Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 76, No 4, 2023

MEDICINE
Ophthalmology

CHALLENGES OF HERPETIC EYE INFECTION

Petja Vassileva, Yordanka Kirilova

Mini Review
Written upon invitation of the Editorial Board

Abstract

Human herpes infections are a major cause of morbidity worldwide. Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) are frequent causes of ocular pathology. Ocular herpes is a recurrent disease, and its complications may lead to blindness. Herpetic viral infection is characterized by its ability to remain latent in the nervous system. Reactivation from the ophthalmic branch of the trigeminal ganglion may lead to recurrent attacks.

Ocular herpes is a disastrous disease causing suffering and anxiety to millions of people, and also represents important economic burden. Recently the incidence of varicella zoster virus (VZV) is increasing for unknown reasons. Published data demonstrate also that more that 50% of patients with ocular and systemic manifestation of VZV are younger than 60 years and immunocompetent. We analyze retrospectively 160 consecutive patients with ocular herpes treated at our referral specialized eye hospital, and proposed original approach to different scenarios of disease development.

Key words: latent herpetic infection, antiherpetic drugs, differential diagnosis HSV/VZV, keratoplasty in corneal perforation, epidemiology of herpetic eye disease (HED)

Introduction. Most humans are infected with herpes simplex virus (HSV type 1) in early childhood, and remain latently infected throughout life. While most individuals have mild or no symptoms, some will develop destructive HSV keratitis. Ocular infection with HSV-1 and its complications account for the majority of corneal blindness in developed nations. Neuronal latency in the peripheral

DOI:10.7546/CRABS.2023.04.01

ganglia is established when transcription of the viral genome is repressed, except for the latency associated transcripts and micro RNAs. The functions of these latency associated transcripts have been investigated since 1987 [1]. Roles have been considered relating to: establishment of latency, reactivation, neuronal protection, antiapoptosis, virulence, asymptomatic shedding, etc.

Viral infections play an increasing role in human pathology with the leading role of herpetic viral disease in ophthalmology. New possibilities for viral identification and etiological diagnosis are being established in everyday clinical practice. Prevalence and incidence of herpetic infection is increasing because of ageing of population, and also as a result of environmental and social factors: unhealthy lifestyle, pollution, misuse of antibiotics, steroids, etc. Important progress is achieved in development of efficient antiviral drugs (AVD). Two main herpetic viruses are most prevalent in human pathology: HSV and VZV, are especially important for ophthalmologists as herpetic infection is at present a leading cause of corneal blindness. New antivirals are already available with beneficial effect in early start of treatment.

Epidemiology. Herpes keratitis is a common disease with a prevalence of 150 in 100 000 inhabitants in western countries, and an annual incidence ranging from 10 to 30 per 100 000 individuals [2]. Globally the lifetime risk of developing herpetic keratitis is 1%. After the first episode the cumulative risk of relapse is 22%, 40%, and 67% at 2, 5 and 7 years, respectively [3]. Forty percent of patients experience 2 to 5 relapses over a lifetime, and 11% experience 6 to 15 relapses. In patients with relapsing keratitis, the 3 main types of keratitis (epithelial, stromal and endothelial) may occur in combination or successively. Fifteen percent of all patients with HSK develop severe complications. Stromal and endothelial keratitis are characterized by vision loss whereas pain is the most significant complication in cases of acute epithelial keratitis.

Most humans are infected with HSV-1 during childhood or early adolescence by contact (digitally, by caressing). At least 90% of the world population is latent with HSV-1 by the age of 60, evidenced by immunological data, and a high percentage of subjects are with HSV-1 DNA in their trigeminal ganglia. Data from USA show that the overall seroprevalence of HSV-1 has decreased by 7% (based on a survey). The authors hypothesize that this decrease could be attributed to improvements of living conditions and better hygiene. Nevertheless, herpetic eye infection remains a serious clinical problem, capable of causing devastating ocular diseases and loss of sight [3].

History. HSV is one of the most common viruses acquired by humans [4], and human herpes infections are a major cause of morbidity worldwide. The members of the family of the *herpesviridae* are phylogenetically very old viruses, among the oldest human pathogens, that coexisted and co-evolved over millions of years with their hosts, and are very adaptive. HSV is endemic in every human society from primitive tribes to megapolises. Humans are the only natural reservoir of

herpes and this disease is mentioned in many ancient sources. The origin of the word is Greek and means "to crawl". This term has been used for more than 25 centuries as description of typical skin lesions by Hippocrates. Mackenzie mentioned herpetic eye disease in 1830 and gave detailed description of bullous lesions on lids and conjunctiva. Later in 1885 Grut presented the pathognomonic symptom of dendritic keratitis, and two forms of herpetic lesion: facial and genital were described [5]. In the beginning of the 20th century Loewenstein [6] proved the contagious character of herpetic disease.

Over 80 different types of herpetic viruses have been describes so far. Eight of them are pathogenic for humans. The strain of virus and those of inoculum influence susceptibility to acute infection by HSV. A higher number of latent virus copies has been suggested to promote reactivation [7].

Accounts of HSV infection date back thousands of years and we are still afflicted today by this virus that is found worldwide. HSV-1 belongs to the family *Herpesviridae* and sub-family *Alphaherpesvirinae* along with HSV-2 and varicella zoster virus (VZV). All three viruses are neurotrophic, and have the unique ability to remain latent in sensory and autonomic ganglia, innervating the site of primary infection for the lifetime of the host [8]. Recent studies on pathogenesis demonstrate that depending on the type of the target cell that is entered by the virion, herpes viruses can take two different paths of infection. Virus progeny is generated only in productive infected cells: this type of infection is associated with host cell lysis. Other cells repressed lytic viral gene expression, and preserve the herpesviral genome for a very long time, a state that is called latency. However, herpes virus latency can be reversed to a productive infection mode: the genome replicates and produces an infectious virus.

Significance. HSV-1 is a ubiquitous virus that is capable of causing a wide spectrum of human diseases, including herpes labialis (cold sores), gingivostomatitis, genital herpes (HSV-2), epithelial and stromal keratitis and encephalitis. Herpetic eye disease (HED) can manifest initially as a blepharitis, conjunctivitis or corneal epithelial keratitis [7]. Recurrent HED develops predominantly as an ulcerative and/or stromal keratitis. Recurrent ocular infections account for the majority of visual morbidity due to irreversible corneal scarring, thinning, neovascularization and eventual blindness. Recurrent ocular HED is the leading cause of infectious corneal blindness in industrialized nations. The HED global infection prevalence and incidence estimates were published by team of WHO and indicate to affection of about over 3 billion people with HSV-1, HSV-2 and VZV. Data for Europe demonstrate affected population of about 13% while in USA data for higher incidence of 22% is reported [9].

Manifestations. In the pathogenesis of HED several important factors participate at a different stage of the disease: viral replication, chronic pathologic immune response, trophic disturbances and secondary infection.

Four major categories of HSV keratitis are defined [10]:

1. Infectious epithelial keratitis (consisting of corneal vesicles), dendritic ulcers, geographic ulcers and marginal ulcers. These lesions result from active viral replication within the epithelium with patients reporting pain, photophobia, and slight watery discharge. Dendritic ulcers are the most common presentation of HSV keratitis.

2. The second category neurotrophic keratopathy, includes punctuate epithelial erosions and neurotrophic ulcers. These entities have a multifactorial etiology and are neither primary infections nor immunologic [4]. Neurotrophic keratopathy often results after a long history of dendritic ulcers and treatment with multiple antiviral agents, cumulating to the cornea innervation being damaged and in conditions of diminished tear production.

3. The third category is stromal keratitis, which can be divided into necrotizing stromal keratitis and immune stromal keratitis. Immune stromal keratitis is more common of the two forms, and is a consequence of recurrent and chronic HSV infection of the corneal stroma. It is thought to be the result of an inflammatory response from CD4+ T cells stimulated against HSV-1 antigens or autoantigens mimicked by HSV-1, to bystander cytokine activation.

4. The fourth category of keratitis-endotheliitis (due to an active infection) is primarily an inflammatory response to the endothelium. Endotheliitis can be further subdivided into disciform diffuse and linear types [11].

Herpes virus structure and classification. Herpes viruses have a unique four-layered structure: a core containing the large, double-stranded DNA genome is enclosed by an icosapentahedral capsid which is composed of capsomers. The capsid is surrounded by an amorphous protein coat called the tegument. It is encased in a glycoprotein-bearing lipid bilayer envelope.

Herpesviruses are divided into three groups: The α herpesviruses, herpes simplex virus types 1 and 2, and varicella zoster virus, have a short replicative cycle, induce cytopathology in monolayer cell cultures, and have a broad host range. The β herpesviruses, cytomegalovirus, and human herpesviruses 6 and 7 are with a long replicative cycle and restricted host range. The γ herpesviruses, Epstein–Barr virus and human herpesvirus 8, have a very restricted host range [12].

Herpetic viruses are classified according to their genomic morphology, host characteristic and cell tropism. The strain of virus and the dose of inoculum influence susceptibility to acute infection by HSV. A higher number of latent virus copies has been suggested to promote reactivation by overwhelming the cellular mechanisms that silence virus transcription. More recent studies performed by Brandt [13] showed that the recombination of different genes from two different viral strains (OD4/CG394 and OD4/994) produced different outcomes of ocular

infection, neurovirulence and mortality. The ocular viral infection most commonly is caused by HSV type 1 and 2 (HSV-1, HSV-2) in patients less than 60 years of age, while VZV affects mostly people above 60 years. The decline in Cell Mediated Immunity (CMI) is associated with Cytomegalovirus (CMV), and may develop in young immunocompromized patients. Epstein–Barr Virus (EBV) is a rare cause for eye infection mostly in immunodefficient patients [14]. The main risk factors for the human herpetic eye disease (HED) include advancing age, immunocompromized status, or immunosuppressive therapy. Patients with the acquired immune deficiency syndrome (AIDS) and congenital immunity disorders are an important group [9]. Recent observations draw attention to hereditary disposition, especially to chronic VZV infection and shingles. Trauma and stressful lifestyle are discussed to play a role in endogenous reactivation of HSV.

Host characteristics. In addition to the strain of the virus the genetic make-up of the host and the host's immune responses also influence susceptibility to HSV active infection and reaction latency. The competence of the host cellular immune response is suggested to be important in controlling reactivation. The cornea's outer surface mucin layer and lactoferrin, and antiviral molecule present in tear film, could help prevent initial active HSV infection. Other factors, including interferon, have been suggested to affect the severity of the active HSV infection. A genetic locus discovered by Lundberg et al. [15], named herpes resistant locus (Hrl), was found to determine susceptibility or resistance to HSV-1. Furthermore, Jouanguy et al. [16] suggested that humans who are genetically deficient in their capacity to either produce or respond to type 1 interferon are subject to more severe HSV active infection. Animal studies and limited observations in humans suggest that a substantial risk of susceptibility to herpetic disease is inherited [17]. A region has been identified on the long arm of human chromosome 21 containing 6 candidate genes for herpes susceptibility, and expression of one or more of these genes is likely to affect the frequency of herpes simplex.

Pathogenesis of herpetic infection/sequence of events. The primary HSV infection affects the orofacial area (Fig. 1A, B). It is transmitted digitally by caressing contacts in the early childhood, and passes mostly subclinically. The virus enters the mucous membrane of the host and its particles move along the nerve fibres. Immediately after entering the host cell lytic phase starts: HSV-1



a b

Fig. 1. A) Bullous HSV on lips; B) HSV blepharitis

shuts off host cell protein synthesis via the virion host shut off protein. Viral DNA then releases into the nucleus via nuclear entry pore, and host RNA polymerase transcribes the viral genes. Within 2–4 h post infection viral protein synthesis begins. At 5–7 h post infection genes important for HSV replication are activated.

HSV latency establishes in the trigeminal ganglion. Latency is the ability of herpetic viruses to retain at least one functional viral genome in a host cell nucleus in the absence of virus replication, assembly or pathological effect. It is suggested that the maintenance and regulation of latency involves a tripartite relationship between neuron, virus and CD8+ T cells [18]. Latency associated transcript has many potential suggested functions. They include HSV reactivation, establishment of latency, survival, virulence, antiapoptosis, neuronal protectional and virulence/apoptosis [19]. However, the exact mechanism of how latency is established and maintained is not known.

Latency occurs as part of a three-step cycle: establishment, maintenance and reactivation. *The first phase* – establishment, occurs during active infection when the virus replicates within the mucosal epithelial cell and enters its sensory neuron, then travels to the sensory ganglia in a retrograde fashion via the cell's microtubule network. Since most HSV-1 infections occur via the ocular, nasal or oral sites they can be latent in the sensory neurons of the TG [19]. *The second phase* – maintenance, lasts the lifetime of the host. During this phase only the expression of LAT is observed abundantly with all other gene expression generally repressed [20]. Two criteria must be met for latency: the infectious virus cannot be present in a neuron or detected by standard isolation procedure, plus the infectious virus must be successfully obtained from trigeminal ganglion TG [21]. *The third phase* – reactivation, can be spontaneous (no known inducer) or induced by external stimuli such as fever, psychological stress, fatigue, hypothermia and hyperthermia, immunosuppression and UV-exposure [22]. This multistep process results in stimulation of viral gene expression. Herpetic gene expression (mRNA and protein) can be detected in sensory neurons, and infectious HSV can be isolated from the trigeminal ganglion (TG), saliva and tears. The viral particle is transported by an anterograde flow to the periphery [23]. The end result is virus transmission and recurrent disease.

Endogenous neuronal viral recurrences may develop later in life [24]. A relative immunity against superinfection exists in healthy epithelial surfaces. As long as the eye remains non-irritated and the epithelial surface intact (no rubbing or trauma) there is an efficient protection and no superinfection is possible. After the so-called "signal" (usually stress) about three days are needed to overcome virus latency control, and the endogenous recurrence may appear. Fortunately, only few people harbouring HSV in the ganglia, will experience the recurrent disease [25]. The high frequency of HSV DNA shedding seems to be from asymptomatic individuals. Asymptomatic shedding is the presence of HSV without any clinical symptoms. Since HSV is able to establish latency for the lifetime of the host,

many healthy individuals apparently shed the virus without having symptoms. In fact clinically only 1–3% of primary ocular herpetic infections are recognized, and most transmission of HSV is due to asymptomatic shedding. Mucosal surfaces (such as the mouth, eyes), skin and genitalia tend to be common sites of HSV shedding. This issue is relevant for discussion of virus detection techniques. There is no guarantee that infectious particles would be present because there is no direct correlation between HSV copy numbers and infectious particles. Various clinical studies have detected infectious HSV in saliva and tears of healthy individuals, being detected in higher rates in adults than in children. A lot of studies cover the asymptomatic shedding in tears, saliva, and it is proved that HSV was shed by a few seronegative subjects [26]. The most likely explanation is that the sensitivity of PCR is at least 1000 times greater than that of HSV serology assay.

There are many studies on the most important pathophysiologic characteristic of HSV-phenomena of latent neuronal latency. Virus particles have the ability to gain access to peripheral sensory nerve, travelling with the endoneuronal plasma flow. They reach and hide in the nuclei of the ganglion cells, and the nuclear replication may follow. Virus particles are stopped by immune defense and retreat into its ganglion cells nuclei. Here they disappear as "naked" virus DNA attached to the host cell DNA in a status of a neuronal latency. HSV establishes neuronal latency most commonly assessed in the TG [3, 10, 21]. The virus remains latent in the sensory and autonomic ganglia of the head and neck that innervate the primary site of infection. The traditional site for the study of latency is TG [23]. Other sites have been demonstrated in humans and include the superior cervical, spinal, geniculate, vestibular, inferior vagal and ciliary ganglion [23]. Reactivation from these non-traditional sites explains the unusual infections linked to the herpes viruses such Bell's palsy, Meniere's disease and acute retinal necrosis.

Corneal latency. The issue of whether HSV can establish non neuronal latency is an area of great debate. The cornea has been proposed to be a possible site of latency. However, HSV latency in the cornea has failed to gain acceptance due to the controversy of whether or not the virus is truly latent in the cornea or is only a transmission point from a sensory neuron [21]. Recent studies have been performed to determine if human donor transplanted cornea transfers HSV to the recipient and/or if PKP (penetrating keratoplasty) causes an endogenous reactivation of HSV in the recipient [27]. The authors estimate that ocular HSV occurs six times more frequently in patients who have had PKP. They suggest that the corneal incision and other corneal trauma during PKP cause reactivation of latent HSV. Since the innervations of the corneal epithelial are 300–600 times those of the skin, disruption of the corneal nerve occurs in PKP, could provide a strong stimulus for reactivation. The transmission of HSV through PKP suggests the possibility of corneal latency.

Reactivation is necessary for completion of the HSV viral cycle. Targeting reactivation can prevent spreading the virus and disease recurrence. This constant

recurrence of herpetic keratitis (HK) causes scar formation on the cornea and the subsequent need for PKP. Stressful stimuli such as UV radiation, fever, stress, hypothermia, hyperthermia and surgical manipulation of the TG can cause reactivation. Not all the neurons in the sensory ganglia reactivate at the same time. It is reported that reactivation is an isolated event that is limited to a few neurons in the sensory ganglia. The frequency at which an individual has reactivations ranges from 0–12 episodes per year, and is positively correlated to the amount of TG latently infected. The exact control of reactivation on the molecular level has not been elucidated; however, mutation of the HSV genome that can negatively impact both latency and replication has an effect on reactivation. Evidence is increasing, in part due to the high frequency of asymptomatic shedding, that reactivation occurs without known triggers [28].

For peripheral disease to occur, at "signals" viral DNA starts to replicate complete viruses which are retransported to the site of primary infection, and various forms of the peripheral herpes disease develop.

Induced reactivation is described: a prostaglandin analogue that is used in glaucoma treatment, latanoprost, has been found to induce reactivation in rabbits and humans [29]. The authors suggested that latonoprost may mediate an inflammatory response in the eye.

Recurrent disease is common: reactivation of HSV can occur intermittently. Upon reactivation, the virus is transported axonally to the periphery of the original infected dermatome, and can recur anywhere along the original infected dermatome [30]. The virus tends to recur at sites with a high proportion of sensory neuron innervation.

Factors that contribute to recurrence and severity of herpetic attacks include the immune status of the host and genetic make-up of both the host and virus. Immunodeficient patients, either acquired or inherited, have higher reactivation and recurrence rates. However, certain immunocompetent hosts have a higher recurrence rate.

The Herpetic Eye Disease Study (HEDS) is a 74-centre study that determined various risk factors and non risk factors for ocular HSV recurrence after following 346 patients for eleven months. All of these patients had experienced an episode of ocular HSV in the previous year. Interestingly a history of epithelial keratitis was not a risk factor for recurrent HSV ocular disease, but a history of stromal keratitis increased the risk of recurrence, and it was positively correlated to the number of previous episodes [31].

Although many recurrent diseases are due to reactivation from latency, some studies have documented reinfection with a different new strain of HSV at the same site of the primary infection as the cause.

Risk factors for recurrence. The pathological stress is the most common and generally accepted cause for the HSV recurrence. It is considered that about one third of the population is at risk. Stress is varied and even patients themselves

cannot define it. The important sources of stress are fever, emotional shock, exhausting situations, sunburn, jet-lag. The "signals" are transmitted through the blood/lymph circulation but its biochemical nature is still unknown. There is also no molecular explanation on the individual resistance to recurrent infection yet. The virulence of the specific viral strain may influence the extensiveness and efficiency of latent infection but the host factors are more important in determining whether the individual with latent infection develops symptomatic reactivation. Age is an important factor, and incidence and severity increase with advancing age. Another variable influencing susceptibility to infection is the environment. Social stress, hypothermia, hyperthermia, skin irritation and exposure to UV light are known triggers for HSV reactivation in animal model [32]. Fever, wind, sunburn, trauma, and surgical manipulation of the trigeminal ganglion have been shown to induce HSV reactivation in humans.

Treatment. Ocular herpetic disease is classified in two groups: viral ocular herpes with active replication of viruses and metaherpetic disease non healed lesions post-herpetic infection. Therapeutic approach depends on exact clinical diagnosis. Various physical, chemical and antiviral agents have been used to treat HSV epithelial keratitis and most of them are no longer used. In 1962 KAUFMAN et al. [32] reported the use of idoxuridin (IDU). The success of this treatment led to the development of other nucleoside analogues. Acyclovir (ACV) was subsequently developed in topical, intravenous and oral formulations. In an extensive review WILHELMUS [33] compared the effect of various therapeutic interventions for dendritic or geographic epithelial keratitis and concluded that ACV is effective. At present we possess new antiviral agents from the same group: acyclovir, valaciclovir, ganciclovir, valganciclovir. They represent purine nucleotide analogues, acting by interfering viral DNA synthesis during transcription of the viral genome and act as inhibitor of viral replication. Present clinical experience demonstrates good efficacy especially with early start of active treatment.

There are three levels for AVD therapy of herpetic eye disease with most common drug at present valaciclovir: for acute severe infection – maximal dosing of 4–6 g per day (for about a month); systemic maintenance treatment – 2 g per day (for about 2—3 months) and systemic prophylaxis for prevention of recurrences – 1 g/day for months/years. Individual regime is applied according to the type and stage of herpetic eye disease (Table 1). Since it is known that ocular herpes tends to recur after ocular surgery, in patients with history of herpetic keratitis, prophylactic treatment is recommended before undergoing ocular surgery. Topical and systemic antiviral therapies are necessary to be used perioperatively (for example, at least one year after penetrating keratoplasty).

Antivirals such as acyclovir, valaciclovir, ganciclovir, valganciclovir have been reported to reduce HSV DNA shedding. There are studies on adverse events indicating possible neuropsychiatric effects in elderly patients. It is recognized that not everyone can tolerate high dose valaciclovir treatment. Interferon monotherapy has been demonstrated to have beneficial effect on epithelial herpetic keratitis [31].

Table 1

Therapy subgroups according to classification

Group	Subgroup	Therapy
I	A viral superficial (epithelial)	Antiviral agents
	B viral deep	Antiviral agents plus steroids*
II	C metaherpetic superficial (epithelial)	Conservative resurfacing
	D metaherpetic deep	Surgical reconstruction

Differential diagnosis HSV/VZV. Two human herpetic viruses – HSV and VZV are the main cause for morbidity worldwide. Both viruses have a lot in common: they provoke recurrent disease due to the phenomenon of latency. Eye complications of viral infection may lead to blindness, but systemic involvement can endanger life (especially VZV). Large and increasing number of adults suffer from shingles.

The VZV is found in a worldwide geographic distribution and causes two distinct viral syndromes. Primary infection presents as varicella, benign childhood illness occurring in annual spring epidemics among susceptible children. Herpes zoster (HZ or shingles) typically manifests as unilateral pain in a dermatomal distribution accompanied by a vesicular rash [34]. HZ usually occurs in older adults, and results from reactivation of the latent VZV within the sensory spinal or cerebral ganglia. The varicella vaccine and zoster vaccine can and will alter the course of both VZV diseases. Varicella can be accompanied by ocular signs. Before the introduction of varicella vaccine in the US about 12 000 to 13 000 patients were hospitalized, and approximately 100 to 150 previously healthy individuals died each year because of VZV complications [35]. The incidence of varicella diminished by 90% after implementation of the vaccine in 1995, and it has permanently changed the epidemiology in the US. Herpes zoster is a second clinical manifestation of VZV infection and occurs only in individuals who have had primary VZV infection – varicella or vaccine type [34].

The HZ disease affects not only the skin, but also internal organs, liver, kidney, brain may be involved. In spite of successful antiviral drug interfering with virus multiplication, the viruses cannot be destroyed.

For practical medicine differential diagnosis between HSV and VZV infection is extremely important. These viruses require different treatment approach: topical antiviral drugs (AVD) are not efficient at all for VZV. Clinically there are also many similarities but also a lot of basic differences: a corneal dendrite is a typical sign pathognomonic for HSV, while in VZV a pseudodendritis is observed. HSV-1,2 have only two localizations: ocular and genital, while VZV has various manifestations in the eye and the whole body. Pathogenesis and course of the dis-

ease are also different: HSV causes recurrent attacks with local activation, while VZV has a chronic course with exacerbations, viremia and superinfection. The latency in HSV is located in sensory ganglia of face and genitalia, while in VZV – in dorsal and sensory ganglia of the whole body. Transmission of the infection also differs. In HSV infection is acquired in childhood and gives start to a lifetime latency. In VZ superinfection plays an additional role. These facts imply to practical medicine important preventive rules: adults should avoid contact with children with chickenpox to prevent superinfection and developing shingles. On the other hand, patients with shingles can cause varicella in people who have not had the disease. Treatment is also different: for HSV local and systemic AVD are recommended, while for VZV only systemic AVD are efficient.

New epidemic of VZV. VZV is a DNA virus with one serotype. It infects only people, and humans are the natural reservoir. It is endemic in all human communities and is one of the oldest known diseases, that coexisted with humans for millions of years. Hippocrates 25 centuries ago has called its most common form intercostal shingles "belt of fire" [5]. In 2016 in the USA 450 000 new cases of VZV were registered, with three times more patients in treatment. Adults diagnosed with shingles in Sofia, Bulgaria, last winter reached about 30 people per day. It is believed that one of three persons will have VZV in their lifetime. The most threatened are people over 75–80 years of age. Recent data demonstrate that for unknown reasons there is a rapidly increasing number of VZV patients in younger age (30–40 years old!) [36].

Clinical experience. Overloaded in our everyday practice with a lot of patients mostly referred for surgical treatment of HED complications, we conducted retrospective analysis of consecutive 160 patients, referred and treated in our hospital. Here we demonstrate typical signs and symptoms of VZV eye infection. Diagnostic criteria included keratitis, keratouveitis, increased intraocular pressure, occlusive vasculitis and neurouveitis.

Detailed medical history to reveal previous herpetic attacks with data for locations, duration and management was gathered. Data on chickenpox disease in childhood and adolescence was collected as well on any experienced skin rash ever since. Medical documentation was studied thoroughly looking for signs of intraocular inflammation in preceding years. Inquiry on accompanying systemic diseases including eventual corticosteroid use was also performed. Additionally, routine comprehensive eye exam, fluorescein angiography (FA) and optical coherent tomography (OCT) were conducted. Consultations with dermatologists, neurologists and internal disease specialists were performed on indications. Specialized serologic and immune methods were applied. Mean age of our pool of patients was 42 years (6–82). We observed a great variety of clinical manifestations: various forms of keratitis, scleritis, uveitis. Referral cases represented over 70% of patients. Misdiagnosis and delayed appropriate treatment with antiviral drugs was common observation. Wide use of corticosteroids elsewhere has worsened the

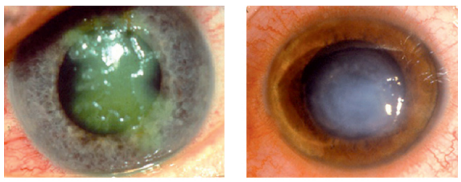


Fig. 2. A) Central corneal ulceration;
B) Disciform keratitis

course and prognosis. Most cases were in advanced stage of disease of intraocular inflammation with visual impairment and severe structural changes. The biggest group of 65 patients (41%) had dendritic ulcer (rarely marginal), stromal keratitis, epithelial erosions and ulcerations were found in 120 patients (175%) (Fig. 2A). Endotheliitis with disciform keratitis had 19 cases (12%) (Fig. 2B). Keratouveitis was diagnosed in 60 patients (38%), and chronic panuveitis in 18 patients (12%). We treated 12 patients (8%) with severe panuveitis. The therapeutic approach included new anti-viral drugs (AVD), resurfacing procedures and ocular surgery when indicated. The therapeutic approach depended on the clinical form and stage of the disease and included topical and oral medications, resurfacing and surgical interventions – amniotic membrane transplantations (AMT) and penetrating keratoplasty (PKP). Application of anti-viral drugs (AVD) as part of personalized complex treatment was performed, and the results were followed and documented for 10–24 months. In some challenging cases with high suspicion of VZV etiology the principles of "diagnosis ex juvantibus" was applied. Diverse clinical picture with overlooked signs, diagnostic problems and risk of recurrences were analyzed.

Most patients had recurrent eye disease with history of numerous attacks for 5–50 years. Common symptoms, complaints and recurrences included: discomfort, photophobia, tearing, sudden vision loss and pain. Signs of acute disease were keratic precipitates, erosion, corneal edema, dendrites, increased intraocular pressure.

A common clinical observation is the misdiagnosis and the delayed treatment. Unfortunately, the majority of patients have had steroid application elsewhere that has led to serious complications. We demonstrate a new form of VZV – chronic panuveitis with good prognosis after AVD treatment. Most of our patients are in the advanced stage. Visual impairment was a result of a cumulative effect of consecutive disease attacks. Prolonged treatment is recommended for prevention of recurrences, severe complications and systemic involvement.

Impaired quality of life with VZV infection. VZV complications cause a decreased visual acuity resulting in a poor quality of life. Numerous disabilities of different character can be observed. Physical problems consist in pain, vomiting, fatigue, weight loss, insomnia. Some people may experience anxiety or

depression. Social isolation and limited communication are very common. People suffer impaired everyday function in hygiene, travel, shopping, cooking, etc. [37].

Most adults had been infected with VZV up to 40 years of age. Clinical picture is varied as the whole body is affected. Eye diagnosis is often delayed because of atypical manifestation of intraocular inflammation [35]. The fact that treatment is most effective if it starts within 72 h since the first symptoms is very challenging.

As result of our clinical expertise we present our insight into the complicated interrelation between VZV and humans from primary infection to varied and severe forms of recurrent disease.

Scenario I – congenital VZV infection. Congenital uveitis develops during pregnancy (Fig. 3). Transplacental transfer of VZV may occur when varicella is acquired by the mother during early pregnancy placing the fetus at risk for congenital varicella syndrome. Serological test should be employed during pregnancy to determine the risk of congenital varicella. It is a rare disease and only few cases are reported.

Scenario II – primary infection. Eye involvement during chickenpox and right after the disease is very common. Skin lesions occur on eyelids, affected by rash with edema and inflammation (Fig. 4A, B). Conjunctivitis is mild and heals for a week. Rarely episkleritis/scleritis (diffuse or nodular) is observed. Optical neuritis may be observed in children about 2 weeks after chickenpox with severe clinical picture: general malaise, optic nerve edema, rapid loss of visual acuity, incapacitating headache. It is self-healing disease, and the role of antiviral treatment or steroids is disputed.

Scenario III – VZV recurrence (HZO/shingles). Symptoms of skin involvement (shingles) are initially non-specific: malaise, headache and subfebrile temperature, burning of the skin, paraesthesia of the sites before the onset of rash. Skin lesions consist of maculopapular eruption, vesicles and yellow pustules for 3–4 days, unbearable, debilitating pain, dry crust formation in 10 to 12 days. Ischemia caused by vasculitis in the deep skin layers leading to scars and pigmentation.

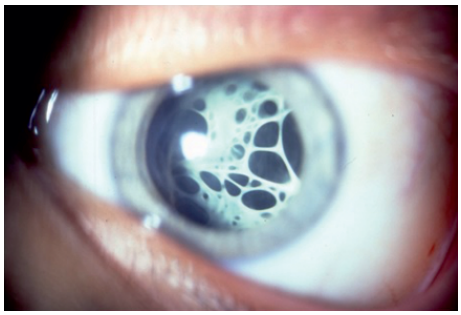
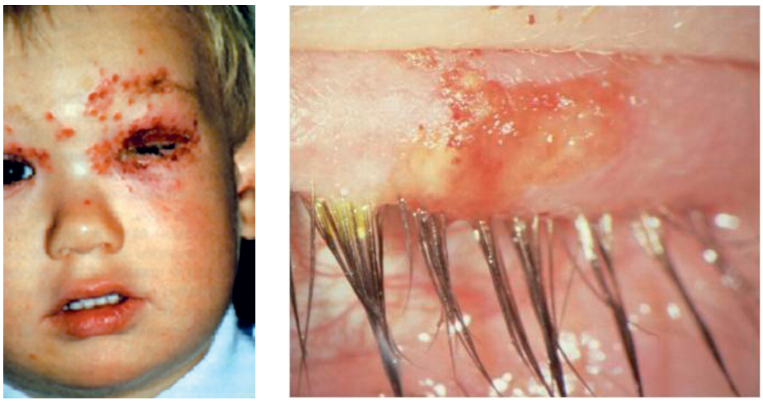


Fig. 3. Congenital VZV uveitis



a b

Fig. 4. A) Child with eye involvement in "chickenpox"; B) Ulcerative VZV blepharitis

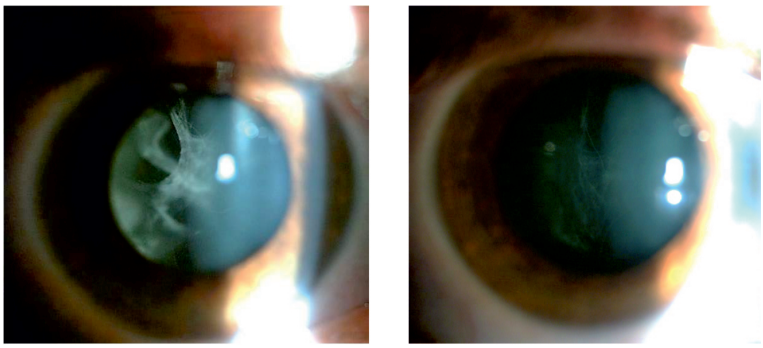
Activating of the latent infection in trigeminal ganglion – most often involvement of n. ophthalmicus – Herpes Zoster Ophthalmicus – HZO (16–20% of all VZV patients). Hutchinson's rule indicates to affection of the nasociliary branch and implies ocular involvement.

Eye lesions are various: acute epithelial keratitis, atypical dendrite, disciform keratitis (usually central). Stromal keratitis starts with infiltrative central lesion and diffuse corneal edema. Severe stromal keratitis in VZV with secondary infection may lead to corneal perforation.

Scenario IV – chronic eye disease after shingles. It is observed in conditions of immune suppression (different risk factors). Such patients may infect people who have not been sick from chickenpox. The clinical picture of anterior uveitis/iridocyclitis is observed, often with sectoral iris atrophy, and increased IOP – secondary glaucoma. We have observed 12 patients (8%) with chronic panuveitis – new entity in uveitis nomenclature. Until now two forms of herpetic uveitis have been described: chronic anterior uveitis, acute herpetic retinitis (ARN, PORN). Chronic panuveitis with exacerbations represents new clinical manifestation in VZV infection (observed by us): inflammation in the anterior segment, vascular changes in the retina with perivascular infiltrates (without necrosis and choroid impairment). Presence of pronounced vitritis is pathognomonic (Fig. 5A, B).

In the patients we studied the diagnosis was not recognized and prolonged administration of systemic and para-bulbar steroids led to worsening. After treatment with AVD excellent functional results were achieved (regardless of dense vitritis and low vision at presentation). Duration of treatment was several months.

Optic neuritis/ischemic optic neuropathy develops during a period of 2–3 weeks after skin lesions (shingles). Severe headache with rapid vision loss is observed. It may be accompanied by retinitis, retinal vasculitis.



a b

Fig. 5. A) Chronic VZV panuveitis with vitriitis: VOD = 0.02; B) Improvment post AVD treatment: VOD = 0.6

Scenario V – ocular infection herpes sine herpete. Chronic eye infection without shingles is most difficult for diagnosis and should be considered a diagnosis of exclusion, when only data for suffering from varicella, usually as adult, is present.

We demonstrate that the herpetic infection recurrences consisted of viral replication, chronic pathologic immune response, trophic disturbances, and in some patients a secondary infection. We consider pathognomonic for the herpetic disease the following signs: an unilateral involvement (in about 90% of the cases), a chronic course with exacerbations, an increased intraocular pressure in 65% of patients, a sectoral iris atrophy (Fig. 7), and a secondary glaucoma threatening with vision loss (Fig. 6).

We faced a lot of challenges during management of such advanced pathology. The epithelial and deep stromal keratitis should be treated urgently, as a corneal perforation may occur, necessiting corneal transplantation in order to save sight (Fig. 9A, B). Another dangerous complication is the development of uveitis, often associated with superinfection, evidence of vitritis and vasculitis, with the predominant affection of arterial vessels. We demonstrate a new form of VZV – chronic panuveitis with good prognosis as a result of AVD treatment (Fig. 5A, B).

The diagnosis of herpetic eye disease is mainly clinical, and is one of the most unrecognized. An important feature is the significant increase of anti-VZV IgG at reactivation stage.

Severe complications often occur after the use of steroids. Our therapeutic approach depends on the clinical form and stage of the disease [28], and includes new anti-viral drugs, resurfacing methods – AMT (Fig. 8), and surgery – penetrating keratoplasty (Fig. 9A, B).

Vaccination strategy for both varicella and HZ is being discussed and evaluated in many recent publications. As the changes in epidemiology in both varicella and shingles disease became more evident in the US, VZV vaccine is the first truly



Fig. 6. Hypertensive VZV keratouveitis

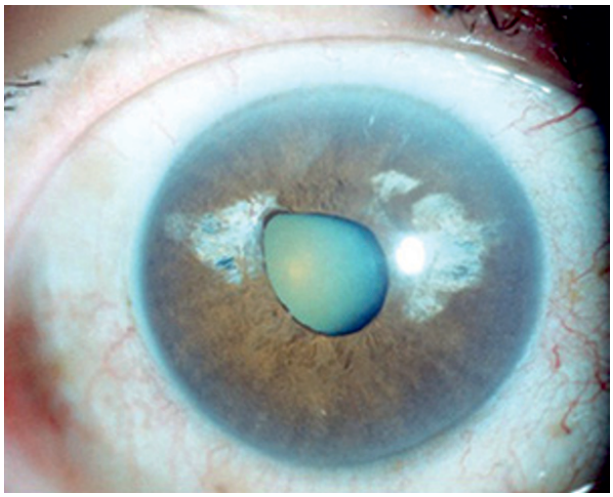


Fig. 7. Iris atrophy in VZV

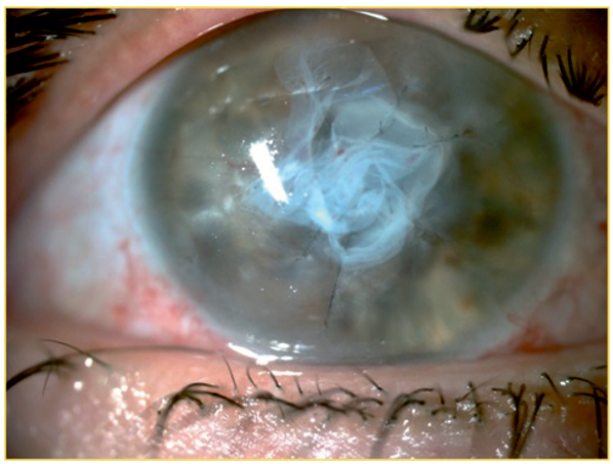
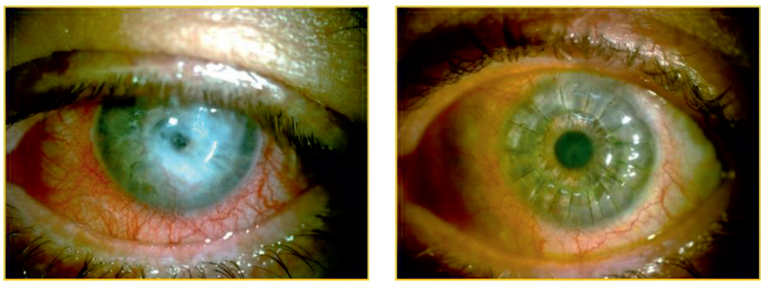


Fig. 8. AMT for central corneal perforation



a b

Fig. 9. A) Central corneal perforation in VZV; B) Corneal transplantation

preventive measure against VZV disease. Timing for application is proposed for early childhood and after 60 years of age. There is no consensus on the benefit of vaccination against VZV [35]. Decreased immunity against VZV occurs with ageing. A live vaccine was approved by FDA in 2011, but it is still not widely used [35].

Summary. The human eye is an important target for infection with herpetic viruses. Diagnosis is often overlooked. There are still controversies regarding current therapy. Still most data are experience based, not evidence based [31]. The phenomenon of latency and life-long coexistence in individuals with herpetic infection has led to high morbidity and variety in the severity of the process, depending on accompanying diseases, lifestyle, environmental influences, etc. Differentiating HSV/VZV is very important for appropriate treatment. Anti-viral therapy is very challenging and there is limited evidence based data on recommended management strategies. Early start – at latest 72 h of first symptoms is of key importance. There are efficient AVD, but often herpetic infection was unrecognized in our pool of patients, and treatment was delayed. For better prognosis herpetic infections should be included in differential diagnosis of patients with all types of intraocular inflammation, especially with ocular surface involvement. Prolonged treatment – months to years, is recommended for prevention of recurrences of this potentially blinding disease with severe systemic involvement. VZV causes pain and suffering for millions of people worldwide each year. At present it is impossible to predict if or when VZV will reactivate, who may develop shingles, how severe an individual case may be, and how long the pain may last. It is important to know that almost all adults aged over 50 are at risk for this often debilitating disease with risk increasing with age. The latency control is an extremely important issue but still it is not elucidated and there is no progress in this field [38]. Some studies point to the role of interferone gama in maintaining latency. It is suggested that release of interleukins during systemic infection can activate VZV [39].

Early and correct diagnosis and timely treatment are most important for this potentially sight threatening disease. At present we possess efficient antiherpetic

medications and vaccination looks promising to prevent or modify the course of VZV infection. Systemic application of AVD during follow-up, depending on disease activity, reduces the incidence of recurrences and improves the quality of life.

REFERENCES

[1] Al-Dujaili L. J., P. P. Clerkin, C. Clement, H. E. McFerrin, P. S. Bhattacharjee et al. (2011) Ocular herpes simplex virus: how are latency, reactivation, recurrent disease and therapy interrelated? Future Microbiol., **6**(8), 877–907.

[2] Xu F., M. R. Sternberg, B. J. Kottiri, G. M. McQuillan, F. K. Lee et al. (2006) Trends in herpes simplex virus type 1 and 2 seroprevalence in the United States, JAMA, **269**(8), 964–973.

[3] Roizman B., D. M. Knipe, R. J. Whitley (2007) Herpes Simplex Viruses. In: Knipe D. M. and Howley P. M. Eds, Fields Virology, Vol. 2, New York, NY, Lippincott Williams & Wilkins, 2501–2601.

[4] Liesegang T. J. (1999) Classification of herpes simplex virus keratitis and anterior uveitis, Cornea, **18**(2), 127–143.

[5] Thygeson P. (1976) Historical observation on herpetic keratitis, Surv. Ophthalmol., **21**, 82–90.

[6] Loewenstein A. (1944) Herpes Corneæ and Virus Infection, Glasgow Med. J., **141**(2), 54–62.

[7] Sawtell N. M. (1997) Comprehensive quantification of herpes simplex virus latency at the single-cell level, J. Virol., **71**(7), 5423–5431.

[8] Hengel H. (2009) Common Characteristics and Distinct Features of Human Pathogenic Herpesviruses. In: Sundmacher R. (ed.) Color Atlas of Herpetic Eye Diseases, Springer, Berlin, Heidelberg.

[9] James C., M. Harfouche, N. J. Welton, K. M. E. Turner, L. J. Abu-Raddad et al. (2020) Herpes simplex virus: global infection prevalence and incidence estimates, 2016, Bull. World Health Organ., **98**(5), 315–329.

[10] Kaye S., A. Choudhary (2006) Herpes simplex keratitis, Prog. Retin. Eye Res., **25**(4), 355–380.

[11] Holland E. J., J. S. Schwartz (1999) Classification of herpes simplex virus keratitis, Cornea, **18**(2), 144–154.

[12] Whitley R. J., S. Baron (1996) Herpes viruses. In: Medical Microbiology, 4th edition, Galveston (TX), University of Texas Medical Branch at Galveston, Chapter 68.

[13] Brandt C. R. (1991) Mixed ocular infections identify strains of herpes simplex virus, J. Virol. Methods, **35**(2), 127–135.

[14] Buchbinder S. P., M. H. Katz, N. A. Hessol, J. Y. Liu, P. M. O'Malley et al. (1992) Herpes zoster and human immunodeficiency virus infection, J. Infect. Dis., **166**(5), 1153–1156.

[15] Lundberg P., P. Welander, H. Openshaw, C. Nalbandian, C. Edwards et al. (2003) A locus on mouse chromosome 6 that determines resistance to herpes simplex virus also influences reactivation while an unlinked locus augments resistance of female mice, J. Virol., **77**(21), 11661–11673.

[16] Jouanguy E., S-Y. Zhang, A. Chapgier, V. Sancho-Shimizu, A. Puel et al. (2007) Human primary immunodeficiencies of type 1 interferons, Biochimie, **89**(6–7), 878–883.
[17] Lopez C. (1975) Genetics of natural resistance to herpes virus infections in mice, Nature, **258**, 152–153.
[18] Divito S., T. L. Cherpes, R. L. Hendricks (2006) A triple entente: virus, neurons and CD8+ T cells maintain HSV-1 latency, Immunol., **36**(1–3), 119–126.
[19] Bloom D. C. (2004) HSV LAT and neuronal survival, Int. Rev. Immunol., **23**(1–2), 187–198.
[20] Perng G. S., C. Jones (2010) Towards an understanding of the herpes simplex virus type 1 latency reactivation cycle, Interdiscip. Perspect. Infect. Dis., 262415.
[21] Kennedy D. P., C. Clement, R. L. Arceneaux, P. S. Bhattacharjee, T. S. Huq et al. (2011) Ocular herpes simplex virus type 1: is the cornea a reservoir for viral latency or a fast pit stop?, Cornea, **30**(3), 251–259.
[22] Toma H. S., A. T. Murina, R. G. Areaux et al. (2008) Ocular HSV-1 latency, reactivation and recurrent disease, Semin. Ophthalmol., **23**(4), 249–273.
[23] Richter E. R., J. K. Dias, G. E. Gilbert, S. S. Atherton (2009) Distribution of herpes simplex virus type 1 and varicella zoster virus in ganglia of the human head and neck, J. Infect. Dis., **200**(12), 1901–1906.
[24] Fatahzadeh M. (2007) Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management, J. Am. Acad. Dermatol., **57**(5), 737–763.
[25] Gaynor B. D., T. P. Margolis, E. Cunningham (2000) Advances in diagnosis and management of herpetic uveitis, Int. Ophthalmol. Clin., **40**(2), 85–109.
[26] Kaufman H. E., A. M. Azcuy, E. D. Varnell, G. D. Sloop (2005) HSV-1 DNA in tears and saliva of normal adults, Invest. Ophthalmol. Vis. Sci., **46**(1), 241–247.
[27] Remeijer R., J. Maertzdorf, P. Doornenbal, J. M. Verjans, A. D. Osterhaus (2001) Herpes simplex virus 1 transmission through corneal transplantation, Lancet, **357**(9254), 442, https://doi.org/10.1016/S0140-6736(00)04011-3.
[28] Vassileva P. (2013) Therapeutic behavior according to the type and stage of ocular herpes, Medinfo, **13**(10), 40–47, (in Bulgarian).
[29] Kaufman H. E., E. D. Varnell, H. W. Thompson (1999) Latanoprost increases the severity and recurrence of herpetic keratitis in the rabbit, Am. J. Ophthalmol., **127**(5), 531–536.
[30] Cunningham A. L., R. J. Diefenbach, M. Miranda-Saksena et al. (2006) The cycle of human herpes simplex virus infection: virus transport and immune control, J. Infect. Dis., **194**(1), 11–18.
[31] Herpetic Eye Disease Study Group (2001) Predictors of recurrent herpes simplex virus keratitis, Cornea, **20**(2), 123–128, https://doi.org/10.1097/00003226-200103000-00001.
[32] Kaufman H., E. L. Martola, C. Dohlman (1962) Use of 5-iodo-2′-deoxyuridine (IDU) in treatment of herpes simplex keratitis, Arch. Ophthalmol., **68**, 235–239.
[33] Wilhelmus K. R. (2015) Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis, Review, Cochrane Database Syst. Rev., https://doi.org/10.1002/14651858.CD002898.pub5.

[34] Kaye D., K. M. Kaye, M. Aleissa, B. Dionne (2019) Herpes zoster: a potentially dangerous but preventable disease, Healio, News, Infectious Disease, Vaccination.
[35] Oxman M. N., M. J. Levin, G. R. Johnson et al. (2005) A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults, N. Engl. J. Med., **352**, 2271–2284.
[36] Weber D. J. (2020) Prevention and control of varicella-zoster virus in hospitals, www.uptodate.com.
[37] Vrcek I., E. Choudhury, V. Durairaj (2017) Herpes Zoster Ophthalmicus: A Review for the Internist, Am. J. Med., **130**(1), 21–26.
[38] Kennedy P. G. E., R. J. Cohrs (2010) Varicella-zoster virus human ganglionic latency: a current summary, Review, J. Neurovirol., **16**(6), 411–418.
[39] Goldstein R. S., P. R. Kinchington (2023) Varicella Zoster Virus Neuronal Latency and Reactivation Modeled in Vitro, Review, Curr. Top. Microbiol. Immunol., **438**, 103–134.

Specialized Eye Hospital for Active Treatment "Acad. Pashev"
51 E. Vaskidovich St
1517 Sofia, Bulgaria
e-mails: centersight@sobalpashev.com
dr.y.kirilova@gmail.com