Red Eye

Differential Diagnosis & Management

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FOREWORD

”Red Eye” is a common disorder. Ophthalmologists see and treat a lot of patients, who suffer from inflammatory and non-inflammatory forms of Red Eye. Eye doctors, especially external disease specialists, have the necessary instruments, as well as enough knowledge and experience, to differentiate between less dangerous forms of Red Eye (dry eyes, different forms of conjunctivitis) and other types (blepharitis, keratitis, scleritis, uveitis, eye trauma, acute glaucoma etc.) that are more dangerous and/or more difficult to treat. The aim of this brochure is to provide help in differentiating between the less and the more dangerous forms of red eyes for those medical doctors (GPs, GPPs, family doctors, district doctors etc.) who do not have special instruments and enough experience to perform special ophthalmological examinations and to base their decisions on the results of such examinations. This is an important goal as, in most countries, considerable numbers of Red Eye patients turn first to general practitioners, who should be able to decide which of these patients can be treated by them, and which need to be referred to an ophthalmologist. Chapter I of this brochure concentrates on differential diagnosis of red eyes without the aid of special instruments, using simple methods. Chapters II, III, and IV discuss in detail the diagnosis and therapy of dry eyes, and allergic and infectious conjunctivitis, with the aim of providing sufficient information and practical advice to enable the less complicated forms of red eyes to be managed. The brochure is basically written for general practitioners and as such it takes an uncommon approach, that makes it different from most of the other red eye and dry eye brochures, protocols and handbooks. We feel, however, that such a booklet may also be useful for ophthalmologists in at least three respects: 1. specialists also have to know what GPs can be expected to do with Red Eye patients; 2. ophthalmologists may also use the suggested methods, if they do not have, in certain situations, proper instruments and still have to make decisions; 3. residents and young ophthalmologists may pick up ideas and practical advice from the recommendations written by devoted and experienced specialists in the field.

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April 25, 2007

I THE DIFFERENTIAL DIAGNOSIS OF THE RED EYE

András Berta

INTRODUCTION

According to statistics, up to 6 % of patients presenting to general practitioners (GPs) suffer from eye disease. One in two of these patients have some kind of inflammatory disease of the conjunctiva or the cornea. Inflammation of the outer segment of the eye is often referred to as “Red Eye”, based on the fact that redness of the normally white conjunctiva is a common symptom of different inflammatory and non-inflammatory diseases of the anterior segment of the eyeball. [1]

Knowledge of the most common diseases that may cause redness of the eye is essential for a GP (also referred to as a panel doctor, district doctor, or family doctor in some countries). It is also important for them to be able to differentiate those red eyes, mainly inflammations of the conjunctiva (different types of conjunctivitis) that can be treated by GPs, from other types of red eye, mainly inflammations of the cornea and the iris (different types of keratitis and iritis) as well as traumatic lesions, and glaucomatous attack, that have to be treated by eye specialists. Inflammations of the eyelids, of the orbit, of the external eye muscles, or of the lacrimal glands are also associated with more or less redness of the conjunctiva, but due to their clearly different clinical appearance are not discussed among the possible causes of “Red Eye”. Subconjunctival haemorrhage (conjunctival suffusion) may appear as a non-inflammatory form of red eye (usually associated with systemic diseases), or may be a part of inflammatory or traumatic lesions of the conjunctiva.

The aims of this brochure are to provide basic information for GPs about inflammatory diseases of the anterior segment of the eye, to describe symptoms, signs and examinations that can be used in the differential diagnosis without the use of sophisticated instruments, and to highlight those types of therapy (eye drops and eye ointments) that can be used by GPs in simple cases of inflamed red eyes.

DEFINITION

“Red Eye” is a general term that refers to a diverse group of diseases for which the most typical clinical sign (the cause of redness) is active hyperaemia (dilatation of conjunctival and

sometimes also the deep intrascleral arterioles). Inflammation in the anterior segment of the eye is most often caused by infection (bacterial, viral or chlamydial), by trauma, by allergy or by dry eyes, but less commonly other aetiologies may be present. Most cases are benign, and can be managed effectively by GPs. The key to the management is the proper diagnosis of the cause of red eye, the administration of adequate and specific treatment, and careful follow up. It is important to keep in mind that questionable, complicated or therapy resistant cases require consultation with an ophthalmologist.

GENERAL SYMPTOMS OF INFLAMED RED EYES

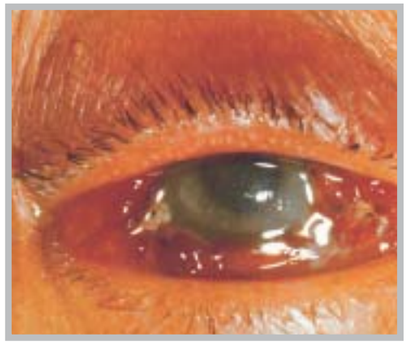

Figure 1 – A patient with unilateral inflamed red eye

The basic description of the signs of inflammation dates back to the ancient world. In book three of the treatise De Medicina of the roman philosopher and encyclopedist, Cornelius Celsus (cca. 14 B.C. – 38 A.D.), the famous descriptive sentence is found: “Now there are four diagnostic marks of inflammation, redness and swelling, with heat and pain”. A Greek physician, Galen (130 – 200 A.D.), added “loss of function” as the fifth cardinal sign of inflammation. These are still the landmarks of the symptomatology of inflammation in general, and have become the basis of the classic description of the inflammatory process, as well. [2]

The classical symptoms of inflammation: redness, swelling, pain and disturbed function are also important signs of eye inflammations. The general symptoms of the inflamed red eye, however, are usually described in ophthalmology textbooks as tearing, photophobia, blepharospasm, hyperaemia, oedema and exudation *(Figure 1)*.

BASIC INFORMATION CONCERNING DIFFERENTIAL DIAGNOSIS OF RED EYES

The differential diagnosis of common causes of inflamed red eyes is also a usual part of ophthalmology text-books, generally presented in the form of tables that give help to differentiate between the most common causes of red eyes: acute conjunctivitis, acute iritis and iridocyclitis, glaucomatous attack (acute angle closure glaucoma), and corneal trauma or acute keratitis. It is suggested that these diverse pathologies can be differentiated based on incidence, the nature of discharge (exudates), visual acuity, presence or absence of pain, type of injection (hyperaemia), the clearness of the cornea, the size of the pupil, whether the pupil constricts to light, intraocular pressure (measured by tonometer or estimated by palpation), and the evaluation of conjunctival smears and cultures. Such a differential diagnostic table can be seen below.

TABLE I THE DIFFERENTIAL DIAGNOSIS OF COMMON CAUSES OF INFLAMED RED EYE

	Conjunctivitis*	Anterior uveitis (iritis or iridocyclitis	Acute Angle Closure Glaucoma	Corneal Trauma	Keratitis	
Incidence	Extremely common	Common	Uncommon	Common	Common	
Discharge	Moderate to copious	None	None	Watery or purulent	Watery or purulent	
Vision	Not affected	Slightly blurred	Markedly blurred	Usually blurred	Significantly blurred	
Pain	None	Moderate	Severe	Moderate	Moderate or severe	
Injection	Diffuse, more toward fornices	Mainly circumcorneal	Diffuse	Diffuse	Intense	
Cornea	Clear	Usually clear	Steamy	Change in clarity related to cause	Change in clarity related to cause	
Pupil Size	Normal	Small	Moderately dilated and fixed	Normal or smaller	Normal or smaller	
Pupillary Light Response	Normal	Poor	None	Normal	Normal or poor	
Intraocular Pressure	Normal	Normal	High	Normal	Normal	
Smear / Culture	Causative organisms	No organisms	No organisms	Organisms only in infected cases	Causative organisms	

*See details in Table II.
Adapted from: Vaughan D., Asbury T., Tabbara K.F: *General Ophthalmology.* A Lange medical book, 12th ed. (1989) [3]

MEDICAL HISTORY

The onset, the duration, the uni- or bilaterality of the disease, possible trauma, former similar events, environmental factors, the presence of systemic or eye diseases, the main and accessory symptoms, factors that aggravate or alleviate the symptoms, the use of eye or systemic medications are all important.

The doctor not only has to ask specific questions, but also needs to be able to evaluate the answers of the patient. Patients often complain of blurred vision just because they have exudates in their eye(s), or even loss of vision just because their eyelids are stuck together by

conjunctival discharge. Patients often describe discomfort, burning or foreign body sensation as “pain”. Sometimes they mention a lot of complaints and the doctor has to find out which of them disturbs the patient the most and which of the subjective symptoms describes the complaints best. In other cases, the patient does not readily give specific information on what he/she really feels but just reports *“I have an eye problem”* or *“I turn to you because of my eyes”*.

Diagnostic clues, characteristic complaints of the patient, that may help the differential diagnosis among the most common causes of red eyes are:

- If the eye itches, it is usually allergy.
- If the eye burns, it can be dry eye.
- If the eye is sticky, it is probably bacterial conjunctivitis.

Many more questions and answers, as well as specific symptoms are discussed in detail in the following chapters of this booklet, dealing with dry eyes and allergic and infectious types of conjunctivitis.

EXAMINATION OF THE PATIENTS

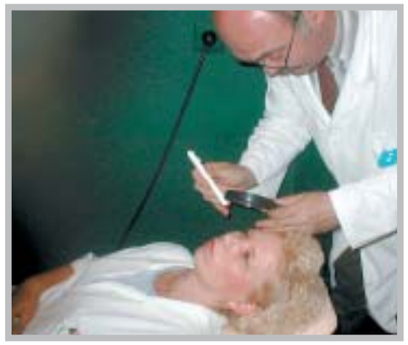

Figure 2 – Examination with side illumination and a magnifying glass

Examination of a patient with a red eye performed by a GP differs from the examination performed by an ophthalmologist in several respects. The GP does not have the instruments with which an eye specialist usually examines the patient (such as a slit lamp, ophthalmoscope, tonometer, perimeter etc.). The GP has to examine the eyeballs, the eyelids and the surrounding areas with the naked eye. The inspection can be assisted with good side illumination (a flashlight, a visit lamp or a table lamp). For better visualization the doctor can use a loupe (magnifying glass) and if he/she is presbyopic (or is wearing glasses) must wear his/her glasses when performing the examination (*Figure 2*). The other major difference is that the GP does not have to diagnose all specific eye diseases. **It is sufficient to decide whether the patient has some type of conjunctivitis (conjunctivitis sicca, allergica or infectiosa), that can be treated by a non-specialist with appropriate eye drops and ointments, or if the patient is (or may be) suffering from other possible causes of red eyes (different types of keratitis, iritis, iridocyclitis, scleritis, eye injuries, glaucoma etc.) that should be treated by an eye specialist.** In any doubtful case, it is always better to be on the safe side and to refer the patient to an ophthalmologist rather than to treat “according to the most probable diagnosis”.

In case of more severe (non-conjunctivitis) type of red eyes, it is also important to decide when, how and where to send the patient (in the lying position in an ambulance immediately to the nearest hospital, by car within a few hours to an institute with an ophthalmological department, next day or with an early appointment to the local eye specialist). Eye injuries and glaucomatous attack may fall into the first category; different types of keratitis, iritis and iridocyclitis into the second; various forms of blepharitis, scleritis, chronic and therapy resistant cases of non-infectious conjunctivitis or keratoconjunctivitis into the third.

After taking a proper medical history (good anamnesis is half diagnosis!), the first and the most important task is to find out if the patient's visual acuity is disturbed (decreased by the red eye) or not. In some countries, GPs renew driving licenses, waterman ship certificates, firearms licenses and disability pensions (evaluate the impact of possible changes in health suitability). To perform this function, they are trained and have the necessary facilities to evaluate the patient’s visual acuity (i.e. have a vision chart on the wall of their examination room, but do not have a trial frame and a set of lenses for correction of refractive errors). Those GPs who cannot check the patient’s visual acuity using a vision chart can perform distance and near visual acuity tests using posters, tables on the wall and printed text like newspapers with letters of different sizes, to find out if the patient is able to read what healthy people can under the same circumstances. Common sense is needed when performing visual acuity testing. Examine both eyes of the patient separately (cover the other eye during the examination). Make sure that the patient keeps his/her eye open and is looking in the right direction. The visual acuity of a patient who normally uses glasses or contact lenses has to be tested with their glasses or contact lenses. If the patient is older than 40 years of age, he/she is presbyopic, i.e. he/she can only read with proper reading glasses. Take into consideration that presbyopic patients may have different glasses for distance vision (5 m, 20 feet and more) and for reading (33 cm). Patients suffering from conjunctivitis should not have visual disturbance (unless their eyes are full of exudates, or their eyelids are stuck to one another by exudates). **Decreased vision in a red eye should always be considered as a sign of a more severe form of inflammation! These patients have to be referred to an eye specialist, and not treated by the GP!**

The second task is to evaluate the smoothness of the surface and the clearness (the transparency) of the cornea. The surface of the cornea is normally smooth because it is covered by continuous epithelium and an even, sufficiently thick and stable precorneal tear film. The smoothness of the corneal surface can be judged by examining (evaluating) the light reflex(es) (the reflections of light sources) that can be seen on the surface of the cornea. If the form of these reflexes is regular, if they have sharp margins, if they remain regular when the eye is moving, the surface is smooth (*Figure 3*). If the light reflexes are irregular, broken or are totally missing, or lose their regularity when the eye is moving then the surface is not regular. Irregularity of the corneal surface is a sign of corneal involvement, either keratitis or traumatic lesion of the cornea (F*igure 4*). The transparency of the cornea can be evaluated by judging how clearly the pupillary margin and the texture of the iris can be seen through different parts of the cornea. Usually the details (the colour, the cryptas and the lacunas, parts that are lighter and darker) can be seen and distinguished on the iris, and the margin, the shape, the size and the regularity of the pupil can easily be evaluated (*Figure 3*). If this is not the case and the above mentioned details cannot be clearly seen, and their sharpness is not the same when the eye moves,

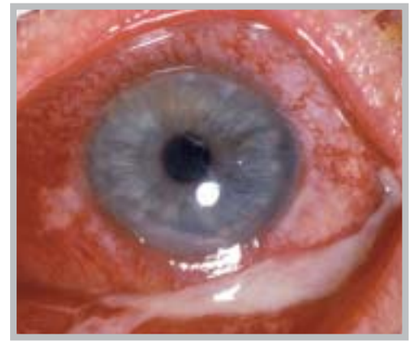

Figure 3 – Bacterial conjunctivitis (clear cornea, purulent exudate)

Figure 4 – Keratoconjunctivitis (broken corneal light reflex, partly cloudy cornea)

it can be a sign of loss of transparency, the partial cloudiness of the normally crystal clear and totally transparent cornea (*Figure 4*). **All cases with corneal involvement are severe red eyes to be treated by an ophthalmologist! All corneal lesions can worsen with time, therefore specific and effective therapy should be started without delay!**

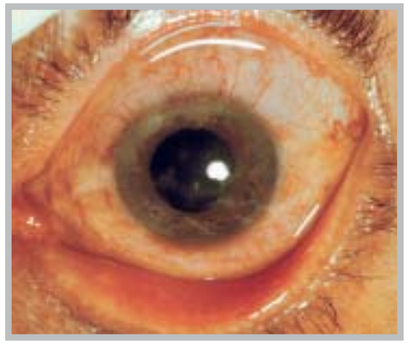

Figure 5 – Dendritic keratitis without staining

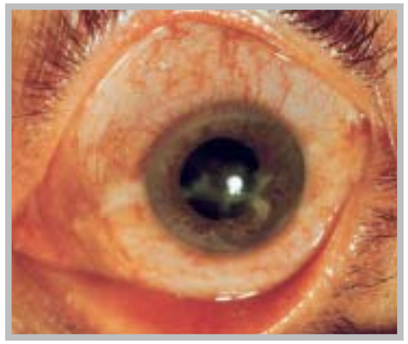

Figure 6 – Dendritic keratitis with fluorescein staining

Fluorescein staining can be helpful in deciding whether the corneal surface is intact or epithelial defects are present. This is especially important to rule out possible herpetic (HSV) infection of the cornea that is hard to see with the naked eye (*Figure 5*), while the characteristic appearance of a branching epithelial defect (dendritic keratitis) is clearly recognisable after instilling one drop of 2 % sodium fluorescein eye drops (*Figure 6*).

Once the two most important questions (possible visual acuity changes and corneal involvement) are answered, further careful inspection of the eyeball and the surrounding areas has to be performed. By pulling down the lower eyelid, the lower conjunctival fornix (exudates, mucous threads, folliculi) and the inner surface of the lower eyelid can be exposed for careful visual examination; by everting the upper eyelid, the inner surface of the upper eyelid (common site for small foreign bodies trapped in the subtarsal sulcus) can similarly be exposed and examined. By examining the lid margins, signs of blepharitis (crusts, scales, ulcers, pustulae) can be found, by palpating the eyelids chalazeon can be detected, by feeling the regional lymph nodes enlargement and tenderness can be identified. Palpation of the eyeball is not a precise mode for evaluating the intraocular pressure, but "hard as a rock" and painful red eye can help the diagnosis of a glaucomatous attack, and a hypotonic eye can confirm the supposed diagnosis of a penetrating eye injury. The pupil is typically constricted (miotic) in acute, and irregular, (due to the presence of posterior synechiae), in chronic forms of iritis and iridocyclitis. A wide pupil and the absence of light response can be present in acute angle closure glaucoma and following blunt injury of the eyeball (traumatic mydriasis). Differences in the size and the light reaction of the pupils can have neurological (head trauma, brain tumor, circulatory changes) or pharmaceutical (use of miotic or mydriatic eye drops) causes.

THE DIFFERENTIAL DIAGNOSIS OF VARIOUS TYPES OF CONJUNCTIVITIS

Once the diagnosis of conjunctivitis is made and the doctor is sure that other more severe causes of red eye can be excluded, the next question is whether it is a dry eye (keratoconjunctivitis sicca, inflammation of the cornea and the conjunctiva due to drying out of the ocular surface), or an allergic, or infectious form of conjunctivitis. The following three chapters deal with the diagnosis and therapy of these diseases in detail. In the last part of this chapter, only some hints are given on how to differentiate between the main types of conjunctivitis. The characteristics and therapy of dry eyes and of different types of allergic and infectious conjunctivitis are dealt with in the remaining chapters of this brochure.

The differentiation between different types of conjunctivitis is usually possible based on evaluation of the appearance of the conjunctiva, the type of hyperaemia, and any conjunctival exudate (diffuse bright red conjunctiva with serous exudate is typical of viral conjunctivitis, diffuse hyperaemia and swelling of the conjunctiva with purulent or mucopurulent exudate and crusts on the lid margins is the usual appearance of bacterial conjunctivitis, while a more swollen rather than hyperaemic conjunctiva with a "milky appearance" and the presence of itching is very characteristic of allergic conjunctivitis). Enlarged preauricular lymph nodes are present in chlamydial and in certain types of viral conjunctivitis. Microscopic evaluation of smears of conjunctival exudates (stained with Haematoxilin or Giemsa) can be helpful in supporting the diagnosis (polymorphonuclear leucocytes and bacteria in bacterial conjunctivitis, eosinophils in allergic conjunctivitis, mononuclear leucocytes in viral conjunctivitis, inclusion bodies in epithelial cells in chlamydial disease, fungi in fungal conjunctivitis are all very characteristic). Most microbiological laboratories offer immediate diagnosis from smears including Gram staining of the bacteria, but those GPs (and ophthalmologists) who have a microscope and a little experience in evaluating blood smears and urinary sediments can also evaluate conjunctival smears themselves. Culturing and antibiotic sensitivity tests not only help in the identification of the causative microorganism but make therapy more precise and more effective.

TABLE II DIFFERENTIAL DIAGNOSIS OF COMMON FORMS OF CONJUNCTIVITIS

	Course of the Disease	Appearance of the Conjunctiva	Exsudate	Smears	Preauricular Lymph Nodes	
Bacterial	Acute or chronic	Hyperaemic	Purulent	Bacteria, polymorphonuclear leucocytes	Usually normal	
Viral	Acute	Highly hyperaemic, suffusions may be present	Serous	Mononuclear leucocytes	Enlarged, tender	
Chlamydial	Subacute to chronic	Moderately hyperaemic	Mucopurulent	Intracellular inclusion bodies	Enlarged, tender	
Allergic	Acute or chronic	More oedematous than hyperaemic	Serous	Eosinophilic leucocytes	Normal	

Adapted from: Hollwich F.: *Ophthalmlogy. A short textbook.* 2nd ed., Thieme (1985) [4]

FURTHER COMMON PROBLEMS IN THE DIFFERENTIAL DIAGNOSIS OF INFLAMED RED EYES:

1. DRY EYE VERSUS CHRONIC INFECTIOUS CONJUNCTIVITIS

There are forms of infectious conjunctivitis that, besides their chronic nature, are characterized by mild and non-characteristic symptoms (minimal or no hyperaemia, minimal or no discharge). The subjective complaints in these cases can be similar to those in mild dry eyes. It is not correct to treat such cases with combined (antibiotic and corticosteroid) eye drops and ointments, which is a common practice in certain countries amongst some GPs. Chronic infectious cases should be treated by topical antibiotics, as they are caused by microorganisms (usually by diplococci or by chlamydia). Dry eye cases have to be treated with artificial tears. It is advisable to refer patients with chronic irritative eye disease to a specialist, to obtain proper diagnosis and further treat the patient according to the advice of the ophthalmologist. [5]

2. MARGINAL/BORDERLINE DRY EYE VERSUS TIRED/OVERUSED EYES

There are patients whose tear secretion and the stability of their precorneal tear film is sufficient under normal conditions. Environmental changes (drought, hot air, smoke or dust in the air etc.), certain activities (reading, staring at a computer screen), however, lead to a decreased blinking rate and the development of subjective complaints (discomfort, burning, foreign body sensation, sensation of dryness etc.) and sometimes also to the appearance of mild objective signs of dry eyes (decreased stability of the tear film and even punctate staining of the corneal epithelium). The problem is complicated by the fact that ophthalmologists in different countries and with different training use varying criteria (and different normal values) when classifying the diagnosis of dry eyes. Therefore, certain patients with mild dry eye symptoms are diagnosed as “dry eye” by one ophthalmologist and “not yet manifest dry eye” by another. The symptoms of marginal/borderline dry eyes resemble those of simple tired/overused eyes. It is bad practice to give either of these two groups of patients vasoconstrictor eye drops. Occasional (only when complaints are present) use of artificial tears helps in marginal/borderline dry eyes, while reducing and possibly eliminating the factors and circumstances that cause or aggravate the symptoms of tired/overused eyes is the best solution in the latter group of patients. [6]

3. OCULAR SURFACE DISEASE

“Ocular surface disease” is the general name given to diseases that change the structural (macroscopic or microscopic), physical or chemical characteristics of the surface of the corneal and conjunctival epithelium, and by doing so interfere with the formation or maintenance of a sufficiently stable precorneal tear film. This is a large and diverse group of diseases of the anterior segment of the eye, ranging from degenerations and dystrophies, through scars, vesicules, bullae, chronic oedema to symblepharons and large irregularities of the corneal curvature. These different diseases may be the cause of, and appear in the form of chronic irritation of the eye. Their common characteristic is that the corneal surface (sometimes only a part of it) is drying out, in spite of the fact that the eye is full of tears or is even tearing. These patients usually benefit from the use of artificial tears (viscous solutions or gels), but may also need specific treatment (therapeutic contact lenses, excimer laser or surgery). [7]

4. TOXIC CORNEAL EPITHELIOPATHY (KERATOCONJUNCTIVITIS MEDICAMENTOSA)

Every dry eye specialist occasionally examines patients who have several weeks’ or even months’ long medical history of uni- or bilateral eye inflammation, and report that they have been treated by several doctors with a number of eye drops and ointments and that their eye(s) did not heal; on the contrary with each new medication their condition became worse. They may even produce the boxes of 10–15 or more drugs, or a list containing the names of all the medications that they have previously used (various antibiotics, anti-inflammatories, sometimes even antivirals, artificial tears, and often combined drops and ointments). The eye(s) of these patients show conjunctival hyperaemia, large numbers of small epithelial lesions on the cornea, and sometimes oedema of the corneal epithelium. The slit lamp appearance of these corneas resembles that of dry eyes, but the eyes are full of tears, and the patients usually have epiphora (persisting, excessive tearing). The condition develops due to the constant and unnecessary use of eye drops and ointments, and is caused by the toxic effect of preservatives contained in most of these eye medications. If the patient stops the use of preservative containing topical drugs, improvement occurs in 1–2 days. The use of preservative free artificial tears may be considered, especially if the patient does not easily accept that “no treatment is the best treatment” for his/her long standing disease. [8]

5. EPISCLERITIS AND SCLERITIS

Episcleritis and scleritis are less common causes of inflamed red eyes. The latter is usually associated with systemic autoimmune diseases (rheumatoid arthritis, Wegener granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), sometimes with other inflammations like polychondritis or herpes zoster infection. Episcleritis is superficial and appears as a circumscribed hyperaemic area on an otherwise white eyeball, while scleritis is deeper and usually causes diffuse, sterile inflammation of the anterior or posterior sclera, and the overlying conjunctiva. Scleritis may be recurrent and sometimes results in the appearance of circumscribed but multiplex necrotic areas of the sclera. The search for underlying systemic disease is essential. Treatment of episcleritis is with topical NSAID eye drops, but the disease is usually self limiting (heals without any treatment). Scleritis is treated with corticosteroids, or with a combination of NSAIDs and steroids. In most cases of scleritis, besides extensive local treatment, the systemic administration of anti-inflammatory drugs is also necessary. [9]

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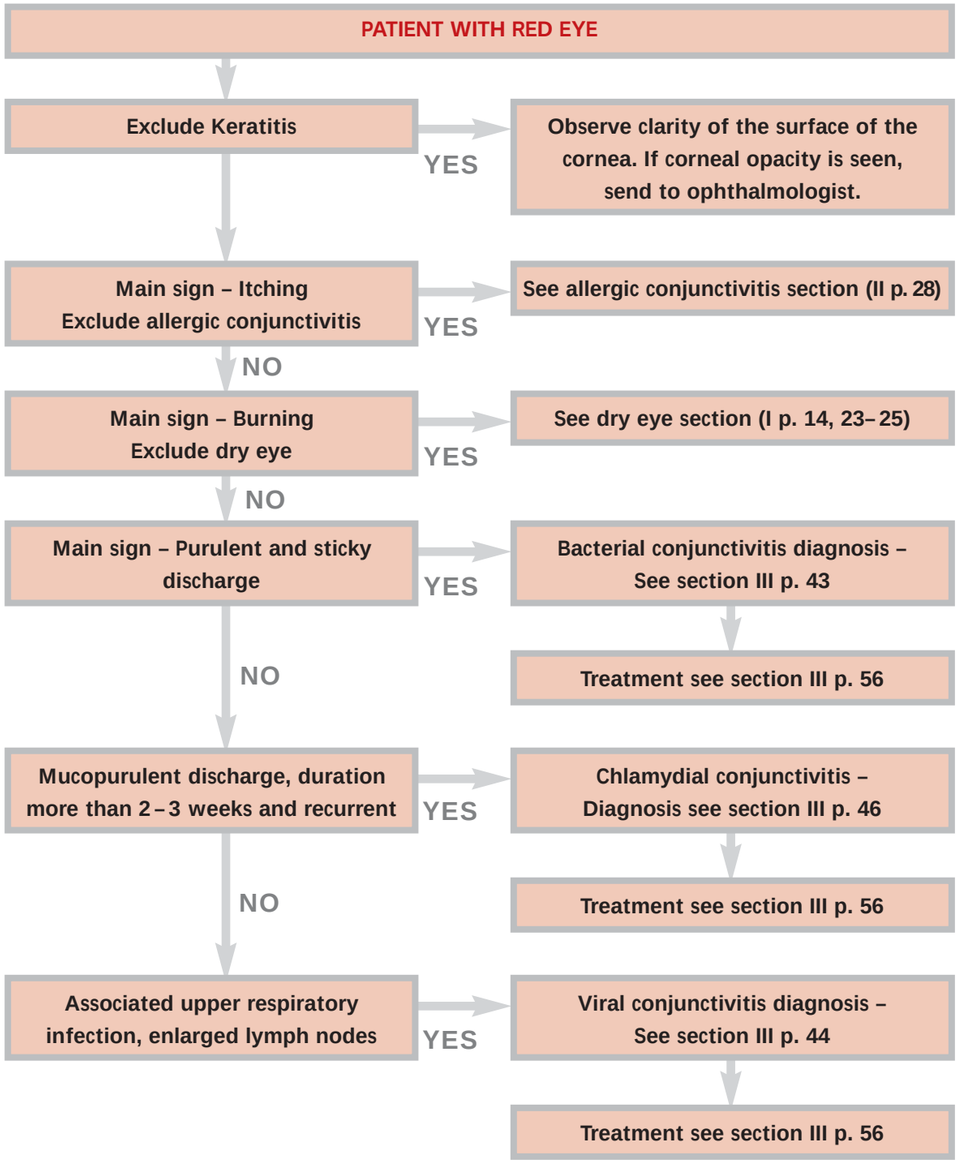
RED EYE FLOWCHARTS Marek E. Prost

FIGURE I PATIENT WITH RED EYE – MAIN DECISION TREE



II DRY EYE

Igor Petriček

INTRODUCTION

WHAT IS DRY EYE?

Virtually everyone has experienced some dry eye-related complaints in his/her life, in most cases completely unaware that those complaints were actually caused by tear dysfunction. Either when driving with an open window, working on the computer, especially in an air conditioned room, or having teary eyes on a cold winter morning. It is one of the most challenging eye disorders, because it is perhaps the most diverse of them all. At one end of the dry eye spectrum are mild, infrequent complaints and on the other, severe, debilitating, eye-threatening inflammation. It is virtually impossible, and highly individual, to draw the line between dry eye conditions that are part of our everyday lives and those that must and should be treated. This fact poses the biggest problem of dry eye diagnosis and treatment, as well as the epidemiology of dry eye.

It is the general practitioner's right, as well as their responsibility, to diagnose and treat dry eye. It is not solely the ophthalmologist's domain, since the largest segment of the dry eye spectrum does not pose a serious threat to the eye and visual function, and remains more symptom than sign-defined. In most cases, dry eye is an age related decrease of tear protection of the eye surface. Other causes of dry eye (autoimmune, neurological etc.) are far less common, although potentially more dangerous.

Therefore, general practitioners should be able not only to recognize and treat uncomplicated dry eye, but also to detect those dry eye-related conditions which may be potentially more dangerous to the eye, and should be referred to the ophthalmologist.

That is the purpose of this guideline.

In order to give the best treatment, while also not overburdening the health system by over-referral, a correct diagnosis must first be made. Using this guideline, general practitioners may be able to correctly diagnose dry eye as the leading cause of a patient's complaints, even without using more sophisticated tools and tests, available only to the ophthalmologist. Also, it is important for them to be able to differentiate which cases of (presumably) dry eye should be referred to the ophthalmologist, in order to either run more thorough diagnostic algorithms, or to modify therapy.

DEFINITIONS OF DRY EYE

There are many definitions of dry eye, depending on the criteria used. Listed here are those most relevant to the approach used in this guideline.

1. Dry eye is a disorder produced by the inadequate interrelation between the lacrimal film and the ocular surface epithelium, caused by **quantitative** and **qualitative deficiencies** in one or both of them (The Madrid triple classification of dry eye was created by a group of experts (Murube, Benitez del Castillo, ChenZhuo, Berta and Rolando), first published in 2003 [1], later it was modified and accepted by a larger group of experts in 2005 [2]).

2. Dry eye is a disorder of the tear film due to **tear deficiency** or **excessive tear evaporation** which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort. [3]

3. Dry eye is a disease of the ocular surface attributable to different disturbances of the natural function and protective mechanism of the external eye, leading to an **unstable tear film** during the open eye state. [4]

EPIDEMIOLOGY OF DRY EYE

How prevalent is dry eye? Is it a serious, eye-threatening condition? Because of this question, which may be answered in various ways, depending on the definition of dry eye applied, exact prevalence data for dry eye in the general population does not actually exist. Vast numbers of studies have analysed dry eye in the general population of various countries, but, since almost every study defined dry eye differently, and thus used different inclusion criteria, all the data is very difficult to compare. Nevertheless, we will list several published studies to enable readers to get a general impression of dry eye prevalence.

Jacobson *et al.* found that the prevalence of dry eye in the Swedish population, in the age group 55–72, was 15 % [7]. A Japanese study led by Hikichi demonstrated that 17 % of screened Japanese patients had dry eye symptoms [8]. A study conducted in Copenhagen showed that the prevalence of dry eye in the age group 30–60 in the general population was 11 % [9]. A study in the elderly conducted in Salisbury, Maryland and published in 1997 reported that 59 % of the screened population complained of dry eye symptoms [10]. The Beaver Dam Study (2000) showed the figure to be 14.4 % [11].

THE TEAR FILM

The tear film is not just water on the eye. It has a very complex structure. Its elements must interact adequately and must be present in sufficient quantity and quality to provide an optimal protective function to the eye surface.

The classical description of the tear film describes it as a trilaminar structure: lipid layer on the surface, aqueous layer in the middle, and mucous layer adjacent to the eye surface [12]. However, recent research has shown that this clear-cut demarcation between layers does not seem to exist. Rather, it is postulated that soluble mucins are dispersed in the aqueous layer, being more concentrated near the ocular surface [13].

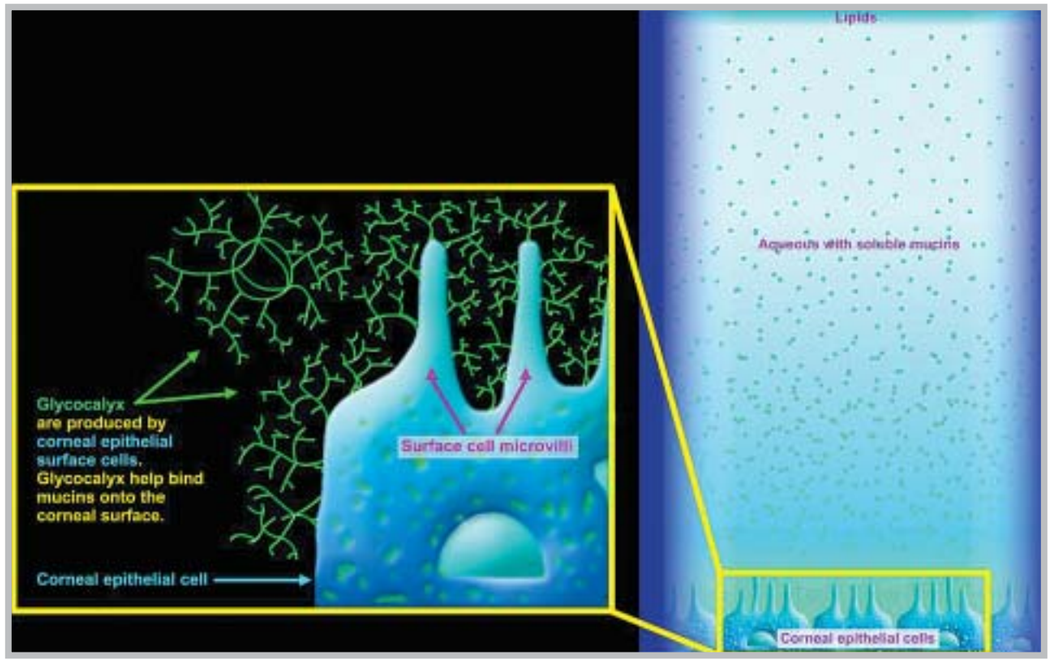


Figure 1 – Structure of the tear film (courtesy of Alcon)

Functions of different elements of the tear film

1. Lipid layer

The lipid layer is the thinnest of all, and is uppermost. It is mostly produced by the meibomian glands in the upper and lower tarsus in the eyelids, and secreted on the lid margins. It consists of lipids that are not identical to skin sebum.

Its main functions are preventing aqueous tear layer evaporation, and providing a smooth, regular optical surface. In the case of an absent lipid layer, aqueous tear evaporation increases four-fold. [14] In addition, it prevents tear overflow over the lid margins. [15]

2. Aqueous layer

The aqueous-mucin layer is the thickest of all the tear layers. The aqueous component is secreted by the lacrimal gland, as well as by the accessory lacrimal glands of Krause and Wolfring. In it are dispersed electrolytes, proteins, metabolites and desquamated epithelial cells. Among the various proteins present, immunoglobulins, lysozyme and lactoferrin are very important, as they have an antibacterial role in the defence of the tear surface. Aqueous tear osmolality is an expression of the total concentration of dissolved particles in a solution without regard to their size, density, configuration or electrical charge. Osmolality is one of the tear film parameters that virtually always increases in all types of dry eye. [16] The main function of the aqueous tear layer is wetting of the ocular surface, thus providing its optimal optical clarity. Besides that, it forms the first line of antibacterial defence and washes away foreign bodies, dust etc.

3. Mucous component

The mucous component consists of proteins, mainly glycoproteins, secreted by the goblet cells of the conjunctiva. Glycoproteins form the glycocalyx, a protein meshwork, that helps bind proteins to the epithelial surface, and promotes ocular surface wettability. [17] Its viscoelasticity also enables it to quickly repair and fill any surface defect or irregularity. [18]

CLASSIFICATION OF DRY EYE

The most comprehensive classification of dry eye is The Madrid triple classification of dry eye [1, 2]. It includes the whole spectrum of causes of dry eye, and uses three criteria: ethiopathogenesis, affected glands and severity. Although a general practitioner or general paediatric practitioner (GP/GPP) should be informed about all the causes of dry eye, it is highly recommended that he/she should endeavour to treat only those listed below in italics – other causes of dry eye should be referred to a subspecialist experienced in treating dry eye.

According to ethiopathogenesis:

1. **Age-related**
2. **Hormonal**
3. **Pharmacologic**

others may be immunopathic, hyponutritional, inflammatory, traumatic, neurologic and tantalic.

According to affected glands:

1. **Aqueo-serous deficiency**
2. **Lipodeficiency**

other types are mucodeficiency, epitheliopathy and non-lacrimal affected exocrine glands.

According to severity:

1. **Grade 1** – symptoms without significant clinical signs
2. **Grade 2** – reversible clinical signs, such as corneal staining and hyperaemia
3. **Grade 3** – irreversible sequelae of dry eye, such as scarring and leucoma.

Rheinstrom (1999) made a more precise differentiation of tear deficient and evaporative dry eye, which is relevant for this guideline. [5] McCulley *et al.* proposed using terms hyposecretory and hyperevaporative dry eye (2003). [6]

Dry eye (keratoconjunctivitis sicca)

Tear deficient (hyposecretive)

- Sjoegren's syndrome
- Non-Sjoegren tear deficiency
  - Lacrimal disease

- Lacrimal obstruction
- Reflex

Evaporative (hyperevaporative)

- Oil deficient
- Lid related
- Contact lens related
- Surface change

CASE HISTORY

The patient's description of his/her symptoms, in case of dry eye, is highly pathognomonic. However, there is no one question which will reveal that dry eye is the leading cause of complaints. Listed below are a number of questions related to dry eye symptoms. If patients, who are suspected of having dry eye, are asked all or most of these questions, correct diagnosis is highly probable, even without detailed clinical examination using instruments and tests available only to the ophthalmologist. Also, by asking the specific questions listed below, subtypes of dry eye may be defined (hyposecretory or hyperevaporative), this is important, since treatment options are different.

SYMPTOMS

1. Duration of symptoms: are they chronic?
Of all anterior eye diseases, dry eye is perhaps most clearly defined as chronic.
An acute onset of symptoms is never related to dry eye.

2. Symptoms predominantly bilateral?
Dry eye symptoms are related to a decrease in function of the apparatus that protects the ocular surface. Therefore, it is never unilateral, except when dry eye is caused by trauma (most frequently chemical) or some neurological diseases.

3. Feeling of dryness in the mouth, presence of rheumatic disease, patient younger than 50?
In case of concomitant dryness of the mouth and rheumatic symptoms, a more serious form of dry eye must be taken into consideration, that is related to systemic disease. Since systemic therapy may be needed, patients with such complaints should be referred to an immunologist and/or rheumatologist.

4. Redness not usually pronounced, intermittent?
One of the typical signs of age related dry eye is the virtual absence of conjunctival hyperaemia, which is present only intermittently. When eyes are really hyperaemic, with an acute onset, the diagnosis of dry eye is highly unlikely. In case of a highly probable diagnosis of dry eye accompanied by pronounced and persistent red eyes, patients should be referred to an ophthalmologist for further testing.

5. Patient older than 50?
Since age related dry eye is the most common type of this condition, the presence of the aforementioned symptoms encountered after the age of 50 are highly pathognomonic of dry eye. Almost all patients older than 70 report some dry eye-related symptoms.

6. Symptoms worsening in winter (central heating, cold air) or in a hot, dry climate?
Increased evaporation of tears due to dry air (central heating) and an increased thermal gradient between the eye surface and ambient environment (cold air in the morning contains less relative humidity, and rapidly becomes dry when heated near the eye surface!) can invariably be the cause of a dry eye where most symptoms worsen in the winter months. Hot, dry climates (desert) also increase tear evaporation.

7. Symptoms worsening when working on a computer, reading, or watching TV? Periodic blurry vision that changes (improves) with blinking, especially after longer periods of reading or watching TV?
Since, on the average, the blink rate decreases fivefold when gazing fixedly, (such as when working on a computer, reading and watching TV), increased tear evaporation exacerbates dry eye symptoms. Tear evaporation increases mainly due to deficient function of the lipid layer, which is secreted from glands in the eyelids when we blink. This complaint is the least age-related one, and occurs in younger age groups more frequently than the other symptoms. Nevertheless, it is definitely related to a decreased protective tear function.

8. Symptoms worsening when driving (ventilation, air conditioning)?
The same conditions occur when driving, with the additional element of increased ventilation and dryness of air due to air conditioning in the car. As when working on a computer, this complaint typically gets reported by younger patients, who lead more active lives.

9. Symptoms worsening during PMS (for premenopausal women)?
Since increased levels of progesterone increase the viscosity of the tear film, borderline dry eye female patients may experience decompensation of their tear film stability during PMS. If properly investigated, this symptom is highly pathognomonic of dry eye.

10. Discomfort while wearing contact lenses?
Contact lenses float in the tear film. In case of tear film inadequacy, the eye surface becomes mechanically irritated by rubbing with the contact lens.

Questions to differentiate hyposecretory from hyperevaporative dry eye:

11. Symptoms worse in the morning/evening?
Worse in the morning (tearing): Hyperevaporative dry eye (lipid layer deficiency)
Worse in the evening (burning): Hyposecretory dry eye (aqueous layer deficiency)

12. Gritty sensation in the eyes, burning, feeling of dryness?
The most common complaint in relation to dry eye is the feeling of hot, burning eyes, with an intermittent gritty sensation, worsening in the evening. This complaint, if properly investigated, is one of the most distinguishing symptoms differentiating dry eye from infective and allergic conjunctivitis. Feeling of dryness is much more rarely reported, but, when present, is almost pathognomonic of hyposecretory dry eye. **A positive answer to this question strongly suggests hyposecretory dry eye.**

13. Tearing in the morning, especially in winter (cold air)?
This complaint is one of the hallmarks of hyperevaporative dry eye. In a way, it is contrary to the very name of this condition- dry eye, and only shows that it is in many ways inappropriate. Lipids, which are secreted by the meibomian glands, prevent hyperevaporation of tears, as well as their passage over the eyelids (tearing). The secretion of the meibomian glands is blink-dependent. Eyes do not blink during the night, therefore, no secretions are produced, and upon waking the tear film is relatively lipid-deficient. In case of decreased lipid secretion (hyperevaporative dry eye), an increased need for secretion of lipids in the morning may cause decompensation of the meibomian glands' capacity to secrete lipids, therefore inducing symptoms of tearing. **A positive answer to this question strongly suggests hyperevaporative dry eye.**

If the answer to most or all of the above is yes, a diagnosis of dry eye should be considered!

MEDICAL HISTORY

The following systemic conditions or procedures may exacerbate dry eye symptoms:

1. menopause
2. autoimmune diseases
   - rheumatoid arthritis
   - systemic lupus erythematosus
   - scleroderma etc.
3. dermatological disease (e.g. ocular pemphigoid)
4. nerve trauma or disease (e.g. Parkinson's disease)
5. refractive surgery (LASIK)

History of medicine use

The use of certain systemic medications is frequently accompanied by dry eye symptoms. Should the patient exhibit symptoms of dry eye, discontinuation of the medication should be taken into consideration if that does not adversely influence the patient's overall medical condition. Examples are:

- Anticholinergic agents
- Antihistamines
- Oral contraceptives
- Antihyperetensives (beta-blockers, reserpine, thiazide, diuretics etc.)
- Antiarrhythmic agents
- Analgesics
- Psychopharmaceuticals (benzodiazepines), antidepressants, neuroleptics
- Oestrogens
- Cytostatics
- Migraine drugs
- Anti acne treatment in conjunction with doxycycline therapy

Physical examination

A general practitioner generally does not have the opportunity to diagnose external eye diseases using a slit lamp, an ophthalmologist's tool. However, physical examination using only the naked eye may in many cases be adequate, and may add valuable information to that already gathered by asking the previously listed case history questions.
Observe conjunctival hyperaemia and discharge; if minimal to moderate: consider a diagnosis of DRY EYE.

Interpretation of tests used in dry eye diagnostics by the ophthalmologist

As previously mentioned, ophthalmologists diagnose dry eye using a slit lamp to observe the eye surface under magnification. They use various tests to diagnose this condition and to differentiate between several subtypes of dry eye, especially the hyperevaporative and hyposecretory types. This is important, since therapy options vary for each dry eye subtype.

Below are listed diagnostic tests that are used by the ophthalmologist. General practitioners are not supposed to use them by themselves, since they lack the necessary equipment and experience. However, they should be able to interpret findings that they receive from ophthalmologists, when they have referred patients to them for more thorough testing.

It must be noted, however, that cut-off values for most of the tests listed are not universally accepted, and that the ophthalmologist's final opinion (diagnosis) should be his/her opinion regarding the observed patient's condition.

1. Fluorescein staining
By using 1 % sodium fluorescein solution, epithelial defects of the eye surface are stained, and may be observed using a slit lamp. Distribution of fluorescein staining may be highly pathognomonic of dry eye.

Bilateral corneal staining,
predominantly on the inferior cornea: **DRY EYE**

Bilateral conjunctival staining,
predominantly in the aperture: **DRY EYE**

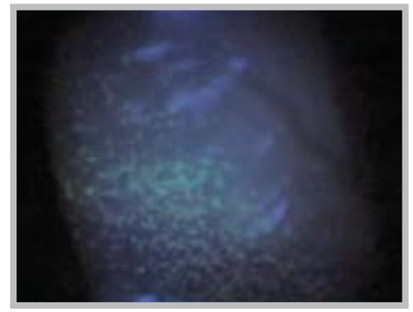


Figure 2 – Fluorescein staining *(courtesy of Alcon) Visible are epithelial defects in the lower portion of the cornea, typical of dry eye*

2. TBUT (Tear Break-Up Time Test)
Tear film stability, together with osmolarity, are two parameters that are changed in every type of dry eye. Therefore, the Tear Break-Up Time test (TBUT) is one of the pivotal tests in diagnosing dry eye. TBUT measures stability of the tear film, by instilling sodium fluorescein solution in the eye and observing the appearance of dark spots in the stained tear film, using a slit lamp. The value is expressed in seconds after opening the eye. Although it is extremely important in diagnosing dry eye, TBUT is notorious for the variability of its results, making it, in many ways, unreliable. The reason for this lies in the fact that measurement is not standardized, as it is performed in many different ways, thus making results non-comparable between practitioners. The values mentioned below are those most universally accepted, but again the ophthalmologist's interpretation should be honoured as the most reliable.

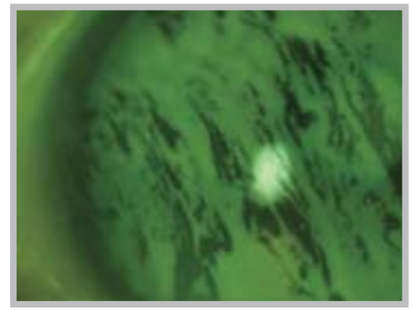


Figure 3 – TBUT Test *(courtesy of Alcon) Visible are multiple breaks in fluoresceine-stained tear film*

TBUT lower than 10 sec: consider diagnosis of dry eye
TBUT lower than 3–5 sec: dry eye is the most probable cause of symptoms

3. Schirmer test

The Schirmer test is the oldest of the diagnostic tools used in diagnosing dry eye. It predominantly measures the secretion of the aqueous segment of the tear film, making it an important tool in diagnosing **hyposecretory dry eye**. It is performed by placing the folded end of a standardized filter paper strip into the lower conjunctival sac, and, after five minutes, measuring the length of the paper that is wetted. Values are expressed in millimeters. In no way can the Schirmer test substitute for the TBUT or other tests as the only test used in diagnosing dry eye, since it measures only one segment of tear film function. The Schirmer test is even more variable in interpretation, since it also is performed with many different modifications (eyes open, closed, with or without anaesthetic), yielding very different results. The values listed below are again those most widely accepted in the literature.

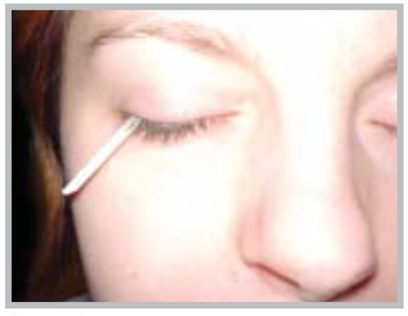


Figure 4 – Schirmer test

> 10 mm	**normal secretion of aqueous segment of tear film**
5 – 10 mm	**marginal finding, inconclusive in ruling out aqueous-deficient dry eye**
< 5 mm	**highly probable aqueous-deficient dry eye**
< 3 mm	**aqueous deficient dry eye**

4. Meibomian Gland Expression

Meibomian Gland Expression is a diagnostic tool that has been introduced into ophthalmic practice fairly recently. It may be very useful in assessing the function of the meibomian glands in the lids, responsible for secretion of the lipid layer of the tear film. Meibomian gland dysfunction (MGD) may be the cause of **hyperevaporative dry eye**. The test is performed with the slit lamp, by gently squeezing upwards the middle portion of both lower eyelids, and noting any secretion thus expressed from the meibomian gland orifices. [19]

1. Clear fluid is expressed from 75 % of orifices	**normal**
2. Clear or milky fluid is expressed from 50 % of orifices	**mild MGD**
3. Less than 50 % of orifices yield any secretion secretion is creamy	**moderate MGD**
4. Less than 25 % of orifices yield any secretion secretion purulent	**severe MGD**

Other tests used in dry eye diagnosis

There are many other tests in use for establishing the diagnosis of dry eye. Their use depends on the experience and the skill of the ophthalmologist and on the equipment available.
The most commonly used tests are listed below:

- Bengal red staining
- Lissamine green staining
- NIBUT (Non-invasive tear break-up test)
- LIPCOF (lid parallel conjunctival folds)
- Tear film detritus assessment
- Lipid Layer Thickness measurement (LLT)
- Tear osmometry
- Evaporimetry
- Tear meniscus measurement
- Tear ferning test

THERAPY

Dry eye cannot be cured.

It is a condition that will stay with the patient for the rest of his/her life. This is an additional reason why this diagnosis should not be made lightly. Once this diagnosis is established and confirmed, the patient should be carefully informed about the goals of dry eye therapy, to avoid disappointment and loss of the patient's confidence.

There are two goals of dry eye therapy:

1. To alleviate symptoms, and thus enhance the patient's quality of life.
2. To prevent development of possible complications of dry eye, such as bacterial or viral infections or more severe corneal and conjunctival complications like perforation or scarring.

GENERAL RECOMMENDATIONS

Several simple and inexpensive recommendations may help the patient alleviate his/her dry eye-related symptoms:

- Avoid situations that are known to worsen dry eye-related symptoms (smoking, dust, strong wind, cold air, dry air).
- Place the computer screen 10 – 20° below eye level, to reduce the eye aperture and therefore reduce tear evaporation.
- Use wide-rimmed eyeglasses that wrap around the face to reduce eye exposure to wind.

The importance in differentiating between hyposecretory and hyperevaporative dry eye resides in the fact that therapy choices are different for each condition. However, it must not be forgotten that these conditions may coexist and are not mutually exclusive, and therefore the patient's condition may require combined therapy.

HYPOSECRETORY DRY EYE

Artificial tears

Artificial tears in their many varieties still form the backbone of dry eye therapy. It is particularly true for hyposecretory dry eye. However, artificial tears have their limitations, and patients should be instructed on how to use them properly.

- Artificial tears do not cure the disease. They are substituting what is lacking, i.e. tears, and will not make decreased tear secretion come back to the normal level. In order to avoid unreasonable expectations and loss of confidence in the practitioner by the patient, he/she should be clearly informed about this.

- Keep in mind that, after instillation, the majority of artificial tears usually protect the ocular surface for 10–20 minutes only, and therefore frequent instillation is necessary. Some newer products are reported to have longer protection times.
- Recommend instilling artificial tears before situations that are known to worsen the symptoms (going outdoors, watching TV etc.).
- In cases of irritation, recommend preservative-free artificial tears. If that does not help, recommend periodic change of brand.
- In case of filamentary keratitis (severe hyposecretory dry eye) consider acetylcysteine eyedrops.
- At bedtime and in cases of more pronounced symptoms during the daytime, it might be useful to prescribe artificial tears in the form of a gel, since they are more efficient in protecting the ocular surface. The main drawback with these products is blurred vision because of the thick gel layer covering the cornea and this can limit the usefulness of gels in everyday use.
- In case of contact lens irritation, recommend frequent instilling of preservative-free artificial tears. In case of serious discomfort and/or clinical signs, consider advising discontinuation of contact lens wear.

HYPEREVAPORATIVE DRY EYE

Artificial tears

- Through excessive evaporation of tears, ocular surface discomfort may be severe. Therefore, artificial tears should be prescribed here not so much as a form of substitution therapy, but more as a symptomatic therapy through their lubricating action.

Meibomian gland secretion stimulation

- Daily use of hot compresses applied over closed eyelids, followed by gentle massage in the direction of the eyelid margins may in some cases alleviate hyperevaporative dry eye symptoms by promoting meibomian gland function.
- During the day, gentle massage of the eyelids by rotatory movements with the palms of the hands may bring temporary relief.

Eyelid margin hygiene

- In case of scales and hyperaemic eyelid margins (blepharitis), recommend eyelid margin hygiene with either 25 % baby shampoo, or saline.

Forceful blinking

- Recommend forceful intentional blinking (to express secretions from the meibomian glands) during computer work or watching TV to reduce tearing.

Short course of topical corticosteroid therapy

- In case of periodic worsening of symptoms, a short course of topical corticosteroids may help the patient.

Course of topical antibiotic therapy to reduce bacterial population

- In case of pronounced blepharitis (meibomian gland orifices blocked, no secretion expressed, eyelid margins hyperaemic, dried secretion on margins), a short course of broad spectrum topical antibiotic (accompanied by eyelid margin hygiene) may reduce symptoms by reducing the bacterial population that feeds on lipids.

OTHER THERAPEUTIC OPTIONS

Apart from those listed above, there are other therapeutic procedures available for treatment of dry eye. However, they are most commonly used in treating more severe forms of dry eye, and therefore are not in widespread use among GP/GPPs and general ophthalmologists.

- Therapeutic contact lenses, combined with artificial tears
- Topical cylosporine-A
- Tarsorrhaphy
- Occlusion of the lacrimal puncta

WHEN DRY EYE PATIENTS SHOULD BE REFERRED TO THE OPHTHALMOLOGIST?

Dry eye patients may be successfully treated and followed up for years by general practitioners. However, in the course of his/her disease, every dry eye patient may potentially develop some other medical condition that may be potentially dangerous to his/her visual function. In those cases, patients should be referred to an ophthalmologist.

Below are listed conditions that are best referred for further testing and treatment to an ophthalmologist.

1. Sudden exacerbation of otherwise chronic signs and symptoms (discharge, hyperaemia, and pain).
2. Symptoms and signs becoming more pronounced unilaterally.
3. Exacerbation of symptoms and signs accompanied by deterioration of visual acuity (denoting corneal involvement).
4. No improvement on given therapy, previously efficient therapy not helping anymore.
5. Concomitant systemic condition (autoimmune disease, systemic therapy that may affect dry eye condition).

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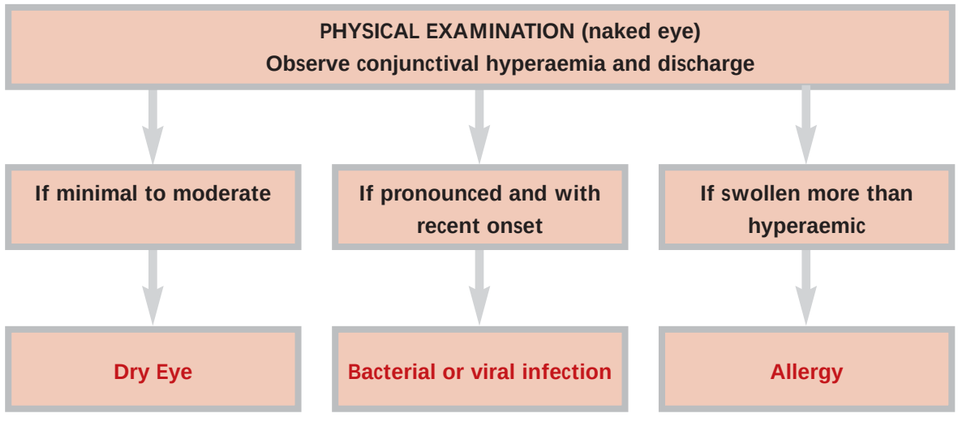
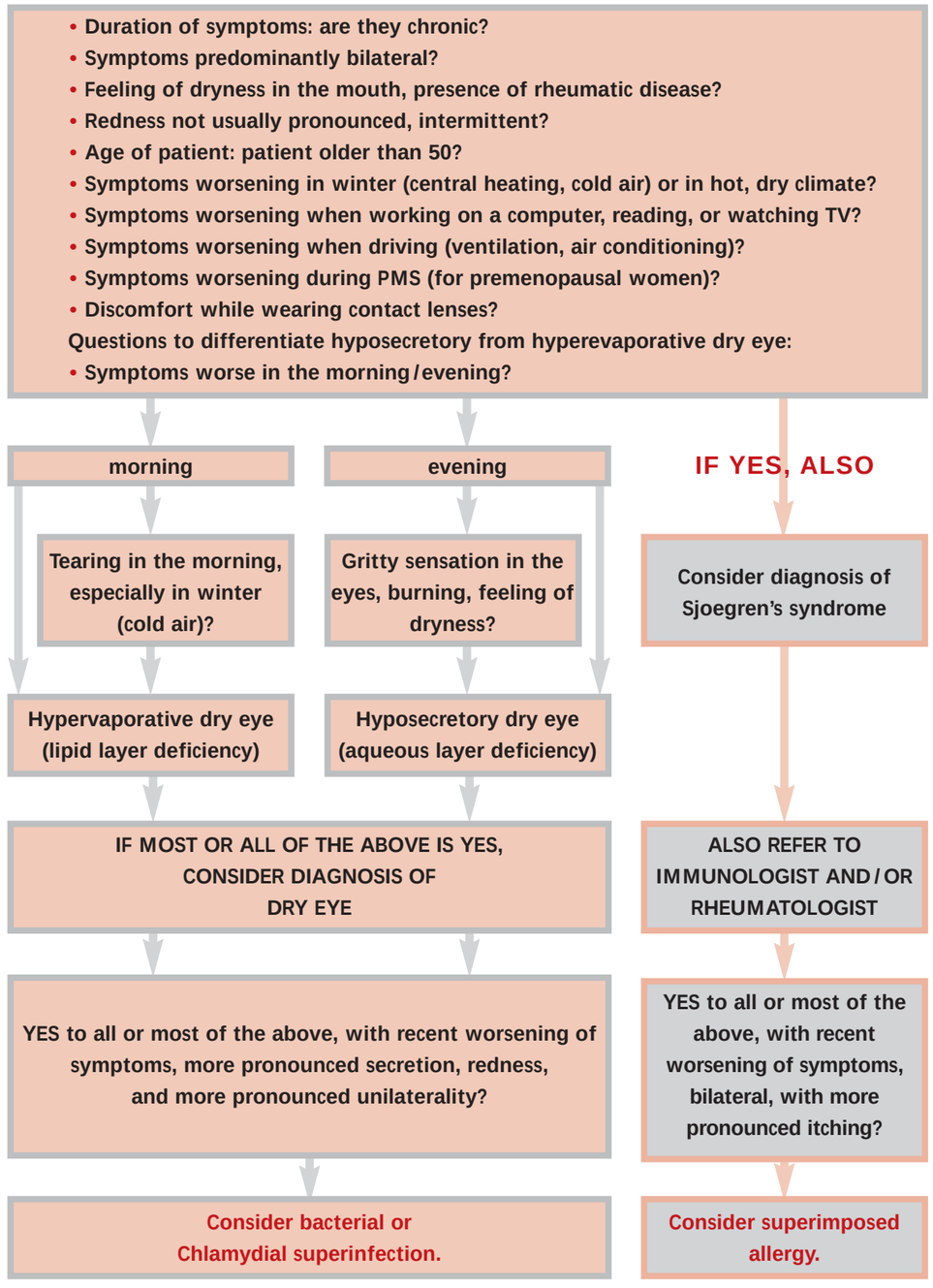
FLOWCHARTS

FLOWCHART I PHYSICAL EXAMINATION



FLOWCHART I DIAGNOSTIC DECISION TREE



III ALLERGIC CONJUNCTIVITIS

Mohamed T. Higazy

INTRODUCTION

The allergic response is considered to be an over-reaction of the body's immune system to foreign substances (allergens). The response can be innate or acquired. The key component to the ocular allergic response is the mast cell. When mast cells interact with specific allergens, the process causes a discharge of chemical mediators into the surrounding tissues. The primary chemical mediator released during degranulation is histamine, which is responsible for increased vascular permeability, vasodilation, bronchial contraction and increased secretion of mucus. Heparin, chymase, tryptase and other substances are also released from mast cells. In severe or prolonged allergic reactions, a "late-phase" response may occur in which cell membranes begin to break down into arachidonic acid, which is further degraded to form prostaglandins, leukotrienes and thromboxane (powerful mediators of inflammation that initiate stimulation of pain receptors and migration of white blood cells). [1]

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are classical examples of the "early-phase" response; however, the "late-phase" response includes atopic keratoconjunctivitis (AKC), and vernal keratoconjunctivitis (VKC).

DEFINITION

Allergic conjunctivitis is an allergic inflammatory response in the conjunctiva. Approximately 70 % of patients with allergic conjunctivitis have an associated atopic disease, such as allergic rhinitis, asthma, or atopic dermatitis.

EPIDEMIOLOGY

In most reports allergic conjunctivitis affects approximately 15 to 20 % of the world's population. [2] This incidence appears to be increasing due to increased air pollution and cigarette smoke, which may be responsible for the increased sensitivity to allergens. [3] Given the high incidence of allergic conditions, it is very common for patients suffering from allergic conjunctivitis to present to general practitioners or general ophthalmologists. Correct diagnosis and treatment is essential to manage such patients.

CLASSIFICATION AND CLINICAL PICTURE OF ALLERGIC CONJUNCTIVITIS

According to Bonini and Bonini (1997) allergic conjunctivitis is classified into: [4]

1. Seasonal allergic conjunctivitis – Acute (SAC)
2. Perennial allergic conjunctivitis – Chronic (PAC)
3. Vernal keratoconjunctivitis (VKC)
4. Atopic keratoconjunctivitis (AKC)
5. Giant papillary conjunctivitis (GPC)

The hallmark of allergic conjunctivitis is itching. A patient having red itchy eyes with no palpable preauricular lymph nodes is most probably having allergy. !

SEASONAL ALLERGIC CONJUNCTIVITIS (SAC) & PERENNIAL ALLERGIC CONJUNCTIVITIS (PAC)

Common airborne antigens including pollen, grass, and weeds may provoke the symptoms of acute allergic conjunctivitis in the form of ocular itching, redness, burning, and tearing. The main distinction between seasonal and perennial allergic conjunctivitis is the timing of symptoms.

Individuals with SAC typically have symptoms of acute allergic conjunctivitis during a defined period of time; in spring when the predominant airborne allergen is tree pollen; in summer when the predominant allergen is grass pollen; or in autumn when the predominant allergen is weed pollen. Typically, persons with SAC are symptom-free during the winter months in cooler climates because of the decreased airborne transmission of these allergens.

In contrast, individuals with PAC may have symptoms that last the whole year; thus, PAC may not be caused exclusively by seasonal allergens, although, they may play a role. Common household allergens such as dust mite, cockroaches, and pet dander are the usual causes of PAC.

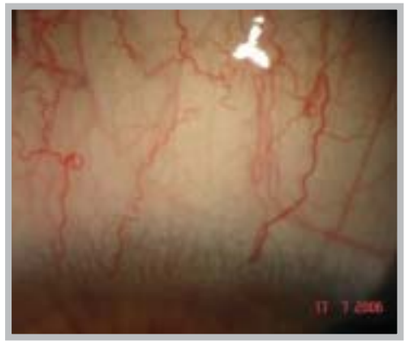


Figure 1 – Milky appearance of bulbar conjunctiva

Classic signs of allergic conjunctivitis include injection of conjunctival vessels as well as varying degrees of chemosis (conjunctival oedema) and eyelid oedema.
The conjunctiva often has a milky appearance *(Figure 1)* due to obscuration of superficial blood vessels by oedema within the substantia propria of the conjunctiva.
Oedema is generally believed to be the direct result of increased vascular permeability caused by release of histamine from conjunctival mast cells.

VERNAL KERATOCONJUNCTIVITIS (VKC)

VKC is a chronic bilateral inflammation of the conjunctiva, commonly associated with a personal and/or family history of atopy. More than 90 % of patients with VKC exhibit one or more atopic conditions such as asthma, eczema, or seasonal allergic rhinitis.

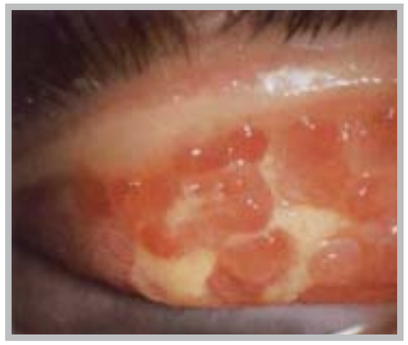


Figure 2 – Cobblestone papillae in VKC

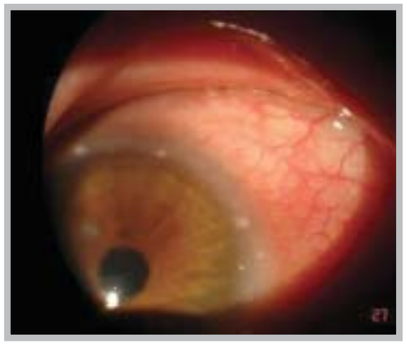


Figure 3 – Horner-Trantas dots in VKC

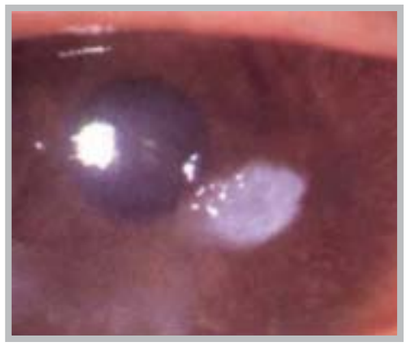


Figure 4 – Shield ulcer in VKC

VKC is characterized by severe itching, foreign body sensation, thick stringy mucous discharge, photophobia and conjunctival injection.

VKC may be subdivided into two varieties, palpebral and limbal. The classic conjunctival sign in palpebral VKC is the presence of giant papillae. They most commonly occur on the superior tarsal conjunctiva. Giant papillae are large, polygonal excrescences with flat tops, and are often described as "cobblestone papillae". A mucous coating may cover the giant papillae *(Figure 2)*. In severe cases large papillae may cause mechanical ptosis

The limbal form of VKC commonly occurs in dark-skinned individuals such as those from Africa or India. As the name implies, papillae tend to occur at the limbus and have a thick gelatinous appearance. They commonly are associated with multiple white spots (Horner-Trantas dots), which are accumulations of degenerated epithelial cells and eosinophils *(Figure 3).*

The cornea may be affected in a variety of ways. Punctate epithelial keratopathy (PEK) may be due to the toxic effect of inflammatory mediators released from the conjunctiva. As the areas of PEK coalesce, they may result in frank epithelial erosion resulting in a shield ulcer, which is typically shallow with white irregular epithelial borders. It is pathognomonic of VKC *(Figure 4)*.

Another type of corneal involvement is vernal pseudogerontoxon, which is a degenerative lesion in the peripheral cornea resembling corneal arcus.

ATOPIC KERATOCONJUNCTIVITIS (AKC)

AKC is a bilateral inflammation of the conjunctiva and eyelids, which has a strong association with atopic dermatitis. Atopic dermatitis is a common hereditary disorder that usually starts in childhood; symptoms may regress with advancing age. Approximately 25 % of cases with atopic dermatitis may develop AKC.

AKC may affect eyelid skin and lid margins, conjunctiva, cornea, and lens. The skin of the eyelids may exhibit eczematoid dermatitis with dry, scaly, and inflamed skin. Lid margins may show meibomian gland dysfunction and keratinization. Staphylococcal colonization of eyelid margins is very common and may result in blepharitis. The conjunctiva may show chemosis and typically a papillary reaction, which is more prominent in the inferior tarsal conjunctiva, in contrast to that seen in vernal keratoconjunctivitis.

Hyperplasia of limbal regions may result in a gelatinous thickening, similar to the limbal variant of VKC. Fibrosis or scarring of the conjunctiva may result in symblepharon formation. Corneal involvement ranges from punctate epithelial keratopathy early in the course of the disease, to neovascularization, stromal scarring, and possibly ulceration.

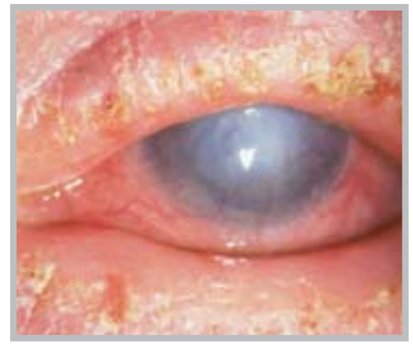


Figure 5 – Atopic keratoconjunctivitis

Lenticular changes in AKC include anterior or posterior subcapsular cataract formation. Lens opacities are usually bilateral and present in the second decade of life but progress very slowly. There may be an association with chronic use of topical corticosteroids.

GIANT PAPILLARY CONJUNCTIVITIS (GPC)

GPC is an immune-mediated inflammatory disorder of the superior tarsal conjunctiva. As the name implies, the primary finding is the presence of "giant" papillae, which are typically greater than 0.3 mm in diameter *(Figure 6)*. It is believed that GPC represents an immunologic reaction to a variety of foreign bodies, which may cause prolonged mechanical irritation to the superior tarsal conjunctiva. Although contact lenses (hard and soft) are the most common irritant, ocular prostheses, extruded scleral buckles, and exposed sutures following previous surgical intervention may precipitate GPC.

The best method of examining a patient who is suspected of having GPC is, after removing their contact lenses if worn, to evert the upper lid to view the tarsal surface with a hand held magnifier. A drop of 2 % fluorescein is instilled into the cul-de-sac and the patient is asked to blink several times, then the lid is re-everted and examination is performed with blue-cobalt light. Fluorescein will outline the giant 0.3–0.5 mm papillae. [5]

Another clinical sign of GPC may be chronic limbal vascularization due to hypoxia associated with prolonged and persistent use of contact lenses.

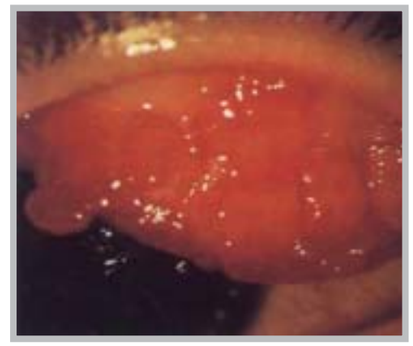


Figure 6 – Giant papillae in the tarsal conjunctiva of a chronic contact lens wearer which are not taking the cobble-stone appearance as in VKC

There are other forms of allergic eye disease that do not fully fit into this classification, as Contact Allergic Conjunctivitis (CAC):

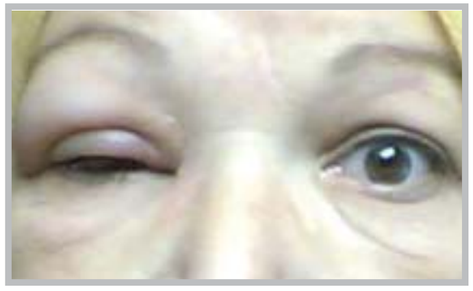


Figure 7 – Puffy eyelid due to neomycin eye drops allergy

Contact allergic conjunctivitis is due to an agent causing an allergic or toxic effect. The causative agent may be ocular medications such as atropine, gentamicin, neomycin, tobramycin, antivirals, epinephrine, pilocarpine, etc., or a preservatives such as benzalkonium chloride, chlorhexidine, EDTA, thimerosal, etc., or chemicals in cosmetics and hair spray. Usually the patient presents with a puffy swollen eyelid *(Figure 7)*. On examination, the palpebral conjunctiva may show a follicular reaction and corneal staining with fluorescein may show punctuate keratopathy.

CASE HISTORY

IMPORTANT POINTS TO BE CONSIDERED:

Age
SAC and PAC usually affect any age. VKC typically affects young males with onset generally in the first decade and duration up to one decade. Its symptoms usually peak prior to the onset of puberty and then subside. AKC typically affects adults (20 – 50 yrs) suffering from atopy.

Sex
VKC has a significant male preponderance.

Race
VKC occurs predominantly in areas with tropical and temperate climates such as the Mediterranean, the Middle East, and Africa. The limbal form of VKC commonly occurs in dark-skinned individuals from Africa and India.

Type of discharge
A serous discharge is most commonly associated with viral or allergic ocular conditions. A mucoid (stringy) discharge is highly characteristic of allergy or dry eyes. A mucopurulent or purulent discharge, often associated with morning crusting and difficulty opening the eyelids, strongly suggests a bacterial infection.

Itching
Itching is the hallmark of allergic conjunctivitis, as well as other forms of allergic eye disease. The itching may be mild to severe. In general, a red eye in the absence of itching is not caused by ocular allergy.
A history of recurrent itching or a personal or family history of hay fever, allergic rhinitis, asthma or atopic dermatitis is also suggestive of ocular allergy. In VKC, itching is the most important and most common symptom. Other commonly reported symptoms are photophobia, foreign body sensation, tearing, and blepharospasm. In contrast to AKC, the eyelid skin usually is not involved. In AKC, the single most common symptom is bilateral itching of the eyelids, but watery discharge, redness, photophobia, and pain may be associated. Primary symptoms in GPC are ocular itching with a mucoid or stringy discharge, very similar to that seen in VKC.

Bilateral nature
Allergic conjunctivitis is almost always secondary to exposure to environmental allergens and, therefore, usually presents with bilateral symptoms. Infections caused by viruses and bacteria (including Chlamydial organisms) are transmissible by eye-hand contact. Often, these infections initially present in one eye, with the second eye becoming involved a few days later.

Family history of atopy
More than 90 % of patients with VKC exhibit one or more atopic conditions such as asthma, eczema, or seasonal allergic rhinitis. AKC has a strong association with atopic dermatitis.

Onset of symptoms
The onset of symptoms is important in diagnosis of allergic conjunctivitis. Individuals with SAC typically have symptoms of acute allergic conjunctivitis for a defined period of time; in spring when the predominant airborne allergen is tree pollen; in summer when the predominant allergen is grass pollen; or in autumn when the predominant allergen is weed pollen. Typically, persons with SAC are symptom-free during the winter months in cooler climates because of the decreased airborne transmission of these allergens. In contrast, individuals with PAC may have symptoms that last the whole year; thus, PAC may not be caused exclusively by seasonal allergens, although, they may play a role. Other common household allergens such as dust mite, cockroaches, and pet dander may be responsible for the symptoms of PAC.

Contact lens use
A persistent foreign body sensation when using contact lenses, resulting in an inability to wear contact lenses for the desired length of time (dropout) is an important symptom in diagnosis of GPC.

History of medication / chemicals use
Contact allergic conjunctivitis is due to an agent causing an allergic or toxic effect. The causative agent may be an ocular medication such as atropine, gentamicin, neomycin, tobramycin, antivirals, epinephrine, pilocarpine, etc., or a preservative such as benzalkonium chloride, chlorhexidine, EDTA, thimerosal, etc., or chemicals in cosmetics and hair spray.

PHYSICAL EXAMINATION & DIAGNOSTIC TESTS

Patients with allergic conjunctivitis present with itching of the eyes, accompanied by tearing and a burning sensation. The reaction is usually bilateral, although unilateral conjunctivitis may occur in a patient who has had direct hand-to-eye contact with an allergen.The periocular tissues are usually swollen and reddened. The conjunctiva is injected, with mild to moderate chemosis, and there is a stringy mucous discharge in the tear film.

Laboratory Tests

Although examination of the ocular discharge in allergic conjunctivitis typically reveals large numbers of eosinophils, this test is almost never performed. Instead, allergic conjunctivitis is generally diagnosed clinically. As with any allergy, skin testing may be performed to identify the offending allergen or allergens, however, it is rarely undertaken.

MAIN TREATMENT GUIDELINES – THERAPEUTIC OPTIONS IN ALLERGIC CONJUNCTIVITIS

ALLERGEN AVOIDANCE

The most effective but least practical treatment is to prevent exposure to the allergen. Since this is not usually possible, patients should be instructed to frequently use cold compresses, artificial tears and ointments to soothe and lubricate the eyes and wash away the allergens. Artificial tear substitutes provide a barrier function and help to improve the first-line defence at the level of the conjunctival mucosa. These products help to dilute various allergens and inflammatory mediators that may be present on the ocular surface, and they help flush the ocular surface of these agents

MEDICAL TREATMENT

The main strategy of medical treatment is to combine different therapeutic pharmacological agents, that are active on different mediators involved in allergy pathogenesis. These pharmacological agents may include:

Topical Vasoconstrictors

Vasoconstrictors are available either alone or in conjunction with antihistamines to provide short-term relief of vascular injection and redness. Common vasoconstrictors include naphazoline, phenylephrine, oxymetazoline, and tetrahydrozoline.

Generally, the common problem with vasoconstrictors is that they may cause rebound conjunctival injection, inflammation and dryness. These pharmacological agents are ineffective against severe ocular allergies and against other more severe forms of allergic conjunctivitis, such as atopic and vernal disease. [6]

Antihistamines

Systemic and/or topical antihistamines may be given to relieve acute symptoms due to interaction of histamine at ocular H1 and H2 receptors.

Two kinds of systemic H1 receptor antagonist are available:

- **a** The first generation drugs, such as chlorpheniramine and hydroxyzine. These easily pass the blood-brain barrier and cause sedation, they also may have anticholinergic activity leading to elevation of IOP and problems with accommodation.
- **b** The second generation drugs, such as astemizole, cetirizine, loratadine, terfenadine are non-sedating.

While systemic antihistamines often relieve ocular allergic symptoms, patients may experience systemic side effects such as drowsiness and dry mouth.

Topical antihistamines competitively and reversibly block histamine receptors and relieve itching and redness but only for a short time. These medications do not affect other proinflammatory mediators, such as prostaglandins and leukotrienes, which remain uninhibited. Topical levocabastine is a second generation anti-H1 agent with a rapid onset of action and good local tolerance and does not affect accommodation or IOP. Newer topical anti-histamines, such as emedastine difumarate 0.5 % have been seen to be very effective in relieving the signs and symptoms of allergic conjunctivitis. [7]

Mast cells stabilisers

Mast cell stabilisers have a mechanism of action that is unclear. They may aid in the phosphorylation of a 78,000-d protein that terminates secretion of mast cell granules; they may increase calcium influx into the cell preventing membrane changes; and/or they may reduce membrane fluidity prior to mast cell degranulation. The end result is a decrease in degranulation of mast cells, which prevents release of histamine and other chemotactic factors that are present in the preformed and newly formed state. Mast cell stabilisers do not relieve existing symptoms and are to be used on a prophylactic basis to prevent mast cell degranulation with subsequent exposure to the allergen. Therefore, they need to be used long term in conjunction with various other classes of medication. Common mast cell stabilisers include cromolin sodium and lodoxamide.

Dual action drugs

If the goal of the therapy is to be both treatment and prevention, an agent which has both antihistamine and mast cell stabilising activities should be considered. There are several products on the market claiming to show this dual effect or even multiple effects.

Among these agents only olopatadine hydrochloride 0.1 % targets tryptase/chymase mast cells, the predominant mast cells in human conjunctival tissue and is the only antihistamine and mast-cell stabiliser approved to treat all the signs and symptoms of allergic conjunctivitis. Studies demonstrate that this formulation effectively controls the signs and symptoms associated with allergic conjunctivitis for at least 16 to 24 hours post-instillation.

Non-steroidal anti-inflammatory drugs (NSAIDs)

These act on the cyclooxygenase metabolic pathway and inhibit production of prostaglandins and thromboxanes. They have no role in blocking mediators formed by the lipoxygenase pathway, such as leukotrienes.

Common NSAIDs that are approved for allergic indications include ketorolac tromethamine and diclofenac sodium. They are useful in reducing itching and conjunctival injection but not very helpful in ridding the eye of excess immune cells. [8]

Corticosteroids

Corticosteroids remain one of the most potent pharmacologic agents used in the treatment of allergic conjunctivitis. They act at the first step of the arachidonic acid pathway by inhibiting phospholipase, which is responsible for converting membrane phospholipid into arachidonic acid. By preventing the formation of arachidonic acid, corticosteroids effectively block both cyclooxygenase and lipoxygenase pathways, in contrast to NSAIDs, which act only on the cyclooxygenase pathway. Corticosteroids do have limitations, including ocular side effects such

as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataract. In addition, the anti-inflammatory and immunosuppressive effects are nonspecific. Corticosteroids exist in various forms and potencies. Relatively weak steroids such as rimexolone, medrysone, and fluorometholone tend to have lower potency with fewer ocular side effects. In contrast, agents such as prednisolone acetate are more potent and have a higher incidence of side effects. A relatively new steroid, loteprednol etabonate, is rapidly metabolized once it enters the anterior chamber of the eye. Therefore, it is extremely useful in treating ocular surface and superficial corneal inflammations. It has a specific indication for ocular allergy and has been shown in clinical studies to have fewer ocular side effects. [9]

However, a general rule-of-thumb is that topical steroids should be prescribed only by ophthalmologists for a short period of time and for severe cases that do not respond to conventional therapy.

Cyclosporine A

This modality has been tried by some ophthalmologists.

Cyclosporine A was approved for the treatment of keratoconjunctivitis sicca and may someday be a treatment option for allergic conjunctivitis. In some studies, it has been shown that management of allergic conjunctivitis with topical cyclosporine A produced satisfactory results and patients experienced symptomatic relief within the first week of treatment. [10,11] In one study, Daniell and co-workers showed that topical cyclosporine A 0.05 % was not beneficial compared to placebo as a steroid sparing agent in steroid dependent allergic conjunctivitis. [12]

Immunotherapy

This treatment modality is usually administered by immunoallergologists who are experienced with this kind of therapy.

Immunotherapy can be beneficial in some patients with allergic conjunctivitis. [13] Immunotherapy, or allergy shots, involves injecting increasing doses of the offending antigen or antigens in an attempt to attenuate the specific allergic response. An immunotherapy extract is prepared on the basis of skin-testing results. The patient then receives increasing doses subcutaneously on a weekly or twice-weekly schedule for about five months. After this so-called build-up phase, the patient is maintained on a stable dose that is administered weekly to monthly for several years. Usually, patients achieve maximal benefit after being on the maintenance dose for one year.

MEDICAL TREATMENTS THAT CAN BE USED BY THE GENERAL PRACTITIONER IN MANAGING DIFFERENT TYPES OF ALLERGIC CONJUNCTIVITIS

Seasonal and perennial allergic conjunctivitis

Various classes of medication may be effective against the symptoms of acute allergic conjunctivitis; each is directed at a specific point in the inflammatory and allergic cascade.

The following can be used:

- Artificial tear substitutes
- Topical antihistamines
- Mast cell stabilisers
- Dual action drugs
- Vasoconstrictors
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Vernal keratoconjunctivitis

VKC should be referred to an ophthalmologist as the therapeutic options are many, and should be chosen on the basis of the severity of the disease. However, the general practitioner as a start point can give the following:

- Mucolytic agents such as acetylcysteine may help minimise the discharge and provide temporary relief.
- Mast cell stabilisers are perhaps the mainstay of treatment of VKC and are safe for long-term use.
- Oral aspirin as adjunctive therapy for intractable cases of vernal conjunctivitis has been shown to be effective. Aspirin acetylates the enzyme cyclooxygenase, thereby preventing the formation of prostaglandin D2. [14]

Referral to an ophthalmologist is mandatory to continue management with the following:

- Topical steroids are the most effective drugs. They should be prescribed by an ophthalmologist at the lowest effective concentration and for the shortest duration possible. A pulsed-therapy regimen is generally recommended such as 1 % prednisolone acetate every two hours for the first week followed by a rapid taper; this may be repeated if symptoms recur.
- Systemic steroids may be used in severe cases, but generally are not necessary for moderate cases of VKC.
- Topical 2 % cyclosporine A in castor oil should be considered as an alternative to steroids and may be effective in reducing some of the signs and symptoms of VKC without adverse effects.
- Treatment of corneal shield ulcer may require the use of antibiotic-steroid ointments.

Atopic keratoconjunctivitis

Treatment of patients with AKC is similar to that of VKC and should be by an ophthalmologist. As with VKC, topical mast cell stabilisers and topical corticosteroids provide significant relief of symptoms. Mast cell stabilisers have to be used for several weeks prior to seeing a clinical effect, and in the interim, topical steroids used in a pulsed fashion may help to control symptoms. Systemic antihistamines that are specific for H1 histamine receptors have been found to be helpful. Systemic steroids are rarely required, except in cases of vision-threatening complications. Systemic cyclosporine A, which has been shown to be effective in the treatment of atopic dermatitis, has shown promise in controlling ocular inflammation in AKC. [15] This treatment modality can only be performed by an immunology department.

Giant papillary conjunctivitis

Treatment of patients with GPC is similar to that of AKC and VKC and should be by an ophthalmologist.

The goal of treatment in GPC is resolution of symptoms and restoration of functional use of contact lenses or ocular prosthetics. Although removal of the responsible foreign body is the definitive treatment, and while that may be appropriate for exposed sutures or scleral buckles,

complete discontinuation of contact lenses or ocular prosthetics may be met with some degree of resistance from patients. Fortunately, contact lens wear does not need to be completely discontinued to minimize the symptoms of GPC. Significant reduction in the signs and symptoms may be achieved by changing the contact lens material and care routine. Disinfecting solutions that contain chemical preservatives should be discontinued. Converting a patient from soft daily-wear contact lenses to disposable or daily-disposable soft contact lenses may prevent the accumulation of proteinaceous deposits, which may be the antigenic stimulus for GPC. [16] Rigid gas permeable contact lenses may provide further relief from symptoms if disposable lenses do not provide an adequate response. This relief is obtained because of the decreased proclivity of the rigid gas permeable contact lenses to develop adherent deposits and coatings. Pharmacologic treatment of GPC includes the use of mast cell stabilisers, topical corticosteroids, and antihistamines similar to that in the other immunologic conjunctival disorders discussed previously. As always, care must be taken when using topical corticosteroids; a pulsed regimen is recommended to minimise adverse reactions.

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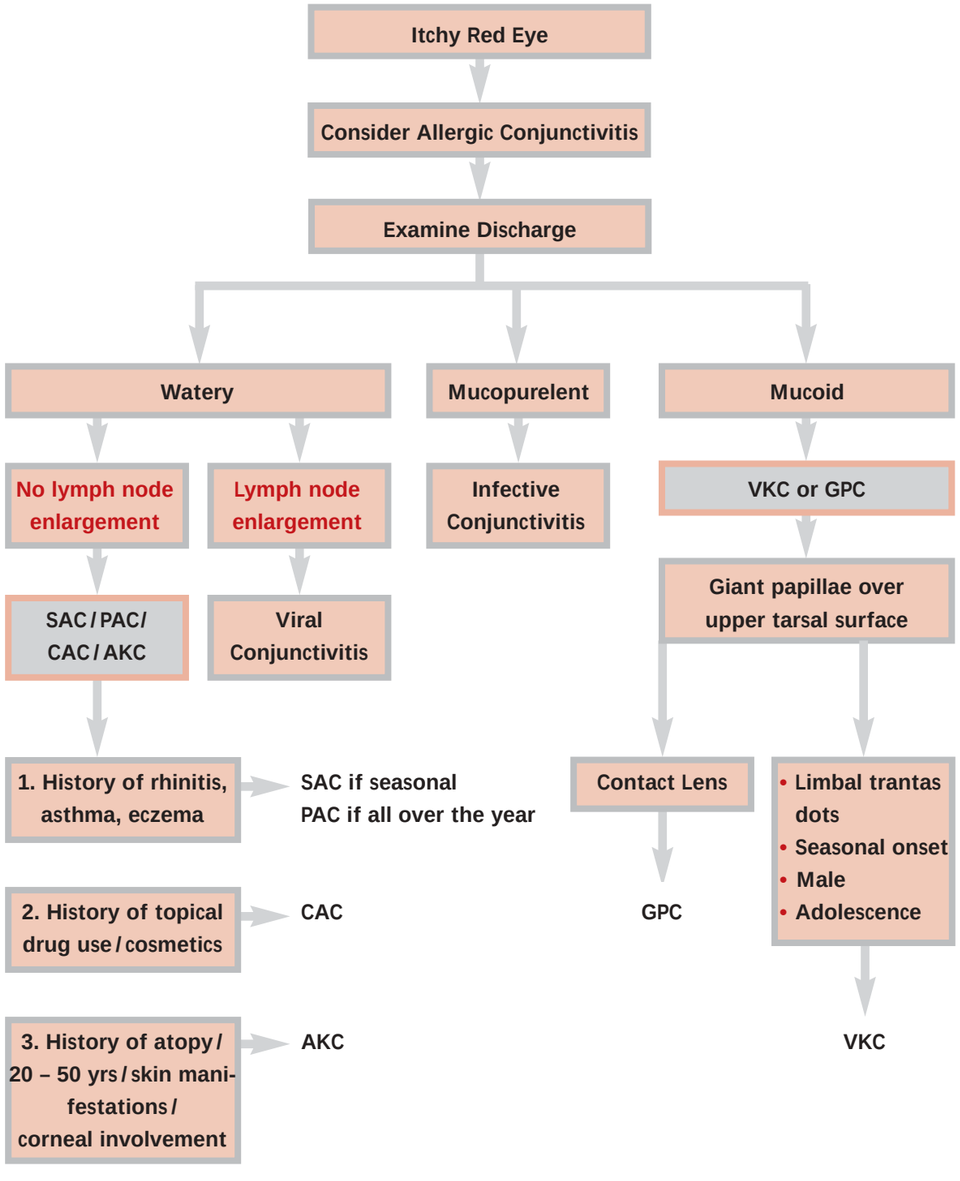
FLOWCHART I DIAGNOSTIC CHART OF ALLERGIC EYE DISEASE



SAC = Seasonal Allergic Conjunctivitis
PAC = Perennial Allergic Conjunctivitis
CAC = Contact Allergic Conjunctivitis
AKC = Atopic Keratoconjunctivitis
VKC = Vernal Keratoconjunctivitis
GPC = Giant Papillary Conjunctivitis

TABLE I A QUICK GUIDE TO DRUGS USED TO TREAT DIFFERENT CASES OF ALLERGIC CONJUNCTIVITIS.

	SAC	PAC	VKC	AKC	GPC	CAC
Artificial Tears	+	+	+	+		+
Vasoconstrictors	±	±				±
Topical Antihistamines	+		+	+	+	+
Mast Cell Stabilisers	+	+	+	+	+	+
Dual Action Drugs	+	+	+	+	+	+
NSAIDs	+	+	+	+		+
Topical Steroids			+	+	+	
Topical Cyclosporine			+	+		
Systemic Steroids				+		
Systemic Cyclosporine				+		
Imm. Therapy	+	+		+		

NSAIDs = Non Steroidal Anti-inflammatory Drugs

IV INFECTIOUS CONJUNCTIVITIS

Marek E. Prost

INTRODUCTION

Infectious conjunctivitis is one of the three leading causes of red eye (the other two are allergic conjunctivitis and dry eye syndrome). Therefore, patients with these disorders are frequently seen by general practitioners in their every-day practice. Most cases of infectious conjunctivitis are self-limiting but some of them may progress and may cause severe ocular complications or they may be associated with involvement of other organs. The aim of this chapter is to present, in a concise form, the most important information on how to establish the proper diagnosis of infectious conjunctivitis and differentiate it from other red eye causes, how to choose appropriate therapy and help to make decisions about which cases can be treated by general practitioners and which should be referred for treatment by ophthalmologists.

DEFINITION

Infectious conjunctivitis is an inflammation of the conjunctiva caused by infective agents. Almost any microbial organism can cause infectious conjunctivitis. Most frequently it is caused by bacteria, viruses and chlamydia. Rarely, conjunctivitis is caused by acanthamoeba and very rarely, by fungal infection. These inflammations are usually secondary to keratitis.

EPIDEMIOLOGY

Infectious conjunctivitis is one of the most frequent causes of red eye. According to a recently published study, performed in nine Eastern European and Middle Eastern countries, red eye patients account for 15 % of all consultations performed by ophthalmologists and 6 % of visits to general practitioners. [11] Among these patients, infectious conjunctivitis was the most frequent cause of red eye seen by ophthalmologists (31.3 %) and the second largest cause in general medical practitioners practices (25 % – the most frequent diagnosis was allergic conjunctivitis: 56 %). [11]

BACTERIAL CONJUNCTIVITIS

This is usually caused by Streptococcus and Staphylococcus species and less frequently by Haemophilus influenzae and enteric gram-negative organisms. [8, 9, 10, 12] In children, Haemophilus influenzae may be the most common cause. [10, 16] The sources of the infection are usually a skin or respiratory tract pathogen or, in neonates, vaginal delivery by an infected mother. Usually, one eye is involved but infection of the second eye may develop in a few days.

Bacterial conjunctivitis can present as an acute, subacute or chronic condition. **Acute bacterial conjunctivitis** usually begins suddenly in one eye with hyperaemia and moderate to copious purulent or mucopurulent discharge *(Figure 1 and Figure 3, Chapter I)*, but infection of the second eye may develop in a few days. [12] Patients initially complain of unilateral then bilateral tearing and vague irritation. Associated mild to moderate eyelid oedema and erythema may give the appearance of pseudoptosis. Purulent discharge may accumulate on the eyelashes, resulting in the eyelids sticking together in the morning on waking. Some bacteria are able to cause conjunctival membranes or pseudomembranes (beta hemolytic streptococci, Bordetella pertussis – diphtheria).

Figure 1 – Acute bacterial conjunctivitis with purulent discharge and conjuctival hyperaemia.

In **subacute or chronic conjunctivitis** patients present with moderate purulent discharge, mild conjunctival hyperaemia and crustings on the eyelids and/or eyelashes (dried purulent discharge). [1, 9] *(Figure 1)* Sometimes a conjunctival papillary reaction may be seen in chronic bacterial conjunctivitis. [8, 9] *(Figure 2)*

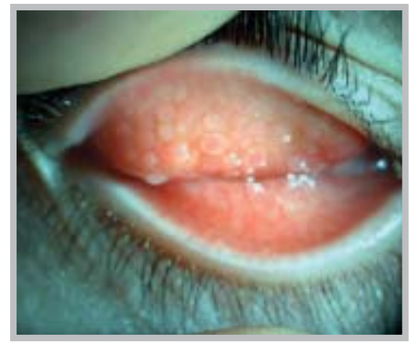


Figure 2 – Conjunctival papillary reaction in chronic bacterial conjunctivitis.

Corneal involvement is very rare in bacterial conjunctivitis. The duration of infection is on average 5–7 days and is usually mild and self-limiting, but in children it may rarely progress to keratitis and infection of orbital tissue (preseptal cellulites). [1] Pre-auricular lymph nodes are not enlarged.

The most typical sign of bacterial conjunctivitis is purulent discharge and eyelids sticking together in the morning upon waking. In neonates and infants it is necessary to exclude nasolacrimal duct obstruction as a cause of bacterial conjunctivitis. A very rare but sight threatening form of bacterial conjunctivitis is hyper-acute conjunctivitis (see addendum).

VIRAL CONJUNCTIVITIS

This is usually caused by adenoviruses (epidemic keratoconjunctivitis and pharyngoconjunctival fever) or herpes simplex, less frequently by varicella-zoster virus, picornaviruses, pox and papilloma viruses. The infections are transmitted by hand to eye contact, contact with upper respiratory tract droplets, infected swimming pools or infected ocular instruments like tonometers. Typical signs of viral conjunctivitis are conjunctival hyperaemia, copious, clear, serous, watery discharge, lid oedema and follicular conjunctival reaction. *(Figure 3 and 4)* It follows a longer course than bacterial conjunctivitis, usually 2–3 weeks. Preauricular lymph nodes are usually involved. Sometimes a history of recent fever, upper respiratory tract infections or pharyngitis helps to establish diagnosis. [13]

Figure 3 – Intensive conjunctival hyperaemia in epidemic adenoviral keratoconjunctivitis.

Figure 4 – Typical follicular reaction in lower palpebral conjunctiva in viral conjunctivitis

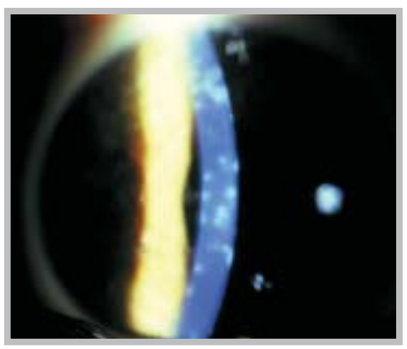


Figure 5 – Small, round, grayish, subepithelial infiltrates in the cornea of patients with epidemic keratoconjunctivitis.

Adenoviral infections are usually highly contagious and occur in epidemics. Patients usually give a history of recent exposure to an individual with red eye at home or work. The onset of infection is abrupt and the second eye is involved in 1–2 days. The disease usually presents with significant conjunctival injection, copious, clear, watery, serous discharge, eyelid oedema and follicular conjunctival reaction. [10] Distinctive signs of adenoviral infection are: follicular conjunctivitis with abrupt onset, watery discharge, lid oedema, subepithelial corneal infiltrates and preauricular lymph node enlargement. [13, 15] Patients with adenoviral conjunctivitis are contagious to others for three weeks after the beginning of the infection. [14] Subtypes of adenoviral conjunctivitis include epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever (PCF).

a. Epidemic keratoconjunctivitis (EKC) is characterized by a sudden onset of signs and symptoms; significant irritation, soreness, red eye, photophobia, foreign body sensation, and excessive watery discharge. Marked eyelid swelling and erythema is often present. In severe cases, conjunctival membranes, pseudomembranes and subconjunctival haemorrhages and chemosis may develop. A typical complication of EKC is the development of small, round, grayish subepithelial infiltrates in the cornea. (*Figure 5*) They appear about two weeks after the onset of the conjunctivitis and may persist for weeks to months, sometimes to years, eventually resolving spontaneously without scarring. They may decrease visual acuity and cause glare. Preauricular lymph nodes are usually enlarged. Sometimes, concurrent upper respiratory tract infection is observed.

b. Pharyngoconjunctival fever (PCF) is characterized by fever, pharyngitis, acute follicular conjunctivitis and regional lymphoid hyperplasia with tender, enlarged preauricular adenopathy. Usually, clinical signs and symptoms are less severe than in EKC and corneal involvement is rare. [15]

Herpes simplex conjunctivitis is caused by HSV type 1. In neonates, infection is due to maternal genital infection with HSV-2. Conjunctival signs are typical for viral conjunctivitis but sometimes a vesicular eyelid rash may accompany herpetic conjunctivitis and is a distinctive sign of this infection. It is often associated with corneal involvement. A typical manifestation is dendritic keratitis with the typical picture of linear branching lesions. *(Figure 6 and Figure 6, Chapter III)* Other forms of corneal involvement are less frequent (epithelial keratitis, neurotrophic keratopathy, interstitial keratitis, necrotizing stromal keratitis, disciform stromal keratitis, endotheliitis). Preauricular lymph nodes are usually involved. Fever and upper respiratory tract infections may precede or accompany herpes simplex conjunctivitis. Distinctive signs of herpetic infection are: vesicular eyelid rash and dendritic epithelial keratitis. [1, 13]

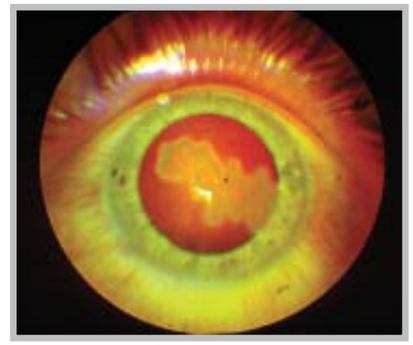


Figure 6 – Typical picture of linear branching figures of epithelial corneal lesions (dendritic keratitis) in herpetic keratitis

Varicella-zoster conjunctivitis is caused by varicella-zoster virus (VZV) and is unilateral. It is characterized by typical vesicular skin eruptions involving the tissues innervated by the ophthalmic division of the trigeminal nerve (eye, ear, mouth, tongue, skin), fever, headache, significant ocular pain and sometimes extraocular signs and symptoms (hyperaesthesia, pain in the affected dermatome, vertigo, hearing loss, taste alteration, paralysis of the facial nerve). [13] Conjunctivitis is associated with corneal involvement in 40–60 % of the cases, iridocyclitis in up to 40 % and elevated IOP in 40 %. These complications usually cause a decrease in visual acuity. Recurrence is a characteristic feature of herpes zoster ophthalmicus. A vesicular eyelid and face rash and significant pain that accompany varicella-zoster infection is a distinctive sign of this infection. [1]

Acute haemorrhagic conjunctivitis is caused by picornaviruses and has been described in Egypt and other African countries, China, India, Japan and Cuba. As EKC it is a rapidly progressive and highly contagious infection. Its signs include swollen lids, conjunctival follicles, chemosis and typical subconjunctival haemorrhages, which can range from petechiae to coalescent, large areas of haemorrhages. [13] Superficial epithelial changes can be seen sometimes in the cornea. The infection usually resolves without sequellae. In infants and children, polio-like paralysis, aseptic meningitis and involvement of different organ systems, ranging from the myocardium to the CNS, respiratory system and skin, have been described.

Molluscum contagiosum is a cutaneous or conjunctival pox viral infection that causes a raised, waxy, umbilicated lesion on the eyelids, near the lid margin and face. An immunocompromised state may predispose to multiple and/or large lesions. [1] Virus particles that are shed into the tear film from eyelid lesions may cause a reaction of the conjunctiva and cornea, resulting in a chronic, follicular conjunctivitis and sometimes punctate corneal epithelial defects with subepithelial corneal opacities and mild superior keratitis. Conjunctivitis is usually unilateral

less often bilateral. Infrequent complications include conjunctival scarring and occlusion of the lacrimal puncta. [13] Usually, there is no enlargement of lymph nodes. Typical umbilical eyelid lesions help to establish the diagnosis.

Verrucae, commonly known as warts, are produced by the papilloma viruses. If skin lesions grow on the eyelid margin and among the lashes, the viral toxins and desquamating epithelial cells may cause a secondary, mild toxic, follicular conjunctivitis.

CHLAMYDIAL CONJUNCTIVITIS

Chlamydia are obligate intracellular organisms, depending on the host cell to carry out metabolic biosynthesis and are counted among the gram-negative bacteria. The species consists of three subgroups: C. trachomatis, C. pneumoniae and C. psittaci. Humans are the reservoir of C. trachomatis and C. pneumoniae; C. psittaci causes zoonosis. By serologic typing, C. trachomatis can be divided into subtypes, of which A, B, Ba and C induce trachoma, subtypes D-K cause inclusion body conjunctivitis (adult and neonatal) and urethritis, prostatitis, cervicitis and salpingitis, subtypes L 1-2-3 produce lymphogranuloma venerum.

Although C. trachomatis is the infectious agent of both trachoma and inclusion body conjunctivitis (adult and neonatal), the clinical presentations and the epidemiologic characteristics of the two diseases are very different. The incidence of trachoma is highest in unhealthy, dirty, crowded, poor hygienic conditions. Transmission generally occurs with contact of conjunctival exudates directly or via flies. Subtypes D-K, as well as the L varieties are transmitted sexually and therefore cause venereal disease, in which ocular involvement represents secondary infection. Chlamydial conjunctivitis consists of three clinical syndromes: trachoma, adult inclusion body conjunctivitis and neonatal chlamydial conjunctivitis.

Trachoma

Trachoma and its complications still represent a serious world health problem and today remains a major cause of preventable blindness. Trachoma affects approximately one-seventh of the world's population.

In its early stages, trachoma presents as a bilateral follicular conjunctivitis with a predilection for the superior tarsal and bulbar conjunctiva. Symptoms are photophobia, tearing and mucopurulent discharge. Conjunctival follicles at the limbus are characteristic of severe trachoma. Primary corneal involvement includes superior pannus formation. Corneal infiltrates (superior, diffuse, limbal) and marginal ulceration may occur. As the disease progresses, the conjunctival scarring can result in entropium and trichiasis, that can lead to corneal ulceration and neovascularization, causing corneal opacification. Corneal changes are the major blinding complications of trachoma. The conjunctival scarring may also cause many other secondary complications, including severe dry eye syndrome and punctal stenosis.

Adult inclusion body conjunctivitis

Chlamydial infection is one of the most common sexually transmitted diseases. Ocular infection commonly occurs by autoinoculation (sexual contact or by hand to eye contact) with infected genital and urinary secretions.

The disease usually is unilateral, but may also be bilateral. It is a chronic, prolonged, recurrent conjunctivitis with exacerbations and remissions. Patients complain of ocular irritation, photophobia and redness. Typical signs include pseudoptosis, mucopurulent discharge, moderate conjunctival hyperaemia and follicular conjunctival reaction, particularly on the inferior fornix. Chlamydial conjunctivitis is often associated with corneal involvement (epithelial keratitis, small pannus), which can cause diminished visual acuity. Preauricular lymph nodes are usually enlarged and tender. Women often have chronic vaginitis or cervicitis, men have symptomatic or asymptomatic urethritis. All patients with suspected or confirmed chlamydial conjunctivitis should be evaluated and co-managed with a gynaecologist or urologist

Neonatal chlamydial conjunctivitis

This infection has been estimated to occur in 2 % to 6 % of all newborns. The high incidence of infection may also be related to the ineffectiveness of silver nitrate in preventing chlamydial infection.

Neonatal chlamydial conjunctivitis is characterized by the onset of a mild to moderate unilateral or bilateral mucopurulent conjunctivitis, 5 to 14 days after the birth. Typical signs are eyelid oedema, chemosis, mucopurulent discharge and conjunctival membrane or pseudomembrane without follicular reaction. Sometimes the cornea is involved, including punctuate opacities and micropannus formation. Systemic chlamydial infection (pneumonia nasopharyngeal infection and otitis) can develop in more than 50 % of infants. An important aspect of treatment is concurrent therapy for the mother and her sexual partner.

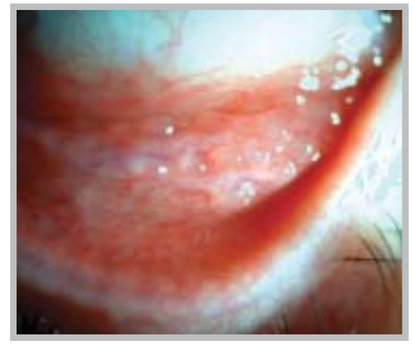


Figure 7 – Multiple conjunctival follicles in a patient with adult inclusion conjunctivitis.

ACANTHAMOEBA KERATOCONJUNCTIVITIS

Acanthamoeba keratoconjunctivitis is an uncommon but sight-threatening condition that mainly affects contact lens wearers. It is caused by free-living protozoans (amoebas) that may be found in soil, dust, fresh water, tap water, hot tubs and swimming pools. Contact lens wearers, using poor disinfection and storage techniques for their lenses (instead of commercially produced solutions), are at particular risk. Very rarely, it can occur after a minor corneal abrasion becomes infected with soil or ground water. The typical classic clinical picture of Acanthamoeba keratoconjunctivitis includes multifocal, patchy, corneal stroma infiltrates coalescing to form a central or paracentral non-suppurative ring in a patient with severe ocular pain out of proportion to the clinical findings. Visual acuity is significantly decreased. Conjunctivitis is always secondary to keratitis.

FUNGAL KERATOCONJUNCTIVITIS

Fungal keratoconjunctivitis can be caused by nonfilamentous fungi e.g. Candida species or filamentous fungi e.g. Aspergillus or Fusarium species. It should be suspected in cases of patients with bacterial or herpetic keratitis unresponsive to standard treatment. It usually develops after trauma involving vegetable matter (such as wood) and sometimes in immunocompromised patients. The clinical picture consists of a gray, stromal, corneal infiltrate with

indistinct, feathery borders. Visual acuity is significantly decreased. Sometimes, satellite lesions surround the primary infiltrate. A purulent discharge in the lower part of the anterior chamber can also be found. Conjunctivitis in fungal infection is always secondary to keratitis.

CASE HISTORY

1. When do your symptoms start?
   Bacterial conjunctivitis usually occurs in the hot, summer months. Viral infections can be associated with upper respiratory tract infections or pharyngitis and therefore occur more frequently in autumn.
2. Do they last more or less than three weeks?
   Chlamydial infections are chronic, recurrent with exacerbations and remissions and last more than three weeks. Viral infections usually take a less prolonged course of two to three weeks and bacterial infections very infrequently last longer than one week.
3. Has there been recent exposure to an infected individual? Adenoviral or picornaviral infections are highly contagious and usually conjunctival infection can be diagnosed in other members of the family or coworkers.
4. Are symptoms constant or intermittent?
   Chlamydial infections are usually chronic and recurrent lasting more than three weeks.
5. What are the main symptoms (sticky purulent, serous or mucopurulent discharge, blurring of vision)? Patients with bacterial conjunctivitis often present with a sticky purulent discharge, viral infections are associated with a serous discharge and chlamydial infections with a mucopurulent discharge. Corneal involvement with blurring of vision occurs more frequently in viral infections (usually adenoviral or herpetic keratoconjunctivitis).
6. Do you have glued eye(s) in the morning?
   Eyelids and/or lashes sticking in the morning upon waking due to a purulent discharge is a typical sign of bacterial conjunctivitis.
7. Does the patient complain of blurring of vision?
   Diminished visual acuity is usually a symptom of corneal involvement. Keratitis is a frequent complication of viral or chlamydial conjunctivitis. In bacterial conjunctivitis, keratitis is extremely rare. In Acanthamoeba and fungal keratoconjunctivitis, visual acuity is significantly decreased.
8. Are other members of the family/partners or likely contacts involved? Viral conjunctivitis (adenoviral and picornaviral) is highly contagious and occurs in epidemics. Chlamydial infections are typically found in sexually active adults and can be transmitted sexually, so examination of his/her sexual partner is necessary. Anterior segment infections caused by Chlamydia trachomatis occur in endemic areas.
9. Underlying general disease:
   The conjunctiva can be affected during or after systemic infections:

bacterial conjunctivitis	• no systemic manifestations,
viral conjunctivitis	• sometimes has a history of recent upper respiratory tract infection or pharyngitis, chickenpox, zoster, lymphadenopathy
chlamydial infections	• pneumonia and/or otitis (children), cervicitis and/or vaginitis (women), symptomatic or non-symptomatic urethritis (men), lymphadenopathy.

PHYSICAL EXAMINATION AND DIAGNOSTIC TESTS

ANTERIOR SEGMENT EXAMINATION

Detailed examination of the anterior segment of the eye is the most important part of evaluation of patients with red eye. Ophthalmologists examine the anterior segment with the use of a slit lamp. GPs or GPPs can examine the conjunctiva and cornea with side illumination and a magnifier (see Chapter I on the differential diagnosis of the red eye). The type of discharge, changes in and on the surface of the palpebral or bulbar conjunctiva, and changes of the regularity and clearness of the cornea should be observed. If changes are seen in the cornea, the patient should be sent to an ophthalmologist for detailed diagnosis. Some features seen with a slit lamp or during examination with side illumination may be specific for various types of infectious conjunctivitis. The signs include: papillae, giant papillae, follicles, membranes or pseudomembranes, corneal filaments, micro-pannus and gross-pannus. For GPs and GPPs it will be difficult to distinguish these changes but they should try to recognize conjunctival follicles during examination with side illumination and a magnifier. These are numerous, smooth, yellowish elevations of the conjunctiva, 2–5 mm in diameter, similar to a small grain of rice, with no vessels inside them. Follicles represent hyperplasia of the subconjunctival lymphoid tissue. *(Figure 4)* They are a common presentation in viral (acute inflammation lasting less than three weeks), chlamydial conjunctivitis (chronic inflammation with exacerbation lasting more than three weeks) and toxic reactions. [10] They should be differentiated from papillae which are a non specific sign, occurring in any kind of inflammation (mainly in bacterial and allergic). They present as elevated, polygonal, hyperaemic areas separated by pale channels with central vessels erupting into a spoke-like pattern. The connective tissue septa that anchors the epithelium to the deeper collagenous tissue limits the size of papilla to less than 1 mm. *(Figure 2)*

ORDINARY BACTERIAL CONJUNCTIVITIS

This type of conjunctivitis can be diagnosed on the basis of medical history and eye examination. Usually slide stains, cultures or cytology are not necessary to prove the diagnosis. [1] Diagnostic tests are indicated in neonatal bacterial conjunctivitis, difficult clinical cases, recurrent conjunctivitis and in patients not responding to medication. It has to be remembered that in patients with bacterial conjunctivitis treated previously with antibiotics, the results of slide stains and cultures are very often negative. In hyper-acute and suspected neonatal conjunctivitis, it is mandatory to perform slide stains, cultures and antibiotic sensitivity as a matter of urgency.

Usually Gram stain is used for direct identification of causative bacteria. [9, 12] Conjunctival smears and corneal scrapings can be cultured on various media, the most popular is blood agar. In neonates and infants, it is necessary to exclude nasolacrimal duct obstruction as a cause of bacterial conjunctivitis.

VIRAL INFECTIONS

Usually clinical diagnosis is used. Viral cultures and immunodiagnostic tests are not very helpful and are infrequently used in clinical practice. [1] They are only performed in diagnostically difficult cases. Obtaining the results of viral cultures takes several weeks.

CHLAMYDIAL INFECTIONS

If the diagnosis can not been made on a clinical basis performance of cytology with Giemsa stain (basophilic intracytoplasmic inclusion bodies in epithelial cells – Halberstaedter – von Provazek bodies), direct immunofluorescent antibody tests (DFA, IFA), ELISA and PCR tests of ocular specimens may be helpful. [1, 2, 3, 7] Doubtful clinical cases should be sent to an ophthalmologist for detailed examination.

ACANTHAMOEBA AND FUNGAL CONJUNCTIVITIS

Both conditions are severe and sight-threatening and therefore patients with suspected Acanthamoeba or fungal conjunctivitis should be send to an ophthalmologist for detailed examination.

In many patients with different types of conjunctivitis cytology (performed with Giemsa staining) allows more rapid diagnosis (not influenced by the previous treatment) than cultures, slide stains or immunological tests. [9, 12] *(Table III)*

MAIN TREATMENT GUIDELINES

ORDINARY BACTERIAL CONJUNCTIVITIS

Neonatal bacterial conjunctivitis and difficult clinical cases should be sent to an ophthalmologist for detailed diagnosis and treatment. In other cases, treatment is usually started with broad spectrum topical antibiotics. Since ordinary bacterial conjunctivitis is very often self-limiting, a less expensive option, like aminoglycosides, may be selected but fluoroquinolones are used more and more frequently nowadays. [1, 9] If this therapy is not effective after seven days, the patient should be sent to an ophthalmologist for detailed diagnosis. Because antibiotic resistance is becoming a growing problem, it is advisable to select bactericidal and not bacteriostatic antibiotics to diminish the probability of the development of antibiotic-resistant bacterial strains. It is also recommended that adequate dosing should be maintained (e.g. aminoglycosides at least three times per day, fluoroquinolones four times per day) to decrease the possibility of exposure of bacterial populations to repeated, sublethal doses of antibiotics which can stimulate development of mutations that are responsible for increased resistance. It is necessary to wash away any purulent discharge before initiating treatment.

HYPER-ACUTE BACTERIAL CONJUNCTIVITIS

The patient should be sent to an ophthalmic center and admitted to hospital. Detailed examination with slide stains, cultures and antibiotic sensitivity has to be performed. Treatment is started immediately with systemic antibiotics (basic therapy) – ceftraxione [adults 1 g IM, children 125 mg IM, neonates 25–50 mg/kg (not to exceed 125 mg) IM or IV single dose]. Topical last-generation fluoroquinolones given hourly can also be administered. [1] Afterwards, therapy is adjusted according to the sensitivity of the cultured organism. Washing of discharge from the infected eyes should be considered.

VIRAL CONJUNCTIVITIS

In adenoviral and picornaviral infections, treatment is only supportive. The recently introduced ganciclovir 0.15 % ocular gel has antiviral activity against some serotypes of adenoviruses. Topical broad spectrum antibiotics can be used to prevent bacterial superinfection. If the patient is complaining of blurred vision, he/she should be sent to an ophthalmologist for detailed examination and exclusion of keratitis. Patients should be advised to wash their hands frequently, use separate towels and avoid close contact with other people.

In herpetic and varicella-zoster infections, topical acyclovir (3 % ointment four times per day for 3 weeks) is the treatment of choice. Ganciclovir (0.15 % gel four times per day for 3 weeks) is comparable in efficacy to acyclovir in the treatment of ocular herpetic infections. [6] Topical idoxuridine (IDU), vidarabine and trifluridine are now less commonly used. Oral acyclovir 200 to 400 mg, given five times per day until the conjunctivitis resolves, is sometimes used in more severe cases. Cases of neonatal herpetic conjunctivitis should be sent to an ophthalmologist and treated with oral acyclovir in conjunction with a paediatrician because they can be associated with systemic HSV infection, which is a life-threatening condition. [1] Zoster infection could be a sight-threatening disease so it should be treated by an ophthalmologist.

In molluscum contagiosum and papilloma, treatment is by surgical excision, incision, cauterization, cryotherapy or curettage. The conjunctivitis and keratitis typically resolve after removal of the skin lesions. [1, 13] Spontaneous resolution is usually seen in 3 to 12 months in immunocompetent patients.

Corticosteroids should be used with caution in viral conjunctivitis because they can worsen viral infections. It is important to wash and disinfect the hands carefully after contact with a patient with viral conjunctivitis because these infections are highly contagious.

CHLAMYDIAL INFECTIONS

If diagnosis can not been made on a clinical basis or there is suspicion of corneal involvement, the patient should be sent to an ophthalmologist. Because of frequent concomitant systemic infections, oral azithromycin (one time single dose 1 gm p.o.) or clarithromycin, tetracycline, doxycyline or erythromycin for two weeks, given to the patient and his or her sexual partner is basic therapy for chlamydial conjunctivitis. Therapy of both patient and his/her sexual partner is necessary. In some countries, only topical treatment is used as follows: topical sulphametacin eye drops 10 % – 30 % four times per day, together with erythromycin 0.5 % ointment or tetracycline 1 % ointment during the night for two weeks. The effectiveness of topical treatment added to systemic therapy is not proven.

Trachoma is one of the leading causes of blindness in developing countries so GPs should always consider sending the patient to an ophthalmologist.

DIFFICULT CLINICAL DIAGNOSIS

If the diagnosis is doubtful the patient should be sent to an ophthalmologist for detailed examination and adequate treatment.

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FLOWCHARTS AND TABLES

FLOWCHART I INFECTIOUS CONJUNCTIVITIS – MAIN DECISION TREE

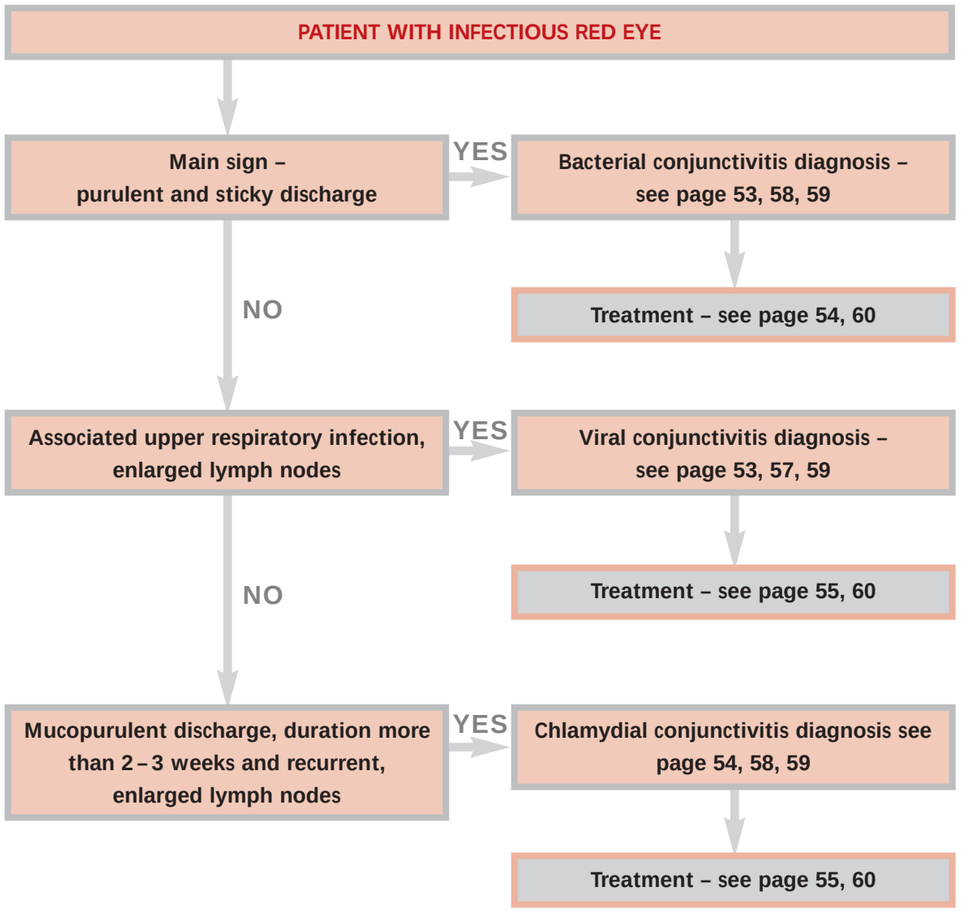

TABLE I MAIN CLINICAL DIAGNOSTIC GUIDELINES

Cause	Main causing factor	Duration	Main ocular manifestations	Systemic manifestations
Bacterial	Usually Streptococci and Staphylococci, less frequently Haemophilus (children) and enteric gram-negative organisms	5–7 days	Sticky purulent discharge, moderate conjunctival hyperaemia, crustings on the eyelids and/or lashes, lids sticking in the morning upon waking due to purulent discharge. Corneal involvement is very uncommon.	None
Hyper-acute bacterial	Often caused by Neisseria species (N. gonorrhoeae, meningitides) less often by other bacteria e.g. Pseudomonas aeruginosa		Develops usually in newborns and less often in adult patient. Bilateral, severe, fulminating conjunctivitis with profuse lid and conjunctival oedema, very copious, yellow-green, purulent discharge. There is a high risk of corneal infiltration and corneal perforation within hours. Can lead to blindness.	In neonates, septicaemia with arthritis and meningitis may develop. In adults, septicaemia with arthritis and pelvic inflammatory disease (rarely). Examine the patient and his/her sexual partner (venereal disease).
Viral	Usually adenoviruses, herpes simplex viruses, less frequently varicella-zoster viruses, picornaviruses, moluscum contagiosum, or pox and papilloma viruses	2–3 weeks	Significant conjunctival hyperaemia, copious, clear, watery, serous discharge, eyelid oedema, follicular conjunctival reaction, sub- and conjunctival haemorrhages (picornaviruses). Typical vesicular eyelid rash in herpes simplex and vesicular skin eruptions in zoster, umbilical eyelid lesions in molluscum infections, verrucae in papilloma virus infection. Often corneal involvement (keratitis). Very contagious.	Frequent history of recent fever, upper respiratory tract infections or pharyngitis. Enlarged preauricular lymph nodes, adenopathia.
Chlamydial	Chlamydia trachomatis, psittaci and pneumoniae	More than 3 weeks with exacerbations and remissions	Mucopurulent discharge, moderate hyperaemia, follicular conjunctival reaction, pseudoptosis. Often corneal involvement (keratitis and pannus). Corneal changes and conjunctival cicatrization the most frequent in trachoma.	Pneumonia and otitis (in children), cervicitis and/or vaginitis (in women), symptomatic or non-symptomatic urethritis (in men), enlarged preauricular lymph nodes. Examine the patient and his/her sexual partner (venereal disease).

TABLE II MAIN DIAGNOSTIC GUIDELINES

Type of conjunctivitis	Suggested diagnostic tests
Bacterial	Diagnosed on the basis of medical history and eye examination. Diagnostic tests are indicated in neonatal bacterial conjunctivitis, difficult clinical cases, recurrent conjunctivitis and in patients not responding to medication.
Hyper-acute bacterial	It is mandatory to perform slide stains, cultures and antibiotic sensitivity as a matter of urgency.
Viral	Diagnosed on the basis of medical history and eye examination. Tests (viral cultures and immunodiagnostic) are not very helpful but can be performed in diagnostically difficult cases only.
Chlamydial	If diagnosis can not been made on a clinical basis performance of cytology (Halberstaedter – von Provazek bodies), direct immunofluorescent antibody test, ELISA and PCR tests of ocular specimens may be helpful.

TABLE III INTERPRETATION OF CONJUNCTIVAL CYTOLOGY RESULTS IN DIFFERENT TYPES OF CONJUNCTIVITIS

Type of conjunctivitis	Cytology of the conjunctival smear
Bacterial	Polymorphonuclear leucocytes
Viral	Mononuclear cells (lymphocytes and monocytes)
Chlamydial	Polymorphonuclear leucocytes, monocytes and perinuclear inclusions (Halberstaedter – von Provazek bodies)
Allergic	Eosinophils and basophils
Fungal	Polymorphonuclear leucocytes and giant cells with organisms
Acanthamoeba	Corneal cysts

FLOWCHART II MAIN TREATMENT GUIDELINES

Ordinary bacterial conjunctivitis	**Start treatment with aminoglycoside or fluoroquinolone eye-drops. If conjunctivitis does not improve in 7 days send patient to an ophthalmologist for detailed examination.**
Hyper-acute bacterial conjunctivitis	**Send immediately to an ophthalmologist – risk of corneal perforation. Obligatory examination of patient's sexual partner.**
Viral conjunctivitis	**Adenoviral infection** **1. Treatment is supportive** **2. Use antibiotic to prevent bacterial superinfection** **Herpes simplex and varicella-zoster infection** **1. Topical acyclovir or ganciclovir is the drug of choice** **2. Use steroids with caution – may worsen viral infection** **Send to an ophthalmologist for treatment if suspicions of corneal involvement (blurring of vision)**
Chlamydial conjunctivitis	**1. Systemic (basic therapy): azithromycin (one time dose 1 gm p.o.) or clarithromycin, tetracycline, doxycyline or erythromycin for 2 weeks for the patient and his or her sexual partner** **2. Topical erythromycin or tetracycline ointment** **3. In some countries only topical treatment is used as follows: topical sulphametacin eye drops 10 % – 30 % 4 times per day, together with erythromycin 0.5 % ointment or tetracycline 1 % ointment during night for 2 weeks.**
Difficult clinical diagnosis	**Send to an ophthalmologist for detailed diagnosis and treatment.**

ADDENDUM – SPECIAL CASES OF CONJUNCTIVITIS

I. HYPER-ACUTE CONJUNCTIVITIS

A very rare but sight threatening form of bacterial conjunctivitis is hyper-acute conjunctivitis caused by Neisseria species (N. gonorrhoeae or meningitides) or less often Pseudomonas aeruginosa infections. The disease is usually bilateral and is characterized by sudden, rapid onset, fulminating conjunctivitis with marked eyelid swelling, severe hyperaemia, chemosis and profuse, thick, yellow-green purulent discharge. Typically, the purulent discharge is copious and quickly recurs when wiped or washed away. There is a high risk of corneal infiltration and corneal necrosis and perforation within hours which can lead to blindness. Gonococcal conjunctivitis usually develops in the newborn and less often in the adult patient. In neonates, septicaemia with arthritis and meningitis may develop. [1, 9] In adults, septicaemia with arthritis and pelvic inflammatory disease may rarely occur. [1] Neisseria gonorrhoeae infections are transmitted sexually and therefore it is mandatory to examine and treat not only the patient but also his/her sexual partner.

II. NEONATAL CONJUNCTIVITIS

Neonatal conjunctivitis requires special diagnosis and therapy because of frequent corneal and systemic involvement. Therefore, treatment should be performed in cooperation with a paediatrician because of the possibility of life-threatening systemic manifestations of the infection. Most cases of neonatal conjunctivitis develop as a result of vaginal delivery by an infected mother and are indicative of inadequate prenatal care. The conjunctivitis can be prevented by prophylaxis of the neonate at birth. It includes the use of topical 1 % silver nitrate solution or 1 % silver acetate in single-dose ampoules (a long-term standard prophylactic agent that is no longer available in many countries), 0.5 % erythromycin or 1.0 % tetracycline ointment or 2.5 % povidone-iodine solution. [5, 6] Silver nitrate solution is not active against chlamydia. Slide stains and cultures of conjunctival smears or scrapings are indicated in all cases of suspected neonatal conjunctivitis. [1]

III. BLEPHAROCONJUNCTIVITIS

Blepharoconjunctivitis (inflammation of the eyelid margin and conjunctiva) is a common ophthalmological disorder as well as one of the most difficult conditions to treat. It can be related to skin or lid diseases (*Figure 8*). [4]

Figure 8 – Crustings, oedema, hyperaemia and small ulcerations of the lid margin in a girl with staphylococcal blepharoconjunctivitis.

TABLE A-I DIFFERENTIAL DIAGNOSIS IN INFECTIONS OF THE CONJUNCTIVA IN NEONATES

Cause	Time of presentation	Clinical features	Comments and treatment
Chemical	1–2 days	Slight hyperaemia, serous discharge	Treatment not necessary
Neisseria gonorrhoeae	2–4 days	Hyper-acute conjunctivitis, severe purulent, yellow-green discharge, lid oedema, chemosis, rapidly progressive, corneal ulcer, risk of corneal perforation in hours. Can cause blindness.	Check for sepsis, meningitis, arthritis. Urgent case, treatment with systemic (basic therapy) ceftraxione 25–50 mg/kg (not to exceed 125 mg) IM or IV single dose if no evidence of disseminated disease. Topical fluoroquinolones or erythromycin. Treat mother and her sexual partner.
Viral (HSV2)	5–12 days	Lid vesicles, copious serous discharge, lid oedema, possibility of corneal changes	Check for cataract, uveitis and disseminated infection. Topical acyclovir. Systemic acyclovir treatment may be necessary in intraocular or disseminated infections.
Chlamydia	5–7 days	Mucopurulent discharge, marked hyperaemia, sometimes micropannus, pseudomembranes and rarely corneal opacity. No follicular reaction.	Check for pneumonia nasopharyngitis and otitis. Treatment with oral (basic therapy) erythromycin 50 mg/kg per day in four divided doses for 2 weeks and topical erythromycin or tetracycline ointment for two weeks. Treat mother and her sexual partner.
Other bacterial **s. pneumoniae staph. aureus proteus, klebsiella, pseudomonas, serratia marcescens.**	1–30 days	Purulent discharge, no corneal changes.	Start treatment with topical aminoglycosides or fluoroquinolones. If not effective switch to newer topical fluoroquinolones. Exclude obstruction of nasolacrimal duct.
Nasolacrimal duct obstruction	ca. 21 days	Bacterial conjunctivitis	Lacrimal sac massage, if not effective perform probing. Topical aminoglycosides for prophylaxis of keratitis.

TABLE A-II BLEPHAROCONJUNCTIVITIS

Cause	Clinical features and comments	Treatment and comments
1. <u>Staphylococcal infection</u> **2. Meibomian gland dysfunction** **3. Contact dermatitis** **4. Eczema** **5. Seborrhoeic dermatitis** **6. Acne rosacea** **7. Angular blepharitis – moraxella lacunata** **8. Unusual causes – molluscum, pediculosis**	1. Lid margin oedema 2. Lid crusting (scales) 3. Hyperaemia of lid margins and conjunctiva 4. Small ulcerations of eyelid margin 5. Collarettes and crustings around eyelashes 6. Loss of eyelashes 7. Recurrent hordeola 8. Corneal marginal ulceration may develop (usually immune response)	1. Lid hygiene 2. Morning removal of crustings 3. Antibiotic ointment (tetracyclines, fluoroquinolones) to lid margin 4. Oral tetracycline for chronic or severe disease [4] 5. Steroid ointment (selected cases)

Most common cause is underlined.