Drugs 2002; 62 (3): 479-490
0012-6667/02/0003-0479/$30.00/0

Viral Skin Infections

Diagnosis and Treatment Considerations

Kyoung C. Park and *Won S. Han*

Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea

Contents

Abstract

Skin lesions are prominent features of many viral diseases. In some instances, characteristic skin lesions suggest a specific viral illness, the diagnosis of which can be quickly established by appropriate procedures. In addition to clinical manifestations, laboratory methods including virus isolation are used to diagnose viral infections. In viral diseases, prophylaxis has proved more successful than the specific treatment of established infection. However, recent progress in molecular biology has facilitated the development of new vaccines and new drugs to treat viral infections.

In this paper we focus on the diagnosis and current options available in the treatment of various viral dermatoses for general clinicians. In viral infections limited to the skin and mucous membranes, diagnosis can be quickly established by careful history taking and physical examination, and can be confirmed by appropriate procedures; however, there is difficulty in differential diagnosis with some viral infections. We present a brief summary of the important clinical features of common viral skin infections. Vaccines have been extremely useful in the prevention of a variety of viral illnesses. Currently, there are 20 approved specific antiviral drugs available for the treatment of viral diseases and here we review those commonly used for the treatment of viral skin infections.

1. General Considerations

Many viral infections have cutaneous manifestations. The following is a list of the numerous groups of viruses that can affect the skin or mucous surfaces, and the diseases:[1]

- Herpesvirus group: herpes labialis, herpes genitalis, varicella, herpes zoster, cytomegalovirus (CMV) infection, infectious mononucleosis, exanthem subitum
- Poxvirus group: molluscum contagiosum, small pox, milkers' nodules
- Papovavirus (papillomavirus) group: verruca
- Paramyxovirus group: measles
- Togavirus group: rubella
- Parvovirus group: erythema infectiosum
- Coxsackievirus group: hand-foot-and-mouth disease, herpangina
- Retrovirus group: human immunodeficiency virus (HIV) infection.

Some viral skin infections are self-limited and resolve spontaneously, but the others may cause severe morbidity and even mortality.

2. Viral Replication and Host Response

Viruses are composed of a central core of nucleoprotein called the nucleoid, which is surrounded by a protective protein coat called the capsid.[2] Viruses are obligatory intracellular parasites that must use the organelles, the energy, and many of the enzymes of the host cell to replicate. In doing so, viruses may act as pathogens. The viral replication cycle is composed of attachment, penetration, uncoating, biosynthesis, virion assembly and release.[3] Viruses replicate by synthesising their various structural components separately and then assembling them into multiple virion. There are several general patterns of viral infection.[4] The most typical is acute infection followed by viral clearance, usually via immune mechanisms. This pattern occurs frequently with exanthems, such as measles. Another pattern is acute infection followed by latent infection, which may then be followed by viral reactivation, such as with herpes zoster. A third pattern is that of chronic infection.

The severity of illness induced by a particular virus varies considerably from person to person and host factors usually account for most of this variation. Antibody response to viral infection represents the major host defence against reinfection by the same virus.[5] Humoral immunity is not thought to contribute to the recovery from most primary viral infections. Specific cell-mediated immunity is also elicited during viral infections and influences the course of many viral infections. Patients with impaired cell-mediated immunity are at risk of developing severe primary viral infection. Inflammatory cells may produce and secrete interferon into the extracellular fluid.[6] Interferons are cytokines that have broad antiviral, immunomodulating and antiproliferative effects.[7] Synthetic preparations [interferon (IFN)-α2a, IFNα2b, and leucocyte-derived IFNαn3] are currently approved for the treatment of viral infections.

3. Clinical Manifestations

3.1 Herpes Labialis and Herpes Genitalis

Recurrent herpes labialis, known commonly as cold sores, is the most common manifestation of herpes simplex virus (HSV) infection. Itching and burning at the vermilion border of the lip heralds the onset of a cold sore. The most common triggering events are sun exposure, trauma to the lip, emo-

tional stress, and fatigue.[8] In the case of ulcers inside the mouth, differentiation from aphthous ulcer is necessary. Herpes begins as clustered lesions, whereas aphthous ulcers begin as widely separated lesions.[9]

Herpes genitalis is the most common cause of genital ulcerations in industrialised countries. The usual time for an outbreak of genital herpes is between 3 and 14 days after sexual relations with a person who has active genital lesions. Lesions in primary infections are usually multiple and bilateral and last 2 to 3 weeks, but recurrent herpes genitalis frequently presents as a single ulcer and lasts only 1 week. Exposure to herpes simplex in a mother's vaginal secretions during delivery can result in a primary herpes simplex infection in the neonate, which is a devastating life-threatening infection that must be diagnosed and treated promptly with antiviral drugs.

3.2 Varicella and Herpes Zoster

Varicella is the primary infection of varicella-zoster virus (VZV) and is highly contagious. It is characterised by generalised pruritic rash that progresses rapidly from macules and papules to vesicles, pustules and crusts. The early vesicle is surrounded by irregular area of erythema, called 'dewdrop on a rose petal'. The rash begins on the face and spreads rapidly to the trunk. A distinctive feature of varicella is the simultaneous presence of lesions in all stages of development. Varicella during pregnancy is a threat to both mother and fetus.[10] Clinical manifestations are more severe in pregnant women and the fetus may die as a consequence of premature labour.

Herpes zoster is the result of reactivation of endogenous VZV that has persisted in latent form within sensory ganglia following an earlier attack of varicella. It is characterised by unilateral localised vesicular eruption and radicular pain that is generally limited to the dermatome innervated by a single sensory ganglion. The rash does not cross the midline. Pain frequently persists for more than 30 days from onset of the rash, called postherpetic neuralgia (PHN). The overall incidence of PNH is 8 to 15%, but it is more than 50% in patients aged ≥60 years.[11,12] Facial palsy frequently complicates cephalic herpes zoster (Ramsay-Hunt syndrome) and bladder dysfunction may follow the sacral herpes zoster. Careful eye examinations are recommended in patients with herpes zoster which involve the ophthalmic division of the trigeminal nerve.

3.3 Cytomegalovirus Infection

Cutaneous lesions associated with CMV are rare and nonspecific in healthy individuals. Underlying disorders associated with CMV cutaneous involvement include HIV infection, malignant neoplasm, burns and iatrogenic immunosuppression. The most specific cutaneous manifestation of CMV is ulceration, especially in the perianal area.[13] Primary maternal CMV infection during the first 24 weeks of gestation carries the highest risk of permanent sequelae for the fetus.

3.4 Infectious Mononucleosis

Infectious mononucleosis is caused by Epstein-Barr virus (EBV) and is associated with the triad of fever, sore throat and lymphadenopathy. Patients treated with ampicillin develop a generalised macular and papular eruption.[14]

3.5 Exanthem Subitum (Sixth Disease)

Human herpesvirus 6 (HHV-6) and 7 (HHV-7) are believed to cause exanthem subitum. The onset of the disease is abrupt and is characterised by a high fever. The fever drops abruptly on the fourth day, coinciding with the rapid onset of a rash. The rash characteristically first appears on the trunk and lasts 1 to 2 days. This disease is commonly mistaken for other causes of fever and rash in children.

3.6 Molluscum Contagiosum

Molluscum contagiosum virus is a poxvirus and a large (200 to 300nm) DNA virus. It generally affects children and individual lesions are discrete, smooth, flesh coloured, dome-shaped papules with

central umbilication. Patients with atopic dermatitis or other conditions with impaired immune function may develop widespread lesions.

3.7 Warts

Warts are very common and result from infection with human papillomavirus (HPV). Their clinical location or morphology usually classifies them. *Verruca vulgaris* are scaly, rough, spiny papules or nodules. Plantar warts may be painful with pressure and must be differentiated from corns and calluses. In warts, punctuate black dots are observed after shaving away the outer keratinous surface.[15] *Verruca plana* are 2 to 4mm, slightly elevated flat topped papules, most frequently seen on the face. *Condyloma acuminata* are epidermal and dermal papules or nodules on the perineum, usually transmitted sexually. Some less-common types of warts are associated with malignancy. *Bowenoid papulosis* are 2 to 3mm multiple papules of the external male and female genitalia, and histopathologically resemble Bowen's disease. *Epidermodysplasia verruciformis* manifest in childhood and may resemble lesions of widespread tinea versicolor. There is a high risk of developing cutaneous squamous cell carcinoma on sun-exposed areas, especially if infected by HPV type 5 and 8.[16]

3.8 Measles

Measles virus is classified as a paramyxovirus. Measles is characterised by high fever, cough, coryza, conjunctivitis, Koplik's spots, and generalised macular and papular rash. Rash is erythematous, discrete, macular and papular, and begins behind the ears and over the forehead and then spreads down over the neck and trunk. The body temperature frequently reaches 40 to 40.5°C (104° to 104.9°F) at the peak. The pathognomonic lesions of Koplik's spots are small, irregular, bright-red spots with central bluish-white specks, usually on the buccal mucosa opposite the second molars, and appear 24 to 48 hours before onset of the rash and may remain discrete for 2 or 3 days.[17]

3.9 Rubella (German Measles)

Rubella results from infection with the Togavirus group, and is characterised by a rash of 2 to 3 days' duration and the enlargement of cervical, suboccipital and postauricular lymph nodes. The rash is first noted on the face, then spreads to the neck and trunk, and consists of pink-red coalescing macules and papules. Approximately 50% of infants who acquire rubella during the first trimester of intrauterine life will show clinical signs of fetal damage. The earlier the infection, the more severe the fetal damage.[18]

3.10 Erythema infectiosum (Fifth Disease)

Erythema infectiosum is characterised by a slapped cheek appearance of the face and an erythematous, lacy eruption on the trunk and extremities. The parvovirus B19 infection may cause a transient aplastic crisis in patients with chronic haemolytic anaemias and cause nonimmune fetal hydrops in pregnancy.[19,20]

3.11 Hand-Foot-And-Mouth Disease

Hand-foot-and-mouth disease is associated with coxsackievirus A16 and is clinically manifested by characteristic vesicular lesions in the mouth and on the extremities. In general, dorsal surfaces and sides of the fingers, hands, toes and feet are more often involved than the palms and soles.[21] In temperate climates, the disease is seasonal and it is more common during warmer months.

3.12 Herpangina

The aetiological agent is usually group A coxsackievirus. The feature of the disease is the presence of gray-white, 1 to 2mm papulovesicular lesions with surrounding erythema in the oropharynx. As multiple viral strains cause herpangina, the clinical syndrome can recur in the same patient in successive years, although permanent immunity occurs to the type-specific agents.

3.13 HIV infection

Two types of HIV have been identified. HIV-1 is the cause of nearly all HIV infection in North America and Europe, and HIV-2 is detected mainly in West Africa. HIV-2 is known to be much less virulent than HIV-1.[22] In HIV infection, a variety of opportunistic viral infections occurs, (e.g. herpes simplex, herpes zoster, warts, molluscum contagiosum, CMV infections, etc). Clinical manifestations are more severe and wide spread than in healthy individuals. Readers are referred to reviews for more information. [22]

4. Diagnosis

In most viral infections limited to skin and mucosal surfaces, a specific diagnosis can be made easily on the basis of clinical manifestations only. But in systemic viral infections with cutaneous manifestations, specific diagnosis is sometimes confusing even for an experienced dermatologist, and clinicians must exclude several nonviral conditions (e.g. drug eruptions and rickettsial diseases). A simple schematic diagnostic procedure is presented in figure 1. Four major approaches are used in the laboratory to diagnose viral infection: virus isolation, microscopy, serology, and detection of viral nucleic acids or viral antigens.[23]

4.1 Virus Isolation

Isolation of virus by culture is a standard method for diagnosis of viral disease and allows further analysis, such as determination of its sensitivity to antiviral drugs. Culture techniques for

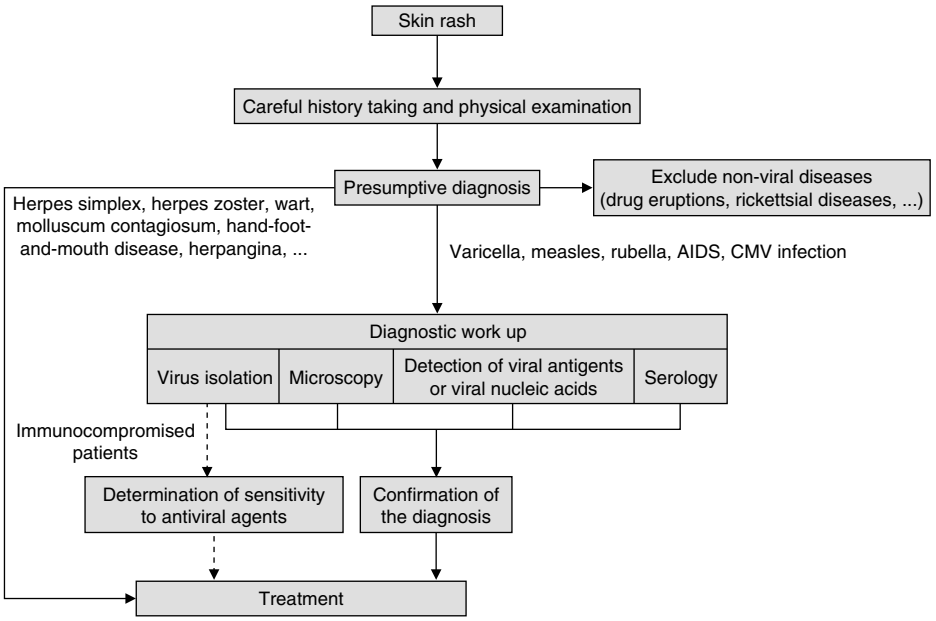

Fig. 1. Diagnostic procedures. Some viral skin infections, such as herpes zoster, can be easily diagnosed by their specific clinical manifestations and managed promptly. However, generalised erythematous maculopapular lesions present a diagnostic challenge. Clinicians must exclude nonviral conditions and may require laboratory work-up for an accurate diagnosis. Determination of sensitivity to antiviral agents may be necessary in immunocompromised patients because resistant strains are relatively common in these patients. Usually, however, the treatment of immunocompromised patients is not delayed until *in vitro* testing is completed. **CMV** = cytomegalovirus.

HSV are quite sensitive, with diagnostic changes in cells often appearing within days of inoculation. However, VZV is much more difficult to grow in culture, so false-negative results are extremely common.[1]

4.2 Microscopy

A valuable clinical approach to make a rapid diagnosis of herpesvirus infection relies on the Tzanck preparation. It is accomplished by taking a smear of cells from the base of the skin lesion, and staining with Wright or Giemsa stain to look for multinucleated giant cells. However, it cannot distinguish VZV from HSV infections.

For lesions that contain large numbers of viral particles, electron microscopy may provide morphologic identification of the virus, but the detection rate is low.

4.3 Serology

In most acute viral illness, serologic analysis requires acute and convalescent sera, which limits its use to only retrospective diagnoses. The acute specimen should be taken as early as possible and the convalescent specimen 2 to 4 weeks later. Serum should be separated immediately from the coagulated blood and refrigerated or preferably frozen at -20°C until tests can be run simultaneously on both specimens. A 4-fold or greater rise in antibody titre between the first and second specimen generally indicates recent infection.[1]

In the case of HIV infection, it is not necessary to take acute and convalescent sera. The enzyme-linked immunosorbent assay (ELISA) test with single serum is the primary screening test of HIV infection. If the ELISA test is positive, Western blot is performed for confirmation. Western blot is considered positive if any two of the p24, gp41, gp120/gp160 proteins are detected.[22]

4.4 Detection of Viral Antigenic Proteins

Radioimmunoassay, ELISA and immunoelectron microscopy identify viral antigenic protein by the use of specific antibody.[1] The identification of specific viral antigen in clinical material permits a more specific diagnosis than direct microscopy. For example, immunological techniques can distinguish between HSV and VZV.

4.5 Detection of Viral Nucleic Acids

Recently, remarkable progress has been made in this field. Polymerase chain reaction (PCR) is revolutionising diagnostic techniques and can specifically amplify minute quantities of viral nucleic acid. The main pitfall of PCR is false-positive results as a result of its extreme sensitivity. In the case of HPV infection, sequences of numerous types of HPV are already known and the primer sequences for PCR are also available.

5. Treatment Considerations

Prophylaxis of viral infection has thus far proved more successful than the specific treatment of established infection. Vaccines have been extremely useful in the prevention of a variety of viral illnesses. Recently, however, remarkable progress in the development of specific antiviral agents has been achieved.

5.1 Antiviral Drugs

As late as the mid-1980s only three antiviral drugs were approved for treatment of systemic viral infections. The development of new antiviral agents has recently entered an accelerated growth phase. Currently, more than 30 antiviral drugs are approved for the treatment of viral infections and half of them are used for the treatment of HIV infection.[24] The main antiviral agents that are commonly used by dermatologists, are summarised in table I.

5.1.1 Aciclovir

Aciclovir is highly active against HSV-1. However, it is slightly less active against HSV-2, and approximately 8-fold less active against VZV *in vitro*.[25] The active antiviral moiety of aciclovir is aciclovir triphosphate, which is a potent inhibitor of certain herpesvirus-induced DNA polymerases. The initial phosphorylation of aciclovir to aciclovir

Table I. . Antiviral agents for the treatment of common viral skin infections

Drug	Clinical indications	Adverse effects	Considerations
Aciclovir	Mucocutaneous HSV infections, varicella, herpes zoster	Crystallisation of the drug in renal tubules	Must avoid dehydration, rapid intravenous administration
Valaciclovir	Mucocutaneous HSV infections, varicella, herpes zoster	Crystallisation of the drug in renal tubules	Converted to aciclovir
Famciclovir	Mucocutaneous HSV infections, varicella, herpes zoster	Uncommon	Prolonged intracellular half-life
Vidarabine	Mucocutaneous HSV infections, varicella, herpes zoster	Anaemia, leukopenia, thrombocytopenia	Must be administered as a constant 12h infusion in a dilute solution
Ganciclovir	CMV infections in immunocompromised patient	Neutropenia, thrombocytopenia	Toxicity is worsened by concomitant use of zidovudine
Foscarnet	CMV infections in immunocompromised patients HSV or VZV infection resistant to aciclovir CMV infection resistant to ganciclovir	Renal toxicity	Hydration and slow infusion reduce nephrotoxicity
Cidofovir	CMV infections resistant to ganciclovir and foscarnet in immunocompromised patients	Renal toxicity	Hydration and slow infusion reduce nephrotoxicity
Idoxuridine Trifluridine	HSV keratoconjunctivitis	Uncommon	Topical use only
Zidovudine	HIV infection	Myelosuppression	Combination therapy is necessary

CMV = cytomegalovirus; **HSV** = herpes simplex virus; **VZV** = varicella-zoster virus.

monophosphate is efficiently carried out by herpesvirus-induced thymidine kinase but not by cellular kinase. Thus, aciclovir monophosphate is concentrated in virus-infected cells.[26] Viruses that are resistant to aciclovir on the basis of thymidine kinase mutations are also resistant to ganciclovir and famciclovir but are generally sensitive to vidarabine, foscarnet and cidofovir. The mechanisms of action of antiviral agents are presented in figure 2.

Aciclovir is almost entirely eliminated by the renal route. Therefore, dosage reductions are required for patients with creatine clearances of <50 ml/min.[27] The major toxicity associated with aciclovir is crystallisation of the drug in renal tubules, which has been reported with high dosage, dehydration and rapid intravenous administration.[28]

5.1.2 Valaciclovir

The oral bioavailability of aciclovir is low (15 to 30%). Valaciclovir was developed to provide increased oral bioavailability. It is rapidly absorbed from the gastrointestinal tract and is converted almost entirely to aciclovir. After a 1g oral dose of valaciclovir, peak plasma concentrations of aciclovir are similar to those achieved with 5 mg/kg aciclovir given intravenously.[29]

5.1.3 Famciclovir

Famciclovir is a prodrug of penciclovir. Penciclovir is phosphorylated to penciclovir triphosphate, which has antiviral activity against HSV-1, HSV-2, VZV, and EBV.[30]

The bioavailability of famciclovir is 77 percent and the intracellular half-life of penciclovir triphosphate is 10 to 20 hours in HSV-infected cells and 9 hours in VZV-infected cells.[31] This is the rationale for the longer interval of administration of famciclovir (every 12 hours) compared with that recommended for aciclovir (every 4 hours).

5.1.4 Ganciclovir

Ganciclovir is markedly more active against CMV than aciclovir.[32] Its most well established use is for the treatment of CMV retinitis in patients with AIDS. The major toxicity is bone-marrow suppression, particularly neutropenia and thrombocytopenia.[33]

5.1.5 Cidofovir

Cidofovir is converted by host-cell enzymes to cidofovir diphosphate, which is a competitive inhibitor of viral DNA polymerases and, to a lesser extent, of host-cell DNA polymerases.[34] It is ap-

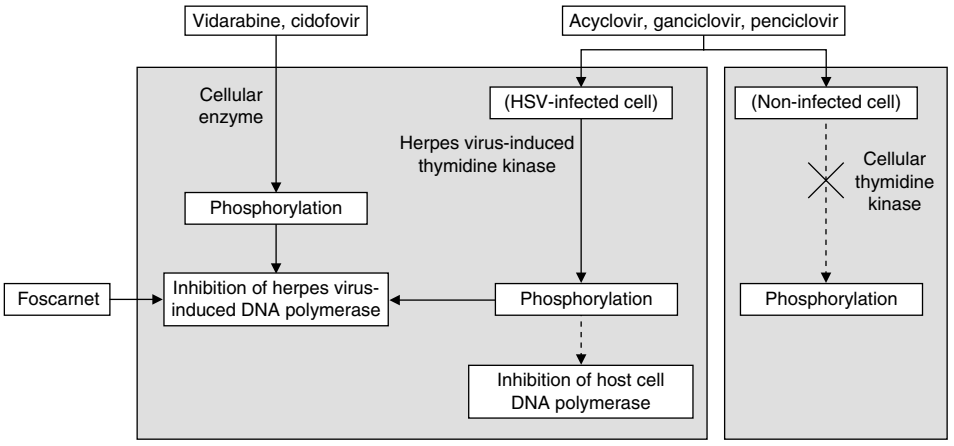

Fig. 2. Mechanisms of action of antiviral agents. Aciclovir, ganciclovir and penciclovir, but not vidarabine, cidofovir and foscarnet, require herpesvirus-induced thymidine kinase for phosphorylation. It is for this reason that aciclovir is ineffective but cidofovir is still effective in the diseases caused by herpesvirus with mutant thymidine kinase.

proved for the treatment of CMV retinitis in patients with infections resistant to ganciclovir and foscarnet.

5.1.6 Foscarnet

Foscarnet does not require phosphorylation for its antiviral activity and noncompetitively inhibits viral DNA polymerases. It is used in the treatment of CMV retinitis in patients with AIDS. Foscarnet is also used for HSV or VZV infections, which are resistant to aciclocir and for CMV infection that is resistant to ganciclovir.[35,36]

5.1.7 Vidarabine

Vidarabine is administered intravenously as a constant 12-hour infusion in a dilute solution.[37] On entering the cell, the drug is phosphorylated by cellular kinase to the triphosphate, which inhibits the herpesvirus-encoded DNA polymerase. At high dosages, vidarabine has been associated with anaemia, leukopenia and thrombocytopenia. Because of difficulty in administration and toxicity, it has largely been replaced with aciclovir.

5.1.8 Idoxuridine and Trifluridine

These are available in the US as a 1% ophthalmic aqueous solution and are approved for the treatment of herpes simplex keratoconjunctivitis.[38]

5.1.9 Fomivirsen

Fomivirsen is approved for the treatment of CMV retinitis in AIDS patients. Being complementary in base sequence, it hybridises with the CMV mRNA and thus blocks the expression.[24]

5.1.10 Zidovudine (Azidothymidine)

Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI) and requires phosphorylation to the triphosphate form. It is particularly effective against DNA synthesis by the reverse transcriptase of HIV and inhibits growth of the virus. The major toxic effect is myelosuppression.

5.2 Treatment of Specific Viral Skin Diseases

5.2.1 Herpes Labialis and Herpes Genitalis

The early application (within the first 8 hours from clinical onset) of topical aciclovir 5% ointment in polyethylene glycol results in a significant effect in the treatment of herpes labialis.[39] Topical penciclovir cream 1% is also effective in the treatment of herpes labialis, whether therapy is initiated early or late.[40] Our experience, however, is that the efficacy of topical antiviral agents is limited. Primary HSV infection is usually more severe than

recurrent disease, therefore we recommend oral aciclovir in most patients with initial disease.

Treatment with oral aciclovir or famciclovir shortens healing time of herpes genitalis.[41,42] Valaciclovir has also been approved for treatment of recurrent HSV genital infections in immunocompetent hosts.[43] Mucocutaneous HSV infections in immunocompromised patients generally respond to either oral administration or intravenous administration of aciclovir.[44,45] Famciclovir is also approved for the treatment of HSV in the HIV-infected patients. Intravenous aciclovir is still the drug of choice for the treatment of life-threatening HSV infection, such as encephalitis or neonatal infection.

5.2.2 Varicella

In healthy children, varicella (chicken pox) is generally benign and self-limited. Calamine lotion and antihistamines may help control the intense pruritus of the rash. Salicylates must be avoided because of their association with Reye's syndrome. Early treatment (within 24 hours of the appearance of rash) with oral aciclovir 20 mg/kg four times a day for 5 days reduces the duration and severity of chicken pox.[46] In adults with varicella, oral aciclovir is recommended. In an immunocompromised host, varicella should be treated with antiviral agents and the recommended treatment is intravenous aciclovir.[12]

Naturally, the prevention of varicella would be preferable to treatment of an existing infection. Varicella-zoster immune globulin has been used in the past to treat immunocompromised patients who have received significant exposure to varicella (recommended dose is 125 U/10kg). Unfortunately, one-third to one-half of these patients still develop clinical infection. Therefore, the recently approved live attenuated VZV vaccine (OKA strain) has been received with much interest. This vaccine appears to be both highly efficacious (96% seroconversion in healthy children in one study) and very well tolerated, with only such mild adverse effects as slight varicelliform rash, fever and infection-site reactions reported.[47] In addition, the incidence of zoster occurring after vaccination seems to be decreased compared with that after natural infection.

5.2.3 Herpes Zoster

Because VZV is less sensitive to aciclovir than HSV, higher doses of the drug should be used. Randomised, double-blind, placebo-controlled trials showed that aciclovir halted progression of herpes zoster.[48] In immunocompetent patients with herpes zoster, famciclovir had a beneficial effect on the resolution of skin lesions and on the duration of PHN.[49] Valaciclovir has also been approved for treatment of herpes zoster in immunocompetent hosts. Treatment of common herpes virus infec-

Table II. . Treatment recommendations for common herpesvirus infections

Diseases	Immunocompetent patients	Immunocompromised patients
Herpes simplex	Topical 5% aciclovir ointment or Topical 1% penciclovir cream or Oral aciclovir 200mg five times daily for 10 days or Oral famciclovir 125mg twice daily for 5 days or Oral valaciclovir 500mg twice daily for 5 days	Oral aciclovir 400mg five times daily for 7 to 10 days or intravenous aciclovir 5 mg/kg q8h for 7 to 10 days
Herpes zoster	Oral aciclovir 800mg five times daily for 7 days or Intravenous aciclovir 10 mg/kg q8h for 7 days or Oral famciclovir 500mg three times daily for 7 days or Oral valaciclovir 1g three times daily for 7 days	Intravenous aciclovir 10 mg/kg q8h for 7 to 10 days Intravenous foscarnet 40 mg/kg q8h until healed [a]
Varicella	Oral aciclovir 800mg five times daily for 7 days Oral famciclovir 500mg three times daily for 7 days or Oral valaciclovir 1g three times daily for 7 days	Intravenous aciclovir 10 mg/kg q8h for 7 to 10 days Intravenous foscarnet 40 mg/kg q8h until healed[a]

a If resistant to aciclovir.

q8h = every 8 hours.

tions (herpes simplex, varicella, and herpes zoster) are summarised in table II.

5.2.4 Cytomegalovirus Infection

Ganciclovir is 50 times more effective against CMV than aciclovir. Because of low oral bioavailability (5 to 9%), relatively large doses of ganciclovir need to be administered orally (1g orally three times daily) to achieve an effect.[50] Oral bioavailability is improved by administration with food. Foscarnet, cidofovir, fomivirsen and maribavir are also used in the treatment of CMV infection.[24]

5.2.5 Infectious Mononucleosis

Infectious mononucleosis is usually a self-limiting disease. Ampicillin or amoxicillin should not be given during the acute phase of infectious mononucleosis because of development of an ampicillin rash.

5.2.6 Exanthem Subitum

Exanthem subitum are mild self-limiting benign conditions of short duration, and usually no treatment is necessary.

5.2.7 Molluscum Contagiosum

In patients with molluscum contagiosum, removal of lesions with a sharp curette is simple and effective. Treatment is not always necessary, since the condition is usually self-limiting and heals without scar.

5.2.8 Warts

Children with common warts may not require therapy. Two-thirds will remit within 2 years.[51] In adults, however, treatment of warts is often disappointing because of a high rate of relapse. Current treatments for warts involve multiple modalities: physical destruction (curette, CO_2 laser), cryotherapy, topical podophyllin, diphencyprone (DPCP) and intralesional bleomycin.[15] A double-blind controlled study showed no beneficial effect for cimetidine.[52]

Numerous recent clinical trials have shown topical imiquimod to be effective and well tolerated for the treatment of anogenital warts.[53] As a topically applied immune enhancer, imiquimod stimulates the innate immune response through induction, synthesis and release of cytokines, including INFα, interleukin-6 and tumour necrosis factor-α.[54] Benefits of imiquimod include less tissue damage and efficacy superior to results of chemodestructive therapies. It is approved by the US Food and Drug Administration (FDA) for the treatment of external anogenital warts.

5.2.9 Measles

A single dose of live attenuated vaccine produces measles antibody in approximately 95% of recipients. From 1989, public health authorities in the US adopted a two-dose immunisation schedule. The first dose is usually given at 15 months of age and the second dose is given prior to school entry or early in elementary school.[55] Uncomplicated measles runs a self-limited course, lasting about 10 days. Immune serum globulin (0.25 ml/kg intramuscularly) may be used to modify or prevent measles if given within 6 days of exposure.

5.2.10 Rubella

Rubella vaccine is usually given together with measles and mumps (MMR) at the age of 15 months and at school entry. It should not be given to a pregnant woman.

5.2.11 Erythema Infectiosum, Hand-Foot-And-Mouth Disease and Herpangina

Erythema infectiosum, hand-foot-and-mouth disease and herpangina are self-limiting and resolve spontaneously over the course of a week. Therefore, no specific treatment is necessary.

5.2.12 HIV Infection

The prognosis of HIV infection has dramatically improved during the past few years with the advent of highly active antiretroviral therapy (HAART). The three main groups of antiretroviral drugs are NRTIs, nonnucleoside reverse transcriptase inhibitors and protease inhibitors.[22] There are now 15 antiviral agents that have been formally licensed for the treatment of HIV infection: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, nevirapine, delavirdine, efavirenz, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir. Several others are under clinical development.[24] The treatment of many

opportunistic viral skin infections in patients with HIV infection is more difficult than in healthy individuals. More details than this are beyond the scope of this paper and the reader is referred to other reviews for more information.

6. Conclusions

Recently, new techniques for the diagnosis of viral infections and several new effective antiviral drugs have been introduced. Making the correct diagnosis may have important clinical implications for treatment as well as for prognosis in patients with viral skin infections.

Acknowledgements

Preparation of this review was supported by Seoul National University Hospital Research Fund. The authors wish to thank ER Seo for her technical assistance.

References

1. Lowy DR. Viral disease: general consideration. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2390-5
2. Penneys N. Diseases caused by viruses. In: Elder D. Lever's histopathology of the skin. 8th ed. Philadelphia (PA): Lippincott-Raven, 1997: 569-89
3. Roizman B. Multiplication of viruses, an overview. In: Fields BN, Knipe DM, Howley PM. Fields virology. 3rd ed. New York: Lippincott-Raven, 1996: 101-11
4. Ahmed R. Persistence of viruses. In: Fields BN, Knipe DM, Howley PM. Fields virology. 3rd ed. New York: Lippincott-Raven, 1996: 219-49
5. Murphy BR, Chanock RM. Immunization against virus disease. In: Fields BN, Knipe DM, Howley PM. Fields virology. 3rd ed. New York: Lippincott-Raven, 1996: 467-97
6. Vilcek J, Sen GC. Interferons and other cytokines. In: Fields BN, Knipe DM, Howley PM. Fields virology. 3rd ed. New York: Lippincott-Raven, 1996: 375-99
7. Sen GC, Lengyel P. The interferon system. A bird's eye view of its biochemistry. J Biol Chem 1992 Mar 15; 267 (8): 5017-20
8. Bader C, Crumpacker CS, Schnipper LE, et al. The natural history of recurrent facial-oral infection with herpes simplex virus. J Infest Dis 1978; 138: 897-905
9. Crumpacker CS. Herpes simplex. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2414-26
10. Enders G, Miller E, Cradock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet 1994; 343: 1548-51
11. Ragozzino MW, Melton 3rd LJ, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine 1982; 6 (5): 310-6
12. Straus SE, Oxman MN. Varicella and herpes zoster. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2427-50
13. Toome BK, Bowers KE, Scott GA. Diagnosis of cytomegalovirus infection: a review and report of a case. J Am Acad Dermatol 1991 May; 24 (5 Pt 2): 860-7
14. Weary PE, Cole 3rd JW, Hickam LH. Eruptions from ampicillin in patients with infectious mononucleosis. Arch Dermatol 1970 Jan; 10 (1): 8691
15. Lowy DR, Androphy EJ. Warts. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2484-97
16. Majewski S, Jablonska S, Orth G. Epidermodysplasia verruciformis. Immunological and nonimmunological surveillance mechanism: role in tumor progression. Clin Dermatol 1997 May-Jun; 15 (2): 321-34
17. Koplik H. The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal mucous membrane. Arch Pediatr 1886; 13: 918
18. Gellis SE. Rubella. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2395-598
19. Young N. Hematologic and hematopoietic consequences of B19 parvovirus infection. Semin Hematol 1988 Apr; 25 (2): 159-72
20. Levy R, Weissman A, Blomberg G, et al. Infection by parvovirus B19 during pregnancy: a review. Obstet Gynecol Surv 1997 Apr; 52 (4): 254-9
21. Haley JC, Hood AF. Hand-foot-and-mouth disease. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2403-7
22. Johnson RA. Cutaneous manifestations of human immunodeficiency virus disease. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2505-38
23. Yolken R. Laboratory diagnosis of viral infections. In: Galasso GJ, Whitley RJ, Merigan TC. Antiviral agents and viral diseases of man. New York: Lippincott-Raven, 1997: 141-81
24. Clercq ED. Antiviral drugs: current state of the art. J Clin Virol 2001; 22: 73-89
25. Schaeffer HJ. Acyclovir chemistry and spectrum of activity. Am J Med 1982 Jul 20; 73 (1A): 4-6
26. Elion GB. Mechanism of action and selectivity of acyclovir. Am J Med 1982 Jul 20; 73 (1A): 7-13
27. Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. Am J Med 1982; 73 (1A): 197-201
28. Sawyer MH, Webb DE, Balow JE, et al. Acyclovir-induced renal failure: clinical course and histology. Am J Med 1988 Jun; 84 (6): 1067-71
29. Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir pro-drug valacyclovir after escalating single and multiple dose administration to normal volunteers. Clin Pharmacol Ther 1993 Dec; 54 (6): 595-605
30. Earnshaw DL, Bacon TH, Darlison SJ, et al. Mode of antiviral action of penciclovir in MRC-5 cells infected with HSV-1, HSV-2 and VZV. Antimicrob Agents Chemother 1992 Dec; 36 (12): 2747-57
31. Pue MA, Pratt SK, Fairless AJ, et al. Linear pharmacokinetics of penciclovir following administration of single oral doses of famciclovir 125, 250, 500, and 750mg to healthy volunteers. J Antimicrob Chemother 1994 Jan; 33 (1): 119-27
32. Plotkin SA, Drew WL, Felsenstein D, et al. Sensitivity of clinical isolates of human cytomegalovirus to 9-(1,3-dihydroxy-

2-propoxymethyl) guqnine. J Infect Dis 1985 Oct; 152 (4): 833-4
33. Markham A, Faulds D. Ganciclovir: An update of its therapeutic use in cytomegalovirus infection. Drugs 1994 Sep; 48 (4): 455-84
34. Neyts J, Snoeck R, Balzarini J, et al. Particular characteristic of the anti-human cytomegalovirus activity of (s)-1-(3-hydroxy-2-phosphonylmothoxyprophy) cytosine in vitro. Antiviral Res 1991 Jul; 16 (1): 41-52
35. Hardy WD. Foscarnet treatment of acyclovir-resistant herpes simplex virus infection in patients with acquired immunodeficiency syndrome: preliminary results of a controlled, randomized, regimen-comparative trial. Am J Med 1992 Feb 14; 92 Suppl. 2A: 30S-5S
36. Drobyski WR, Knox KK, Carrigan DR, et al. Foscarnet therapy of ganciclovir-resistant cytomegalovirus in marrow transplantation. Transplantation 1991 Jul; 52 (1): 155-7
37. Whitley R, Alford C, Hess F, et al. Vidarabine: a preliminary review of its pharmacological properties and therapeutic use. Drugs 1980 Oct; 20 (4): 26782
38. Pavan-Langston D. Major ocular viral infections. In: Galasso GJ, Whitley RJ, Merigan TC. Antiviral agents and viral diseases of man. 3rd ed. New York: Raven, 1990:183-233
39. Spruance SL, Schnipper LE, Overall Jr JC, et al. Treatment of herpes simplex labialis with topical acyclovir in polyethylene glycol. J Infect Dis 1982 Jul; 146 (1): 85-90
40. Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. JAMA 1997 May 7; 277 (17): 1374-9
41. Bryson Y, Dillon M, Lovett M, et al. Treatment of first episode of genital herpes simplex infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. N Engl J Med 1983 Apr 21; 308 (16): 916-21
42. Sacks SL, Aoki FY, Diaz-Mitoma F, et al. Patient-initiated, twice daily oral famciclovir for early recurrent genital herpes. JAMA 1996 Jul 3; 276 (1): 44-9
43. Spruance SL, Tyring SK, DeGregorio B, Miller C, Beutner K. A large-scale placebo-controlled dose-ranging trial of peroral valacyclovir for episodic treatment of recurrent herpes genitalis. Arch Intern Med 1996 Aug 20-26; 156 (15): 1729-35
44. Wade JC, Newton B, Mclaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex infection after marrow transplantation. Ann Intern Med 1982 Mar; 96 (3): 265-9
45. Shepp DH, Newton BA, Dandliker PS, et al. Oral acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised marrow transplant recipients. Ann Intern Med 1985 Jun; 102 (6): 783-5
46. Wallace MR, Bowler WA, Murray NB, et al. Treatment of adult varicella with oral acyclovir: a randomized, placebo-controlled study. Ann Intern Med 1992 Sep 1; 117 (5): 358-63
47. McCrary ML, Severson J, Tyring SK. Varicella zoster virus. J Am Acad Dermatol 1999; 41 (1): 1-16
48. Balfour Jr HH, Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med 1983 Jun 16; 308 (24): 1448-53
49. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995 Jul 15; 123 (2): 89-96
50. Spector SA, Busch DF, Follansbee S, et al. Pharmacokinetic, safety, and antiviral profiles of oral ganciclovir in persons infected with human immunodeficiency virus: a phase I/II study. J Infect Dis 1995 Jun; 171 (6): 1431-7
51. Messing AM, Epstein WL. Natural history of warts: a two year study. Arch Dermatol 1963; 87: 306-10
52. Yilmaz E. Alpsoy E, Basaran E. Cimetidine therapy for warts: a placebo-controlled, double-blind study. J Am Acad Dermatol 1996 Jun; 34 (6): 1005-7
53. Edwards L. Imiquimod in clinical practice. J Am Acad Dermatol 2000 Jul; 43 (1 Pt 2): S12-7
54. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol 2000 Jul; 43 (1 Pt 2): S6-S11
55. Cooper LZ. Measles. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw-Hill, 1999: 2398-403

Correspondence and offprints: Dr *Kyoung C Park*, Department of Dermatology, Seoul National University College of Medicine, 28 Yungon-dong, Chongno-gu, Seoul, 110-744, Korea.
E-mail: gcpark@snu.ac.kr