Course in External Ocular Disease

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Bacterial Conjunctivitis

Dr. Everardo Barojas Weber

ANATOMICAL CHARACTERISTICS OF THE CONJUNCTIVA

The tarsal conjunctiva is closely adhered to the tarsus, the bulbar conjunctiva is easily displaced from the fornix up to nearly the limbus (2 mm). The subepithelium is constituted of loose conjunctival tissue and some inflammatory cells; this tissue continues to the sclera and tarsus where it is transformed into dense fibrous tissue.

CONJUNCTIVAL BACTERIOLOGY

Bacteria do not develop easily in the conjunctiva because of the lower temperatures which produce tear evaporation and because of the moderate vascularization. Tears help with lysozymes, which have effective bacteriostatic and a mechanical factor, which is more important. The conjunctiva normally contains non-pathogenic organisms, which can be confused with pathogenic organisms because of their similarities: **Corynebacterium xerosis** is similar to **Corynebacterium diphtheriae,** but the differentiation requires culturing; diplococci is similar to pneumococci. **Staphylococcus epidermidis** is the most frequently encountered in the lid margin. Some types of Hemophilus can be found in the cul de sac.

CONJUNCTIVAL HYPEREMIA

Transitory: Caused by foreign bodies, alterations in the position of the lashes, etc.

Chronic or recurrent: Caused by environmental conditions, refractive errors, alterations in metabolism, allergic processes, etc.

Changes in secretion characteristics should be taken into consideration to make a diagnosis of infection.

The symptomatology is multiple, when the tearing is intense and unilateral, the lacrimal apparatus should be examined.

CONJUNCTIVAL INFLAMMATION

This can be present with or without infection. When there is no adequate response to antibiotic treatment, then one would think the process is not infectious. The type of secretion is important to the diagnosis and initiation of treatment.

Chemosis indicates accumulation of exudate under the epithelium and is present in acute cases. In children when the inflammatory problem is unilateral one cannot neglect the possibility of foreign body. Staining the cornea with fluorescein can help in the diagnosis. The preauricular node is characteristic of viral processes but can also be encountered in bacterial infections (gonococcus); the purulent secretion characteristic of bacterial processes can present itself in viral infections (inclusion conjunctivitis).

The inflammatory process which is not produced by bacteria, virus, fungi, or parasites should be investigated for possible allergy, toxicity to medications, nutritional factors, or alterations of the cornea, eyelid, or tear-duct associated problems. The cli-

nical history is of prime importance in children, as it can used to analyze a previous trauma, a respiratory infection, or skin lesions of the eyelids.

INVESTIGATION OF THE CONJUNCTIVAL INFECTIOUS PROCESS

Culturing secretion: With sterile cotton moistened in 5% glucose solution, collect the secretion of the cul de sac and place in the appropriate media.

Scraping the epithelium: After local anesthetic, scrape the epithelium with a sterile platinum blade and place the matter on a slide for giemsa stain. Also, this can be used for cultures or for investigation of virus in tissue cultures (HeLa cells, rabbit kidney cells, or chick embryos).

Neutralizing antibody titers: Only for viral investigations. The cells accumulated in the scraping of the conjunctiva can be used to make a diagnostic decision of the type of cells.

Polymorphonuclear antibodies	Bacterial — staphylococci, gonococci Viral — inclusion, lymph, veneral, trachoma
Mononuclear antibodies	Herpes simplex, epidemic keratoconjunctivitis
Plasma cells	Trachoma
Eosinophils	Allergic and vernal conjunctivits
Basophils	Allergy, trachoma
Multinuclear cells	Virus
Inclusion bodies	Virus

Causes of Bacterial Conjuctivitis
Grady Memorial Hospital, Atlanta (1973-1974)

Gram-positive cocci	
Staphylococcus aureus	87
Other staphylococcus	10
Streptococcus pneumoniae (pneumococcus)	19
Streptococcus pyogenes	2
Streptococcus viridans	6
Gram-negative cocci	
Neisseria gonorrheae	6
Gram-negative diplobacillus	
Various types of moraxella	4
Gram-ngative rods	
Various species of hemophilus	42
Acinetobacter calcoaceticus	9
Proteus sp.	4
Klebsiella pneumoniae	3
Serratia marcescens	1
Others	8

TREATMENT OF BACTERIAL CONJUNCTIVAL INFECTIONS

Staphylococcus, estreptococcus and hemophilus infections: First topical treatment: Polymixin B, Bacitracin, and Neomicin. Neomicin is more inconvenient because it is toxic to the corneal epithelium. The sulfonamides are less active. Staphylococcus has rapid resistance to erythromycin. Chloramphenicol is not toxic but it has less of an effective spectrum than the combination of antibiotics. Gentamicin should be reserved for infections resistant to other antibiotics.

Classic treatment of Morax-Axenfeld bacillus is zinc sulfate 0.25 — 0.5% and tetracycline ointment. Systemic antibiotics can be justified in diphtherium and gonococcal processes.

Diphtherium	Penicillin procaine 300,000 units to 1 million, I.M./day Erythromycin 1-2 grains/day Tetanus antitoxin: Adults: 20-40,000 units Children (less than 2 yrs): 5-6,000 units Children (older than 2 yrs): 7-8,000 units
Gonococcus	Penicillin procaine 3-600,000 units I.M./day If there is resistance to tetracycline: Tropically: silver nitrate 1%, penicillin procaine 100,000 units per ml, tetracycline 5mg per ml

CLASSIFICATION OF BACTERIAL CONJUNCTIVITIS

Acute:	Serous Catharral Mucopurulent Membranous
Chronic:	Simple chronic Angular Follicular Specific infection

Catharral and mucopurulent conjunctivitis: This is characterized by general redness, abundant secretion from the cul de sac and eyelashes, filamentous secretion of the cornea. This can be produced by multiple organisms, the most frequent of which is **Staphylococcus aureus,** in children it is pneumococcus, and in warm climates, Koch-Weeks bacillus. It is contagious with direct contact.

Purulent conjunctivitis: There are two types: adult and newborn. In the adult there is direct contamination of the genitals. The symptomatology is more intense with chemosis and frequent corneal lesions. They can have painful and purulent preauricular node. It is very important to use prophylactic measures for the contralateral eye.

This disease is less frequent in the newborn and can be produced by **Neisseria gonorrheae,** staphylococcus or **Chlamydial oculogenitalis** (more frequent in the USA). Although secretion before 8 days is suspect since normally there are no tears, the symptoms are a large amount of purulent secretion, lid edema and corneal lesion. The incubation period in **C. oculogenitalis** is greater than 6-8 days.

Membranous conjunctivitis: The membranes in the inflammatory process of the conjunctiva are fibrinous, though they can be superficial (pseudomembranous) or in the same epithelium (membranous). The infections can be present in diphtheria or in cases where there is not diphtheria but severe streptococcus. The principal characteristics of the process is the tendency for necrosis and formation of symblepharon. Also, it is possible to have a nodular, suppurative preauricular node.

Simple chronic conjunctivitis: This can present as sequelae to an acute process or as secondary to multiple factors. The symptomatology is varied. There can be ocular itching and burning with sandy sensation, differentiated from keratoconjunctivitis sicca. The principal signs are diffuse redness and thickening of the conjunctiva but with minimal secretion.

Angular conjunctivitis: Irritation of the conjunctiva in the interpalpebral space with excoriation of the skin of the palpebral angles. The principal cause is moraxella. There is little secretion or discomfort. It is frequent to see peripheral ulcers.

TBC conjunctivitis: This can present in multiple ways, the most characteristic form is an epithelial ulceration of the chronic type. There is no preauricular node. In the young this process can be an exogenous primary infection. The treatment must be local surgery with systemic medications.

Sarcodosis conjunctivitis: This presents like a nodular lesion in the cul de sac. The diagnosis is made by biopsy. Systemic treatment.

Syphilitic conjunctivitis: It is possible to find a primary chancre in the conjunctiva or secondary to palpebral ulcer with regional nodularity.

Viral and Chlamydial Keratoconjunctivitis

Dan. B. Jones, M.D.

I. Causes of viral keratoconjunctivitis

		Predominant	Less Common
DNA			
	Herpes virus	Herpes simplex Varicella-zoster	Epstein-Barr Cytomegalovirus
	Adenovirus	Types 3, 7, 8, 19	Types 4, 11, 14
	Poxvirus		Vaccinia Variola Molluscum contagiosum
RNA			
	Myxovirus		Influenza Newcastle disease Mumps Rubella Rubeola
	Papovavirus		Verruca
	Picornavirus		Acute hemorrhagic conjunctivitis (Enterovirus EV^{70})

II. Potential mechanisms of disease

A. Replicating virus

B. Hypersensitivity reaction

1. Incomplete virus; viral antigen
2. Components of host tissue

C. Altered host structure

III. Herpes zoster keratoconjunctivitis

A. Basic features of the virus

1. Man is the only host; affinity for cells of ectodermal origin
2. Primary disease = varicella (chicken pox); occurs in a host without immunity
3. Recurrent disease = herpes zoster; presumed latency state in nerve ganglia; spread along dermatome pattern
4. No effective antiviral therapy; intravenous vidarabine may be efficacious in certain immunocompromised hosts
5 Zoster immune globulin used only to prevent or modify vacella in non-immune host
6. Laboratory diagnosis
   a. Giemsa stain of scrapings from base of vesicles; multinucleated giant cells and intranuclear inclusions

b. Tissue culture: cytopathic effect in 1-3 days
c. Indirect immunofluorescent antibody determination: 2-4 hours

B. Clinical features

1. "Non-specific" conjunctivitis; rarely follicular
2. Vesicles may occur at the lid margin
3. Severity of conjunctival and corneal involvement **not** directly related to:
   a. Cutaneous involvement of nasociliary distribution
   b. Severity and distribution of cutaneous disease
4. Mechanisms of corneal disease
   a. Replicating virus (?)
      1) Punctate epithelial keratitis
      2) Macroepithelial ulceration
      3) **No specific therapy**
   b. Hypersensitivity reaction
      1) Punctate subepithelial and epithelial keratitis
      2) Stromal keratitis
      3) Scleritis; sclerokeratitis
      4) **Therapy:** corticosteroids
   c. Altered structure
      1) Punctate and plaque-like epithelial keratopathy
         a) Mimics herpes simplex dendritiform keratitis
         b) **Therapy:** 10% acetylcysteine drops, low viscosity tear substitutes, soft contact lens
      2) Trophic ulceration
         a) Controversial mechanisms: role of dennervation versus disruption of preocular tear film
         b) **Therapy:** tear substitutes, occlusion, soft contact lens, tarsorrhaphy: complex problem

IV. Adenovirus keratoconjunctivitis

A. Basic features of the virus

1. Double stranded DNA
2. Stable at 25C-40C; resistant to lipid solvents
3. 33 well defined human serotypes
   a. Types 1. 2, 5, 6 generally endemic in the U.S.A.; produce pharyngoconjunctival fever, pharyngitis, and pneumonia in children
   b. Types 3, 4, 7, 8, and 19 usually associated with epidemics
4. Incubation period: 5-8 days
5. Prolonged virus excretion: 10-12 days in the conjunctiva
6. Laboratory identification
   a. Tissue culture: cytopathic effect in 2-28 days
   b. Indirect immunofluorescent antibody test: 2-4 hours
   c. Serology: form-fold or greater change in CF (group) antibody in acute and convalescent sera
7. No effective antiviral agent

B. Clinical features

1. "Classic" differentiation of pharyngoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC) not always valid; ie., illness may precede or accompany EKC
   a. PCF: Types 3, 7, 1, 4, 14
   b. EKC: Types 8, 11, 19
2. Preauricular lymphadenopathy; lid edema
3. Conjunctival involvement
   a. Unilateral or bilateral

b. Serous discharge
c. Graded severity: hyperemia and chemosis may "mask" follicle formation
d. Minimal follicle response in the super tarsal conjunctiva
e. Hemorrhagic component
f. Membrane formation
g. Potential for conjunctival scarring
h. **Therapy:** topical decongestants; no evidence of efficacy of corticosteroids; limitation of dissemination

4. Mechanisms of corneal disease
   a. Replicating virus (?): punctate epithelial keratitis: no efective therapy
   b. Hypersensitivity reaction (?)
      1) Progressive intraepithelial and anterior stromal (subepithelial) keratitis
      2) Deep stromal keratitis (rare)
      3) **Therapy:** topical corticosteroids for **suppression** of severe epithelial or anterior stromal infiltrates

V. Chlamydial keratoconjunctivitis

A. Basic features of the agent

1. Obligate intracellular parasite; able to induce self phagocytosis
2. Differ from viruses by the presence of both DNA and RNA; discrete cell wall resembles gram-negative bacteria
3. Multiply by binary fission
4. Developmental cycle of 48 hours: elementary body (inactive metabolically) → initial body (active metabolically) → condensation to elementary body (classic inclusion body)
5. Antigens inhibit lysosomal fusion with phagosomes which contain the agent
6. Mechanism of latency probably attributable to low levels of multiplication held in check by host defenses
7. Spectrum of human disease
8. Laboratory diagnosis
   a. Conjunctival scraping stained by giemsa: high incidence (56%) of false-negative scrapings in adult inclusion conjunctivitis
   b. McCoy tisue culture method for isolation
   c. Fluorescent antibody stain of conjunctival scrapings
   d. Serological tests
      1) Micro immunofluorescence
      2) Complement fixation test

Table 1 — Human Diseases Caused by Chlamydia

Species	Serotype*	Disease
C. psittaci	Many unidentified serotypes	Psittacosis
C. trachomatis	L-1, L-2, L-3	Lymphogranuloma venereum
C. trachomatis	A, B, Ba, C	Hyperendemic blinding trachoma
C. trachomatis	D, E, F, G, H, I, J, K	Inclusion conjunctivitis (adult and newborn), nongonococcal urethritis, cervicitis, salpingitis, proctitis, epididymitis and pneumonia of newborns

* Predominant, but no exclusive association of serotype with disease.

B. Ocular infections **other than** trachoma

1. Neonatal conjunctivitis
   a. Incidence of chlamydial infection of the cervix itn pregnant women may range from 5-13%; 40-50% of exposed infants develop conjunctivitis
   b. Ineffectiveness of silver nitrate
   c. Incubation period: 5-12 days post partum; early infection can occur if placental membranes rupture before delivery
   d. Acute signs indistinguishable from bacterial forms of conjunctivitis; lid edema, serous to muco-purulent discharge conjunctival hyperemia, membrane development
   e. Follicles **may** develop if disease persists untreated for 3-6 weeks
   f. Minimla sequelae: conjunctival scarring, superficial pannus
   g. Other forms of neonatal infection
      1) Rhinitis
      2) Pneumonia
      3) Otitis media
   h. **Therapy:** topical tetracycline or erythromycin ointment; oral erythromycin (50mg/Kg/day); oral tetracycilne for the mother and sexual partner
2. Adult inclusion conjunctivitis (TRIC punctate keratitis)
   a. Role of the genital tract or reservoir if the agent
   b. Incubation period 5-19 days
   c. Clinical features
      1) Unilateral or bilateral
      2) Preauricular lymphadenopathy
      3) Mucopurulent discharge
      4) Mixed papillary follicular conjunctival reaction
      5) Limbal edema
      6) Micropannus formation
      7) Coarse, pleomorphic, randomly distributed punctate epithelial keratitis; evolution to anterior stromal infiltrates
      8) Iritis = rare
      9) Chronic course if untreated: 6-9 months
      10) Post inflammatory conjunctival scarring
   d. **Therapy:** Tetracycline or erythromycin ointment, 5 times daily (limited effectiveness); tetracycline, 1.0-1.5 gm daily for 3 weeks or doxycycline, 100 gm daily for 7 days (may substitute oral erythromycin)
   e. In the presence of specific antichlamydial therapy, topical corticosteroids may be utilized to suppress the keratitis

Ocular infections secondary to herpes simplex

Dr. Rubens Belfort, Jr.

INTRODUCTION

Ocular herpes simplex presents increasing importance in general ophthalmology because the diagnosis is more adequate, there is higher control of bacterial infection, and there is a higher survival rate of patients with compromised immunological systems. Herpes simplex is DNA virus that belongs to the same group as herpes zoster, varicella, cytomegalovirus, and Epstein-Barr virus. It is an infection with high prevalence in the world. In São Paulo, Brazil, 70% of the population have antiherpes antibodies. At the age of two years, high positivity is already noted. In the USA about 90% of the population has the infection.

There are two types of herpes simplex virus: 1 and 2. Type 1, or classic, is the more frequent and it is related to the

mouth and the eye. Type 2 can be seen in the eye or in the genitalia, being the most important cause of veneral disease and also of congenital disease with systemic conditions in the eye such as retinitis and cataracts. Some cases of keratitis are similar to herpes simplex type 1.

The natural history is better known fancy in a specific. sub-clinic, or localized now. The primary infection appears in incondition. Rarely is herpes simplex a primary infection in the eye. After an infection by herpes simplex, the herpes may persist hidden in the central nervous system for many years. In some people the virus may show up in the surface of the organism such as the ocular conjunctiva or it can be excreted in the tears. In some people due to unknown mechanisms probably related to the prostaglandin E_2, there are some clinical pictures of secondary herpes simplex such as in the skin, genitalia, lips, eyes, etc., with herpetic infections in the epithelial cells with replicating viral and necrosis. It is also known that some factors may be the cause of these recurrences such as fevers, ultraviolet light, trauma, steroids, immunosuppressants, and alterations in the hormones.

DIAGNOSIS, CLINICAL PICTURE, AND TREATMENT

Ocular herpes simplex presents as large pleomorphism. It is an agent that resembles many ophthalmological entities. Table 1 shows the most important points for its diagnosis. A Dendritic lesion is not pathognomonic for herpes simplex. Low corneal sensitivity can be seen in some other situations such as diabetes, herpes zoster, corneal dystrophies, chronic corneal edema, use of contact lenses, keratoplasty, aphakia, etc. Except for some special situations the laboratory is of poor help because of the difficulties in the interpretation of the results and some technical difficulties.

Table 1 — Diagnosis of Ocular Herpes Simplex

HISTORY:	Previous corneal ulcers, extraocular herpes, immunodeficiencies, treatment with steroids
OCULAR EXAMINATION:	Dendritic lesions, low or absent corneal sensitivity, biomicroscopic findings
LABORATORY EXAMINATION:	Cytological examination (giemsa, Papanicolau, immunofluorescence), electromicroscopy and virus cultures

Table 2 presents the clinical pictures more common with ocular herpes simplex. We will talk about the most important ones.

Primary ocular herpes simplex: This is an acute follicular conjunctivitis with membranes and with enlargement of the preauricular node. Also, skin lesions in the lids unilateral ulcerative blepharitis, dendritic keratitis or punctate keratitis with lesions of 1-2 mm of diameter. This lasts for a few weeks. The clinical picture is generally benign with clinical observation or with IDU. It is more severe in patients with immunodeficiencies or under treatment with steroids.

Secondary ocular herpes simplex: Dendritic keratitis: Visual discomfort with superficial herpes simplex is seen very little in adults. This is the opposite to what is seen in children and in some forms in adults when they are accompanied by uveitis. Its diagnosis is done with the slit lamp and with staining with fluorescein. Epithelial herpes simplex can be treated with de-epithelialization or with antiviral drugs, both have some advantages and disadvantages but both give the same result. Among the methods of de-epithelialization we prefer the mechanical one which is done in the affected area and also around the ulcer. Immediately we put cycloplegics in the eye and we also patch it. The patient is seen 24 hours later and we keep the occlusion as long as he remains with the ulcer.

Table 2 — Clinical Patterns of Herpes Simplex*

PRIMARY HERPES SIMPLEX:	extraocular, ocular		
SECONDARY HERPES SIMPLEX:			
Extraocular		Superficial:	dendritic geographic stromal ulcer
Ocular	Corneal	Profound:	disciform with or without ulcer necrotic with or without ulcer bullous post-herpetic keratitis
	Keratouveitic		
	Uveitic:	Anterior Posterior Diffuse	

* All of the corneal forms can be accompanied by iridocyclitis.

Treatment with antiviral drugs can be done with IDU, ARA-A, or with F_3T. Both IDU and ARA-A seem to have similar potency and toxicity but the viral resistance and sensitivity are not the same for these two drugs. You can use ARA-A when the therapy with IDU is not working well. The F_3T or Trifluorothymidine is probably the best anti-herpetic medication known so far but it is not easily obtained. It seems to have a low toxicity and a good penetration in the stroma and into the anterior chamber when you put a drop in the cornea. This is the opposite to IDU or ARA-A that remain in the epithelium and anterior stroma. We use IDU drops every hour during the day and in ointment form at night or ARA-A ointment four times a day for 10 days before we consider the case as resistant to medication. These medications have some secondary effects in the eye such as follicular conjunctivitis, opacities, microerosions in the cornea, skin alterations, scarring of the conjunctiva, loss of the cul de sac and occlusion of the punctum. These medications also predispose the eye to infections by opportunistic bacteria.

Geographic ulcers: Large herpetic ulcers, amoeboids with ill-defined edges are called geographic. These ulcers are initially treated in the same way as dendritic ulcers. If this treatment fails, we use firm occlusion with antiviral ointment for a longer period. In some difficult cases we use therapeutic contact lenses of permanent wear, using IDU drops four times a day, antibiotics, and mydriatics twice a day. Sometimes they are very difficult to treat. They may recur in herpetic infections which reulcerate because of alteration in the epithelial basement membrane causing post-herpetic keratopathy (previously called meta-herpetics).

Post-herpetic keratopathy: Ulcers are caused by detachment of the epithelium from the basement membrane. Characteristically, these patients also have low corneal sensitivity and can be infected or inflamed directly in relation to the herpes. Slit lamp examination shows an ulcer with elevated edges due to the piling up of cells. The epithelium around the ulcer is adhered and looks like ground glass. The treatment consists of stopping the present medications such as anti-herpetics, steroids, and placing a soft contact lens, applying sterile physiologic saline many times a day, and antibiotics and cycloplegics twice daily. After the ulcer is cured, you have to continue with the use of the soft contact lens for a long period of time and also after you discontinue it, you have to use a lubricating ointment at night in order to protect the corneal epithelium.

Herpetic disciform keratitis: It is a disciform lesion with low or absent corneal sensation, edema of epithelium and stroma, striae in Descemet's membrane, and keratitic precipitates. The differential diagnosis includes herpes zoster, varicella, vaccinia, and corneal trauma. It may be seen in the fifth day after corneal epithelial lesion and may disappear without any treatment in a few weeks. They may progress and produce interstitial keratitis and necrotizing keratitis. Don't use steroids in the disciform herpetic keratitis and treat the patient with cycloplegics and psychological support. We use steroids when the epithelial ulcer presents stromal necrosis, the patient has important uveitis, the process does not change for many weeks, or when there is some decrease in vision and is interfering with the patient's activities. It is important to know the difference between edematous process in the cornea that responds well to steroid therapy, from fibrosis or scarring in the cornea which is refractory to that type of treatment. Our treatment includes Dexamethasone eye drops 2-4 times a day, mydriatics, cycloplegics, and IDU every three hours in order to avoid recurrence of the epithelial disease. After a few days, start the patient to the point of using one drop of applications and diluting it. Try to get the patient to the point of using one drop of Dexamethasone once a week. Avoid sudden changes in the therapeutic trial because patients with herpes are very sensitive to steroids.

Necrotizing herpetic keratitis: These are similar to bacterial or fungal abscesses and look like white cheese with dense infiltrations, neovascularization, important fibrosis, uveitis, and are sometimes associated with a disciform process. The treatment has a poor response. Steroids are contraindicated and antiviral drugs are worthless. Treatment in the acute phase is limited to the prevention and control of complications such as secondary glaucoma, destructive uveitis, melting, descemetocele, and perforations.

Herpetic keratouveitis: The clinical picture has many symptoms such as pain, tearing, photophobia, active corneal lesion with scarring, compromise of corneal sensitivity, ciliary congestion, 1-2+ cells and flare in the anterior chamber, KPs behind the corneal lesion, myotic pupil which is difficult to dilate with mydriatics. There can be some ocular hypertensive episodes. You can see hypopyon secondary to intense infiltration with polymorphonuclear leukocytes and hyphema due to vascularization

Therapeutic principles in iridocyclitis include:

a) Control of the destructive effects of inflammation
b) Don't use long-term or release steroids or deposit steroids
c) Use steroid when the patient has already been treated with steroids
d) Use the smallest doses possible to control secondary destruction, tapering them off slowly

Therapy of herpetic iridocyclitis: 1) Unique strategic therapy, 2) blocking of factors that produce pain and photophobia, 3) avoid posterior synechiae, 4) constant control of intraocular pressure, 5) psychological support.

Therapy for severe herpetic iridocyclitis without necrosis or ulcer: IDU drops every three hours or ARA-A four times a day, Dexamethasone three times daily, and diluted steroid in a ratio of 1:10 as soon as possible. It is necessary, use Prednisone V. O. 40 mg/day.

Treatment for severe herpetic iridocyclitis with necrosis or ulcer: IDU drops every three hours or ARA-A four times a day. Prednisone 40-60 mg/day, therapeutic soft lens, medications against collagenase, surgery if it is necessary.

Therapy for secondary glaucoma due to herpes simplex: a) Epinefrin, diamox, steroids, timolol; b) osmotics; c) cyclocryotherapy.

Surgical treatment for complications and consequences due to herpes simplex:

1) Keratoplasty
2) Conjunctival flap
3) Corneal adhesives

There are some immunological medications under investigation and they do not prevent the recurrence such as: interferon, levamisole, transference factor.

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Tear Dysfunction States

Michael A. Lemp, M.D.

I. Components of the tear film
   A. Lipid
   B. Aqueous
   C. Mucin

II. Structure and formation of tear film
   A. Through layered structure
   B. Tear film stability

III. Tear deficiency states
   A. Aqueous deficiency
   B. Mucin deficiency
   C. Lipid abnormalities
   D. Lid surfacing dysfunction
   E. Epitheliopathy

IV. Diagnostic tests
   A. Slit lamp examination
      1. Scanty marginal tear strip
      2. Increased tear film debris
      3. Superficial punctate erosions
      4. Epithelial filaments
      5. Coarse mucous plaques
      6. Symplepharon
   B. Rose bengal staining
   C. Schirmer tests
   D. Tear film breakup (BUT)
   E. Tear lysozyme levels
   F. Tear osmolarity
   G. Conjunctival biopsy
   H. Labial biopsy
   I. Fluorescein dilution

V. Treatment
   A. Supplementation of tears
      1. Tear substitutes
      2. Sustained release inserts
   B. Preservation of tears
      1. Punctal occlusion
      2. Punctal plugs
      3. Moist chamber
   C. Hormones
   D. Bandage lenses
   E. Surgery

Bacterial Keratitis

Dan B. Jones, M.D.

I. BASIC SCHEME FOR MANAGEMENT

- A. Suspect bacterial keratitis
- B. Determine the severity of disease
- C. Perform the correct laboratory studies
- D. Initiate antimicrobial therapy
- E. Modify the initial antimicrobial therapy
- F. Control the inflammatory response
- G. Correct the structural alterations

II. PATHOGENESIS OF KERATITIS

- A. The concept of opportunistic infections ond the outmoded "pathogen" theory
- B. Predisposing factors
  - 1. Exogenous
    - a. Trauma
    - b. Foreign material
    - c. Drug or irradiation-induced alteration in host defenses
  - 2. Host
    - a. Alteration in defenses
      - (1) Local
      - (2) Systemic
    - b. Antecedent corneal disease
      - (1) Epithelial ulceration
      - (2) Stromal necrosis
    - c. Tear dysfunction state
    - d. Corneal hypesthesia or analgesia
    - e. Malposition of the lids
- C. Responsible organisms
  - 1. Common: the dominant four classes
    - a. **Staphylococcus aureus; S. epidermidis**
    - b. **Streptococcus pneumoniae;** other streptococci
    - c. **Pseudomonas aeruginosa**
    - d. **Enterobacteriaceae:** Proteus, Enterobacter, Serratia
  - 2. Less common: special considerations
    - a. Neisseria: **N. gonorrhoeae, N. meningitidis**
    - b. Moraxella
    - c. Azotobacter
    - d. Mycobacterium species
    - e. Non-sporeforming anaerobic bacteria
    - f. Nocardia, Streptomyces
- D. Mechanisms of disease
  - 1. The organism
    - a. Invasion of tissue
    - b. Release of toxic substances
      - (1) Exotoxins
        - a) Exotoxin A
        - b) Protease
        - c) Hemolysin
        - d) Collagenase
      - (2) Endotoxin
  - 2. The host
    - a. Release of lysosomal enzyme
    - b. The "respiratory burst"

III. CLINICAL DIAGNOSIS

A. Determinants of the severity of keratitis and clinical signs
   1. The strain of the organism
   2. The host
   3. The conditions under which the two are combined
   4. Duration of the process
   5. Antecedent therapy

B. Signs **suggestive** of infection
   1. Previously normal eye
      a. Rapide development (24-48 hours) of keratitis following trauma
      b. Sharply demarcated epithelial ulceration and deep stromal abscess; most typical of staphylococcus and **Streptococcus pneumoniae**
      c. Mucopurulent exudate adherent to the ulcer surface
      d. Liquefactive stromal necrosis; highly suggestive of pseudomonas
      e. Diffuse epithelial edema and stromal cellular infiltrate of the distal cornea
      f. Iritis, development of hypopyon (**not** a distinctive sign)
   2. Abnormal eye: pre-existing epithelial ulceration
      a. Increased pain
      b. Increased area of epithelial ulceration
      c. Development of or increase in stromal suppuration
      d. Development of or increase in anterior segment inflammation

IV. LABORATORY DIAGNOSIS

A. Basic principles
   1. Follow one technique for all suspected microbial keratitis
   2. Maintain complete patient control to assure adequate sampling of the area of corneal suppuration
      a. Akinesia by local injection in noncooperative adults
      b. General anesthesia in children
   3. Obtain multiple samples from areas of suppuration for **each** stain and media
   4. **Fix** the smears of corneal scrapings promptly in methyl alcohol; **not** by heat
   5. Inoculate material directly to fresh media which has been warmed to room temperature

B. Procedure
   1. Conjunctival cultures (prior to application of proparacaine hydrochloride 0.5%)
      a. Bilateral
         (1) Blood agar plate
         (2) Chocolate agar plate
         (3) Sabouraud's agar plate
      b. Ipsilateral: thioglycollate broth
   2. Corneal scrapings (after application of proparacaine hydrochloride 0.5%)
      a. Smear for stains
         (1) Gram (bacteria and fungi)
         (2) Giemsa (fungi)
         (3) Reserve for special stains: acid-fast, PAS, methenamine silver
      b. Culture
         (1) Blood agar plate
         (2) Chocolate agar plate
         (3) Thioglycollate broth
         (4) Sabouraud's agar plate
         (5) Brain heart infusion broth

V. INITIAL THERAPY

A. Potential guidelines for selection of the type and routes of initial antibacterial therapy
   1. Status of the cornea prior to the development of keratitis
   2. Antecedent antibacterial therapy
   3. Severity of the keratitis
   4. Specific biomicroscopic features
   5. Utilization of corneal scrapings
      a. Stains
      b. Limulus lysate assay for endotoxin (gram-negative rods)

B. Severity grade for keratitis

Feature	Grade		
	I	II	III
Location	Non-axial	Central or peripheral	Central or peripheral
Area	< 2 mm	> 2 mm < 6 mm	> 6 mm
Depth	Superficial 1/3	Superficial 2/3	Extending to inner **1/3**
Structural alteration	Nil	Not approaching the inner 1/3	Threatened or existing perforation
Anterior segment inflammation	Minimal	Moderate or severe	Severe; hypopyon; fibrinous exudate

C. Guidelines for selection of initial antibiotics
   1. Criteria for selection of **specific therapy** based on the gram stain morphology (see Table 1).
      a. Grade I or II severity keratitis
      b. No antecedent antibacterial therapy
      c. Adequate sampling from the area of suppuration
      d. Confidence in the interpretation of the gram stain

Table 1 — Initial antibiotics in bacterial keratitis

ORGANISM IN GRAM STAIN		PRIMARY AGENTS	ALTERNATE AGENTS
SPECIFIC THERAPY			
Gram-positive cocci	**Top**[1]	A cephalosporin	Bacitracin
	Subc[2]	Cephaloridine	Methicillin
	IV[3]	Methicillin and penicillin G	A cephalosporin[4]
Grom-positive rods	**Top**	Penicillin G	
	Subc	Penicillin G	
	IV[3]	Penicillin G	
Gram-negative cocci	**Top**	Penicillin G	Erythromycin or tetracycline
	Subc	Penicillin G	Erythromycin
	IV[5]	Penicillin G	**IM**[6] Spectinomycin
Grom-positive rods	**Top**	Gentamicin and carbenicillin	Gentamicin and colistin
	Subc	Gentamicin and carbenicillin	Gentamicin and colistin
	IV[3]	Gentamicin and carbenicillin	Gentamicin[8] and colistin or polymyxin B
BROAD THERAPY			
None or mixed	**Top**	A cephalosporin[4] and gentamicin	Bacitracin and gentamicin
	Subc	Cephaloridine and gentamicin	Methicillin and gentamicin
	IV[3]	Methicillin and gentamicin[8]	A cephalosporin[4] and gentamicin[7,8]

1 **Top** = topical
2 **Subc** = subconjunctival injection
3 **IV** = intravenous administration. Reserve for Grade III severity keratitis
4 Insufficient data to distinguish among injectable cephalosporin derivatives. Cephaloridine is less irritating to tissue but should **NOT** be used for intravenous therapy.
5 Intravenous penicillin G should be administered for all suspected Neisseria conjunctivitis or keratitis.
6 Intramuscular spectinomycin should be administered for suspected Neisseria conjunctivitis or keratitis in a patient with penicillin allergy. Recent appearance of penicillinase producing strains of **N. gonorrhoeae** may prompt increased utilization of spectinomycin.
7 Increased nephrotoxicity is assocaited with parenteral gentamicin and certain cephalosporin antibiotics (cephaloridine and cephalothin).
8 Intravenous gentamicin must be given **slowly** over at least 90 minutes.

(Revised January, 1979)

2. Indications for use of **broad therapy** (See Table 1)
   a. Absence of organisms in gram stain in Grade I or II severity keratitis

   OR

   b. Antecedent antibacterial therapy in Grade II severity keratitis **regardless** of the gram stain morphology

   OR

   c. Grade III severity keratitis **regardless** of other factors
3. Considerations for possibly delaying administration of antibiotics in the absence of organisms in gram stain
   a. Grade I severity keratitis
   b. Suspicion of fungal keratitis
   c. Suspicion of other mechanisms for keratitis
      (1) Drug induced
      (2) Herpes simplex stromal keratitis

D. Concentrations and dosages (See Table 2)

E. Guidelines for frequency and route of administration based on severity of keratitis

1. Grade I severity: Concentrated drops: 15-30 minutes intervals
   Consider subconjunctival administration
2. Grade II severity: Concentrated drops: 15 minutes intervals
   Subconjunctival administration; once or twice daily
3. Grade III severity: Concentrated drops: 15 minute intervals
   Subconjunctival administration twice daily
   Intravenous antibiotics

Table 2 — Concentrations and dosages of principal antibacterial agents

Antibiotic	Trade Names	Dosage		
		Topical	Subconjunctival	Intravenous[2]
Bacitracin	Bacitracin	5,000-10,000 units/ml	10,000 units	———
Carbenicillin	Geopen	4.0 mg/ml	100 mg	300-400 mg/Kg[3]
Cephaloridine	Loridine	50 mg/ml	100 mg	———
Cefazolin	Ancef, kef zol	50 mg/ml	100 mg	4.0 gm/day
Colistin	Coly-Mycin M[1], Coly-Mycin S	5-10 mg/ml	25 mg	———
Gentamicin	Garamycin	8-15 mg/ml	20-40 mg	3.0-7.0 mg/kg/day[4]
Methicillin	Celbenin, Staphcillin	———	100 mg	200 mg/Kg/day[3]
Neomycin	Mycifradin	5-8 mg/ml	250-500 mg	———
Penicillin G	(multiple)	100,000 units/ml	0.5-1.0 megaunits	2.0-6.0 megaunits/4 hr
Vancomycin	Vancocin	50 mg/ml	25 mg	1.0 gm/12 hr

1 Coly-Mycin M is sodium colistin for parenteral administration; Coly-Mycin S is colistin sufate for topical administration
2 Adult dosages; for use in children refer to other sources
3 Divided into 6 doses (4-hourly intervals)
4 Must be given slowly over 90 minutes; 3 divided doses

(Revised January, 1979)

F. Other therapy
   1. Atropine 1% and neosynephrine 2.5-10% drops, 4-6 hourly intervals
   2. Oral diamox for ocular hypertension
   3. Sedation and analgesia

VI. MODIFICATION OF INITIAL THERAPY

A. Determinants: do **not** alter effective therapy based solely on the laboratory determinations
   1. Results of the corneal cultures and sensitivities determination
   2. The clinical response
   3. Tolerance of the antibiotics
   4. Status of the cornea prior to the development of keratitis, i.e. consideration of the role of corticosteroids

B. Measures of improvement
   1. Blunting of the perimeter of the stromal suppuration
   2. Reduction in the density of stromal suppuration
   3. Reduction in cellular infiltrate and edema in the surrounding stroma
   4. Reduction in anterior chamber inflammation
   5. Progressive re-epithelialization

C. Modification of antimicrobial therapy based on the results of the corneal cultures (Table 3)

Table 3 — Modification of antibiotic therapy in **bacterial keratitis**

ORGANISM	PRIMARY AGENTS		ALTERNATE AGENTS	
Staphylococcus; sensitivities unknown or penicillin resistant	**Top**[1]	A cephalosporin[4]	**Top**	Bacitracin or Vancomycin
	Subc[2]	A cephalosporin	**Subc**	Methicillin or Vancomycin
	IV[3]	Methicillin	**IV**	A cephalosporin
Penicillin-sensitive staphylococcus, pneumococcus, or streptococcus	**Top**	Penicillin G	**Top**	A cephalosporin
	Subc	Penicillin G	**Subc**	A cephalosporin
	IV	Penicillin G	**IV**	A cephalosporin
Neisseria gonorrhoeae	**Top**	Penicillin G	**Top**	Erythromycin or Tetracycline
	Subc	Penicillin G	**Subc**	Erythromycin
	IV	Penicillin G[5]	**IM**[6]	Spectinomycin
Pseudomonas	**Top**	Gentamicin and Carbenicillin	**Top**	Tobramycin and Colistin
	Subc	Gentamicin and Carbenicillin	**Subc**	Tobramycin and Colistin
	IV	Gentamicin and Carbenicillin or Ticarcillin	**IV**	Tobramycin and Colistin
Enterobacteriaceae, unidentified	**Top**	Gentamicin and Neomycin	**Top**	Tobramycin and Amikacin[7]
	Subc	Gentamicin and Amikacin[7]	**Subc**	Tobramycin and Amikacin[7]
	IV	Gentamicin	**IV**	Tobramycin and Carbenicillin
Anaerobic non-sporeforming bacteria, unidentified	**Top**	Penicillin G and Chloramphenicol	**Top**	Clindamycin[8] and Chloramphenicol
	Subc	Penicillin G	**Subc**	Clindamycin[8]
	IV	Penicillin G	**IV**	Chloramphenicol
			Oral	Metronidazole[8]

1 **Top** = topical
2 **Subc** = subconjunctival injection
3 **IV** = intravenous administration. Reserve for Grade III severity keratitis
4 Insufficient data to distinguish among injectable cephalosporin derivatives. Cephaloridine is less irritating to tissue but should **NOT** be used for intravenous therapy
5 Intravenous penicillin G should be administered for all suspected Neisseria conjunctivitis or keratitis
6 Intramuscular spectinomycin should be administered for suspected Neisseria conjunctivitis or keratitis in a patient with penicillin allergy. Recent apperance of penicillinase-producing strains of N gonorrhoeae may prompt increased utilization of spectinomycin.
7 The safety and efficacy of amikacin have not been determined in various forms of keratitis
8 Efficacy of these agents has not been adequately established in anaerobic keratitis

(Revised January, 1979)

D. Plan for reduction in antimicrobial therapy
   1. Termination of subconjunctival injections
   2. Termination of intravenous therapy
   3. Reduction in frequency of topical applications by the halving method
   4. Conversion to less concentrated drops or ointments

E. Proceed with **tube dilution** sensitivity testing of the responsible organism

F. Causes of progressive keratitis despite appropriate antimicrobial therapy
   1. Advanced disease prior to initiation of therapy
   2. Suboptimal use of effective antibiotics
   3. Inactivation of antibiotics in the delivery system
   4. Drug toxicity
   5. Acquired resistance of the organism
   6. Unrecognized mixed infection
   7. Tissue destruction by necrotizing enzymes
      a. Exogenous
      b. Endogenous

VII. CONSIDERATIONS FOR UTILIZATION OF CORTICOSTEROIDS

A. **Objective:** to prevent tissue necrosis and consequent irreversible structural alterations

B. Basis for administration
   1. Progressive stromal necrosis despite **apparent** control of the replicating micro-organism
   2. Prior administration of corticosteroids: rebound stromal keratitis

C. Requisites
   1. Adequate delivery of **specific antimicrobial therapy**
   2. Ability to examine the patient at frequent intervals
   3. Absence of other alterations of host defense mechanisms

D. Plan for administration
   1. Trial period for 24-48 hours: prednisolone 1%, 4-6 hourly intervals
   2. Increased dosage if no adverse effect: prednisolone 1%, 1 or 2 hourly intervals
   3. Addition of periocular injection of short-acting corticosteroids (dexamethasone, 4 mgm) if required
   4. Avoid oral corticosteroids

VIII. UTILIZATION OF HYDROPHILIC SOFT CONTACT LENSES

A. Indications
   1. Non-healing epithelial defects
   2. Severe stromal ulceration with or without active microbial disease
   3. Corneal perforatin < 2 mm

B. Principles
   1. Fulltime wear
   2. Avoid excessively tight lens
   3. Maintenance of other medical therapy

IX. PENETRATING KERATOPLASTY

A. Indications
   1. Progressive disease despite adequate delivery of specific antibacterial agents and control of inflammation
   2. Extreme corneal thinning or perforation not manageable by alternate methods

B. Special considerations
   1. Maximum pre-operative antimicrobial therapy
   2. Maximum control of inflammation
   3. Adequate size and placement of the graft to circumscribe the area of microbial replication
   4. Establishment of adequate posterior-to-anterior chamber flow
      a. Lysis of posterior synechiae
      b. Peripheral iridectomy
   5. Interrupted 10-0 monofilament nylon sutures
   6. Post-operative antimicrobial therapy

Fungal Keratitis

Dan B. Jones, M.D.

I. Clinical features

A. Determinants of the severity of the corneal disease
   1. The strain of the organism
   2. The host
   3. The conditions under which the two are combined
   4. The duration of the process

B. Filamentous keratitis
   1. Variable geographic distribution; more common in the southern and southwestern United States
   2. Usually follows outdoor trauma with vegetable matter
   3. Prior administration of corticosteroids or antibiotics **not** a requisite for development
   4. Typical biomicroscopic features
      a. Grey-white color
      b. Elevation of intact epithelium.
      c. Delicate feathery stromal infiltrate
      d. Multifocal suppuration = satellite lesions
   5. Advanced disease resembles severe microbial keratitis
   6. Most common responsible genera
      a. Aspergillus
      b. Fusarium
   7. Laboratory features
      a. Branching septate, hyphal fragments (2-6 microns wide) in direct smear
      b. Mycelial colony growth on solid media; feathery mycelium in liquid media

C. Yeast keratitis
   1. Universal distribution
   2. Multiple predisposing factors: the compromised host
   3. Typical biomicroscopic features
      a. Yellow-white color
      b. Dense suppuration
      c. Focal lesions
      d. Resembles bacterial keratitis
   4. Most common genus = Candida
   5. Laboratory features
      a. Budding yeast (2-4 microns) or pseudohyphae in direct smear
      b. Pasty, opaque colonies on solid media; resemble bacteria

II. Pathological features

A. Ulceration of the epithelium, Bowman's membrane, and outer stroma

B. Migration of inflammatory cells around the organisms and into the anterior chamber
C. Coagulative necrosis of the affected stroma with edema of the collagen fibers and loss of keratocytes
D. Multiple abscesses separated from the main lesion
E. Partial or complete ring abscesses
F. Hyphae usually parallel to the corneal lamellae
G. Penetration of the hyphae through unbroken Descemet's membrane
H. Perforation of the cornea

III. **Laboratory diagnosis**

A. Conjunctival culture: "background flora"
1. Blood agar plate
2. Sabouraud's agar plate
3. Thiol broth

B. Corneal scrapings
1. Smears for direct stains
a. Gram: 2 slides
b. Giemsa: 2 slides
c. Reserve for special stains: 2 slides
2. Direct inoculation of media
a. Blood agar plate: incubated at 37°C: additional blood agar plate incubated at room temperature (25°C) if Sabouraud's agar not available
b. Chocolate agar plate: incubated at 37°C
c. Thiol broth: incubated at 37°C
d. Sabouraud's agar plate: incubated at room temperature (25°C)
e. Brain heart infusion broth: incubated at room temperature (25°C); platform shaker if available

IV. **Antifungal therapy**

A. **Aim of specific therapy;** To inhibit fungal growth by the **prolonged administration** of an effective nontoxic agent to allow the normal host defense mechanisms to eradicate the infection

RESULT OF SMEARS	INITIAL THERAPY
NO hyphal fragments or yeasts; benign infection	Attempt to delay therapy until confirmation by positive culture; repeat scraping in 24-48 hours
NO hyphal fragments or yeasts; **severe** infection, mechanisms accounting for negative smear	**Topical:** Natamycin 5% (pimaricin)
HYPHAL FRAGMENTS	**Topical:** Natamycin 5%
YEAST or PSEUDOHYPHAE	**Topical:** Flucytosine 1% Natamycin 5% **Oral:*** Flucytosine (150 mg/kg/day: 4 divided doses)

* Severe infections with deep stromal abscess; possible intraocular extension

B. Guidelines for selection of agents
1. Initial examination: selection based on results of corneal scrapings
2. Judgement of improvement
3. Management after obtaining results of antifungal sensitivity determinations
a. If current therapy **EFFECTIVE,** continue **UNLESS** evidence of drug toxicity: the need for prolonged administration

b. If current therapy **INEFFECTIVE**, select alternate therapy on the basis of in vitro testing
c. Be prepared to seek assistance from centers possessing investigative compounds

C. Role of corticosteroids
1. Consideration of acute inflammatory pathway. Adequate stimulus plus adequate host response gives active inflammation.
2. Stimuli to inflammation in fungal disease
   a. Replicating: fungi
   b. Non-replicating: enzymes, fungal antigens, drugs, mycotoxins(?)
3. Aim of corticosteroid therapy: to control active inflammation in order to minimize or eliminate structural alteration
4. Basic rules for utilization
   a. No systemic steroids
   b. Effective antifungal agents must be given before local steroid can be introduced
   c. Steroid therapy implies
      (1) Ability to follow patient carefully
      (2) Adequate skills available for emergency surgery

D. Surgical management
1. Surgery main defense against fungal infection in the pre-antifungal era, i.e., corneal grafting and conjunctival flap procedures
2. Despite the advent of more effective agents surgery remains an integral part of the management in
   a. Acute phase
   b. Management of complications
   c. The final visual result
3. Indications for excisional keratoplasty in hyperactive stage of fungal keratitis
   a. Descemetocele
   b. Perforation
c. Rapidly expanding or deepening ulcer despite appropriate antimycotic therapy
   d. Inability to inactive inflammation
   e. Drug toxicity
4. Management of complications: fungal glaucoma

Table 1 — Concentrations and dosages of principal antifungal agents

AGENT	MANUFACTURER	DOSAGES			
		TOPICAL	SUBCONJUNCTIVAL	INTRAVENOUS	ORAL
AMPHOTERICIN B FUNGIZONE	Squibb, USA	1.0-2.5 mgm/ml (prepared from intravenous formulation)	Too toxic	Initiate with test dose; follow strict guidelines; not to exceed 1.0 mgm/kg/day	Not available
FLUCYTOSINE (ANCOBON)	Hoffman LaRoche, USA	10 mgm/ml (investigational)	Not adequately investigated	Not available	150 mgm/kg/day in 4 doses
NATAMYCIN (PIMARICIN)	Alcon Laboratories	50 mgm/ml suspension	Toxic; not absorbed	Not available	Not available
MICONAZOLE MONISTAT	Ortho Pharmaceutical	10 mg/ml drops (intravenous formulation), 2% ointment (dermatological preparation; Micatin, Johnson and Johnson)	5 mg (0.5 ml of undiluted parenteral preparation)	Follow guidelines; 30 mgm/kg/day in divided doses	Not available