oral Acyclovir is more efficient than 3% ointment in post-keratoplasty prophylactic regime.

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Clinical Case Report

Medicine

OPEN

Herpes simplex virus linear endotheliitis in a post-keratoplasty patient

A case report

Jeongah Shin, MD[a], Ho Ra, MD[b], Chang Rae Rho, MD, PhD[a,*]

Abstract

Rationale: To report a case of herpes simplex virus (HSV) linear endotheliitis in a 57-year-old male who had undergone keratoplasty 10 years ago. The characteristic linear keratic precipitates (KPs) resembled the Khodadoust line in graft rejection. The differential diagnosis is essential, because the treatment regimen is different between HSV linear endotheliitis and graft rejection.

Patient concerns: The patient developed a sudden onset of ocular pain and a decrease in visual acuity in his right eye. The patient had received penetrating keratoplasty in the eye 10 years ago.

Diagnoses: The ocular disease was evaluated using several ocular examinations, including best-corrected visual acuity (BCVA), intraocular pressure, slit lamp examination, fundus examination, and aqueous humor tap. Characteristic linear endothelial KPs were found both in the host cornea and graft cornea. Stromal edema was evident in both the donor and recipient corneas. The aqueous humor was sampled for viral polymerase chain reaction (PCR) analysis. The sample was investigated for the possible presence of HSV-1, HSV-2, cytomegalovirus, and varicella zoster virus. The PCR was positive for HSV-1 and negative for HSV-2, cytomegalovirus, and varicella zoster virus.

Interventions: The patient was treated with both antiviral and steroid treatments for 1 month. Thereafter, prophylactic antiviral treatment was continued.

Outcomes: The subjective symptoms had improved and the cornea edema and the linear endothelial KPs had disappeared. The BCVA improved from 20/200 to 20/80.

Lessons: HSV linear endotheliitis is the most severe form of HSV endotheliitis. This case showed characteristic endothelial KPs, which were different from the Khodadoust line of graft rejection.

Abbreviations: BCVA = best-corrected visual acuity, HSV = herpes simplex virus, IOP = intraocular pressure, KP = keratic precipitate, PCR = polymerase chain reaction.

Keywords: acyclovir, cornea, endotheliitis, herpes simplex virus, steroid

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PCR +ve for HSV-1 DNA in aqueous tap.

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Tip 6

- D.D. of endothelial rejection with Khodadoust line:

Linear viral endotheliitis.

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	Live virus	"Immune reaction"	"Meta-herpetic"
Epithelium	Dendrite, geographic		Epithelial defect
Stroma	Necrotizing keratitis	Immune keratitis	Microbial and non-microbial ulcerative keratitis
Endothelium		Disciform keratitis	
Anterior chamber	Keratouveitis	Keratouveitis	

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	Treatment type		
Disease type	Primary treatment	Complementary treatment	Potentially beneficial
Epithelial keratitis	Topical antivirals	Oral antivirals	Debridement Interferon
Stromal Keratitis (necrotising and non-necrotising)	Topical corticosteroids	Oral antivirals	Topical antivirals Topical cyclosporine
Disciform/endothelial keratitis	Topical corticosteroids	Oral antivirals if intis present and for recurrence prevention	Topical antivirals
Neurotrophic keratitis	Artificial tears Collagenase inhibitors Autologous serum Antibiotics if infected	Surgery Botulinum toxin	Growth factors

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Tip 7
PTK or PRK for HZV?

Management of Corneal Scarring Secondary to Herpes Zoster Keratitis

Omar M. Hassan, MD, Asim V. Farooq, MD,† Ketki Soin, MD,* Ali R. Djalilian, MD,* and Joshua H. Hou, MD‡*

However, any ocular surface procedure in the setting of neurotrophic keratopathy must take into account the risk of postoperative persistent corneal epithelial defect and melt. Neurotrophic keratopathy develops in approximately 12.8% of HZK cases, and patients with unilateral HZK can develop bilateral changes in corneal nerve morphology.[11,12]

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PTK/PRK for HSV scar!?

- Success rate up to 80%.
- Increased risk of HSV recurrence?
- **Risk of recurrence outweighs potential benefits of treating HSV scars with PTK, UNLESS the alternative is PKP.**

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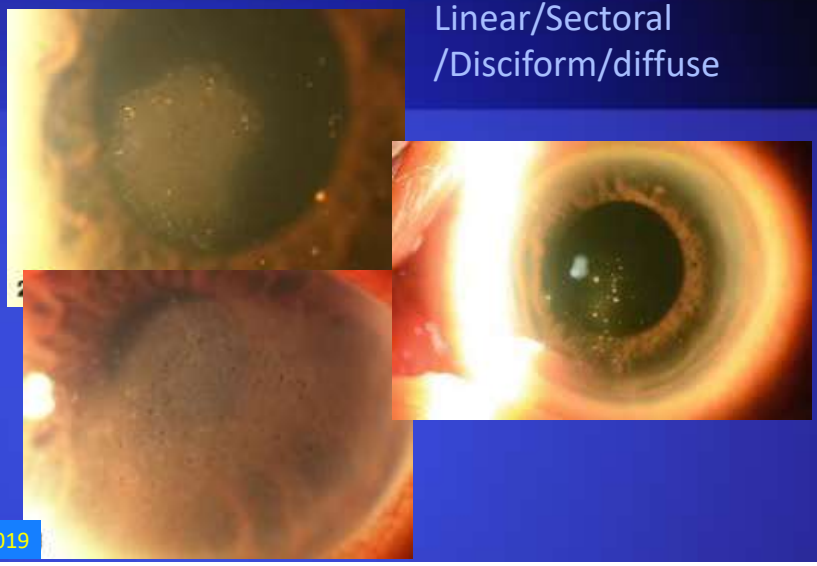
Endotheliitis: Linear/Sectoral /Disciform/diffuse



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NSK

- Thinning, ulceration, and dense infiltration of the stroma, accompanied by an overlying epithelial defect with minimal discharge.
- Topical and systemic acyclovir for treatment of NSK facilitates healing of ulceration.
- Topical steroids after initial antiviral therapy are safe and decreases inflammation and improve visual recovery.

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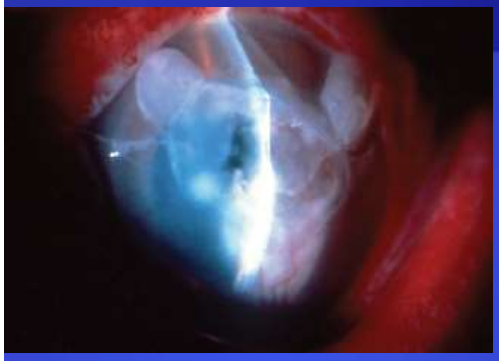
Tip 8



- Mooren's ulcer-like pattern

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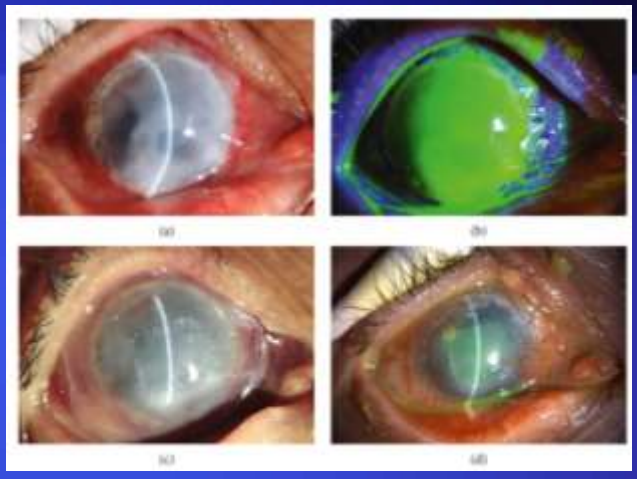

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Interstitial keratitis

- The vast majority of cases are an immune stromal keratitis (ISK), which involves the antibody-complement cascade against retained viral antigens in the stroma.

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Tip 9

Acta Ophthalmologica

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Topical cyclosporine-A versus prednisolone for herpetic stromal keratitis: a randomized controlled trial

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[3]Shiley Eye Institute, University of California San Diego, La Jolla, CA, USA

Conclusions: Cs-A 2% and prednisolone acetate 1% topical eye drops are effective for treatment of HSK.

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options, topical corticosteroid use may be limited by side effects, including potential recurrence of herpetic disease, increased intra-ocular pressure (IOP), development of glaucoma, and cataracts (Titcomb 2013; Zanjani et al 2017). In addition, some patients have persistent inflammation despite using topical corticosteroids (Rao 2006). An alternative immunosuppressant drug targeted at T-cells might be a potential substitute for corticosteroids if its efficacy is proven.

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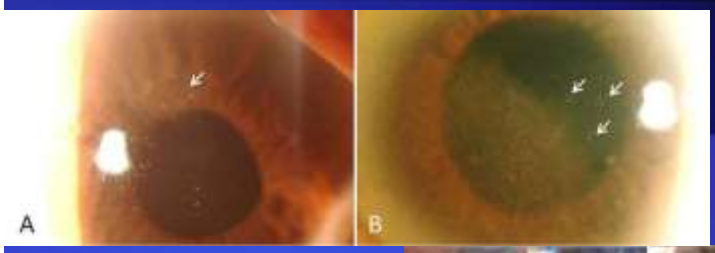
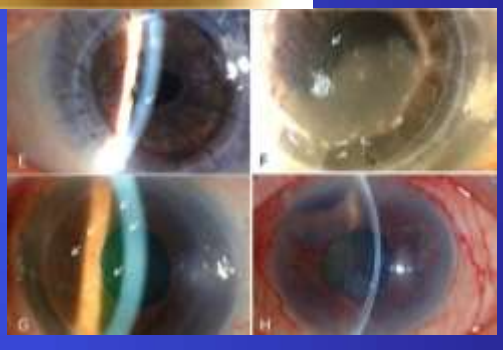
CMV Endotheliitis





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Tip 10

DD: Posner- Schlossman syndrome

- Unilateral & Recurrent.
- Mild discomfort or blurring of vision
- Increased IOP with open angles
- Mild AC reaction & fine white (KPs)
- Crises lasting from several hours to weeks.

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- CMV is not sensitive to acyclovir, valacyclovir, or penciclovir. At this stage, if a diagnosis of CMV anterior uveitis is being considered, PCR testing should be performed prior to initiating **valganciclovir or ganciclovir**.

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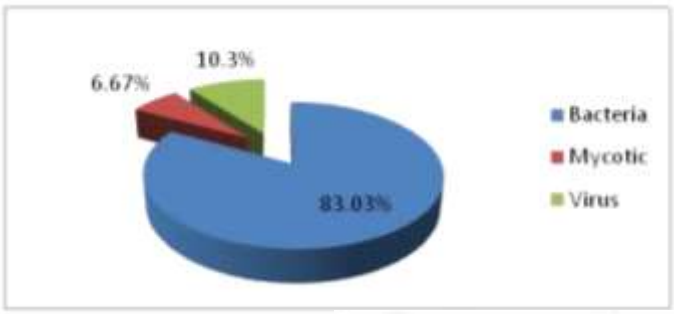
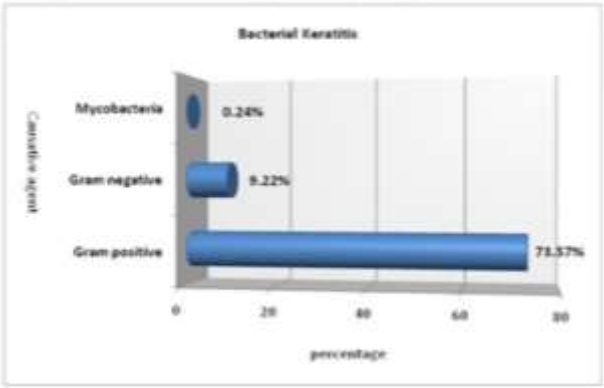


2025 cases from 2000-2010



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Tip 11

Resistant corneal infection

Resistant organism

- Poor choice of antibiotic .
- Wrong dose/Short duration of antibiotic
- Concomitant use of steroids eye drops
- **Atypical mycobacteria-Viral-Fungal-Acanthamoeba.**
- Immunocompromized patient.
- Bacterial strain with **chromosomal mutation; gene transformation** e.g Resistant Staph spp. in USA, Pseudomonas in India,P. against fourth generation fluoroquinolones.

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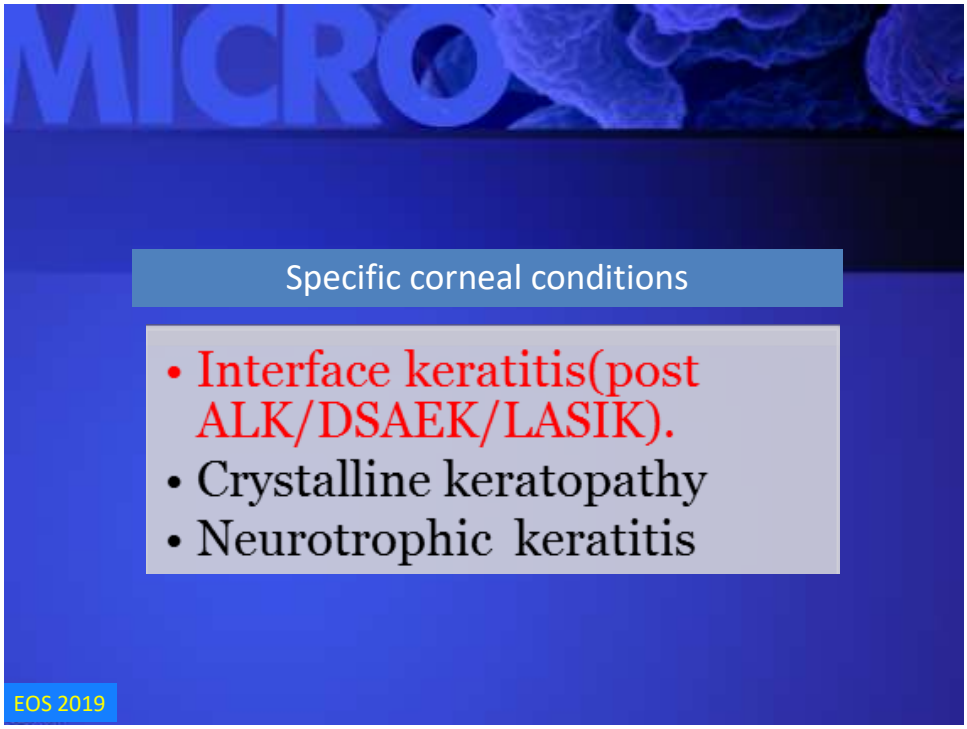
MICRO
Specific corneal conditions
• Interface keratitis(post ALK/DSAEK/LASIK).
• Crystalline keratopathy
• Neurotrophic keratitis
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MICRO
Wrong diagnosis of infection
• Toxic keratopathy
• Sterile infiltrates
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Tip 12

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Management of corneal infection- with no hyphae seen on KOH 10% smear-

Broad spectrum (Gati/ Moxi -floxacin) and duo therapy -fortified antibiotic drops(Vancomycin and Ceftazidime 5%)	No improvement within 48 hours & negative cultures on blood ,chocolate agar

Consider non bacterial causative organism in case of -ve cultures

Suspension of treatment for 24 hours	Re-scrape with inoculation on broader range of culture media

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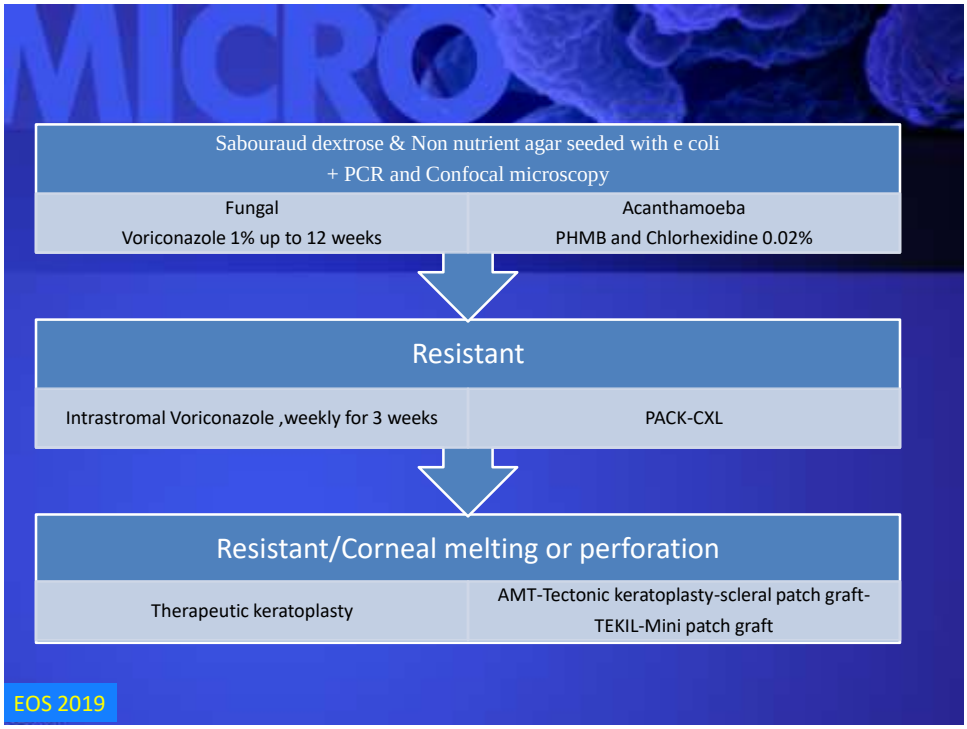
MICRO
Sabouraud dextrose & Non nutrient agar seeded with e coli
+ PCR and Confocal microscopy
Fungal
Voriconazole 1% up to 12 weeks
Acanthamoeba
PHMB and Chlorhexidine 0.02%
Resistant
Intrastromal Voriconazole ,weekly for 3 weeks
PACK-CXL
Resistant/Corneal melting or perforation
Therapeutic keratoplasty
AMT-Tectonic keratoplasty-scleral patch graft-
TEKIL-Mini patch graft
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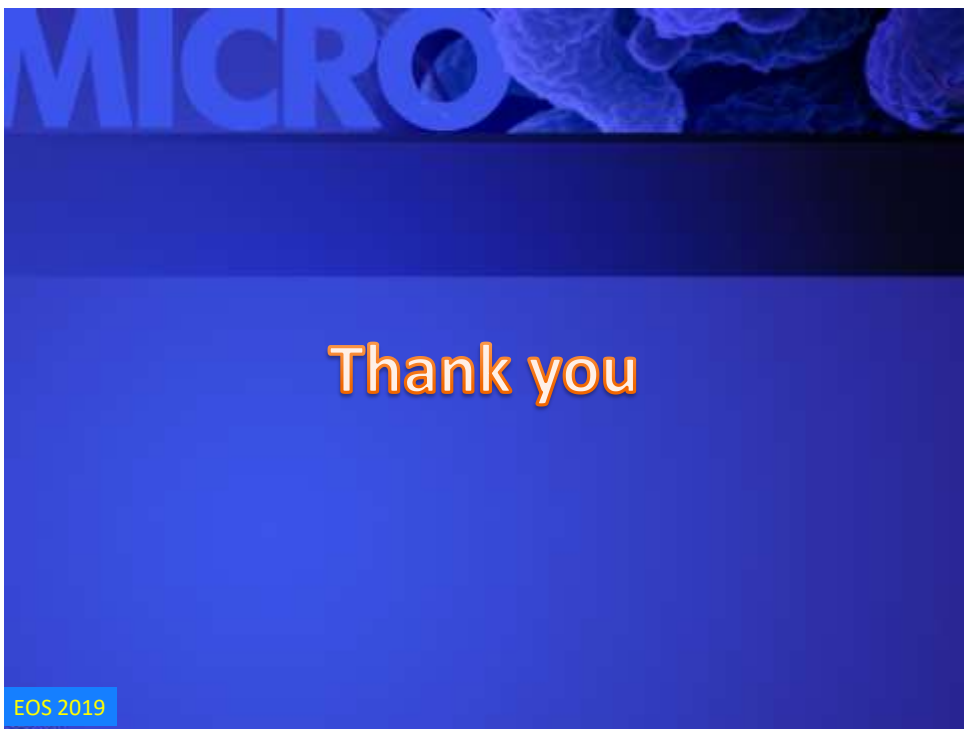
MICRO
Thank you
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