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TOPICS IN Ocular Antiinfectives

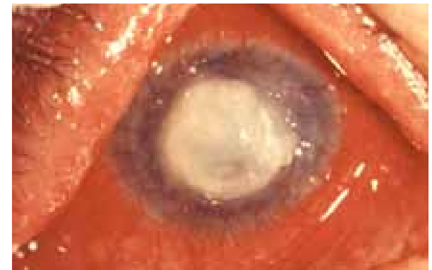
Advances in the Prevention of Ocular Herpes Simplex Disease and Its Recurrence

C. STEPHEN FOSTER, MD, FACS, FAAO, FACR

Advances in the understanding of herpetic latency and reactivation can help clinicians protect patients against ocular herpes simplex disease and its sight-threatening sequelae.

Most ophthalmologists are aware that the herpes simplex virus (HSV) is near ubiquitous in the general population. We all know, too, that HSV can establish lifelong latency in the trigeminal ganglia, from which reactivation and production of mature HSV virions can occur, with migration down the axonal trunks that innervate the eye to cause keratitis and other forms of herpetic ocular disease.

Less widely understood are the cellular processes that underpin herpetic latency and the factors that serve to either maintain latency or trigger reactivation. Understanding herpes simplex latency—and how to best preserve it—is vital if we are to prevent recurrent HSV eye disease, which remains a major cause of infectious blindness and a leading indication for corneal transplant (Figure 1).[1]



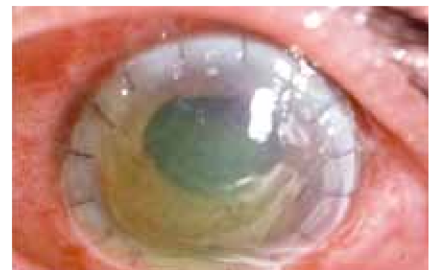


FIGURE 1 Severe stromal herpetic scarring (top) is a leading indication for corneal transplant (bottom), as in this eye shown before and after penetrating keratoplasty.

Inside the Trigeminal Ganglion

By the time we become adults, most of us have been infected with HSV and harbor genetic material from the virus inside the nuclei of our trigeminal ganglion cells.[1] It is common for clinicians to think of this herpetic "hibernation" as passive, but this is far from true. Continued latency depends on the ongoing transcription of messenger RNA to produce latency associated transcripts, or LATs. Anything that disturbs this continual LAT transcription can trigger herpetic reactivation.[2]

What are these triggers? Known provocateurs include fever, trauma, exposure to strong UV light, immune depression, and hormonal disturbance. What these hold in common, on a cellular level, is that they all increase the elaboration of cyclic AMP (adenosine monophosphate). This cellular messenger molecule, in turn, interacts with a response element in the promoter region of the LAT gene. So events that raise cyclic AMP levels have the potential to provoke reactivation of herpes viruses from latency.[2]

Cyclic nucleotides like AMP operate in a yin-yang relationship. So, on the other side of the coin, factors that

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elevate levels of cyclic GMP (guanosine monophosphate) promote LAT creation and strengthen latency. Studies show that long-term use of antiviral drugs such as acyclovir has just such an action and, so, reduces the recurrence of active herpes simplex disease—including ocular involvement.[2]

Maintaining Latency

This contradicts the generally held belief that antivirals prevent ocular herpetic disease solely by blocking the replication of active virions in the eye *after* latency has been lost. Antiviral drugs do this, but just as important may be their molecular effect inside the ganglion cell, where these drugs strengthen latency.

An even bigger myth concerns the mechanism by which steroids exacerbate ocular herpetic disease. The long-held belief has been that ophthalmic steroids fuel ocular herpetic disease only if virions are already actively replicating in the cornea. In fact, experiments show that steroids induce the loss of latency and as a result trigger viral gene expression within latently infected cells.[3,4] This effect may be indirect, as exposure to steroids can kill lymphocytes, and we know that particular subpopulations of lymphocytes (gamma/delta CD8 T-cells) play an important role in maintaining viral latency.

An appreciation of these multifactoral aspects of latency can help the clinician understand the importance of consistent, life-long antiviral therapy for protecting patients who have experienced significant and/or recurrent ocular HSV disease. It likewise reminds us that steroid use in the herpes-infected patient—although sometimes necessary—should never be approached lightly and requires coverage with an antiherpetic agent and close clinical monitoring.

The HEDS Trials

I began using oral acyclovir for the prevention of ocular herpes recurrence in the 1980s, after watching my colleagues in dermatology safely keep their patients on oral acyclovir for years

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STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread "off-label" use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.[1]
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.[2]
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.[3]
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.[4]
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).[5,6]
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

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TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES

Upon completion of this unit the reader will be able to:

1. State the factors that strengthen or weaken herpes simplex latency.
2. List the antiherpetic medications that strengthen latency.
3. State two factors expected to increase the incidence of zoster disease over the next 50 years.
4. Discuss the factors that make heightened clinical awareness and prompt treatment crucial for preventing zoster's sight-threatening ocular complications.

FACULTY AND DISCLOSURE STATEMENTS

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CORE CONCEPTS

- Maintaining latency of HSV in the trigeminal ganglion is an active process that requires ongoing transcription of latency associated transcripts (LATs).
- Agents that disrupt LAT transcription and promote HSV reactivation include steroids, trauma, strong UV light, fever, immune depression, and hormonal disturbance.
- Systemic antiherpetic drugs have at least 2 actions: They strengthen viral latency and block viral replication.
- Laser refractive surgery is contraindicated in patients with prior ocular herpetic disease.
- Medically necessary ocular surgery warrants perioperative prophylaxis with oral anti-herpetics in patients with prior ocular herpetic disease.
- Add topical ganciclovir gel to oral antiherpetics when using steroids to control the postoperative inflammation of invasive procedures.
- Consider lifelong prophylaxis with oral antiherpetic drugs for patients with one or more occurrences of herpetic keratitis.

to suppress outbreaks of genital herpes. Subsequently, Neal Barney and I demonstrated that long-term oral acyclovir could increase the success rate of corneal grafts performed on patients who had lost their vision to severe herpetic scarring—recurrent herpes being a common cause of graft failure in these patients.[5,6]

A year later, we published the results of a similar study demonstrating that long-term oral acyclovir could reduce recurrence rates of herpetic uveitis.[7] The considerable attention that these studies garnered helped inspire the multicenter, NIH-funded trial that became known as the Herpetic Eye Disease Study (HEDS).

Generous funding and careful design enabled HEDS to produce statistically powerful results that convincingly answered many of the questions ophthalmologists had about the prevention and treatment of herpetic infections. HEDS demonstrated, for example, that long-term acyclovir (400 mg twice a day) was safe and effective in reducing rates of recurrence of all types of ocular HSV (19% recurrence over 1 year with acyclovir vs 32% with placebo).[8] An even greater benefit was seen in the prevention of sight-threatening stromal disease, with acyclovir maintenance therapy halving the annual recurrence rate (14% with acyclovir vs 28% with placebo). In addition, HEDS confirmed that concomitant use of acyclovir helped prevent herpetic disease flare ups when steroids were used to control associated ocular inflammation.[9]

Advances since HEDS

The recent FDA approval of ophthalmic ganciclovir gel 0.15% represents an important advance in the treatment of herpetic keratitis. For the first time in the US, we have an ophthalmic antiviral without significant epithelial toxicity.

Although the idea of using a well-tolerated topical drug instead of a systemic one for prophylaxis is appealing, we must remember that prophylaxis is less about blocking the replication of active virions in the eye than it is about maintaining latency in the trigeminal ganglia. In theory, a topical antiherpetic drug could help maintain latency within keratocytes, which have been found to contain latent virus.[10] However, the most important site of latent herpes virus is the regional ganglia of the trigeminal nerve, and there is no evidence that a drug applied to the ocular surface could reach this target.

The HEDS trials employed oral acyclovir for systemic prophylaxis. Since then two, more-bioavailable prodrug forms of acyclovir have come into widespread use—valacyclovir and famciclovir. Relatively little data exists to enable us to say that either valacyclovir or famciclovir provides superior protection over acyclovir, though valacyclovir permits less frequent dosing (Table 1).[11]

Noncompliance increases whenever one asks a patient to take a drug more than once a day. In my experience with acyclovir prophylaxis, the solution has been to permit patients to take the entire daily dose (800 mg) at breakfast. I have been doing this for some 15 years, without seeing any compromise in protection.

Lifelong Prophylaxis

I typically prescribe lifelong prophylaxis with acyclovir or valacyclovir for *any* patient who has had a single episode of herpes keratitis. I base this on a simple risk/benefit calculation: I weigh the superb safety profile of these antiherpetic drugs against the potentially devastating consequences of recurrent herpes keratitis.

The one rare but significant side effect associated with systemic antivirals is renal toxicity. This is not a significant risk in the patient with normal kidney function who takes the drug at recommended doses. However, there have been reports suggesting that high doses of valacyclovir may pose a little understood mortality risk in patients who are HIV-positive.[12]

TABLE 1

Prophylactic use of antiherpetic agents

Drug	Recommended Prophylactic Dose
Acyclovir	400 mg po BID. Double dosage when using steroids
Valacyclovir	500 mg po QD. Double dosage when using steroids
Famciclovir	250 mg po BID. Double dosage when using steroids
Ganciclovir gel 0.15%	1 drop QID in addition to oral prophylaxis when steroids are used to control postoperative inflammation (begin 1 day preoperatively and continue 1 month)

As an added safeguard, I recommend monitoring kidney function in all patients on long-term antiherpetic prophylaxis. My own protocol involves twice yearly blood work, including a complete blood count and assays for liver enzymes, blood urea nitrogen, and creatinine.

Additional Prophylactic Measures

Many patients report that they are more prone to herpetic outbreaks during times of stress; studies, however, are mixed as to whether this correlation exists.[13,14] Certainly, stress reduction offers a safe and reasonable intervention, as does general health maintenance. The prevention of UV-triggered outbreaks gives patients yet another reason to wear UV protective sunglasses.

Herpes and Ocular Surgery

Intraocular surgery is a known trigger of herpetic ocular disease, as is the exposure to intense UV light that takes place in excimer laser refractive surgery.[15,16] Consequently, preoperative assessment should always include a careful examination for signs of herpetic corneal scarring as well as inquiries concerning prior diagnosis and/or symptoms suggestive of herpetic ocular disease.

Keratitis is the most common manifestation, but is by no means the only form of recurrent ocular herpes infection. Infected patients can experience recurrent conjunctivitis, episcleritis, scleritis, and uveitis, though such atypical involvement often goes undiagnosed. As a result, my suspicion of recurrent ocular herpes is heightened whenever I uncover a history of recurrent ocular inflammation of undiagnosed cause.

I consider elective laser surgery wholly contraindicated in patients with a history suggestive of ocular herpetic disease. A prior history of frequent labial herpes outbreaks may indicate a moderately increased risk of ocular involvement; consequently, I recommend perioperative prophylaxis for these patients should they desire refractive surgery.[16,17]

For medically necessary, invasive procedures such as cataract removal, perioperative protection is crucial for the patient not already on lifelong prophylaxis. A systemic antiherpetic drug should be initiated at least 2 days prior to surgery and continued for at least a month postoperatively. Case reports indicate that cataract surgery can trigger ocular herpetic disease in latently infected patients.[17] So consider prophylaxis when other factors such as frequent labial herpes or immunosuppression suggest elevated vulnerability.

If steroids are used to control postoperative inflammation, the usual prophylactic dose of oral antiviral should be doubled for as long as the patient remains on the steroids. Finally, I add topical ganciclovir (1 drop 4 times a day beginning a day prior to surgery and continuing for a month) to the perioperative prophylaxis for corneal procedures such as grafting.

In summary, it behooves us as physicians to incorporate an understanding of herpetic latency and reactivation into our care of patients with a known or suspected history of herpes simplex disease. In doing so, we can better protect them from potentially sight-destroying complications.

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The Changing Epidemiology of Ocular Shingles

Christopher N. Ta, MD

Between now and mid-century, the aging of the American population and the introduction of childhood varicella vaccination have the combined potential to increase the incidence of adult herpes zoster disease and its ocular complications. Heightened awareness can help clinicians diagnose and treat herpes zoster in its earliest stages, which can lower the risk of painful and sight-threatening sequelae.

CORE CONCEPTS

- Latent VZV resides in the trigeminal ganglia and can reactivate when cellular immunity weakens, which can lead to herpes zoster ophthalmicus.
- The aging of the population and adoption of childhood vaccination against varicella (chickenpox) are expected to increase the incidence of herpes zoster ophthalmicus for the next 30 to 50 years.
- The zoster vaccine reduces the risk of developing zoster disease and its ocular complications.
- Prompt and adequate treatment with antivirals reduces the risk and severity of ocular complications.

Herpes zoster disease, or "shingles," results from reactivation of the varicella-zoster virus (VZV), which on initial infection causes varicella, or chickenpox. Like its cousin herpes simplex, herpes zoster establishes lifelong latency in the trigeminal ganglia. It can reactivate at any age, but does so most commonly in late life with the natural waning of cellular immunity.[1] Herpes zoster ophthalmicus can result when the reactivated virions travel down the ophthalmic branch of the trigeminal nerve.

Close to 30% of adults will experience at least one episode of zoster disease in their lifetime, producing approximately 1 million cases per year in the United States.[2] Without antiviral treatment (ideally within 72 hours of the first skin lesion), approximately 50% of patients with zoster of the V1 distribution of the trigeminal nerve will develop ocular involvement.[3]

Herpes zoster ophthalmicus, or ocular shingles, can involve all parts of the ocular system, from the cornea and conjunctiva to the retina and optic nerve (Table 1). Corneal complications occur in some 65% of ocular cases and can result in significant vision loss and the need for keratoplasty.[4]

In comparison to herpes simplex keratitis, zoster keratitis is associated with a higher degree of neurotrophic cornea (Figure 1). Tragically, this results in a higher rate of graft failure when zoster-associated scarring necessitates corneal transplant.[5] A common consequence of zoster disease is post-herpetic neuralgia, a syndrome of enduring pain that can range from mild and intermittent to agonizing and intractable.[3]

In addition to age, known risk factors for VZV reactivation include immune-compromising conditions such as HIV infection, systemic corticosteroid use, and chemotherapy treatment. Poor nutrition, stress, and fatigue may increase susceptibility to some degree. Topical ophthalmic corticosteroids do *not* appear to trigger zoster reactivation or fuel infection, as they do with herpes simplex.[3]

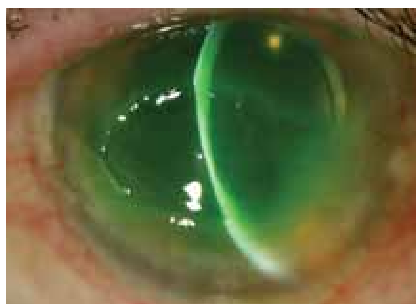

FIGURE 1 Compared to herpes simplex keratitis, zoster keratitis is associated with a higher degree of neurotrophic cornea. (Photo courtesy of Huynh Van, Stanford University).

Changing Epidemiology

Awareness of ocular zoster disease is increasingly important today as incidence is expected to rise in the coming years and may have already begun to do so. Two factors are driving this increase: the aging of the population and the introduction of childhood vaccination against varicella (chickenpox).[6]

In 1995, the varicella vaccine became a routine part of the early childhood immunization schedule in the United States. Until then, infection was a near-universal part of childhood.[7] In immunocompetent persons, initial infection produces strong T-cell mediated immunity, which effectively maintains VZV latency in the ganglion cells of the trigeminal nerve. Such cell-mediated immunity wanes over time, most dramatically in old age.

Two natural mechanisms help boost immunity to latent VZV. One is exposure to children (or anyone else) with active chickenpox. The other is periodic, internal exposure to low-level viremia, which generally involves asymptomatic escape of small numbers of VZV virions from the ganglion cells.[2,8]

The widespread adoption of the childhood chickenpox vaccine has rapidly removed the first of these latency boosters. A number of mathematical models predict this will increase the incidence of zoster disease in the adult population for the next 30 to 50 years, after which rates should dramatically decline, as today's vaccinated children themselves reach old age.[9,10] Though the current chickenpox vaccine contains weakened live virus, studies indicate that the vaccine strain is far less likely than wild varicella-zoster to establish trigeminal latency, reactivate in later life, or cause severe zoster disease.[9] So

TABLE 1

The ocular complications of herpes zoster.

Involvement	Signs	Time since rash onset
Eyelid/conjunctiva		
Blepharoconjunctivitis	Cutaneous macular rash respecting midline and involving eyelids	Day 0
	Conjunctival edema, inflammation	2 to 3 days
	Vesicular lesions and crusting	6 days
Episclera/sclera		
Episcleritis/scleritis	Inflammation and pain	Weeks to months
Cornea		
Punctate epithelial keratitis	Swollen epithelial cells	1 to 2 days
Dendritic keratitis	"Medusa-like" epithelial defect with tapered ends	4 to 6 days
Anterior stromal keratitis	Multiple fine infiltrates	1 to 2 weeks
Deep stromal keratitis	Deep stromal inflammation	1 month to years
Neurotrophic keratopathy	Punctate corneal erosions Persistent epithelial defects Corneal ulcers	Months to years
Anterior chamber		
Uveitis	Iris inflammation and scarring	2 weeks to years
Retina		
Acute retinal necrosis/progressive outer retinal necrosis	Coalescent patches of retinal necrosis Occlusive vasculitis Acute retinal necrosis	Varies
Cranial nerves		
Optic neuritis	Swollen, edematous optic nerve head	Varies
Oculomotor palsies	Extraocular motion abnormalities	Varies

Adapted from Shaikh S, Ta CN. Evaluation and management of herpes zoster ophthalmicus. *Am Fam Physician.* 2002 1;66(9):1723-30.

we have good reason to believe that universal vaccination will eventually render herpes zoster ophthalmicus an uncommon disease.

Meanwhile, some epidemiological studies suggest that the interim increase in adult zoster disease has already begun and that it is pushing incidence into younger age groups. A recent report from Australia, for example, documents a 2% to 6% annual increase in herpes zoster among adults age 40 and older since the nation's 2005 adoption of childhood varicella vaccination.[10]

A Vaccine for Zoster

At present, our best means of boosting varicella-zoster immunity and, so, preventing zoster disease is the zoster vaccine, which gained FDA approval in 2006. With a potency around 14 times that of the childhood varicella vaccine, the zoster vaccine underwent clinical testing in studies that enrolled over 38,500 immunocompetent subjects, all of whom were 60 years or older and had a history of chickenpox. In double-blind, randomized, placebo-controlled testing, the live vaccine reduced disease incidence by 51.3%, burden of illness by 61%, and incidence of postherpetic neuralgia by 66.5%.[11] Based on the above clinical studies, the vaccine's current FDA approval, and most insurance coverage, is restricted to patients age 60 and older. Subsequent studies in persons in their 50s have demonstrated safety and immunogenicity.[12] In fact, studies parsing epidemiology and immunological response suggest that the ideal age for zoster vaccination may be between 50 and 55 years—the age span in which zoster incidence begins to increase exponentially but immune response to vaccination remains strong.[13]

Anticipating Ocular Zoster

The anticipated rise in zoster incidence underscores the need for ophthalmologists to maintain a high index of suspicion when patients complain of pain or tingling in the forehead or scalp or report a recent history of such symptoms.

Ocular zoster's potential for significant morbidity underscores the need for prompt recognition and treatment. When initiated within 72 hours of the first skin lesions, appropriate doses of oral antivirals reduce the incidence and severity of ocular complications. Importantly, antiviral therapy for zoster requires significantly higher doses of antivirals (800 mg oral acyclovir 5 times daily or 1 gm valacyclovir 3 times daily for 7 to 10 days) than that required to treat ocular herpes simplex, which can present somewhat similarly.[15]

In addition, the risk of triggering zoster mandates that we closely monitor the patients we place on systemic immunosuppression—for example, the patient taking oral prednisone for scleritis—particularly if the patient is middle-aged or older.

Differential Diagnosis and Treatment

In some cases, distinguishing ocular zoster from herpes simplex is fairly straightforward, as when the patient has a vesicular rash on the forehead. But ocular zoster disease can occur without the classic rash, and distinguishing between zoster and simplex keratitis (without other features) can be challenging.

With epithelial keratitis, the clinician can make distinctions based on the appearance of the dendrites with staining (Figure 2). In herpes simplex keratitis, dendrites tend to stain intensely with fluorescein and have distinct terminal bulbs, while the pseudodendrites of zoster keratitis stain less intensely and

have tapered ends (no terminal bulbs). When in doubt, I do not hesitate to prescribe the higher zoster dose (double that for ocular herpes simplex), as both acyclovir and valacyclovir have low toxicity in persons with normal renal function.

Some clinicians add topical treatment with ophthalmic ganciclovir gel, recently FDA approved for the treatment of herpes simplex keratitis. We do not, however, have studies that demonstrate topical ganciclovir's efficacy against zoster keratitis.

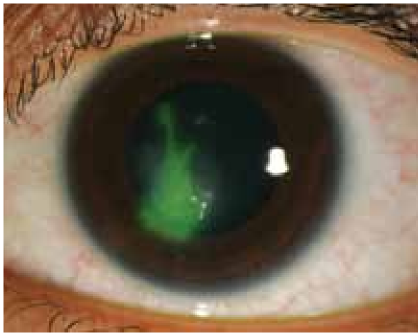

FIGURE 2 The pseudodendrites of zoster keratitis stain less intensely than do herpes simplex dendrites and have tapered ends (vs terminal bulbs). (Photo courtesy of Huynh Van, Stanford University).

A distinction to keep in mind is that while herpes simplex keratitis generally involves a combination of active infection and inflammation, the infectious phase of ocular zoster disease tends to be relatively brief followed by a prolonged inflammatory response. And as a result, inflammation control is important and can be safely accomplished with topical steroids without antiviral coverage after the initial 7 to 10 days of treatment. However, recent evidence suggests that chronic herpes zoster keratitis may have an infectious component, as shown by positive PCR. In these cases, long-term use of antiviral therapy may be warranted.

Finally, we must remain mindful that some of the most serious ocular complications of zoster disease can develop long after the patient's initial presentation (Table 1). It is common, for example, to diagnose zoster stromal keratitis weeks to months after initial presentation, and uveitis may appear months to years later.

As a result, clinicians should continue to monitor their zoster patients for an extended period. In my practice, I schedule a follow-up visit 2 to 3 weeks after initial treatment and, in the absence of worrisome signs, schedule another follow-up visit 2 months later.

Conclusion

Herpes zoster ophthalmicus is not something that most eyecare practitioners see every day, but we can expect to be seeing more of this potentially blinding and painful disease in the coming years—particularly among our oldest patients but also among the middle-aged. With prompt diagnosis and appropriate treatment, we can reduce their risk of sight-threatening sequelae and of postherpetic neuralgia. We should also be encouraging our older patients to avail themselves of the new zoster vaccine. The best news of all, perhaps, is that childhood vaccination may spare future generations from this bane of old age.

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1. Maintenance of herpetic latency depends on which of the following?
   A. Killing of virions on the ocular surface
   B. Long-term steroid use
   C. The continual suppression of LATs
   D. The continual transcription of LATs

2. Known triggers of herpes simplex reactivation share what in common?
   A. All increase the production of cyclic GMP
   B. All block the production of cyclic AMP
   C. All increase the production of cyclic AMP
   D. None of the above is true

3. Oral acyclovir:
   A. Strengthens viral latency
   B. Blocks viral replication
   C. Both A and B above are true
   D. Neither A nor B above are true

4. Patients on long-term prophylaxis with systemic antiherpetic agents should be monitored for:
   A. Normal renal function
   B. Normal cardiovascular function
   C. Normal pancreatic function
   D. All of the above

5. Foster recommends prophylactic use of ophthalmic ganciclovir gel:
   A. As a substitute for oral agents for lifelong prophylaxis
   B. In addition to oral agents for lifelong prophylaxis
   C. As a substitute for oral agents for prophylaxis in corneal grafting
   D. In addition to oral agents for prophylaxis in corneal grafting

6. Approximately how many people develop herpes zoster disease in the United States each year?
   A. 10,000
   B. 100,000
   C. 1 million
   D. 10 million

7. Without prompt antiviral treatment, zoster disease produces ocular complications in approximately what percentage of patients?
   A. 90%
   B. 50%
   C. 10%
   D. 0.5% to 1.0%

8. Reactivation of the varicella-zoster virus most commonly involves which of the following immunological factors?
   A. White cell response to local trauma
   B. Immune suppression due to prednisone use
   C. Waning T-cell immunity
   D. Aging antibodies

9. The widespread introduction of the chickenpox vaccine is expected to change zoster epidemiology in which of the following ways?
   A. Increase zoster incidence among today's adults
   B. Lower the age at which zoster is commonly seen
   C. Decrease zoster incidence in the second half of the century
   D. All of the above are true

10. At present, our best means of preventing zoster disease is:
    A. Oral acyclovir
    B. Oral valacyclovir
    C. The zoster vaccine
    D. The varicella vaccine

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ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
    Objective 3: 1 2 3 4 5
    Objective 4: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: ____________________

____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

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