REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Herpes Zoster Ophthalmicus: A Review for the Internist

Ivan Vrcek, MD,[a] Eileen Choudhury, MD,[b] Vikram Durairaj, MD[a]

[a]TOC Eye and Face, Austin, Tex; [b]New York Eye and Ear Infirmary of Mount Sinai.

ABSTRACT

Herpes zoster ophthalmicus occurs due to reactivation of the varicella zoster virus in the ophthalmic branch of the fifth cranial nerve. This disease primarily affects the elderly as well as the immunocompromised and can result in a wide range of ophthalmic morbidity. Systemic antiviral therapy is the mainstay of treatment; however, consultation with an ophthalmologist is typically indicated. Herein we present a review of this common entity including epidemiology, pathophysiology, evaluation, treatment, follow-up, and an update on the current body of literature.

 • *The American Journal of Medicine (2017) 130, 21-26*

KEYWORDS: Herpes zoster ophthalmicus; Hutchinson sign; Shingles

Varicella is caused by primary infection from human herpesvirus type 3. Following primary infection, which often occurs in childhood, the virus remains dormant in neurosensory ganglia. It may be reactivated, typically years or decades later, resulting in the cutaneous disease commonly known as shingles or herpes zoster. According to the Centers for Disease Control and Prevention (CDC), there are an estimated 1 million cases of herpes zoster annually in the US,[1,2] and nearly 1 in 3 people will develop shingles during their lifetime.[3] Herpes zoster classically results in a unilateral neurocutaneous reaction in the dermatome served by a particular neurosensory nucleus, causing pain and a pustular rash; serious complications such as superinfection, long-term pain, and ophthalmic involvement can result in significant morbidity. Up to 4% of patients presenting with herpes zoster require hospitalization to aid in management of complications.[3]

Herpes zoster ophthalmicus represents 10% to 20% of herpes zoster cases.[1,3] Herpes zoster ophthalmicus occurs when human herpesvirus type 3 reactivation presents in the first division of the trigeminal nerve, also known as the ophthalmic division. Reactivation may manifest with pain and a periocular cutaneous rash limited to the periorbital region; however, 50% to 72% of patients demonstrate involvement of the eye itself.[1,4-6] Such involvement ranges from a cutaneous reaction limited to the eyelids to corneal ulceration or retinal disease resulting in permanent loss of vision. Careful evaluation and treatment of patients with herpes zoster ophthalmicus is imperative to decrease long-term morbidity. This review is intended to provide useful clinical information about the epidemiology, pathophysiology, clinical manifestations, and treatment of this common disease entity, as well as an update on new developments and future directions of treatment.

EPIDEMIOLOGY

A recent study utilizing a database with access to the medical records of over 4 million patients in the US revealed a total of 9152 incident cases of herpes zoster in a 12-month period. This translates to an overall age- and sex-adjusted incidence of 3.2 cases per 1000 person-years. The sex distribution was approximately 59.9% female and 40.1% male. The peak incidence was between the ages of 50 and 79 years, with a skew toward older individuals, with the highest rates observed among patients over age 80 years (10.9 cases per 1000 person-years).[7]

The incidence of herpes zoster ophthalmicus, in particular, has not been the subject of a nationwide study; however, both the Miami Veterans Administration Healthcare

Funding: None.

Conflict of Interest: None of the authors have any conflict of interest, financial or otherwise, to report.

Authorship: All authors have had access to the data and played a role in writing the manuscript.

Requests for reprints should be addressed to Vikram Durairaj, MD, TOC Eye and Face, Austin Medical Plaza, 3705 Medical Parkway Suite 120, Austin, TX 78705.

E-mail address: vdurairaj@tocaustin.com

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2016.08.039

System and Kaiser Permanente in Hawaii have evaluated their rates of herpes zoster ophthalmicus.[7,8] The Miami study collected data over a span of 4 years, revealing 90 patients with herpes zoster ophthalmicus. The majority (97%) were immunocompetent, and the frequency of herpes zoster ophthalmicus with eye involvement was 0.05%.[7] The Kaiser study documented 134 cases in 1 year in a population of 217,061 patients. This is an overall incidence of 30.9 per 100,000 person-years.[8] These studies are retrospective and likely underestimate the incidence of this common entity.

CLINICAL SIGNIFICANCE

- Herpes zoster ophthalmicus is a common entity presenting to community and academic internists with regularity.
- There are hallmark signs and symptoms that should alert an examiner to the presence of herpes zoster ophthalmicus.
- Early involvement of an ophthalmologist can be useful in avoiding vision-threatening sequelae.
- The Zostavax vaccine is recommended for persons 50 to 59 years old.
- Varicella zoster immune globulin is available for postexposure prophylaxis.

PATHOPHYSIOLOGY

Varicella infection is associated with 2 distinct syndromes. The first is primary infection, which is more common in children and is associated with a febrile illness and a pustular rash that is highly contagious and self-limited. During primary infection, viral particles are believed to spread from the infected skin along sensory nerve endings, ultimately reaching the nerve ganglia. An alternative hypothesis suggests that hematologic spread during the viremic phase leads to access to the ganglia.[9]

Following primary infection, the host's immune system suppresses viral replication; however, viral particles can then remain dormant for years, most commonly in spinal root and cranial nerve ganglia. Reactivation results when host immunity fails to suppress the virus, which can be due to stress, immunosuppression, or direct trauma. Reactivation leads to the classic dermatomal rash and neuropathic pain in the distribution of the dermatome of the involved cranial or spinal nerve. Additionally, inflammation in the ganglion itself can lead to neuronal necrosis. At the time of reactivation, the immune system demonstrates a T-cell proliferation with subsequent production of interferon-alfa and herpes virus-specific antibodies.[10]

The territory of the ophthalmic division of the fifth cranial nerve includes the eyelid, brow, forehead skin, and the skin of the tip of the nose. The ophthalmic division gives rise to 3 terminal branches: the lacrimal, frontal, and nasociliary branches. The nasociliary branch innervates the skin of the tip of the nose and divides further into the long ciliary nerves, which provide sensory innervation to the globe, including the cornea and uvea. For this reason, involvement of the tip of the nose, or Hutchinson sign, is highly correlated with ophthalmic involvement.[11]

As the virus replicates, viral particles migrate peripherally along the sensory nerves, triggering a local inflammatory immune response. In the early stages of replication and inflammation, this pain is often mildly neuropathic in nature, with sensations of burning and tingling; however, as the virus continues to replicate, the inflammation becomes severe, leading to intense pain in the affected dermatome. Once the virus reaches the skin, it penetrates the epidermis, resulting in a pustular lesion. Ophthalmic involvement follows a similar paradigm, as viral replication along the long ciliary nerves results in inflammation that can involve the cornea, sclera, conjunctiva, iris, retina, and optic nerve. As the virus migrates along these nerves, inflammatory sequelae can cause optic neuritis, retinal necrosis, and uveitis, as well as corneal stromal and epithelial sequelae.[12,13]

CLINICAL MANIFESTATIONS

The clinical manifestation of herpes zoster is divided into 3 phases: preeruptive phase, acute eruptive phase, and chronic phase. The preeruptive phase is characterized by neuropathic-type symptoms, often described as burning, tingling, or shooting-type pain that may initially be mild and typically is limited to a particular dermatome. A viral prodrome may accompany these symptoms with symptoms of fatigue, malaise, fever, photophobia, and headache.

The pustular, vesicular rash that is typical of herpes zoster defines the acute eruptive phase. This tends to have a duration spanning 10-15 days. In herpes zoster ophthalmicus, this rash commonly involves the periocular skin, such as the eyelids, medial canthal area, and classically, the tip of the nose, known as Hutchinson sign (**Figure 1**).

Eyelid involvement typically manifests as a cutaneous macular rash that may develop secondary bacterial infection resulting in yellowish crusting and discharge. Conjunctival involvement results in injection and chemosis (boggy edema of the conjunctiva), with a papillary reaction involving the bulbar conjunctiva. The cornea most commonly demonstrates punctate epithelial keratitis and the hallmark pseudodendrite, composed of heaped-up epithelial cells with negative fluorescein staining (**Figure 2**). Notably, the pseudodendrite is similar in appearance but, importantly, distinct from the dendrite of herpes simplex epithelial disease. The dendritic epithelial defect seen in herpes simplex virus is a true epithelial defect in that the epithelium is absent in this area and viral particles can be seen in the terminal bulbs of the dendrite itself. The pseudodendrite of herpes zoster ophthalmicus is instead heaped-up epithelial with "negative staining" that results from fluorescein collecting at the edges of the epithelium, rather than staining an epithelial defect.

Further corneal disease can be composed of an anterior stromal keratitis with stromal infiltrates that may coalesce to

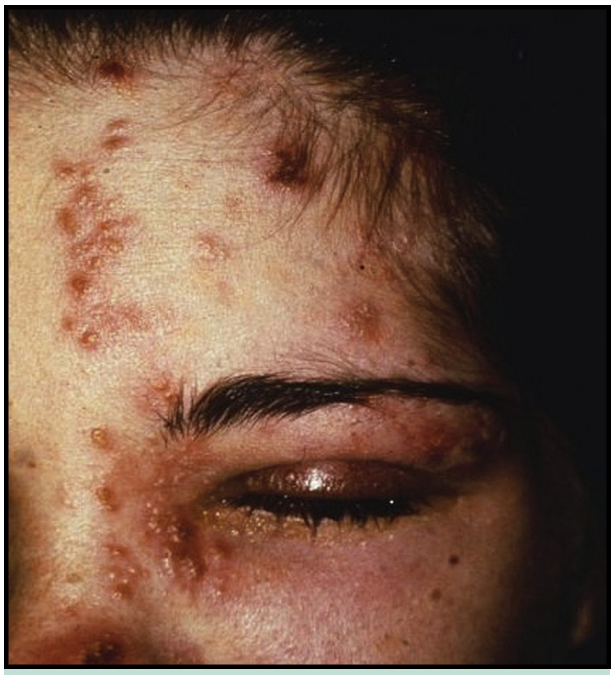

Figure 1 Patient with herpes zoster ophthalmicus demonstrating Hutchinson sign.

form a nummular keratitis. Nummular keratitis typically is composed of multiple small circular white opacities in the cornea. Herpes zoster infection of the corneal endothelium leads to a disciform stromal keratitis that is classically associated with elevated intraocular pressure due to trabeculitis. Disciform keratitis has the appearance of a relatively large circular white opacification of the cornea (**Figure 3**). Extensive corneal involvement can result in corneal neovascularization with subsequent lipid extravasation resulting in corneal opacification. Keratitis is the most common ophthalmic complication, followed by uveitis/iritis, conjunctivitis, and scleritis/episcleritis.[14]

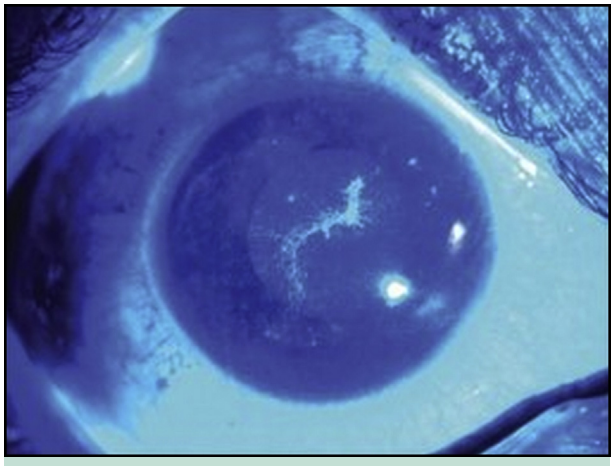

Figure 2 Patient with a corneal pseudodendrite.

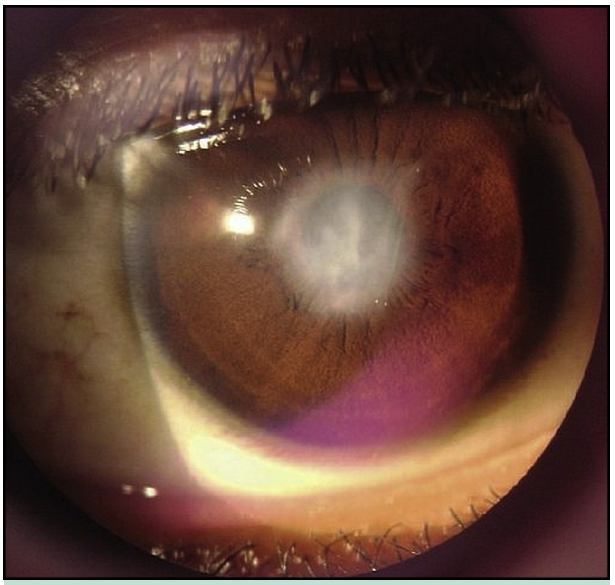

Figure 3 Patient with disciform keratitis.

Uveal involvement typically results in an anterior chamber cellular reaction and can progress to synechiae formation with scarring and adhesion of the iris to either the lens or the angle structures inside the anterior chamber. Classically, herpes zoster results in sectoral iris atrophy, as opposed to the patchy iris atrophy seen in herpes simplex infection.

Herpes zoster ophthalmicus can result in devastating retinal pathology as well, particularly in immunocompromised patients. Acute retinal necrosis is a devastating manifestation of herpes zoster reactivation in the retina in immunocompetent hosts. Manifestations include rapid necrotic inflammation of the retina resulting in severe sequelae, often, permanent vision loss. Retinal detachment is a frequent complication, occurring in up to 50% of patients.[14] Progressive outer retinal necrosis is the name given to this disease in immunocompromised hosts and is often similar to acute retinal necrosis; however, it demonstrates more severe and often more rapid retinal necrosis, often without pain and vitritis, due to immunocompromise (**Figure 4**). These entities can present bilaterally with devastating visual consequences. Complete ophthalmic examination with a dilated fundoscopic examination is indicated in these patients.

The chronic phase is characterized most commonly by an entity known as postherpetic neuralgia, which can last 30 or more days. It is characterized by a neuropathic-type pain that can be debilitating and severe. Ocular surface manifestations can include persistent corneal epithelial defects that become secondarily infected. Ocular surface pain can persist indefinitely. If the patient develops retinal involvement, the cicatrizing changes involving the retina are typically chronic and irreversible. Postherpetic neuralgia is the most common chronic complication of herpes zoster infection and is seen in 9%-45% of cases.[1]

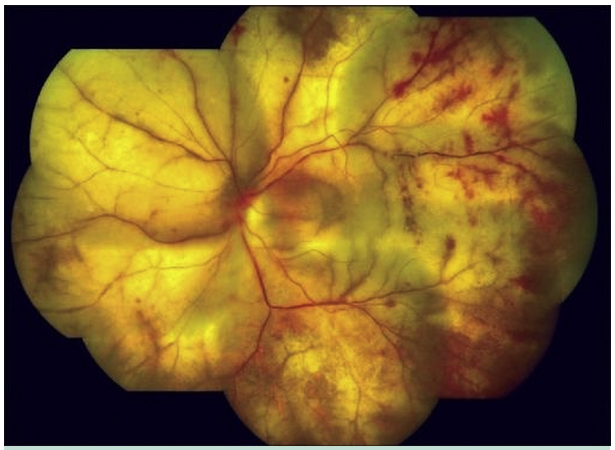

Figure 4 Patient with progressive outer retinopathy due to herpes zoster ophthalmicus.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for eyelid inflammation with decreased vision and a red eye is broad. Key factors narrowing the differential in this case include: a dermatomal rash, pseudodendritic (as opposed to true dendritic) corneal epithelial defect, and a vesicular rash with involvement of the tip of the nose (Hutchinson sign). In terms of corneal manifestations, the differential diagnosis includes herpes simplex epithelitis, severe dry eye with filamentous disease, exposure keratopathy, and corneal abrasion. The retinal manifestations can be similar to retinal involvement in sarcoidosis, cytomegalovirus retinitis, Behçet disease, endophthalmitis, and lupus retinopathy. Consultation with an ophthalmologist or retinal specialist should be pursued urgently if there is concern for retinal involvement, as a delay in treatment can result in irreversible vision loss.

EVALUATION

The evaluation of a patient suspected of having herpes zoster ophthalmicus begins with a complete history. When possible, a history of primary varicella infection should be solicited. A complete vaccination history should also be obtained. Careful questioning to elicit potential immunocompromise should be undertaken, as the disease entity can be more severe and prolonged in immunocompromised individuals. A detailed review of systems to exclude other entities in the differential diagnosis should be performed as well. The physical examination should be complete and thorough to evaluate for dermatomal involvement of herpes zoster. When suspicious of herpes zoster ophthalmicus, particular attention should be given to the tip of the nose to detect Hutchinson sign. Varicella virus serologies are not part of the typical work-up because diagnosis can usually be made by history and physical examination alone. If testing is necessary, a Tzanck smear or Wright stain may be used to determine whether lesions contain a herpes-type virus, although they do not distinguish between varicella and herpes simplex infections.

A complete ophthalmic examination is indicated when herpes zoster ophthalmicus is suspected. When performing an ophthalmic examination, it is helpful to proceed methodically, first checking the vision, intraocular pressure, and pupil reaction. Next, extraocular motility and confrontation visual fields should be examined. The external examination includes evaluation of the eyelids and adnexa. What follows is a sequential methodical evaluation of the eye itself, starting with the anterior-most structures and proceeding posteriorly. First, the conjunctiva and sclera are examined, taking care to evaluate the palpebral conjunctiva. Next, the cornea is examined, preferably with fluorescein staining. The anterior chamber, iris, and lens should be evaluated next. A dilated fundoscopic examination should be performed to evaluate the presence of retinal disease. If there is a suspicion for ophthalmic involvement, a consultation with an ophthalmologist is recommended due to the significant morbidity that can occur.

MANAGEMENT

Following a complete history and physical examination, management goals in the patient with herpes zoster ophthalmicus include shortening disease course, providing analgesia, and preventing potential complications. Treatment ultimately depends on the degree of ocular involvement. However, nearly all patients with acute manifestation of herpes zoster ophthalmicus require treatment with systemic antiviral medications, as the disease process is not limited to the ocular surface. Systemic antivirals have been shown to reduce viral shedding from skin lesions, reduce the chance of viral dissemination, and reduce the incidence and severity of ocular complications. Therapy started within 72 hours can also decrease the duration of postherpetic neuralgia, which may occur later in the disease process. Topical antivirals are typically not used for treatment of herpes zoster ophthalmicus. Immunocompromise should always be explored, as herpes zoster is 4-5 times more common in these patients; however, the majority of patients with herpes zoster and herpes zoster ophthalmicus are immunocompetent.[7]

Options for treatment include oral acyclovir, famciclovir, and valacyclovir. Famciclovir (500 mg 3 times a day) and valacyclovir (1 g 3 times a day) have been shown to be as effective as acyclovir (800 mg 5 times a day),[15] both in the treatment of herpes zoster and in reduction of complications. The simpler dosing regimen of famciclovir and valacyclovir may enhance patient compliance. Intravenous acyclovir is recommended in immunocompromised hosts, particularly to prevent disseminated disease such as encephalitis.[16]

The standard duration of antiviral therapy is 7-10 days. However, varicella DNA has been shown to persist in the cornea for up to 30 days, particularly in elderly individuals.[17] This implies that in immunocompromised and elderly patients, antiviral therapies may reasonably be continued, although no clinical trials have proven their efficacy in this particular patient population.

The use of oral corticosteroids in conjunction with antiviral agents is recommended, as this has been shown to reduce the duration of pain during the acute phase of the disease.[18] Topical steroids can be helpful in certain ocular complications of herpes zoster ophthalmicus, including stromal keratitis, uveitis, or scleritis/episcleritis.[18] It must be noted that the use of ophthalmic topical steroids can have serious complications, including worsening of epithelial disease leading to corneal ulceration and perforation. Ophthalmic steroids should be used cautiously, typically in direct consultation with an ophthalmologist.

Our usual treatment protocol is to initiate a 10-day course of oral valacyclovir 1 gram 3 times daily. If there is corneal involvement, we recommend frequent artificial tear use as well as erythromycin ophthalmic ointment 4 times daily to prevent superinfection and to keep the ocular surface lubricated. Further treatment with topical antivirals or topical steroids is individualized and requires a comprehensive ophthalmic examination.

PREVENTION

The US Food and Drug Administration, in 2006, approved the Zostavax vaccine (Merck, Kenilworth, NJ) in patients over the age of 60 years. In a randomized, double-blind, placebo-controlled trial of the vaccine, it has been shown to decrease the incidence of herpes zoster and postherpetic neuralgia by 61% and 66.5%, respectively, and may result in a decrease in future rates of herpes zoster ophthalmicus.[19]

In 2011, the US Food and Drug Administration lowered the approved age for use of Zostavax to 50-59 years. This approval was based on a multicenter study, the Zostavax Efficacy and Safety Trial. At its October 2013 meeting, the Advisory Committee on Immunization Practices reviewed results of the trial from a cost-effectiveness analysis comparing health outcomes, resource utilization, costs, and quality-adjusted life years related to herpes zoster, postherpetic neuralgia, and other complications in unvaccinated patients and patients vaccinated at age 50, 60, or 70 years. Based on this analysis, vaccination at age 60 years would prevent the most shingles cases, followed by vaccination at age 70 years, then age 50 years. However, vaccination at age 70 years would prevent the most cases of postherpetic neuralgia, followed by vaccination at age 60 years, then age 50 years. From a financial perspective, vaccinating at age 70, 60, and 40 years would, respectively, cost $37,000, $86,000 and $287,999 per quality-adjusted life years saved. Based on these results, the Advisory Committee maintained its current recommendation that the herpes zoster vaccine be routinely offered for adults $\geq$60 years of age.[18]

The CDC recommends use of varicella zoster immune globulin preparation for postexposure prophylaxis in patients at high risk of severe disease who lack immunity to varicella or for whom vaccination is contraindicated. This includes neonates or those who are immunocompromised or pregnant. The CDC recommends administration of immune globulin as soon as possible after exposure to varicella and within 10 days. Patients affected by herpes zoster are advised to remain under contact and respiratory isolation until full crusting of lesions is achieved, to prevent transmission to others.

FUTURE DIRECTIONS

Several innovative treatments for herpes zoster ophthalmicus and its complications are under development. Inflammatory destruction of nerves affected by herpes zoster can result in corneal hypoesthesia and neuropathic keratopathy. Eye drops containing tetrapeptides derived from substance P and insulin-like growth factor-1 have demonstrated rapid epithelial healing of corneal defects and regeneration of corneal nerve fibers, renewing corneal sensitivity and reducing incidence of corneal hypoesthesia.[19] In addition, sterile eye drops containing thymosin β4 have been reported to reduce geographic defects and reduce ocular irritation in patients affected by herpes zoster ophthalmicus.[19] Finally, the use of amniotic membrane for healing epithelial defects of the corneal surface has shown some success,[17] and may be considered as a reasonable alternative for treating severe neurotrophic corneal defects.

CONCLUSION

Herpes zoster ophthalmicus is a common and potentially devastating entity that may demonstrate significant ophthalmic morbidity if not adequately diagnosed and treated. This review describes the pathophysiology, evaluation, treatment, and prevention of herpes zoster ophthalmicus. First-line interventions include treatment with systemic antiviral medication, such as acyclovir, and testing to uncover potential immunocompromise. Consultation with an ophthalmologist is typically indicated, as much of the ophthalmic morbidity of herpes zoster ophthalmicus can be limited if early ophthalmic evaluation is initiated.

References

1. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology*. 2008;115(2 suppl):S3-S12.
2. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med*. 2005;20(8):748-753.
3. Ragozzino MW, Melton LJ, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)*. 1982;61(5):310-316.
4. Harding SP. Management of ophthalmic zoster. *J Med Virol* 1993;(suppl 1):97-101.
5. Harding SP, Lipton JR, Wells JC. Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement. *Br J Ophthalmol*. 1987;71:353-358.
6. Langston DP. Herpes zoster ophthalmicus. *Neurology*. 1995;45(suppl 8):S50-S51.
7. Tran KD, Falcone MM, Choi DS, et al. Epidemiology of herpes zoster ophthalmicus: recurrence and chronicity. *Ophthalmology*. 2016;123(7):1469-1475.

8. Borkar DS, Tham VM, Esterberg E, et al. Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study. *Ophthalmology*. 2013;120(3):451-456.
9. Kinchington PR, Leger AJS, Guedon J-MG, Hendricks RL. Herpes simplex virus and varicella zoster virus, the house guests who never leave. *Herpesviridae*. 2012;3:5.
10. Starr CE, Pavan-Langston D. Varicella-zoster virus: mechanisms of pathogenicity and corneal disease. *Ophthalmol Clin North Am*. 2002;15(1):7-15, v.
11. Zaal MJ, Volker-Dieben HJ, D'Amaro J. Prognostic value of Hutchinson's sign in acute herpes zoster ophthalmicus. *Graefes Arch Clin Exp Ophthalmol*. 2003;241(3):187-191.
12. Arvin AM. Varicella-zoster virus. *Clin Microbiol Rev*. 1996;9:361-381.
13. Arvin A. Aging, immunity, and the varicella-zoster virus. *N Engl J Med*. 2005;352:2266-2267.
14. Yawn BP, Wollan PC, St Sauver JL, et al. Herpes zoster eye complications: rates and trends. *Mayo Clin Proc*. 2013;88(6):562-570.
15. Marsh RJ, Cooper M. Oral acyclovir in acute herpes zoster. *Br Med J (Clin Res Ed)*. 1987;294(6573):704.
16. Balfour HH Jr. Varicella zoster virus infections in immunocompromised hosts. A review of the natural history and management. *Am J Med*. 1988;85:68-73.
17. Seitz B, Heiligenhaus A. "Herpetic keratitis". Various expressions require different therapeutic approaches. *Ophthalmologe*. 2011;108(4):385-395 [quiz: 396-397].
18. Johnson JL, Amzat R, Martin N. Herpes zoster ophthalmicus. *Prim Care*. 2015;42(3):285-303.
19. Hales CM, Harpaz R, Ortega-Sanchez I, et al. Update on recommendations for use of herpes zoster vaccine. *MMWR Morb Mortal Wkly Rep*. 2014;63(33):729-731.