Diagnostic Methods and Management Strategies of Herpes Simplex and Herpes Zoster Infections

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KEYWORDS

• Herpesvirus • Diagnosis • Complications • Immunosuppression • Treatment

KEY POINTS

- The distribution of herpes simplex and herpes zoster varies; however, the primary lesion is a vesicle on an erythematous base often preceded by sensory alterations.
- Always consider herpes zoster in the differential diagnosis when an elderly patient presents with dermatomal pain or altered mental status.
- Polymerase chain reaction assays are preferred for a rapid diagnosis with high sensitivity.
- Immediate treatment with antivirals is recommended for herpes simplex and herpes zoster. Early antiviral intervention can decrease the incidence of postherpetic neuralgia.

INTRODUCTION

Herpesviruses are medium-sized double-stranded DNA viruses. Of more than 80 herpesviruses identified, only 9 human herpesviruses have been found to cause infection in humans. These include herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), human cyto-megalovirus (HCMV), Epstein–Barr virus (EBV), and human herpesvirus (HHV-6A, HHV-6B, HHV-7, HHV-8). HSV-1, HSV-2, and VZV can be problematic given their characteristic neurotropism which is the ability to invade via fusion of its plasma membrane and reside within neural tissue. HSV and VZV primarily infect mucocutaneous surfaces and remain latent in the dorsal root ganglia for a host's entire life. Reactivation causes either asymptomatic shedding of virus or clinical manifestation of vesicular lesions.[1–3]

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The clinical presentation is influenced by the portal of entry, the immune status of the host, and whether the infection is primary or recurrent.[1] Affecting 60% to 95% of adults, herpesvirus-associated infections include gingivostomatitis, orofacial and genital herpes, and primary varicella and herpes zoster. Symptomatology, treatment, and potential complications vary based on primary and recurrent infections as well as the patient's immune status.

OROFACIAL HERPES SIMPLEX AND GENITAL HERPES

Primary Herpetic Gingivostomatitis

Orolabial herpes infection is essentially caused by HSV-1 infection, although HSV-2 infection can occur (**Figs. 1–3**). Most initial orolabial infections are subclinical and, therefore, go unrecognized. Latest data from the National Health and Nutrition Examination survey showed that during 2015 to 2016, the prevalence of HSV-1 was 47.8% and of HSV-2 was 11.9% among those aged 14 to 49.[2]

A small proportion of newly infected patients develop primary herpetic gingivostomatitis (PHGS). Classically, PHGS begins as transient perioral vesicles that quickly rupture, producing painful superficial ulcerations. The perioral vesiculo-ulcerative lesions are often preceded by a sensation of burning or paresthesia at the site of inoculation. Initial primary infections often occur within 1 to 26 days after inoculation and can last for 10 to 14 days. Although most orolabial infections are asymptomatic, they can be preceded by a prodrome of fever, chills, fatigue, muscle aches, and cervical and submandibular lymphadenopathy.[3–5]

Recurrent Herpes

Recurrent herpes labialis (RHL) affects up to one-third of the American population and typically presents at the vermillion border of the lip in 90% of cases. Recurrence may occur on eyelids, cheeks, perioral skin, nasal mucosa, or oral mucosa. If it recurs intraorally, it mostly recurs on keratinized mucosa, such as on the hard palate, gingiva, and occasionally dorsum of the tongue. Conditions associated with oral ulcers include orolabial herpes infection, aphthous ulcers, herpangina, hand-foot-mouth disease, lichen planus, drug-induced ulcers (with drugs like beta-blockers, antimetabolites, and alkylating agents, among others), erythema multiforme, pemphigus vulgaris, and Behcet's Disease (**Table 1**). For RHL specifically, papules on an erythematous base progress to vesicles and within 72 to 96 hours become ulcerated and crusted before healing.

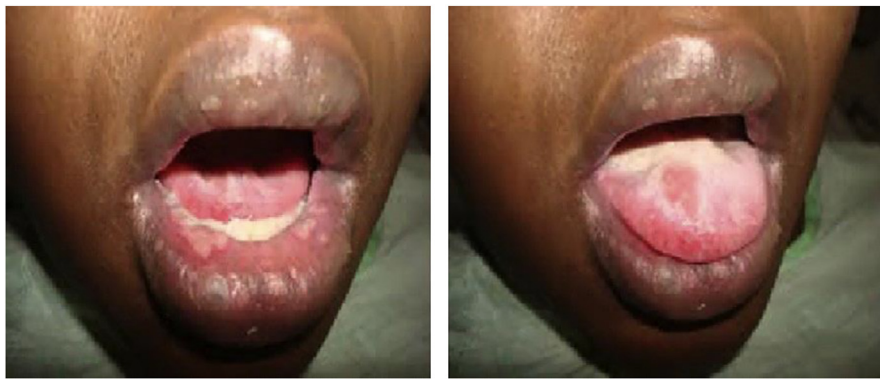

Fig. 1. Primary herpetic gingivostomatitis with coalescing grouped erosions with scalloped borders. The diagnosis was confirmed by viral culture.

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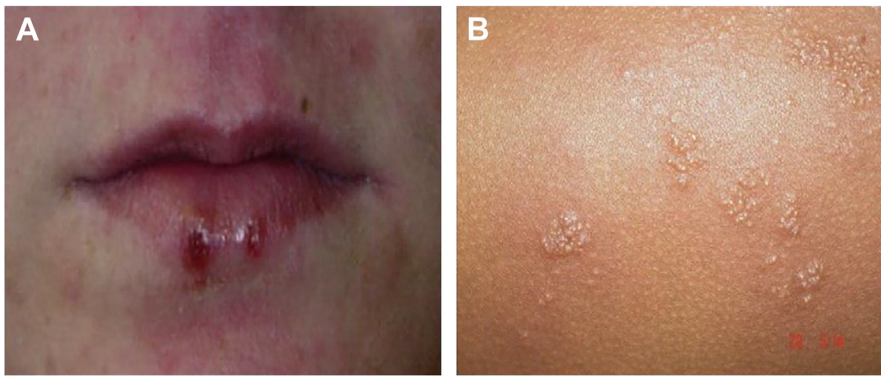

Fig. 2. (*A*) Recurrent herpetic labialis. (*B*) Recurrent cutaneous herpes.

About 60% of people experience a prodrome of tingling, itching, and burning within 24 hours of skin lesions. Overall, symptoms and duration are milder and shorter than primary infections.[3] Common triggers are illness, surgery, sun exposure, trauma, emotional stress, and menses. At least one-half of all immunocompetent individuals who experience an episode of HSV infection will have a recurrent episode in their lifetime.[4]

Genital Herpes Simplex Virus Infection

HSV-2 is the most common strain in genital herpes (**Fig. 4**); however, the percentage due to HSV-1 infection is increasing in developed countries.[7] This may be due to the fact that among people 14 to 19 years of age, the seroprevalence of HSV-1 has decreased by 30% over the past 30 years; thus, an increasing proportion of adolescents lack protective HSV-1 antibodies when they become sexually active.[8] Independent risk factors for HSV-2 seropositivity include female sex, older age, lifetime number of sexual partners, lower education or income level, cocaine use, and black or Hispanic race.[9] Approximately half of patients with symptomatic genital lesions report headache, fever, malaise, dysuria, or tender inguinal lymphadenopathy. However, most patients with initial genital herpes do not have conspicuous lesions and systemic symptoms.[8] Atypical presentations include edema, crusts, fissures, erythematous patches, or transient irritation, and back pain without genital lesions.

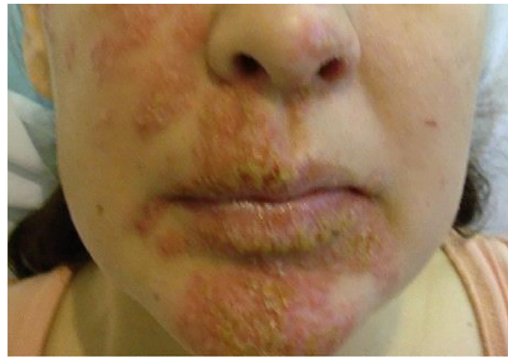

Fig. 3. Recrudescent herpes infection following a neurosurgical procedure.

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Table 1
Differential diagnosis of oral ulcers

Orolabial herpes infection	Keratinized mucosa (hard palate, gingiva)
Aphthous ulcers	No vesicles, nonkeratinized, and moveable mucosa
Herpangina	Acute, multiple ulcers, posterior oral cavity, mild systemic symptoms, more common in children
Hand-food-mouth disease	Anterior oral cavity, hand, and foot lesions
Lichen planus[a]	Wickham striae[b], other skin or genital mucosal lesions
Drug induced	Beta-blockers, mycophenolate, anticholinergic bronchodilators, clopidogrel, nonsteroidal anti-inflammatory drugs, captopril, antimetabolites, taxanes, alkylating agents, vinca alkaloids
Erythema multiforme[a]	Often spared gingiva, widespread, irregular ulcers, blood-crusted lips, with or without targetoid skin lesions
Pemphigus vulgaris[a]	Posterior oral cavity and gingival ulcers
Behcet's disease	Uveitis, genital ulcers, acneiform lesions, pseudofolliculitis, erythema nodosum-like lesions, arthritis

[a] Biopsy is needed to confirm the diagnosis.
[b] Wickham striae are pathognomonic for lichen planus and appear as white reticulated patches on the buccal mucosa.
Data from Refs.[5,6]

Potential complications are urinary retention, aseptic meningitis, pharyngitis, and psychological morbidity.[10] The differential diagnosis for genital ulcers includes genital HSV in addition to other infectious and inflammatory causes (**Table 2**).

Transmission of Orofacial Herpes and Genital Herpes

Transmission of orofacial, intraoral, and genital herpes occurs by direct contact between mucous membranes, respiratory droplets, or impaired skin with mucosal secretions or ulcerative lesions of a person with active primary or recurrent infection. Clinicians often misuse the term "recurrence." Viral reactivation that results in asymptomatic viral shedding is considered a recurrence, whereas viral reactivation that produces clinical disease or symptoms is termed "recrudescence."[15]

Symptomatic lesions are more infectious because they contain higher virus titers; however, asymptomatic shedding is the predominant mode of transmission. Studies have shown that only approximately 20% to 50% of people with HSV-2 serology

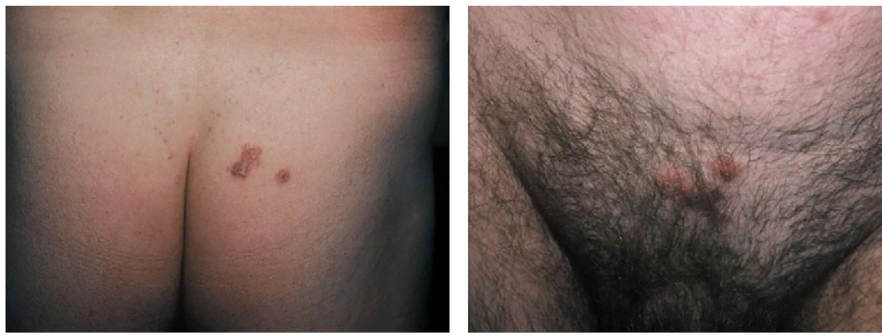

Fig. 4. Primary genital herpes caused by HSV-2.

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Table 2
Differential diagnosis of genital ulcers

Differential Diagnosis	Clinical Features
Infectious causes	
Syphilis	Painless chancre with nontender LAD
Chancroid	Painful ulcer and LAD
Lymphogranuloma venereum	Painless ulcer, lymphadenitis
Donovanosis	Painless ulcerations, no LAD
Scabies	Excoriated red papules, burrows
Candida	Shallow, bright red
Cutaneous Crohn disease	Genital edema, linear "knife-like" ulceration, abdominal symptoms
Behcet's disease	Painful oral ulcers, uveitis, pathergy, arthralgias, gastrointestinal symptoms
Contact dermatitis	Complex topical products (ie, scented feminine hygiene products)
Reactive arthritis	Arthritis, uveitis, urethritis, cervicitis, buccal, mucosal and glans penile ulcers
Lichen planus	Inner aspect labia majora or glans penis
Pemphigus vulgaris	Oral ulcers and flaccid bullae/erosions on skin
Pyoderma gangrenosum	Painful ulcers with purpuric borders and undermined margins
Erythema multiforme	Herpes simplex virus, *Mycoplasma* associated, drug-induced

Abbreviation: LAD, lymphadenopathy
Data from Refs.[11–14]

are aware that they are infected.[16] Asymptomatic or unrecognized viral shedding is responsible for transmission of more than half of primary cases.[17]

Asymptomatic shedding varies by location, subtype, and primary or recurrent status. High-risk periods of asymptomatic shedding for genital herpes occur most commonly in the first 3 months after primary infection, during the prodrome, and the week following a symptomatic recurrence.[18–20] Infections that are primary, HSV-2 positive, and located to the perineum have a longer duration of shedding.[21,22] Having symptomatic genital herpes does not increase the risk of subclinical shedding compared with patients who are seropositive without a history of clinically evident disease.[22,23]

Anticipatory Guidance for Patients Regarding Herpes Simplex Virus-1 and Herpes Simplex Virus-2 Transmission

Patients with recrudescent genital herpes should be counseled to practice safe sex behaviors, including abstinence during outbreaks, and using condoms in all sexual encounters. Asymptomatic seropositive patients pose a greater challenge. However, when educated on the signs and symptoms of genital herpes, many "asymptomatic" patients begin to recognize clinical symptoms. Although asymptomatic seropositive patients experience less viral shedding than symptomatic seropositive patients, they can still transmit genital herpes in an unpredictable manner. Daily antiviral suppressive therapy has been shown to decrease HSV recrudescence, viral shedding, and transmission in serodiscordant sexual partners.[24]

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Should everyone be screened for HSV-1 and HSV-2 with a blood test? This is a controversial public health question. Many clinicians fear the psychosocial consequences of mass serotesting and labeling millions of people with an incurable disease in addition to significant burdens to the health care system. Mass screening may be associated with severe anxiety to patients, increased psychological counseling, more costs related to testing, and an increase in suppressive therapy regimens related to increased diagnoses. Serologic testing may also be associated with a high rate of false-positive test results.[25] Patients with HSV have also expressed concerns related to personalized stigma, disclosure concerns, negative self-image, and concern with public attitudes.[25] The latest US Preventive Services Task Force (USPSTF) in 2016 recommend against routine serologic screening for genital HSV infections in asymptomatic adolescents and adults, including those who are pregnant.[26]

It is generally considered appropriate to initiate suppressive therapy for serodiscordant couples in which 1 partner is seropositive and the other is not and for patients who have psychological distress to their diagnosis.

HERPES SIMPLEX VIRUS INFECTION IN THE IMMUNOCOMPROMISED PATIENT

Patients who are immunocompromised (ie, those who are human immunodeficiency virus [HIV] positive, have undergone bone marrow or solid organ transplants, or are dependent on hemodialysis) have a heightened risk of acquiring opportunistic infections. Additionally, they may exhibit atypical symptoms of common infections like herpesvirus infections. While the clinical manifestations of HSV-1 and HSV-2 infections are similar between those with normal and compromised immune systems, the latter group may present variations in symptomatology. Infections in the immunocompromised patient group are more frequent, symptomatic, progressive, poorly responsive to therapy, associated with longer duration of shedding, involve multiple sites, and are at higher risk for viremic dissemination. Intraoral lesions are more extensive, surrounded by white elevated border and involve both keratinized and nonkeratinized mucosa. Genital HSV-1 and HSV-2 can be more atypical, such as painful verrucous nodules and persistent ulcers. Cutaneous HSV infection lesions have presented with ulceration of “knife-like” skin fissures in the abdominal, infra-abdominal, and inframammary skin folds, the interlabial and the gluteal cleft, and the inguinal crease.[5,27]

ECZEMA HERPETICUM

Eczema herpeticum (EH) describes herpes-infected dermatitis. Atopic dermatitis (AD) is the most common dermatitis implicated in EH with about 3% of patients developing this complication over their lifetime, but herpes simplex can secondarily infect many other chronic dermatoses. Other dermatoses that can be affected are pemphigus foliaceus, mycosis fungoides, ichthyosis vulgaris, Hailey–Hailey disease, irritant contact dermatitis, pityriasis rubra pilaris, and burns. Hematological abnormalities with a report of EH include cutaneous T-cell lymphoma and Sézary disease.[28] Classically, patients present with disseminated widespread monomorphic vesicles accompanied by fever, malaise, and lymphadenopathy. The vesicles crust over and heal by 6 weeks in most cases. However, often the presentation is more subtle, fissured disseminated plaques, flaring atopic dermatitis with punched out erosions, and a component of periorbital involvement with blepharitis can all indicate an occult herpes infection. The head, neck, and trunk are the most affected sites.

The use of topical corticosteroids has not been shown to increase the risk of EH. Topical calcineurin inhibitors may predispose a patient who is at increased risk and

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are contraindicated in acute EH. Antiviral therapy should be set up as soon as EH is suspected as EH can potentially be fatal with a mortality rate of 10% to 75% in its severe form.[29] Clinicians must maintain a high index of suspicion for herpes infection when a patient with chronic dermatosis presents with a flaring dermatosis or widespread monomorphic vesicles within the chronic dermatosis. All patients should be questioned about recent herpes outbreaks.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis (HSE) has an incidence of 1 to 3 per million.[30] There is a bimodal age distribution affecting patients younger than 20 and older than 50 with a peak between 60 and 64. More than 90% of HSE in immunocompetent patients are HSV-1 related. Only 1.6% to 6.5% of HSE cases are HSV-2 related and typically occur in immunosuppressed patients.[30,31] HSE is the most frequent cause of sporadic necrotizing encephalitis in adults. Worldwide it accounts for 5% to 10% of all cases of encephalitis.[32]

HSE is generally not considered a sign of immunocompromise except in cases of bone marrow transplantation and acquired immunodeficiency syndrome (AIDS).[33,34] There are a number of reports of HSE following neurosurgery (eg, cervical spine laminectomy, acoustic neuroma resection).[35,36] Recent studies have elucidated *toll-like receptor*-(TLR 3) interferon pathways resulting in increased susceptibility to HSE. Both animal models and humans also indicate that cytolytic viral replication and immune-mediated responses (including cytotoxic T lymphocytes and immune mechanisms mediated by TLR 2) contribute to the pathology of HSV.[37]

Patients in the following settings should have cerebrospinal fluid (CSF) examination for HSV: patients presenting with fever, headache, and malaise for several days with progression to behavioral changes, seizures, focal neurologic signs, or cognitive difficulties, especially in patients with neuroimaging alterations (particularly in the medial temporal lobes, insular cortex, and orbital frontal lobes).[34] Central nervous system (CNS) manifestations might occur before the skin eruptions.[38] A personal history or an exposure history of "cold sores" or genital herpes should be elicited. In patients with AIDS, HSE may present with personality and behavioral changes but without fever or headache.[39]

The current gold standard confirmatory test for HSE is polymerase chain reaction (PCR) to detect HSV DNA in the CSF, whose sensitivity is approximately 96% with a specificity of 99% in experienced laboratories. Analysis on CSF frequently demonstrates WBC count of 100 to 200 cells/mm^3 with mild to moderately elevated CSF protein levels ($\sim$100 mg/dL) and normal glucose.[32] Diagnosis of HSE can be difficult, viral DNA by PCR can be negative initially. CSF cell count is normal in 5% to 10% of patients, computed tomography (CT) results are normal in the first week of illness in up to 33% of patients and MRI can be normal in up to 10% of patients.

ANTI-N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY ENCEPHALITIS

Autoimmune encephalitis or anti-N-methyl-d-aspartate (NMDA) receptor (NMDAR) antibody encephalitis is a newly described cause of encephalitis within the last decade. It is critically important to distinguish this disease entity from HSE as therapeutic approaches are very different. Anti-NMDAR immunoglobulin (Ig)G serology in the blood and CSF coupled by symptoms of choreoathetosis, memory, behavioral changes, and seizures in the setting of previously diagnosed HSV encephalitis can aid in this distinction. The optimal management of autoimmune encephalitis is still unclear. Key questions, such as whether intravenous immunoglobulin is beneficial as a

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first-line therapy, remain to be clarified by randomized controlled trials. In contrast, intravenous acyclovir for HSE is a life-saving treatment and has reduced mortality from above 70% to around 10% to 20%.[32,37]

Varicella-zoster virusVaricella-zoster virus (VZV) produces 2 clinically distinct diseases. Primary infection with VZV causes varicella or "chickenpox," a vesicular rash most seen in young children. Unlike HSV-1 and HSV-2, primary VZV infection has a systemic phase of viremia. Inhalation of infectious particles colonizes respiratory lymphoid tissue and then spread systemically to the dermis via cutaneous vasculature.[40] This neurotropic virus later becomes latent, primarily in neurons in peripheral autonomic ganglia throughout the entire neuroaxis including dorsal root ganglia (DRG), cranial nerve ganglia such as the trigeminal ganglia (TG), and autonomic ganglia including those in the enteric nervous system. Reactivation of VZV infection results in herpes zoster or "shingles" which occurs up to decades following primary inoculation, presenting as a painful dermatomal vesicular rash. Unlike HSV, VZV tends to reactivate with increasing age and people older than 60 years are 8 to 10 times more likely to develop herpes zoster. VZV cell-mediated immunity declines with age despite unchanged or increased antibody titers. Reactivation of VZV may also cause a wide variety of neurologic syndromes, the most significant of which is a vasculitis, which is treated with corticosteroids and the antiviral drug acyclovir. Other VZV reactivation complications include encephalitis, segmental motor weakness and myelopathy, cranial neuropathies, and Guillain–Barré syndrome in which the viral reactivation occurs in the absence of the characteristic dermatomal distributed vesicular rash of herpes zoster.[41–44]

Primary Varicella

Primary varicella (VZV) or "chickenpox" is predominantly a disease of childhood. The incidence has dramatically decreased since the advent of the childhood vaccine in 1995. Although uncommon, adults can contract primary varicella. A seronegative adult can contract primary varicella from a person with varicella by inhalation of respiratory secretions, contact with skin lesions, or from mucocutaneous contact with someone with herpes zoster. Patients who are susceptible and exposed to VZV should be placed under airborne and contact precautions (**Table 3**).[45] According to the Centers for Disease Control and Prevention, an immunocompetent patient is considered contagious 2 days before the onset of a rash until about 5 days after rash onset and all lesions are dry and crusted.[46] Immunocompromised patients may be contagious for a longer period. Psychosocial needs must be balanced with infection control in long-term care facilities because of psychosocial risks associated with restriction.[46]

Primary varicella infection in adults or in an immunocompromised patient may be more severe. The conjunctiva and the upper respiratory tract mucosa are the most common portals of entry. The virus undergoes a primary viremia between days 4

Table 3
Isolation guidelines for varicella

	Immunocompetent	Immunocompromised
Localized herpes zoster	Standard precautions Completely cover lesions	Standard precautions + airborne (until disseminated herpes zoster is ruled out)
Disseminated herpes zoster	Standard precautions + airborne contact	Standard precautions + airborne contact

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and 6 in the regional lymph nodes, and then travels to the liver and spleen before hematogenous spread to other organs (eg, lungs, CNS, and skin).[47]

In addition to a low-grade fever and malaise, patients can develop a pruritic rash that evolves through several stages. Erythematous macules and papules present early in the disease course on the scalp and face. Within 12 to 24 hours, the rash may progress to the characteristic vesicles on an erythematous base and then ultimately pustules and crusted scabs.[44] Patients may exhibit lesions in various stages of healing, develop new lesions every few days, and display centripetal rash spread (ie, from the face to the trunk and extremities).[44] Adult primary varicella resembles the childhood type, but can have larger and an increased number of lesions as well as prolonged fever, and other constitutional symptoms. Primary varicella in immunocompromised patients may be more severe and even fatal.[44,48]

The most common cutaneous complication is bacterial superinfection secondary to *Staphylococcus aureus* or *Streptococcus pyogenes,* which can contribute to scarring.[48] Cases of staphylococcal and streptococcal toxic shock and severe soft tissue infections such as varicella-associated necrotizing fasciitis have been reported. Beta hemolytic streptococcal necrotizing fasciitis requires early, aggressive surgical debridement and targeted antibiotics.[49]

Adults and immunocompromised patients have a higher risk of developing complications from chickenpox compared to healthy children (eg, pneumonitis and neurologic sequelae). The mortality rate of adult varicella pneumonia ranges between 10% and 30% and up to 50% in those requiring mechanical ventilation.[50] The most common neurologic symptoms of primary VZV include acute cerebellitis and stroke (especially in childhood).[51] Other neurologic symptoms include myelitits, meningitis, and acute demyelinating radiculoneuropathy. Most cases with neurologic sequelae occur a week following rash onset, but symptoms may also develop without a rash.[51] Presenting symptoms may include the abrupt or gradual onset of fever, headache, vomiting, lethargy, seizures, meningismus, and coma.[51] CSF evaluation sometimes shows a low-grade lymphocytosis and elevated protein.[52] Fortunately, the cerebellar ataxias are self-limited and most patients recover within 1 to 3 weeks without permanent deficits.

Varicella encephalitis is the most serious CNS complication with mortality ranging from 5% to 10% and up to 80% in immunocompromised patients.[53] Other rare systemic complications of primary varicella in adults include myocarditis, glomerulonephritis, appendicitis, pancreatitis, hepatitis, Henoch–Schonlein vasculitis, orchitis, arthritis, optic neuritis, keratitis, and iritis.[54]

Herpes Zoster (Shingles)

Herpes zoster typically affects people older than 60 years secondary to decreased VZV-specific cell-mediated immunity (**Figs. 5** and **6**). Risk factors include chemotherapy, immunosuppressive agents (eg, prednisone used in transplant recipients and treatments for autoimmune disorders), biologics, and HIV/AIDS. It can be the first manifestation of HIV.[55]

Classic herpes zoster is characterized by an acute onset, sharp radicular pain, and the eruption of grouped vesicles on an erythematous base distributed in up to 3 dermatomes. Cutaneous lesions tend to respect the midline, which is a helpful feature to differentiate from HSV infection. Lesions on the chest (thoracic dermatomes) are the most common, followed by the face (trigeminal dermatome).[41]

Pain is often accompanied with pruritus, decreased sensation, and allodynia within the affected dermatome(s). In more than 90% of cases, pain precedes the skin eruption by days to a week.[56] It is easy to misdiagnose the pain as myocardial infarction,

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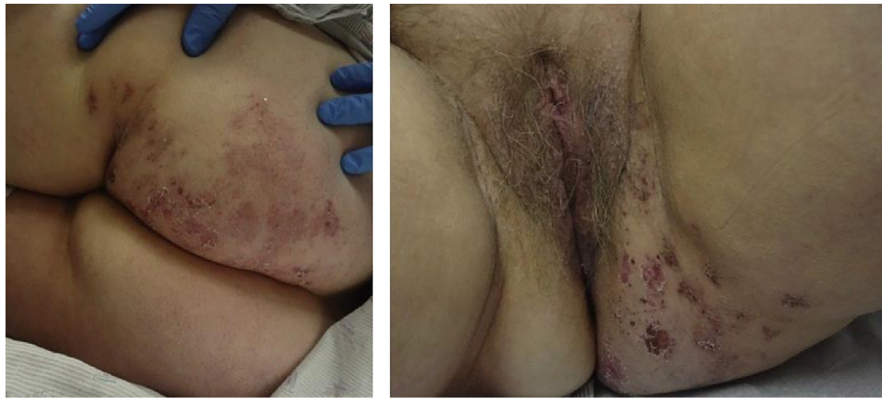

Fig. 5. Perineal herpes zoster.

pleurisy, cholecystitis, appendicitis, duodenal ulcer, ovarian cyst, herniated intervertebral disc, thrombophlebitis, or even biliary or renal colic. Zoster sine herpete describes a zoster-like neuropathic pain in a dermatomal distribution without an accompanying rash.[57] Reported cases noted rising titers of VZV-specific antibody

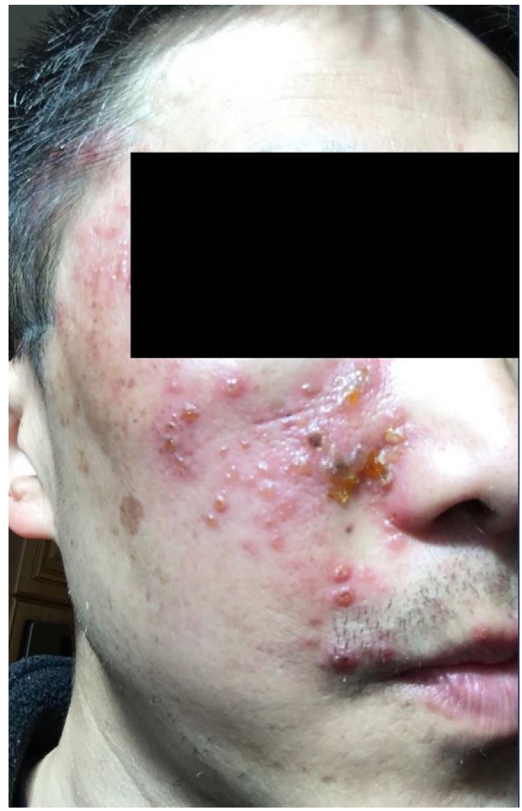

Fig. 6. Herpes zoster involving V2 dermatome.

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in the serum and CSF as well as VZV DNA detected in the CSF and peripheral blood mononuclear cells by PCR.[41] Disseminated VZV is clinically like disseminated HSV and immunocompromised patients are at a significantly higher risk. Dissemination is defined as 20 or more individual vesicles distributed beyond the primary and adjacent dermatomes. Multisystem organ involvement (eg, lung, liver, and CNS) follows cutaneous dissemination in about 10% of high-risk patients.[58] Like primary varicella, the pain and extent of skin involvement in herpes zoster is more severe in the elderly and immunocompromised.

Neurologic Complications of Herpes Zoster

Possible neurologic sequelae of VZV reactivation are protean and include postherpetic neuralgia (PHN), cranial neuropathies, vasculopathy, myelitis, necrotizing retinitis, and zoster sine herpete. These complications can present as transient ischemic attacks, ischemic or hemorrhagic stroke, aneurysm, contralateral hemiparesis, bowel or bladder incontinence, chest pain, and blindness (**Box 1**).

PHN is the most common cause of morbidity in patients older than 60 years. It is defined as pain that persists for months to years after resolution of the herpes zoster cutaneous eruption.[62] There is a disproportionate frequency of PHN in patients older than 60 years (67%) compared to the number of herpes zoster cases (38%) in this age group.[63] The frequency and severity of PHN increases with age. About 20% of people aged 60 to 65 who have had acute herpes zoster developed PHN, compared to over 30% of people aged 80 or older. Cranial neuropathies and vasculopathy-associated neurologic symptoms can occur weeks after acute zoster.[41]

VZV infection of large or small cerebral arteries may cause an occlusive or inflammatory VZV vasculopathy with varied clinical presentations. When affecting the first division of the trigeminal nerve, the patient can experience delayed contralateral hemplegia days to weeks following herpes zoster. There is often no rash at the time of neurologic symptoms (headache, fever, mental status changes, and focal deficits). PCR can detect viral DNA in the CSF and MRI T2-weighted images may reveal focal enhancement at involved sites.[71–73] Viral invasion of vessels can produce cerebral aneurysms, hemorrhage, myelitis, and retinal necrosis. Although uncommon, when CNS sequelae are present, immunocompetent patients tend to develop large-vessel granulomatous arteritis, whereas immunocompromised patients are more apt to develop small-vessel encephalitis.[41]

Box 1
Neurologic complications

CNS Location	Clinical Presentation Including Neurologic Signs and Symptoms
Oculomotor (CNIII) > Trochlear (CNIV) > Abducens (CNVI)	Ophthalmoplegia, optic neuritis, or both[59–61]
Trigeminal (CNV)	Keratitis, vesicles on nasal tip (Hutchinson sign),
Ophthalmic division	blindness
Maxillary and mandibular divisions	Osteonecrosis and spontaneous exfoliation of teeth[64,65]
Facial (CNVII)	Unilateral facial muscle weakness, rash of ipsilateral external ear, anterior two-thirds tongue, or hard palate (Ramsay Hunt syndrome))[41,66]
Cervical spine	Arm weakness >>> diaphragmatic paralysis[67–69]
Lumbosacral spine	Leg weakness >>> bladder, bowel dysfunction[70]

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Herpes Zoster in Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

Herpes Zoster (HZ) is an HIV-associated opportunistic infection. HIV infected populations have a 3-fold to 20-fold higher risk of contracting HZ than HIV-seronegative individuals.[74] The presence of VZV antibodies shows past exposure to chickenpox or vaccination, but in HIV-infected individuals, it is the low CD4 count and lack of antiretroviral therapy (ART) use, not VZV antibody levels, that better predict future shingles outbreaks.[75] Even though the introduction of ART has improved the survival of those living with HIV, the incidence of HZ among HIV cohorts remains higher than that of the general population.[74]

Clinically, patients with HIV may develop zoster in more than 1 dermatome. Cutaneous lesions can be atypical, such as hyperkeratotic, ulcerative with a black eschar, chronic in nature, and lacking a dermatomal distribution.[76,77] Certain severe complications are almost exclusively seen in HIV/AIDS or patients with impaired cell-mediated immunity. Chronic VZV encephalitis can occur months after a herpes zoster outbreak and present subacutely with headache, fever, mental status changes, seizures, and focal neurologic defects, as well as visual field cuts. The underlying pathology is a VZV-induced small-vessel vasculitis and demyelination. MRI is the best modality to investigate this type of acute encephalitis. There are anecdotal reports that high-dose intravenous acyclovir may be of benefit and adjunctive treatment with steroids remains a matter of debate; however, the clinical course is often progressive and results in death. A progressive and potentially fatal myelitis is also a possibility in the immunocompromised subset. Studies have shown a mortality rate between 4% and 25%. Factors associated with poor outcomes include mechanical ventilation and older age.[76,78] Overall, HIV patients with zoster show increased neurologic (eg, aseptic meningitis, radiculitis, and myelitis) and ophthalmologic complications, particularly peripheral outer retinal necrosis.

LABORATORY DIAGNOSIS OF HERPES SIMPLEX VIRUS AND VARICELLA-ZOSTER VIRUS

Several factors contribute to the ability to isolate herpes simplex and herpes zoster. Host factors, as well as selecting the appropriate test and executing the proper collection, transport, and storage of the specimen, are important. Lesions from immunosuppressed patients have a higher virus load than those from immunocompetent patients. Regardless of the host, an early vesicle has the highest viral yield compared with healed crusted lesions. Similarly, it is easier to detect virus in a primary infection compared with a secondary infection (primary infections have higher titers of virus). Each test has its own advantages and disadvantages. Combining 2 or more methods can increase sensitivity of detection.[79]

There are numerous laboratory tests available to identify herpetic infections. They can be categorized into 5 main methods: morphologic, immunologic, serologic, virologic, and molecular.[80,81] Physicians confirm their diagnosis using diverse laboratory techniques such as Tzanck smear, HSV culture, direct immunofluorescence (IF), or PCR. When it comes to diagnosis, molecular biological techniques are preferentially chosen because of their ease of use, reliability, and high sensitivity. Indeed, PCR is positive in 100% of cases when performed on early lesions, and positivity rates remain higher than 80% on later lesions as well (over 30 days).[82]

Viral culture is considered the gold standard diagnostic modality. Other diagnostic tests are often compared with viral culture when evaluating sensitivity and specificity. Rapid viral culture is available for HSV and VZV, which shortened the time for isolation

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to 4 days.[82] With newer PCR protocols (eg, real-time, nested) that take approximately 1 day to process, it has been proposed that PCR replace viral culture as the gold standard diagnostic test.[83]

Morphologic: Tzanck Smear and Tissue Biopsy

Tzanck smear is a common in-office procedure that is rapid and inexpensive but performer dependent. A fresh vesicle is more likely to result in a positive Tzanck smear than a pustule or crusted ulcer.[84–86] The base of a vesicle is scraped and then the cellular contents are mounted on a slide and stained with Giemsa, Wright, or Papanico laou. A positive smear demonstrates multinucleated giant cell formation, margination of nuclear chromatin, and molding of the nuclei by light microscopy. Tzanck smear cannot differentiate between HSV and VZV, and it requires an experienced interpreter.

A punch or shave skin biopsy from the edge of a lesion is positive if it displays characteristic viral cytopathic effect, such as ballooned or multinucleated keratinocytes with nuclear molding and margination of chromatin. Necrotic hair follicles can be a clue to adjacent herpetic infection as well. The sensitivity and specificity of a lesional skin biopsy are similar to a lesional Tzanck smear.[87] Like a Tzanck smear, a skin biopsy with routine staining cannot delineate HSV-1 from HSV-2 or VZV without immunohistochemical staining. Histologic examination is a reasonable choice to confirm HSV in an old, atypical lesion and to exclude other disease processes with similar clinical features.[81]

Immunomorphologic: Immunofluorescence and Immunoperoxidase Staining

Immunomorphologic techniques are used to identify viral antigens. Direct immunofluorescence uses direct application of viral antigen-specific fluorescein-tagged antibodies to a specimen. This method is rapid, sensitive, and specific and can be done on frozen or formalin-fixed paraffin-embedded sections. It can distinguish between HSV-1, HSV-2, and VZV. Immunoperoxidase technique is not as sensitive but is more specific. It can be performed on fixed or fresh tissue.[88] For VZV, immunofluorescence is more sensitive than viral culture or Tzanck smear. Combining viral antigen methods with viral culture can more rapidly detect HSV or VZV than biopsy, as it may take time for cytopathic effect to evolve.

Serologic Tests

Serologic tests are used to detect previous infection with HSV-1 or HSV-2 when a viral culture is not feasible, or the clinical presentation is unclear. Serologic tests use specific viral proteins, purified or recombinant.[89] These tests use serum to detect the presence of antibodies against HSV 1 and HSV-2. Due to the limited timeframe for the treatment of HSV, these tests must be obtained within the period of acute illness and 3 to 4 weeks later.

By the time a primary infection is established using this method, it is not clinically helpful, as the patient is outside the effective treatment window but provides information to guide future treatment. Fewer than 5% of patients with recurrent HSV infection will have a significant rise in antibody level.[90] Although antibody titers can fluctuate, these fluctuations do not reliably predict recurrent episodes or asymptomatic viral shedding.[91,92] There are certain circumstances in which serologic testing makes sense. The presence of old lesions and inadequate transport of specimens (and therefore compromised quality of specimen) are instances in which a serologic test may help. Serology is also valuable in screening pregnant women who may require acyclovir prophylaxis for HSV-2.

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The diagnosis of genital herpes causes significant psychological distress. Despite a characteristic clinical history (eg, prodromal symptoms, recurrent crusted papules), a negative culture or indeterminate examination is a source of frustration for a patient. In this instance, establishing seropositivity to HSV-2 by serology can provide the patient with objective confirmation of genital herpes. Conversely, the absence of seropositivity can exclude the diagnosis of genital herpes.[93] Serologic diagnosis of HSV-2 should ideally be performed only if patients and providers are aware of the test's high sensitivity but low specificity.[94] In a study by Munday and colleagues, serologic testing contributed to diagnosis in 79% of cases of recurrent genital ulcerations.[95] Seropositivity of HSV-1 is more difficult to interpret. Historically, HSV-1 was considered restricted to orolabial infections; however, there is an increased prevalence of HSV-1 genital infection. A seropositive HSV-1 result cannot delineate an orolabial from a genital infection with certainty.[93]

Serologic tests are either type specific (differentiates HSV-1 from HSV-2) or non–type specific. Non–type-specific serologic modalities include complement fixation tests, direct hemagglutination, fluorescent antibody to membrane antigen, and enzyme-linked immunosorbent assay (ELISA). Complement fixation test has been the most used and is considered the standard serologic test for HSV identification but is less sensitive than other serologic tests. Western blot is considered the epidemiologic gold standard, but it is expensive, labor intensive, and performed at research centers only. Although historically ELISA tests were not the most reliable, newer assays in the past 10 years have improved significantly. Recombinant ELISA assays have excellent sensitivity and specificity. The sensitivity and specificity of the recombinant assay for HSV-1 immunoglobulin G (IgG) were 93.1% to 98.0% and 99.3% to 100.0%, respectively, whereas the sensitivity and specificity of the novel assays for HSV-2 IgG are 100.0% and 94.6% to 97.6%. respectively.[96]

Type-specific tests are neutralization tests, protein-specific assays, and Western blot (immunoblot) analysis. Type-specific tests are more challenging, as both HSV-1 and HSV-2 share many immunogenic antigens. Preexisting HSV-1 seropositivity impairs the sensitivity of HSV-2 serologic response. Seropositivity to HSV-2 can be blunted by the presence of type-common antigens recognized in earlier HSV-1 infections.[93] Western blot is best used for this clinical scenario. Identification of the type of HSV provides clinically helpful prognostic information to the patient, as type 1 versus type 2 exhibits different rates of shedding, recurrence, and transmission. Newer techniques such as the testing of dried blood samples (DBS) allow for a noninvasive sample collection and longer shelf life.[89] Currently, standardized testing protocols for DBS are being developed for review and approval by regulatory agencies.[97]

Virologic & Molecular

While viral cultures are considered to be the gold standard for diagnosing HSV and VZV, viral PCR tests allow for a more sensitive and rapid diagnosis.[98,99] By day 4 of a recurrent lesion outbreak, it is unlikely to obtain positive cultures from an ulcer or crusted lesion and the sensitivity of a positive viral culture is about 50% for genital ulcers.[21] HSV grows faster than VZV and therefore more than 50% of inoculations are positive within 24 to 48 hours and more than 90% are positive within 3 to 4 days. However, VZV takes 7 days to 2 weeks to process by traditional viral culture. New culture techniques (shell vial technique and blind passage) provide a rapid and more sensitive method, which takes only 4 days and increases the rate of VZV isolation from tissue.[100]

Tips for obtaining viral culture and viral PCR.

- Identify a new vesicle if possible.

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- Unroof intact vesicle with a sharp (eg, 11 blade or 25-gauge) needle and be aware that vesicle fluid may splash. Vigorously scrape base of ulcer, as this increases likelihood of obtaining specimens with live virus.[80]
- If lesions are crusted, remove necrotic debris with sterile saline before scraping base for culture.[80,101]
- Use viral culture medium (should be refrigerated until use) and a plastic applicator with a Dacron (or rayon) tip. If viral media is not available, the culture swab should be kept moist with non-bacteriostatic sterile saline.
- If transport time is longer than 8 hours, the swabs should be removed after swirling in the medium.
- A wood applicator with cotton tip should never be used, as they may harbor substances that kill the virus.
- Specimen should be refrigerated at 4°C until inoculation.

PCR is a very sensitive molecular technique to isolate viral DNA. It can distinguish HSV-1 from HSV-2 and VZV. It can detect occult HSV, atypical presentations of HSV, and zoster sine herpete. PCR is the test of choice for VZV, as it is more rapid, highly sensitive, and specific (compared to culture).[81] A classic clinical presentation of herpes zoster may not necessitate laboratory testing; however, if the eruption is more than 3 day old or atypical, it may be prudent to proceed with PCR testing.

DIAGNOSIS OF NEUROLOGIC MANIFESTATIONS

Herpes Simplex Encephalopathy

The sensitivity and specificity for CSF PCR HSV-1 DNA are 98% and 94%, respectively, compared with histology on brain biopsy.[80] The most fruitful window to obtain a positive CSF PCR in HSE is between 2 and 10 days after the onset of illness.[102] CT scanning can be normal in the first 4 to 6 days of illness. MRI is more sensitive than CT, demonstrating high-signal-intensity lesions on T2-weighted, diffusion-weighted, and fluid-attenuated inversion recovery images earlier in the course.[103,104]

Zoster Encephalopathy

Detecting VZV DNA by PCR and VZV IgM and IgG antibodies to VZV in the CSF are confirmatory. Antibodies in the CSF alone without amplification of VZV DNA are supportive in the appropriate clinical setting. Serum antibodies are not relevant because most adults have persistent antibodies to VZV in their serum.[105]

WOLF POSTHERPETIC ISOTOPIC RESPONSE

Immunity-dependent disorders can occur in a zoster-affected dermatome, or after an HSV or varicella infection (**Box 2**). This phenomenon is called Wolf's postherpetic isotopic response (PHIR). An altered secretary immunopeptide milieu is hypothesized to be the cause of PHIR. Zoster-affected sensory neurons may display dysfunctional neuropeptide release, affecting local immune responses.[107]

MANAGEMENT OF HERPES SIMPLEX VIRUS AND VARICELLA-ZOSTER VIRUS

The immune status of the patient, comorbidities, the type of infection (primary vs recurrent), and the extent of the infection (dermatomal vs disseminated) all influence the management of herpes viral infection (**Tables 4** and **5**). Nucleoside analogs that inhibit viral DNA synthesis are the main-stay of herpes viral infections. Acyclovir, valacyclovir, and famciclovir are all in this class of medication, but vary based on dosing schedule and bioavailability. Acyclovir has poor bioavailability (10% to 20% compared

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Box 2
Skin diseases with predilection for previously VZV-infected dermatomes

Granulomatous reactions
- Granuloma annulare
- Sarcoidosis

Malignant tumors
- Breast cancer
- Basal cell carcinoma
- Squamous cell carcinoma
- Angiosarcoma
- Kaposi sarcoma
- Metastases from cutaneous or visceral malignancies

Inflammatory reactions
- Lichen planus
- Lichen sclerosus et atrophicus
- Graft-versus-host disease
- Drug rash
- IgA linear dermatosis
- Psoriasis

Infections (bacterial, fungal, viral)

Acneiform lesions

Rosacea

Pseudolymphoma

Mucinosis

Data from Wolf R, Brenner S, Ruocco V, et al. Isotopic Response. Int J Dermatol 1995;34(5):341-8.[106]

to its prodrug, valacyclovir).[115] Oral valacyclovir can achieve a similar plasma level as intravenous (IV) acyclovir. IV acyclovir is contraindicated in renal disease given its association with crystalline nephropathy.[116] Famciclovir has been shown to be superior to valacyclovir in reducing herpes zoster pain.[117] The benefit of antiviral therapy is most effective when initiated within the first 72 hours of disease onset. The number of recurrences of HSV each year helps guide the decision to initiate suppressive therapy. Chronic suppressive treatment may be indicated in patients who experience 6 or

Table 4
Adverse effects of antiviral therapies

Medication	Side Effects
Acyclovir	Nausea, vomiting, rarely headaches and diarrhea in long-term use—PO Phlebitis, reversible crystalline nephropathy—IV
Valacyclovir	Headache—PO Thrombotic microangiopathy in patients with long-term HIV
Famciclovir	Headache, nausea, vomiting
Foscarnet	Renal toxicity, electrolyte imbalances (hypocalcemia), nausea, vomting, anemia, penile ulcers
Cidofovir	Highly nephrotoxic - IV

Abbreviations: IV, intravenous; PO, oral.
Data from Refs.[5,108,109]

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Table 5
Treatment schedules

	Acyclovir	Valacyclovir	Famciclovir
Herpes labialis			
Recurrent	400 mg 5 times/d for 5 d	2 g q 12 h for 1 d PO	1500 mg × 1 dose
Chronic suppression	400 mg BID-TID	500 mg daily PO or 1 g daily PO	500 mg BID PO
Immunosuppressed	400 mg TID 5–10 d	1 g BID for 5–10 d PO	
Genital HSV			
Primary	200 mg 5 times/d or 400 mg TID for 7–10 d PO	1 g BID for 7–10 d PO	250 mg TID for 5–10 d PO
Recurrent	200 mg 5 times/d for 5–10 d or 400 mg TID for 5 d or 800 mg TID for 2 d PO or 800 mg TID for 5 d PO	0.5 g BID for 3 d or 1 g qd for 5 d PO	1 g BID for 1 d or 500 mg for 1 d then 250 mg BID for 2 d then 125 mg BID for 5 d PO
Immunosuppressed	400 mg TID for 5–10 d	1 g BID for 5–10 d	500 mg BID for 5–10 d
Chronic suppression	400 mg BID PO	1 g daily or 500 mg daily	250 mg BID
Immunosuppressed	400–800 mg BID or TID PO	500 mg BID PO	500 mg BID
Cutaneous HSV			
Primary			
Recurrent in HIV	400 mg TID for 5–10 d PO	1 g BID for 5–10 d	500 mg BID
Chronic suppression in HIV	400–800 mg BID or TID PO	500 mg BID PO	500 mg BID
Varicella			
Primary	10 mg/kg IV q8 h or 20 mg/kg (1 g max) TID × 5 d PO		
Immunosuppressed	VZIG within 72 h[a]		
Herpes zoster			
Primary	5–10 mg/kg body weight TID for 7 d IV or 800 mg 5 times/d for 7 d PO	100 mg TID for 7 d PO	500 mg TID for 7 d PO
Disseminated	10–15 mg/kg IV q 8 h × 7 d or 500 mg/m^2 IV q 8 h × 7 d		

(*continued on next page*)

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Table 5
(continued)

	Acyclovir	Valacyclovir	Famciclovir
Eczema herpeticum			
Mild[29,109,110]	Children: 3–60 mg/kg TID Adults: 400 mg TID	Children: 20 mg/kg/day Adults: 500 mg TID	
Severe[111]	Acyclovir IV 5–10 mg/kg q 8 h		

Abbreviations: bid, twice a day; HSV, herpes simplex virus; IV, intravenous; PO, oral; q, every; tid, 3 times a day; VZIG, varicella zoster immunoglobulin.

[a] In immunocompromised seronegative patients, VZIG if administered within the first 72 h can prevent dissemination.

Data from Refs.[29,108–114]

more recurrences of HSV a year, have severe pain or disfigurement, difficulty swallowing, or a protracted disease course.[108]

Topical antivirals are an additional treatment modality (**Table 6**). Randomized placebo-controlled clinical studies assessing acyclovir topical treatments (creams vs ointments, 5% vs 10%) show mixed outcomes. Most evidence shows topical acyclovir ointment is not effective in treating recurrent herpes labialis because of poor penetration. Five percent acyclovir cream can reduce the duration of lesions if applied during the prodromal stage, but does not reduce pain.[112] 1% penciclovir cream can decrease duration of the lesions and pain if applied every 2 hours after the onset of prodromal symptom.[118] Topical docosanol (10%) can reduce healing time of recurrent herpes labialis when applied 5 times a day for 10 days.[119,120] Foscarnet cream (3%), when used on pre-vesicular lesions, reduces HSV shedding, lesion size, and duration, as well as prevents the development of vesicles. However, it requires compounding and is expensive and should be reserved for acyclovir-resistant HSV infections.[121] Topical therapies may be an option for patients with renal insufficiency.

ACYCLOVIR RESISTANCE

Acyclovir resistance occurs in the immunocompromised population, whereas it is quite rare in immunocompetent patients. Bone marrow transplant recipients have a higher incidence than patients with HIV. Its prevalence is 4.1% to 7.1% in immunocompromised patients.[122] Docosanol cream and topical foscarnet do not exert antiviral effects by way of thymidine kinase and therefore are still viable options in

Table 6
Topical treatments for recurrent herpes labialis

Recurrent herpes labialis	Acyclovir Ointment[a] Every 3 h for 7 d 0.5-in. ribbon/4 in.[2] Acyclovir/hydrocortisone 5%/1% cream 5 times/d for 5 d	Penciclovir[a] Every 2 h for 4 d	Docosanol 5 times/d until healed	Foscarnet Every 2 h for 5 d

[a] In adults older than 18 y.

Data from Brady RC, Bernstein DI. Treatment of herpes simplex virus infections. Antiviral Res 2004;61:73–81.[112,113]

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acyclovir- resistant infections. Cidofovir, although currently approved by the Food and Drug Administration (FDA) only for CMV retinitis in patients with AIDS, is used in acyclovir-resistant cases of herpes simplex infections. It must be administered intravenously with probenecid and aggressive hydration, as it is nephrotoxic. Cidofovir gel (1.0%) once daily for 5 days has been a useful therapy for acyclovir-resistant genital and perianal HSV in patients with AIDS; it produces statistically significant reduction in viral shedding, lesion size, and pain.[123] Foscarnet has also been used at 40 mg/kg IV every 8 to 12 hours for 2 to 3 weeks until all lesions are healed.

A new class of antiherpetic drugs which includes amenamevir and pritelivir are non-nucleoside, antiviral drug called "helicase-primase inhibitors" that block an essential enzyme complex for replication of viral genomic DNA.[124] Amenamevir has also demonstrated efficacy against acyclovir-resistant HSV isolates. Amenamevir was approved in Japan as once-daily treatment for 7 days for herpes zoster in July 2017.[125] Other novel agents such as the polyphenol mangiferin has recently been investigated in Brazil as an alternative treatment for acyclovir-resistant HSV strains.[126]

POSTHERPETIC NEURALGIA

Is it Preventable?

Prevention of PHN with oral antiviral drugs has not been shown to be effective after 6 months of treatment; nor has been the use of systemic steroids. Systemic steroids do not decrease the incidence of PHN; however, in conjunction with antivirals, it can reduce the acute pain of herpes zoster.[127–130] Acyclovir and valacyclovir have shown similar reductions in time to skin healing in herpes zoster, but valacyclovir has shown a 34% faster resolution of zoster-associated pain compared with acyclovir.[131] The addition of gabapentin to valacyclovir within 72 h of rash onset does not provide significant additional relief from acute herpetic pain nor prevention of PHN. In fact, a 2019 randomized controlled trial found that patients taking gabapentin reported worse health-related quality of life and poorer sleep quality.[132] Prior Zoster vaccine live ZVL is 65% effective in preventing PHN in all age groups. No difference has been shown between immunosuppressed and immunocompetent groups.[133]

Topical Agents:

- Lidocaine: Use 5% patches, up to 3 patches simultaneously for a maximum of 12 hours within a 24-h period.
- Trolamine salicylate and *Aloe vera*: Apply directly to the painful area.
- Capsaicin: Apply a single 8% capsaicin patch over the non-crusted, uninjured area. Leave in place for 60 minutes.

Oral Medications:

- Gabapentin:
  - Start with 300 mg orally.
  - Can be increased up to a maximum of 3600 mg per day (divided into 3 doses).
  - Note: Gabapentin combined with morphine provides better pain relief than gabapentin alone.
- Pregabalin:
  - Initial dosage: 150 mg/day in divided doses.
  - Can be increased to a maximum of 300 mg/day within a week.
  - Dosage range: 150 to 300 mg daily (either 75-mg to 150-mg doses twice a day or 50-mg to 100-mg doses 3 times a day).
- Tricyclic Antidepressants:
  - Amitriptyline (Elavil): Start with 10 to 25 mg orally at bedtime. Can be increased to a maximum dosage of 150 to 200 mg/day.

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- Other options: nortriptyline, maprotiline, desipramine.
- Carbamazepine: 600 to 1200 mg daily.
- Controlled-release oxycodone: 10 to 40 mg orally every 12 hours.
- Controlled-release morphine sulfate: Can be combined with tricyclic antidepressants.
- Levetiracetam: Start with 500 mg orally daily. Dose can be titrated up by 500 mg weekly until a maximum dosage of 1500 mg twice daily is reached.
- Diazepam: 2 mg taken 3 times a day. This can supplement any of the aforementionede therapies.

Treatment with analgesics, antivirals, and a 3-day to 5-day course of prednisone 60 mg daily is recommended in immunocompetent patients 50 years or older and is essential when treating ophthalmic-distribution zoster

VACCINATION

In 1995, a live-attenuated vaccine for varicella became available for children. The introduction of a universal vaccination in the United States has led to a dramatic reduction in the varicella incidence, its associated complications, hospitalizations, and fatality rate.[134] A combination measles, mumps, rubella, and varicella vaccine (MMRV) was licensed in the United States in 2005 for healthy children aged 12 months to 12 years.[135] In mega-analysis studies, the MMRV vaccine demonstrated well-tolerated safety profiles. However, it is worth noting that some children who received the MMRV vaccine may have an increased risk of fever and febrile seizure 6 to 12 days after the first vaccine dose when the peak in replication of the live-attenuated measles virus occurs.[136,137]

In 2021, the Advisory Committee on Immunization Practices recommended the recombinant zoster vaccine (RZV), 2-dose, subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$), in adults aged $\geq$18 years who are or will be at increased risk for herpes zoster because of immunodeficiency or immunosuppression caused by known disease or therapy.[138] The Shingrix (recombinant zoster vaccine), FDA approved in 2017, is now the preferred vaccine, over Zostavax (zoster vaccine live), a shingles vaccine in use since 2006. The vaccine consists of 2 doses (0.5 mL each), administered intramuscularly, 2 to 6 months apart.[139] The protective efficacy of the vaccine lasts for at least 4 years and is well preserved in adults aged $\geq$ 70 year.[138,140,141] It is recommended to delay vaccination until after pregnancy. Vaccine may be given regardless of breastfeeding status.[142] In a 2016 randomized, placebo-controlled phase trial, RZV showed a good safety profile. Overall incidences of potential immune-mediated diseases, serious adverse events, and deaths were similar in the vaccine and placebo groups.[143]

Prophylactic genital herpes vaccine has been showing promising results in the prevention of HSV-2 in guinea pig models. More studies are underway to assess its safety and efficacy for prevention of HSV-2.[144]

SUMMARY

Herpes simplex and herpes zoster infections are incredibly common. Because of the neurotropic nature of these viruses, infection is lifelong. Recognition of early signs of infection is necessary to implement effective treatment and prevent complications. Various laboratory tests exist to confirm infection; however, outcomes depend on the stage of the lesion and proper collection technique. Immunosuppressed populations require special attention, as herpes infections may appear atypical and severe.

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This group is at higher risk for disseminated disease. Immunocompetent adults older than 60 should get vaccinated for VZV, as neurologic sequelae can be serious.

CLINICS CARE POINTS

- **Orofacial herpes:** While most initial orolabial herpes infections are subclinical and often unrecognized, recurrent herpes labialis can be preceded by a prodrome of tingling, itching, and burning, with common triggers including illness, sun exposure, and emotional stress.
- **Post herpetic neuralgia:** While systemic steroids don't reduce the incidence of postherpetic neuralgia (PHN), they can lessen the acute pain of herpes zoster when used alongside antivirals.
- **Vaccination:** Be aware of the potential for an increased risk of fever and febrile seizure in some children 6 to 12 days after the first dose of the MMRV vaccine.
- **Herpes simplex encephalitis:** When evaluating patients with fever, headache, behavioral changes, seizures, or focal neurologic symptoms, especially with neuroimaging alterations in the medial temporal lobes, consider cerebrospinal fluid examination for HSV as herpes simplex encephalitis may be present, even if initial tests like PCR are negative.
- **Primary Varicella:** Adults and immunocompromised individuals contracting primary varicella are at a higher risk for severe manifestations and complications, including pneumonia and neurologic sequelae.
- **Herpes Zoster (Shingles):** Due to its prodromal pain, herpes zoster can be misdiagnosed as other conditions such as myocardial infarction or pleurisy; clinicians should be alert to differentiate based on symptomatology and the possibility of subsequent rash appearance.
- **Neurologic complications of herpes zoster:** Neurologic complications of herpes zoster can range from postherpetic neuralgia, which is more prevalent in older patients, to cranial neuropathies and vasculopathy, and may manifest even weeks after the acute zoster outbreak without any visible rash.
- **Herpes Zoster in Human Immunodeficiency Virus:** HIV-infected individuals with a low CD4 count and no antiretroviral therapy are at a heightened risk for future herpes zoster outbreaks, irrespective of their VZV antibody levels.
- **Laboratory diagnosis of HSC and VSV virus:** For optimal viral yield in diagnosis, target early vesicles over healed crusted lesions. Proper specimen collection, transport, and storage are crucial. Newer vesicles in immunosuppressed patients tend to have a higher viral load. While viral culture has been the gold standard for diagnosis, PCR offers higher sensitivity, especially for atypical presentations or older lesions. PCR can accurately differentiate between HSV-1, HSV-2, and VZV, and remains highly sensitive even on lesions over 30 days old.
- **Management of Herpes Simplex Virus and Varicella-Zoster Virus:** The efficacy of antiviral therapy is maximized when initiated within the first 72 hours of disease onset. While topical acyclovir ointment has limited effectiveness for recurrent herpes labialis due to poor penetration, 1% penciclovir cream can decrease the duration of lesions and associated pain when applied frequently after the onset of prodromal symptoms.
- **Acyclovir Resistance:** Acyclovir resistance is more common in the immunocompromised population, with bone marrow transplant recipients having a higher incidence than patients with HIV. Docosanol cream and topical foscarnet remain effective treatments for acyclovir-resistant infections as they don't act via thymidine kinase. Novel antiviral agents, like amenamevir and pritelivir, from the "helicase-primase inhibitors" class, offer potential treatments for acyclovir-resistant HSV, with amenamevir already demonstrating efficacy against resistant strains.
- **Genital Herpes Simplex Virus Infection:** Not all patients with initial genital herpes present with overt lesions; consider atypical presentations such as edema, fissures, or back pain without genital manifestations. Differential diagnosis for genital ulcers extends beyond HSV and should encompass other infectious and inflammatory causes.

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- **Transmission of orofacial herpes and genital herpes:** Daily antiviral suppressive therapy can decrease HSV recrudescence, viral shedding, and transmission to serodiscordant partners. Routine serologic screening for genital HSV in asymptomatic individuals is not recommended due to potential psychosocial consequences, healthcare burdens, and high rates of false-positive results.
- **HSV infection in Immunocompromised patients:** Immunocompromise d patients such as those with HIV or post-transplant, may exhibit atypical and more severe manifestations of HSV infections, requiring vigilant monitoring and prompt therapeutic intervention.
- **Eczema herpeticum:** Clinicians must maintain a high index of suspicion eczema herpeticum in patients with chronic dermatosis, especially when presenting with flared conditions or widespread monomorphic vesicles and initiate antiviral therapy promptly due to its potentially fatal nature.

DISCLOSURE

The authors have no relevant disclosures.

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