Viral Skin Diseases in the Pediatric Practice:
Update on Management, Immune Response Modifiers, and Other Therapies

PROCEEDINGS OF A CLINICAL ROUNDTABLE

Cutaneous Manifestations of Viral Infections: An Overview
Perspective on Human Papillomavirus in Children
Herpesviruses and the Pediatric Practice
Current Views on Molluscum Contagiosum
Less Common Viral Exanthems of Special Interest

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Introduction

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CME Test and Post-Test Evaluation

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- Dr. Eichenfield discusses the investigational use of imiquimod and cantharidin for treating molluscum contagiosum.

- Dr. Levy discusses the investigational use of cidofovir for treating warts and molluscum contagiosum.

- Dr. Orlow is a consultant to 3M.

- Dr. Tyring has received clinical grants from and is a consultant to 3M. He discusses the investigational use of imiquimod and cantharidin for treating molluscum contagiosum.

- Dr. Paller is a consultant to 3M. She discusses the investigational use of imiquimod and cantharidin for treating molluscum contagiosum and the investigational use of imiquimod and cantharidin for treating verruca vulgaris.

- Dr. Paller is a consultant to 3M, and she discusses the investigational use of imiquimod and cantharidin for treating molluscum contagiosum.

- Dr. Tyring has received clinical grants from and is a consultant to 3M. He discusses the investigational use of imiquimod for treating non-genital warts and molluscum contagiosum.

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Educational Needs:

Viral diseases may cause a number of types of mucocutaneous manifestations, the expressions of which may be confusing. It is important for clinicians to be able to identify the types of lesions most closely associated with the various diseases. However, visual inspection alone is insufficient for making a diagnosis, so familiarity with the current laboratory diagnostic methods is essential. Finally, clinicians must remain up-to-date regarding the treatment of the most common viral infections seen in children—including those caused by human papillomaviruses, herpesviruses, and poxviruses. Recent advances in clinical studies with the immune response modifier imiquimod and other therapies will be discussed.

Learning Objectives:

- Name the types of lesions that may be seen in viral infections, along with the most common diseases with which each is associated.

- Discuss the uses of viral cultures, microscopic examination of infected tissue, viral antigen detection, DNA and RNA detection, and serology in the diagnosis of viral diseases in general.

- Describe the current management issues in pediatric infections involving human papillomaviruses, herpesviruses, and poxviruses.

- Summarize the research findings regarding newer therapies for common viral infections in pediatrics, including the use of the immune response modifier imiquimod.

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Introduction
Amy S. Paller, MD, Chair

Children with viral skin diseases represent a major component in the busy practices of both pediatricians and dermatologists. Most common of the manifestations of these infections are warts, caused by human papillomaviruses (HPV), and the poxvirus molluscum contagiosum. Primary care physicians should be able to recognize these common viral infections of children. Referral to a dermatologist or pediatric dermatology specialist should be based on the complexity of the case, the response of the patient to initial therapies, and the experience of the primary clinician.

This supplement is intended as an overview of and quick reference source for recognizing and treating the cutaneous viral infections most likely to be seen in a health care provider's office. To that end, a panel of experts (whose names and affiliations appear on page 2) was convened for a roundtable discussion of this topic. Several of the topic areas are followed by a Discussion section, with informal comments and opinions of the panelists.

Warts
Warts are common in young school-age children and teenagers. Although occasionally uncomfortable, warts are usually painless, but they can be embarrassing for the child when noticeable, and parents often want warts removed. The result of a viral infection, warts can spread to others; autoinoculation also may occur, resulting in spread to new areas on the infected child. Warts are often ignored, as our immune systems eventually recognize the papillomavirus as foreign and can cause spontaneous resolution in most cases, with a mean duration of 2 years.

The trial recently described in the medical literature and lay media about the use of duct tape, a relatively simple intervention, was small in number but deserves further investigation. Common warts are primarily treated with physical modalities, most commonly cryotherapy and salicylic acid. During the last several years, attention has focused on immunologic modalities, thought to stimulate the body's immune system to recognize and clear the warts. These include oral cimetidine therapy and topical immunotherapy with contact sensitizers, particularly squaric acid dibutyester, and the immune response modifier imiquimod.

Anogenital warts in children have also received attention. In 1991, based on the recognition of the association between anogenital warts and possible child abuse, the Committee on Child Abuse and Neglect of the American Academy of Pediatrics (AAP) proposed guidelines suggesting that any case of anogenital warts resulted from probable abuse and needed reporting. Subsequent investigation showed that most anogenital warts in fact do not result from sexual abuse, especially in children under 3 years of age. As a result, the 1999 guidelines from this AAP committee note that anogenital warts should raise suspicion, but that reporting should be undertaken based on the age of the patient, history, and other physical findings.

The latest news about warts is the convincing evidence that a recently developed vaccine directed against HPV-16 infection may reduce the rates of cervical cancer. Perhaps this work may be expanded to include immunization against common warts in our repertoire of immunizations for children and ultimately lead to the eradication of warts from our practices.

Molluscum Contagiosum
In contrast to warts, molluscum contagiosum is not well known despite the frequency of its occurrence. More problematic in our many patients with atopic dermatitis, in whom molluscum contagiosum may exacerbate dermatitis, a variety of techniques are now available to treat this poxvirus infection.

Despite lack of current U.S. Food and Drug Administration approval, cantharidin is now considered a safe and effective therapy for treating molluscum, and it can be applied painlessly in the office setting. However, the efficacy and safety of cantharidin depend heavily on the skill and experience of the individual who applies this vesicant, a factor that underscores the need for a clinician to be trained in its use. Imiquimod has also received attention as a new immunologic means to clear molluscum in children, with encouraging results to date.

Other Common Viral Infections
The herpesvirus family of viruses is also responsible for skin lesions that often cause parents to seek medical attention for their children. Among the most common of these historically is chickenpox. The incidence of this highly contagious infection has been markedly reduced with the growing acceptance of the varicella vaccine. Herpes simplex type 1 affects at least 50% of preschool children and often manifests later in childhood or adolescence as the recurrent herpetic eruptions commonly referred to as “cold sores.”

Finally, several parvoviral and enteroviral infections have received much attention during the past decade, as have certain exanthematous patterns that can be seen with several viral organisms; papular acrodermatitis of childhood and unilateral laterothoracic viral exanthem.

References
Cutaneous Manifestations of Viral Infections: An Overview

Viral infections occur in both children and adults either as a manifestation of a direct infection of the skin or as the result of a systemic infection. The types of viruses that may infect children range from herpesviruses (causing neurologic infection and perhaps cutaneous lesions) to papillomaviruses and the poxviruses (causing, for example, warts and molluscum contagiosum, respectively) to systemic viral infections (including measles and rubella).

Manifestations of viral infections range from simple erythematous, macular presentations to papules, vesicles, pustules, ulcers, and crusting (Table). Clinicians should be aware of the presentations of these cutaneous manifestations, particularly now because of the emerging possibility of both smallpox infection and disseminated vaccinia. The poxviruses, especially, may mimic or be mimicked by lesions from other causes, and the medical community should know the differences in the morphology of the lesions as well as in the presentation, timing, and progression of these eruptions. The American Academy of Dermatology recently disseminated a packet of information to help physicians recognize smallpox, and an article was published recently that described a case of a man who presented to a hospital emergency room with lesions that clinically resembled smallpox. Although the patient actually had a disseminated herpesvirus infection, the reader is referred to the commentary in this article from a representative of the U.S. Centers for Disease Control and Prevention (CDC), which describes the mechanisms now in place for rapid diagnosis, including the ability to send samples to the CDC quickly if there is a serious question.

Viral Transmission

One means of viral transmission is direct inoculation. It is known that herpesviruses are less likely to infect intact skin than abraded skin. Recent discussions of poxviruses, particularly vaccinia (which would be used to prevent smallpox), involve the question of whether vaccinia would be more likely to infect and disseminate on abraded skin.

Some viruses may be inoculated through the skin but then manifest systemically. For example, once herpesviruses are directly inoculated, neurologic infection follows. Recurrent herpetic lesions are the cutaneous signs of systemic infection. Another herpesvirus, varicella, is acquired by direct contact or via the respiratory route and is manifested secondarily in the skin.

Confirming Suspected Viral Disease

The differential diagnosis of a viral infection is based on the patient’s history, systemic signs and symptoms, and the clinical signs and symptoms related directly to the skin. As the Table shows, certain exanthems (or skin manifestations) are typically associated with specific viruses. Whether an eruption is pruritic or painful can help differentiate a viral from a nonviral infection. Contact dermatitis, for example, is typically more pruritic, and herpes zoster would be more painful. After that initial clinical assessment has been made, the issue of whether and what type of laboratory investigation is indicated.

Five general methods of laboratory diagnosis are available to confirm the diagnosis of suspected viral disease: viral cultures, microscopic examination of infected tissue, detection of viral antigens, detection of DNA or RNA, or serology.

When a herpesvirus infection is suspected, a Tzanck test can be helpful. Although it is not definitive for identifying a herpesvirus infection when multinuclear giant cells are...
Perspective on Human Papillomavirus in Children

Warts are cutaneous and mucosal lesions caused by infection with various types of human papillomavirus (HPV). Of the almost 100 subtypes of HPV that have been identified to date, those that are of most concern in pediatric populations are HPV types 1, 2, 3, 6, and 11, and, possibly, types 16 and 18.

Classically, HPV-1 has been associated with palmoplantar warts. HPV-2 has been associated with so-called common warts (verruca vulgaris) elsewhere on the body, as well as on the hands and feet (but not on the plantar or palmar surfaces), and HPV-3 with flat warts (verruca plana). Genital warts (condylomata acuminata) are typically caused by HPV types 6 and 11 and often occur in association with infection with HPV types 16 and 18, which may predispose to cervical neoplasia in females. About a decade ago, the assumption was made that the appearance of anogenital warts in children was de facto evidence of abuse. Because of more recent data demonstrating that the majority of perianal warts in children was de facto evidence of abuse,1 the American Academy of Pediatrics advised a revision of this view in 1999.2

It is not uncommon for clinicians to see children with warts at multiple sites—for example, flat warts on the face and common warts on the hands simultaneously. Although this phenomenon has not been studied formally, it suggests that some children have a susceptibility to HPV infection.

Epidemiology and Natural History of Warts

Warts generally infect males and females equally. Most commonly, warts are seen in school-age children. Occasionally, infants acquire warts in the perinatal period. Transmission of HPV is chiefly by direct skin contact, but infection also may be acquired via fomites. No viremia occurs with HPV infection because the virus infects only epithelial cells. The type of cell that is typically infected depends on the particular wart under discussion.

Many warts do resolve spontaneously, with a classic study by Massing and Epstein suggesting that up to 50% of lesions clear without treatment within 2 years.3 Those that do not resolve without treatment either persist or may increase in number and size. The longer warts persist, the more likely the parent is to bring a child for consultation and possible treatment.

Management of Warts in Children

Multiple medical and surgical therapies are used for the management of warts, but few randomized trials have been done on which to base the use of such treatments. No single therapy is uniformly successful in all patients with warts. No treatments are specifically approved for common warts in children. (For excellent reviews of the treatment modalities used for warts and the evidence accumulated to date to support the use of the various local modalities, the reader is referred to an article by Gibbons and colleagues4 and the Cochrane Database System Review.5)

Commonly used options include destructive modalities, including surgical removal by curettage or electrodesication, and cryotherapy. These destructive modalities are associated with several problems in children. The first is that topical anesthesia is not always sufficient, and an injected anesthetic may be required when performing curettage or electrodesication. Also, surgical destruction can increase the risk of scarring, especially if the warts are located over an extensor joint. Further, when cryotherapy is done in the manner most likely to be effective—prolonged freezing with liquid nitrogen, repeated every 2 to 3 weeks—it causes discomfort, at minimum, and may be extremely painful.

Cantharidin was once a popular treatment for warts and is gaining popularity for the treatment of molluscum contagiosum lesions (see “Current Views on Molluscum Contagiosum,” page 11), despite the fact that a commercially available version is not approved for use in the United States. However, with warts, cantharidin commonly leads to the development of the so-called donut phenomenon, a clear center with a border at which the wart recurs and, some-

References


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times, from which it spreads. Thus, cantharidin cannot be recommended for the treatment of warts.

Pulsed dye laser has been used for warts, based especially on the rationale that warts contain dilated and tortuous capillaries and that this technology is useful for treating vascular lesions. The benefit of this therapy is that scarring seems to be minimal. The main disadvantages are that treatment can be painful, so injected anesthesia is often required, and the fact that the greatest chance of efficacy requires multiple treatments.

A variety of other topical modalities also have been used for common warts, with varying degrees of success in individual cases. These include low-grade irritants such as lactic acid, tretinoin, and formalin, and the commonly used over-the-counter remedy, salicylic acid.

Facial warts, which are typically flat warts, are often treated with topical creams or gels to avoid the risk of scarring or hypopigmentation from destructive modalities. For these lesions, agents such as podofilox, imiquimod, or tretinoin are used with some frequency, if not with the highest level of success.

Filiform warts also occur frequently on the face. If only one or two warts are present and are prominent—especially if the patient is a young child—freezing may be considered. If the lesion is small and the base is fine, application of liquid nitrogen may be accomplished with a small applicator stick.

Condylomata Acuminata in Children
Generally, it is not advisable to aggressively treat anogenital warts in children unless a problem such as bleeding or obstruction of orifices occurs. Rather, home treatment, with podofilox or imiquimod applied by the parents, or possibly light cryotherapy may be considered. The rationale for this approach is that painful treatments are not justified because the lesions may clear and the child should be spared unnecessary discomfort in that area of the body, especially since the patients in whom the lesions persist will require treatment later.

Immunologic Approaches to Treatment
Immunotherapy to provoke the body’s own immunologic response is among the most recent additions to the clinician’s roster of options. These approaches include topical agents—imiquimod (approved by the U.S. Food and Drug Administration for use in genital warts in adults) and tretinoin, as well as contact sensitizers, oral cimetidine, and intraleisional injections of Candida albicans and mumps antigen.

Imiquimod is an immune response modifier with broad antitumor and antiviral activity. Tretinoin, a medication commonly used for acne, tends to irritate the skin, and it is thought that this inflammatory response may be harnessed to boost the cutaneous immunologic reaction to the virus. The use of oral cimetidine as an immunomodulator to treat childhood warts’ remains controversial, although some patients seem to respond very well.

Contact sensitization is another means of inducing an immune response. A number of agents have been tried, including dinitrochlorobenzene, squaric acid dibutylester, and even urushiol, the active agent in poison ivy that causes contact dermatitis.

The efficacy reported with squaric acid, about 65%-70%, indicates that it may be a good alternative to more destructive techniques. In addition, the clinical experience of this panel indicates that recurrences are rare in cases in which wart clearance is achieved with this agent. This modality seems to be especially useful in younger patients, particularly those with multiple warts. Clearance occurs within a mean period of about 7 weeks after the initial application.

The side effects seen in the patient series described in the cited study were limited to contact reactivity at the site of sensitization and/or at the site of the warts in particular. Two problems with squaric acid dibutylester immunotherapy—or any immunotherapy with contact sensitizers—are that these agents must be compounded at a pharmacy equipped to provide such a service and that applications of these agents must be done in the office setting, usually once a week.

Many clinicians are aware of intralesional bleomycin as a treatment for recalcitrant warts, but the injection itself is exquisitely painful, even when anesthesia is used, and is usually followed by considerable discomfort. Intralesional injection of candidin or mumps antigen have been tried, based on the theory that a T-cell immunity response would be induced. Patients with strongly positive skin tests seem most likely to respond to such treatments. However, evidence of efficacy is insufficient to justify the use of these agents in the average child with warts.

Discussion
DR. PALLER: Since the study on duct tape was published, is anyone using more duct tape or are you just having patients ask more about it? And why do you think it might work?

DR. LEVY: I have always used occlusion, and I don’t think it matters what type of tape you use. As for mechanism of action, I’m not quite certain whether the effect is maceration or the contact dermatitis that some of the children develop.

DR. ORLOW: I would like to comment briefly on that study. I’m not a big proponent of freezing warts in children because of the pain involved. I’m also not impressed by how well it works. Nonetheless, in that particular study, the freezing was done for only 10 seconds every 2 to 3 weeks. That was a sort of straw man in terms of a comparator group.

DR. PALLER: I agree. Also, it was a very small study group, and the percentage of patients who responded to cryotherapy was small, compared to the efficacy reported in the literature for cryotherapy.

DR. ORLOW: In addition, we can’t discount the power of suggestion in children. There was an open-label study published recently showing that garlic works.

DR. PALLER: Do we have some further comments on immunologic or immunomodulatory therapy for warts in children? We are trying imiquimod, always under occlusion, for common warts on sites other than the face and genitalia, where thickly keratinized warts usually are not seen.
I'm interested in that concept under the occlusive dressing, and that a salicylic acid patch over imiquimod and one of my colleagues is applying any kind of irritation. Many children achieve clearance without clearance of warts. We have seen that redness does not necessarily correlate to the patient, they need to call me. A little bit of red is okay, but if it’s bothersome to parents, however, because some are so interested in getting rid of the wart or the molluscum that they will treat right through to erosions and ulcerations. It’s important to explain to them that a little bit of red is okay, but if it’s bothersome to the patient, they need to call me.

DR. ORLOW: I think it’s important to stress that redness does not necessarily correlate with clearance of warts. We have seen many children achieve clearance without any kind of irritation.

DR. LEVY: One of my colleagues is applying a salicylic acid patch over imiquimod and under the occlusive dressing, and that seems to be effective.

DR. PALLER: I’m interested in that concept of imiquimod topped by the salicylic acid. Salicylic acid is an agent that has been shown to inactivate other agents. Dr. Tying, do you know if there has been any investigation in this area?

DR. TYRING: We don’t have any good data to answer that question definitively. Inactivation of imiquimod by salicylic acid is not unlikely, but the way we should be using those agents in combination is not together, but, rather, alternating. For example, for a patient with a "worst-case-scenario" plantar wart, we use as many approaches as possible—that is, paring, freezing, imiquimod under occlusion. By adding salicylic acid to the regimen, the possibility exists that its mechanism of action may add to the efficacy of the treatment. In such difficult cases, we have the patients apply salicylic acid during the day and, at night, instruct them to scrape away macerated skin before applying imiquimod. The rationale with this strategy is that enough salicylic acid is removed to prevent inactivation of imiquimod, but the keratolytic effect promotes penetration of imiquimod into the infected cells.

For any warts outside the face and the genital area, combination therapy is the way to go...[and] any combination that is logical for different mechanisms of action should be considered.

So although we can’t prove additive or synergistic benefits of the combination of salicylic acid and imiquimod, I think when you alternate it, it has that potential. On the other hand, if these agents are used together, there is the potential for antagonism.

DR. PALLER: I have one quick practical suggestion to pass along: I tell parents to use a flat toothpick to apply imiquimod to lesions. This minimizes waste, because the amount needed is removed, and the sachet with the remaining cream can be folded, paper-clipped, and saved for subsequent doses.

DR. ORLOW: The amount of cream provided in each sachet is designed to be sufficient to cover one application for an adult with genital warts. Often this is an amount larger than what is needed for treating common warts or a small area of molluscum lesions (see "Current Views on Molluscum Contagiosum," page 11). If I feel that a smaller amount is needed for each application, I tell the parents to prick the sachet with a needle and then just squeeze out what they need, saving the rest for subsequent doses.

DR. PALLER: Any other comments about the treatment of warts?

DR. ORLOW: I think that perhaps the most important thing to say about warts in general is "primum non nocere." The punishment should fit the crime, and the things that we do for warts should be no worse than the warts themselves.

References


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Herpesvirus and the Pediatric Practice

Of the eight human herpesvirus (HHV) types that have been identified, three are seen most commonly in children: herpes simplex virus (HSV) types 1 and 2 and varicella-zoster virus (VZV).

Herpes Simplex Viruses

HSV-1 has long been known as the virus that causes herpes labialis, or oral herpes, and HSV-2 as the virus that causes herpetic genital herpes, or genital herpes. Many patients, and some physicians, presume that this means that HSV-1 infections occur only above the belt and that HSV-2 is found only below the belt. However, either type can affect any part of the body. In children, HSV-1 occurs most commonly, often acquired by direct orofacial contact with an infected individual who has an active infection but no visible lesion. In fact, most adults are seropositive for HSV-1 but have no idea how they acquired the infection.

Because anatomic site is not necessarily an indicator of the causative HSV type, it is not possible to determine clinically which type a patient has. Distinguishing between the two types of HSV is not relevant for therapy, but it may be relevant when a child has a herpetic eruption in a genital area. Before conclusions are drawn about sexual abuse or sexual activity, a viral culture should be done to try to determine the HSV type responsible for the infection.

Prevalence of Genital Herpes in Teenagers

Data on the current incidence of type 2 infection in teenagers from the U.S. Centers for Disease Control and Prevention over the past 2 decades have demonstrated a 30% increase in the seroprevalence of antibodies to type 2 in individuals down to the age of 12 years in both sexes, and in all races and socioeconomic groups. It is important to recognize that genital herpes is a risk factor for human immunodeficiency virus (HIV) infection, not only because of the sexual activity that exposes an individual to the potential pathogens for multiple sexually transmitted diseases (STDs) but also because the herpes infection, specifically, degrades the epithelial barrier and is associated with an infiltrate of CD4+ cells. According to a recent report, individuals with genital herpes have a fivefold increased risk for acquiring HIV if they have sex with an HIV-seropositive person.

Prevention of HSV Infection

Because it is so prevalent and typically is acquired so early in life, prevention of type 1 infection is extremely difficult. The focus, therefore, is on prevention of HSV-2 infection. Since many individuals become sexually active in adolescence, prevention of HSV-2 infection is well within the scope of concern of the pediatrician. Intervention would be most effective, of course, prior to the onset of sexual activity. A vaccine has been developed that appears to prevent oncogenic papillomavirus infections in women at risk for cervical cancer, and Stanberry and colleagues have demonstrated that a vaccine can safely and effectively prevent HSV-2. However, the vaccine worked only in women, a fact that has not yet been explained. Future studies will focus on mucosal immunity, a factor that may account for this difference.

How does this relate to the pediatric population? It is the teenager or preteenage girl who would benefit most from this vaccine if and when it becomes available in 5 or 10 years. Assuming that the vaccine is proven safe and effective, the question then will be whether parents will be willing to consider the possibility that their teenage or preteenage daughters might be at risk for acquiring this virus.

Recurrence of Herpetic Lesions

When an individual has a primary gingival stomatitis from HSV-1 as a child—and 99% of fever blisters are from HSV-1—the chance of recurrence is much greater than 50%. Recurrences, which are not limited to the lip but may occur anywhere in the labial or facial area, may be precipitated by stressors such as emotional stress, exposure to sunlight, and menstrual periods.

In the genital area, HSV-1 is associated with approximately a 50% chance of recurrence, but recurrences are usually infrequent—about once a year—and the eruption is usually mild. In contrast, HSV-2, which is responsible for 70% of first episodes in the genital area, causes at least 95% of the cases of recurrences.

Varicella-Zoster Virus

VZV infection, commonly called chickenpox, was seen in 4 million children a year in the United States until 1995. That year, the first vaccine was marketed to prevent acquisition of this herpesvirus. Although chickenpox is considered by many laypersons to be a relatively insignificant “skin problem,” the infection can cause severe systemic sequelae, including secondary bacterial infections and possibly death from varicella pneumonia.

Pediatricians have reported the development of a modified form of varicella in vaccinated children. It is important to remember that the varicella vaccine is not 100% effective, but it is officially recognized as almost 100% effective in preventing severe chickenpox and 90% to 95% in preventing chickenpox of any severity. This means that some who have been successfully vaccinated will develop a few vesicles, and these vesicles could be from either a wild-type strain of chickenpox that infects the vaccinated person or from the strain in the vaccine itself.

In either case, parents should be aware that this could develop but should also know that the outbreak is almost never as severe as it would have been without vaccination. However, although severe varicella in vaccinated children certainly seems to be uncommon, the diagnosis should never be ruled out if the clinical signs and symptoms suggest chickenpox, even in a vaccinated child.

Postexposure Vaccination and Treatment

The American Academy of Pediatrics now recommends that postexposure vacci-
nation should be considered for any child who is seronegative and is 12 months of age or older. Postexposure vaccination also should be considered for adult contacts in the household who are seronegative and not pregnant. Vaccination in the first few days after exposure will attenuate the disease and in some cases prevent it.

A debate is ongoing about whether a child should be treated with an antiviral medication if chickenpox develops. The only drug that is well studied for children with chickenpox is acyclovir. It may speed up the healing, may prevent scarring, and hopefully would prevent the complications of bacterial secondary infection and varicella pneumonia. It is at least likely, if started within the first day or two of the illness, to allow children to get back to play or school a couple of days earlier. Treatment a few days earlier and therefore allow the parent or guardian to get back to work or school a couple of days earlier. Treatment does not prevent the formation of immunity to VZV because by the time the first vesicle appears, the virus has been in the body for approximately 2 weeks.

Although no studies have been published to date to support the treatment of a teenager or adult with chickenpox, this is generally considered to be a medical necessity to reduce the high risk for dangerous complications. The treatment of immunocompromised individuals is imperative. Valacyclovir or famciclovir may be used at dosages published for the treatment of herpes zoster.

Herpes Zoster in Children

The recurrence of chickenpox in children—herpes zoster, or shingles—is not unfamiliar to pediatricians. Although shingles is more likely to occur in a child with immunodeficiency, it is not necessarily a marker of reduced immunocompetence.

Shingles can occur either as a consequence of infection with the wild-type varicella virus in infancy, in utero, or in early childhood, or following vaccination with the live attenuated varicella vaccine. When herpes zoster occurs in the first months of life, almost certainly the baby was infected in utero; the development of herpes zoster during childhood is a fairly reliable predictor of varicella infection in the first year of life.

The studies done on cultures from vesicles of children with shingles who had received the vaccine have demonstrated that the vaccine itself may cause the recurrence as shingles. A study from Japan suggests that individuals who are infected with the wild-type varicella develop shingles 10 times more frequently than those who are vaccinated. The severity of herpes zoster infection recurring after wild-type varicella infection also is greater than that experienced by vaccinees, so the occurrence of herpes zoster from the vaccine strain of VZV may not be a great problem.

Most adolescents and almost all adults are seropositive for CMV, but the virus almost always is latent in immunocompetent individuals.

Epstein-Barr Virus

The fourth HHV type, commonly known as Epstein-Barr virus, usually is manifested as infectious mononucleosis in children and rarely is seen as Kikuchi’s syndrome or Burkitt’s lymphoma. There is no specific vaccine or treatment.

Cytomegalovirus

Cytomegalovirus (CMV), HHV-5, is an important herpesvirus because it is the number one infectious cause of fetal abnormalities in the United States as well as the number one cause of blindness in individuals with acquired immunodeficiency syndrome (AIDS). Primary maternal infection with CMV during pregnancy causes infection in 55% of fetuses in utero. Most adolescents and almost all adults are seropositive for CMV, but the virus almost always is latent in immunocompetent individuals.

Other Human Herpesviruses

HHV-6 is the cause of sixth disease, and exanthem subitum is the clinical presentation. Exanthem subitum, or roseola infantum, usually appears as a very transient, erythematous macular eruption that is associated with high fevers, and an occasional patient also presents with diarrhea and/or periorbital edema. The infection is self-limited, and there is no specific treatment or prevention, per se, for HHV-6.

Infection with HHV-6 probably is much more common than is generally realized because the exanthem is probably present in only a small percentage of individuals. It has been shown that, in a large percentage of cases, HHV-6 infection is associated with significant febrile illness, including seizures, in the first few years of life. Only a small subset of these patients have the exanthem. Further, most adults have antibodies to HHV-6, with no memory of having had a clinical manifestation of this infection.

Diseases associated with HHV-7 have not yet been identified, but it has been proposed that this herpesvirus may work in tandem with HHV-6 to cause pityriasis rosea.

HHV-8, the most recently described HHV, is the cause of Kaposi’s sarcoma and possibly other epithelial tumors.

Treatment Options for Herpes Simplex Infections

Three antiviral agents are available to treat HSV-1, HSV-2, and VZV infections in patients of all ages. Acyclovir has been available for 2 decades. In 1995, valacyclovir, the prodrug of acyclovir, was introduced. At the same time, famciclovir, the prodrug of penciclovir, became available. Penciclovir is available only in the topical form, for the treatment of herpes labialis. Acyclovir is available in topical, oral, and intravenous forms. Valacyclovir and famciclovir are available only in the oral form.

All of these drugs are safe and effective because they are activated by the virus. The first step, whether the infection is from HSV-1, HSV-2, or VZV, is that the thymidine kinase coded for by that virus activates either the acyclovir (given as acyclovir or acyclovir as a metabolite of valacyclovir) or penciclovir (given as penciclovir or penciclovir as a metabolite of famciclovir). The cellular enzymes phosphorylate the second and third steps. As a result, the active agent is either acyclovir or penciclovir triphosphate, and the active drug is present only in the infected cell. However, it is important to remember that none of these three drugs is a cure. They work only when taken episodically, to treat outbreaks, or as suppressive therapy.

Only acyclovir comes in liquid form, and the manufacturers of other products have reported no plans to market an elixir of their drugs. Because many children are unable to ingest a pill, capsule, or caplet, and because calculating the correct dosages of valacyclovir and famciclovir can be difficult, acyclovir is the drug most often used in young patients.

In young children who are having outbreaks once a month or every 2 months, suppressive therapy may be worthwhile. Episodic treatment usually is more appro-
priate if outbreaks are less frequent. However, this decision should be individualized; for some patients, particularly if the lesions tend to be severe, even five or fewer outbreaks a year present either physical or emotional difficulties, and so suppressive treatment is warranted. In addition, the greatest benefit from episodic therapy occurs when it is instituted during the prodromal phase of an outbreak. Institution of the antiviral regimen at this point may abort the lesion or may speed up the healing if a lesion develops.

**Herpes Simplex in Teenagers**

In teenagers with genital herpes, acyclovir, valacyclovir, and famciclovir are available for episodic therapy, which can, at best, speed up healing by 1 to 2 days. These agents are more effectively used as suppressive therapy. The recommended dosages for suppression of herpes outbreaks in teenagers and adults are as follows: acyclovir, 400 mg twice daily; famciclovir, 250 mg twice daily; valacyclovir, 500 mg once daily.

Perhaps the most important message about long-term suppression for teenagers with genital herpes is that it can protect the infected person’s partner. The study by Corey and colleagues showed that the daily use of an antiviral medication markedly reduced transmission of HSV to partners who had no history of genital herpes and who were seronegative for HSV-2. This study was done using valacyclovir, but it also should hold true for acyclovir and famciclovir.

Valacyclovir recently was approved by the U.S. Food and Drug Administration (FDA) to suppress outbreaks of herpes labialis in individuals over age 12. In the study that led to FDA approval, 10 subjects were enrolled in the basis of having had three or more outbreaks of herpes labialis in the previous year. One group was given valacyclovir, 2 g twice daily for the first day, then 1 g twice daily for the second day; the second group received 2 g twice daily on the first day and placebo on the second day; and the third group used placebo on both days. Patients were instructed to initiate treatment as soon as they experienced itching, tingling, or other prodromal symptoms, or at the outbreak of a visible lesion. The investigators found that 2 days of therapy was no better than 1 day, but 1 day hastened healing of lesions by almost 2 days. In addition, many individuals were able to abort their outbreaks by taking the medication as soon as they experienced prodromal symptoms.

**Discussion**

**DR. PALLER:** Do we know for certain whether suppressive therapy for HSV with antivirals may induce resistance?

**DR. TYRING:** Up to this point, it does not seem to. Although we have seen some acyclovir resistance in our HIV-positive patients, resistance seemed unrelated to previous use of a nucleoside analog. Cultures done in recent acyclovir studies showed resistance rates no different from those found in cultures done during the first acyclovir studies, some 2 decades ago. So the rate of acyclovir resistance, which would predict the rate of famciclovir and valacyclovir resistance, has not changed for otherwise healthy individuals.

**DR. ORLOW:** I find that parents are typically reluctant to have their child on suppressive therapy, and at times it’s hard to convince them of the value of this strategy.

**DR. PALLER:** Acyclovir is such a safe drug that we can often turn that around. My personal experience with suppressive therapy is that it’s generally well tolerated. What I do is treat for 6 months and then stop treatment to see what happens. I have found that, over time, the overall incidence of the herpetic outbreaks decreases, so children don’t necessarily have to stay on the medication for very long periods of time.

**DR. TYRING:** We have a mass of safety and efficacy data, gathered over more than 20 years of experience with acyclovir and for 8 years with the other two antivirals. All of the liver and kidney function tests, as well as complete blood counts, failed to demonstrate any relationship between use of these agents and clinical or laboratory abnormalities. So, long-term antiviral therapy is safe, but the natural history of the virus is that an individual eventually will have fewer and fewer outbreaks. Most patients won’t need these drugs for their entire lives because the recurrence rate will decrease to levels that will allow most people to eventually switch over from suppressive to episodic therapy.

**DR. PALLER:** Dr. Tying, what about the use of suppressive therapy in children with atopic dermatitis who have eczema herpeticum?

**DR. TYRING:** Eczema herpeticum is among the more severe “atypical manifestations” of HSV, and certainly we use antiviral drugs to treat adults and children. We don’t have dosage recommendations from well-controlled studies in patients with eczema herpeticum of any age, but extrapolating from our knowledge of HSV, we use similar dosages. If a patient has a very mild case of eczema herpeticum, we can use outpatient oral therapy. If it’s a very severe case, the patient would have to be hospitalized for intravenous administration of acyclovir. These drugs are safe and effective for that use.

**DR. PALLER:** I have a comment on the varicella vaccine. We get so many calls from parents of children with atopic dermatitis, questioning whether they should have their child undergo vaccination. I think it’s particularly important for these patients to undergo vaccination to try to prevent this very itchy process that tends to exacerbate atopic dermatitis.

**References**


Current Views on Molluscum Contagiosum

Molluscum contagiosum is a common, benign viral infection of the skin that occurs worldwide. The molluscum contagiosum virus (MCV) is classified as a poxvirus. Several types of MCV and variants have been identified, but the type that affects the vast majority of the pediatric population is MCV-1. The infection occurs in young childhood—occasionally in infancy—through adolescence as well as into adulthood, in both otherwise healthy and immunosuppressed individuals.

In an epidemiologic study headed by Eichenfield (not yet published), data from three centers were pooled and analyzed. The data included age, gender, number of lesions, degree of involvement, and any manifestations of systemic disease or state of immunosuppression. Patients with molluscum were divided into four groups: children below 3 years of age, those from 3 to 5 years of age, those from 5 to 8 years of age, and those greater than 8 years of age. The analysis showed that the age of presentation was under 3 years of age in 28%, 3 to 5 years of age in 25%, 5 to 8 years of age in 27%, and greater than 8 years of age in 20%. No great differences were seen among the racial groups, nor between genders, findings that are consistent with other epidemiologic studies in this area.

Regarding the role of immunosuppression, the data showed that almost all molluscum occurs in patients without immunosuppression. In fact, patients with MCV lesions and immunosuppression were the exception rather than the rule.

Number and Anatomic Distribution of Lesions

In that same study, the investigators found that 63% of patients had fewer than 15 lesions and 30% had between 15 and 30 lesions. Thus, the majority of patients have a small number of MCV lesions.

The most common location of lesions is the trunk—principally the chest wall near the axillae and the flanks, plus the periaxillary areas of the upper arms, although not usually the mid-back, umbilical, or sacral areas. In the cited study, 72% of patients had truncal lesions and almost 25% had lesions on the face, scalp, or ears. However, it is important to remember that MCV lesions may occur anywhere on the body.

Recognizing Molluscum Lesions

The hallmark of MCV infection is a central core in the lesions that contains a white material—the site at which the virus is present. The most common differential diagnosis is warts, distantly followed by unusual presentations of other viral infections, adnexal tumors, epidermoid inclusion cysts, milia cysts, and pyogenic granulomas. In the vast majority of cases, the diagnosis is not difficult to make.

MCV Infection and Atopic Dermatitis

Many clinicians have observed that the preponderance of cases of MCV infection occur in patients with either atopic dermatitis or an atopic diathesis, although no studies have been published to date supporting this impression. It has been reported that MCV infection can induce an eczematous dermatitis in about 10% of children, and this can lead to an exacerbation of preexisting atopic dermatitis.

In the epidemiologic study by Eichenfield and colleagues cited above, 23% of the patients had a history of atopic dermatitis. The cases were pooled from pediatric dermatology settings, so patients with atopic dermatitis may be somewhat overrepresented in this study, but these data clearly show that MCV infection probably is more common in atopic patients.

Almost all pediatric dermatologists and many pediatricians have observed the phenomenon of so-called molluscum dermatitis, or eczematized molluscum, with dry, red skin developing around MCV lesions, even in patients with no history of atopic dermatitis. In such cases, a clinician may mistakenly make a diagnosis of unilateral laterothoracic viral exanthem or nonspecific exanthem with eczematous response.

Another phenomenon that may be related is inflammatory molluscum lesions, which often resemble inflammatory acne papules. These cases are misdiagnosed as “infected,” although frank infection sometimes occurs.

Acquisition of MCV

The issue of MCV transmission is complex because the virus lives in the human body only in keratinocytes and, therefore, is transmitted only through direct physical contact. This statement is qualified by the reports and observations of apparent transmission in wet environments such as swimming pools, although it is unclear whether such transmission occurred through water or by skin-to-skin contact in a wet environment. The question of whether the virus may be transmitted through fomites—such as a wet towel—has not been answered and is problematic to study because MCV is difficult to grow in a laboratory setting.

In addition, it seems—but is not proven—that some individuals have an inherent susceptibility to acquiring MCV infection. For example, most clinicians have had cases of siblings who have been bathed together over time, one with molluscum lesions and the other not developing any signs of infection. In other cases, children acquire MCV infection from casual contact with an infected classmate. Therefore, it appears that both virus and susceptibility must be present for infection to occur.

Treatment Modalities

Despite the fact that MCV infection is extremely common, no agents have yet been approved by the U.S. Food and Drug Administration. Indeed, the rationale for the use of treatments for molluscum is based largely on clinical experience, and very few controlled trials for commonly used agents are available. The modalities currently in use include watchful waiting, destructive modalities, immunomodulation, and—rarely used—systemic antiviral therapy.

In mild to moderate cases, primary care
clinicians can be comfortable treating in the office initially with salicylic acid, lactic acid, or potassium hydroxide, or prescribing podophlox or imiquimod for home applications. In severe or refractory cases, patients should be referred to a dermatologist for evaluation and treatment.

It is important to recognize that results with any treatment modality can be confounded by the virus’s incubation period. The appearance of some papules may be delayed for a month or more from the time of exposure. Therefore, new lesions may occur near the site where previous, individual lesions have been destroyed.

Further, parents should understand that MCV lesions may leave a small scar after resolution, regardless of whether treatment is undertaken or which type of modality is chosen. Often these scars resemble a needle-prick mark. Large lesions, particularly inflamed MCV lesions, often leave a pock mark.

Observation

Because the majority of infections in immunocompetent patients resolve spontaneously within 2 years of the first infection, observation without intervention is an option to consider. The disadvantages of nonintervention are the facts that lesions do last longer in a few patients and that some patients begin with a few lesions and develop many more over time.

Destructive Modalities

Destructive modalities that have been used for MCV lesions include curettage, freezing, and the application of chemodestructive agents. Topical anesthetics make the use of curettage a painless procedure in patients with a few lesions. Cryosurgery is an alternative, but it may cause unacceptable discomfort, particularly for young children.

Although no data have been published on the occurrence of scarring, the clinical impression of these authors is that surgical removal, especially curettage, is more likely to leave pitting than natural resolution or other types of treatments.

Cantharidin, which is no longer available as a ready-made compound in the U.S. market, is gaining popularity as an option for the treatment of MCV lesions. Some recently published retrospective studies support its usefulness for this infection.2,3 However, this is an extremely potent medication that should never be given to parents to apply at home and, in fact, should be applied in the office only by clinicians trained in its use.

Other chemodestructive agents include salicylic acid, lactic acid, and potassium hydroxide. When applied at home, treatment typically is time-consuming, and if the number of lesions is large, compliance is unlikely. Acids applied to young children in the office should be preceded by a topical anesthetic if the child experiences pain on application of the agent. Liquid or gel podophlox, approved for use in genital warts, has been reported to be effective in the treatment of molluscum contagiosum.4 This medication can be irritating, and an optimum treatment schedule for childhood molluscum is not known.

Immunologic Therapies

Many pediatricians use tretinoin for MCV lesions in an attempt to provoke an inflammatory response against MCV. Although this drug may be tried in selected patients who fail other treatments, tretinoin should not be considered as first-line therapy because it tends to cause irritation that results in the spread of the MCV lesions. This is seen especially in the periaxillary and the groin areas because of occlusion.

More recently, immunomodulatory agents, including the immune response modifier imiquimod, have become available, and their use results in a more specific cutaneous inflammatory response. A number of case reports and series and small trials have been published on the utility of imiquimod in patients with MCV lesions.5,6 Until good double-blind data are available, clinical experience with this agent indicates that imiquimod can cause irritation in a few patients but is a safe option to consider. Moreover, imiquimod is a treatment that can be applied safely by parents at home. Some children respond extremely well with cimetidine.7 The experience of some clinicians is that patients with molluscum lesions and atopic dermatitis may do especially well with cimetidine.8 Unfortunately, the taste of the liquid form of this medication limits its use.

Antiviral Therapy

One antiviral medication, cidofovir, which is highly effective against many DNA viruses (and particularly poxviruses), has been used with success in MCV infection.9 This drug is available only in intravenous form and so must be compounded for topical use. Cidofovir is extremely expensive—with one course of treatment costing thousands of dollars—and thus generally should be considered only for use in immunodeficient patients with very recalcitrant molluscum lesions.

Discussion

DR. ORLOW: I would like to get the opinions of others on the panel about topical corticosteroid use in patients with atopic dermatitis and MCV lesions. Although many of our colleagues in pediatrics and dermatology caution parents to avoid putting topical corticosteroids on areas with molluscum lesions, my experience has been that the use of low-potency topical corticosteroids improves the dermatitis and sometimes results in the molluscum virus no longer finding a fertile territory to infect. The clinical trials with the topical immunomodulator tacrolimus and pimecrolimus have not shown any indication that they increase the number of molluscum lesions.

DR. EICHENFIELD: I agree that treatment of the dermatitis can be useful.

DR. PALLER: I also agree that it is important to try to decrease the dermatitis, which tends to promote MCV infection. However, I wonder whether an agent rubbed on the skin can cause autoinoculation of the molluscum virus. There are no data on this.

DR. EICHENFIELD: I think there is less of a risk of spreading the virus with rubbing on those medications than it would be with a child scratching eczematous skin surrounded by molluscum lesions.

DR. ORLOW: What about the use of imiquimod in atopic patients?

DR. PALLER: My experience with imiquimod

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Less Common Viral Exan temas of Special Interest

In addition to the other viruses discussed in this supplement, two other virus groups deserve mention: paroviruses and the enterovirus family.

Parovirus B19

Parovirus B19 is now known to be the causative agent of erythema infectiosum, named in the early 1900s as fifth disease, one of the classic childhood exan temas (see Table).

This disease typically affects patients between 4 and 15 years of age. The peak incidence of erythema infectiosum is in the winter and spring.

The classic presentation is brightly erythematous cheeks—the so-called slapped-cheek appearance. Usually at about day 4 after the onset of facial erythema, a rash appears on the extremities. Although the eruption may be papular at first, it soon takes on the lacy, reticular erythematous appearance that typifies erythema infectiosum. Not uncommonly, the rash persists for weeks—sometimes for up to 2 months—with a waxing and waning course and often recurring in the heat or sunlight, or with physical exertion.

Although usually asymptomatic, the rash of erythema infectiosum is pruritic in about 15% of children. Most affected children are otherwise well; some children experience low-grade fever, headache, and arthralgias, but these symptoms most commonly occur in adolescents and adults with the disease.

**Individuals without immunity are at risk for acquiring parovirus infection if they are exposed to an infected individual during the viremic stage of illness.**

At-Risk Populations

Two groups of individuals are at greatest risk for harm from parovirus infections: patients with shortened erythrocyte survival—particularly those with sickle cell disease or those who have decreased erythrocyte production—and the fetuses of pregnant women who have not acquired immunity to the infection. The target cell of parovirus B19 infection is the erythroid progenitor cell, so that an aplastic crisis can occur in patients with sickle cell disease, hereditary spherocytosis, thalassemias, and other disorders with shortened survival of red blood cells or decreased erythrocyte production. The viral disorder can be fatal in these patients, but symptomatic therapy and blood transfusions are usually sufficient to ensure survival until anti-B19 antibodies are generated, usually in 10-15 days. Spontaneous improvement follows antibody development.

Approximately 50% of pregnant women have had a previous parovirus B19 infection and are immune; in many cases, infections are asymptomatic, so patients may not be able to provide a reliable report of infection. Individuals without immunity are at risk for acquiring parovirus infection if they are exposed to an infected individual during the viremic stage of illness. The risk to the fetus is highest if the infection is acquired at less than 28 weeks' gestation, when fetal anemia, nonimmune hydrops fetalis, and fetal death may occur. Overall, the risk of fetal death from parovirus infection is 1% to 9%. It is important to recognize that the viremia that is associated with contagion in a patient with erythema infectiosum occurs prior to any cutaneous manifestations. By the time the slapped-cheek and other rash es occur, the patient is no longer contagious.

If a pregnant woman has been exposed to an individual with parovirus infection prior to the cutaneous stage or shows any signs of an acquired infection, acute and convalescent parovirus B19 serum titers should be obtained. If a patient shows any evidence of infection, the fetus should be followed by ultrasonography for signs of hydrops. In addition, detection of B19 antigens in amniotic fluid is now possible. If a fetus seems to be affected, in utero administration of digitalis and red blood cell transfusions are treatment options.

**Table. Classic Childhood Exan temas**

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<thead>
<tr>
<th>First disease</th>
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<tr>
<td>Second disease</td>
<td>Scarlet fever</td>
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<td>Third disease</td>
<td>Rubella</td>
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<tr>
<td>Fourth disease</td>
<td>Filatov-Dukes syndrome</td>
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<tr>
<td>Fifth disease</td>
<td>Erythema infectiosum</td>
</tr>
<tr>
<td>Sixth disease</td>
<td>Exan them subitum (roseola infantum)</td>
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Mollusc um Contagiosum

Continued from previous page

has been that it hasn’t caused irritation in my atopic patients more often than in the rest of my patients.

References

Viral Exanthems
Continued from previous page

**Papular-Purpuric Gloves and Socks Syndrome**

In the last decade, another cutaneous manifestation of parvovirus B19 infection was recognized: the papular-purpuric gloves and socks syndrome (PPGSS). Although originally linked strictly to parvovirus infection, this condition has now been associated with other viral agents, including human herpesvirus 6 (HHV-6) and cyto-megalovirus. This is a self-limited eruption that often begins with intense erythema and edema of the palms and soles, sharply demarcated at the wrists and ankles. The morphology of these lesions progresses to petechiae and purpura. Patients often describe associated pruritus and burning. In some patients, a vesicular exanthem can be seen on close inspection on the palate, pharynx, tongue, and/or inner lips.

Fever, headache, myalgias, arthralgias, and lymphadenopathy have been described in association with these cutaneous signs and symptoms. Spontaneous resolution of this condition usually occurs within 1 to 2 weeks.

In contrast to the situation with the slapped-cheek manifestation of parvovirus B19 infection, the period of contagion with PPGSS occurs during the period of cutaneous eruptions and does not end before resolution of the lesions. This is an especially important difference to pregnant women or other individuals who may not be immune to parvovirus B19.

**Enteroviruses**

Nonpolio enteroviral infections are the leading cause of exanthematous diseases in children during the summer and fall months. This group of viruses includes coxsackievirus groups A1 to A24 and B1 to B6, echoviruses 1 to 34, and enteroviruses 68 to 72. Enteroviruses can lead to myriad cutaneous and visceral manifestations, so this discussion will be limited to those that are most important in the pediatric population, namely polymorphous, macular, or papular eruptions and, less commonly, vesicular or urticarial lesions.

Echovirus type 9 has been associated with diffuse petechiae or purpura. This is a condition that is often accompanied by aseptic meningitis, so it may be difficult to distinguish it clinically from meningococcemia.

Hand-foot-and-mouth disease (HFMD) most commonly occurs in young children and is characterized by an erosive stomatitis with vesicles on the palms and soles. A maculopapular erythematous eruption on the buttocks, thighs, and external genitalia may be associated. The oral vesicles and erosions are usually seen somewhat broadly within the mouth, occurring on the buccal surfaces, the tongue, palate, uvula, gingivae, or anterior tonsillar pillars. Fever and malaise may be seen in this condition as well. The virus most frequently associated with HFMD is coxsackievirus A16, but other coxsackieviruses and enterovirus 71 have also been implicated.

Herpangina, another enteroviral disorder, is also characterized by an exanthem and fever, but without the cutaneous component. Therapy for both HFMD and herpangina is supportive.

If a pregnant woman has been exposed to an individual with parvovirus infection... or shows any signs of an acquired infection, acute and convalescent parvovirus B19 serum titers should be obtained.

**Morphologic Viral Manifestations of Special Interest**

**Papular Acrodermatitis of Childhood (PAC)**

Papular acrodermatitis of childhood (PAC) was originally described in 1955 as Gianotti-Crosti syndrome and was reported to be an exanthem that occurred in association with hepatitis B infection, as originally described with Gianotti-Crosti syndrome, actually is quite rare in the United States. The association with hepatitis B infection; in the United States, the infection is self-limited, but they should also be cautioned that clearing of this condition may take up to 4 months.

**Unilateral Laterothoracic Exanthem**

Unilateral laterothoracic exanthem (Figure 2), also called asymmetric periflexural exanthem, is also recognized by its pattern of presentation. Most patients with unilateral laterothoracic exanthem are between 1 and 4 years of age. The eruption typically occurs initially in a localized, unilateral distribution. Most commonly, the laterothoracic trunk and axillae are involved, and because of the appearance and distribution aids in making the diagnosis. Serologic evaluation is not necessary unless the physical examination suggests infection with hepatitis virus or Epstein-Barr virus—for example, if hepatosplenomegaly or significant lymphadenopathy are present.

The lesions clear spontaneously between 3 and 12 weeks after they appear, with about 4 weeks being the average time to resolution. Parents can be reassured that this infection is self-limited, but they should also be cautioned that clearing of this condition may take up to 4 months.

The condition is recognized by its clinical manifestations (Figure 1): monomorphous, variably edematous, erythematous papules that range in size from 2 to 6 mm in diameter, with larger lesions tending to occur in young infants. The papules, which may be pruritic, typically occur in a symmetrical distribution on the cheeks, buttocks, and extensor areas of the extremities, with relative sparing of the trunk. This characteristic distribution aids in making the diagnosis. Serologic evaluation is not necessary unless the physical examination suggests infection with hepatitis virus or Epstein-Barr virus—for example, if hepatosplenomegaly or significant lymphadenopathy are present.

![Figure 1. Papular Acrodermatitis of Childhood (PAC)](image)

This exanthem is characterized by monomorphous, variably edematous, erythematous papules ranging in size from 2 to 6 mm. In Europe and Japan, PAC is associated with hepatitis B infection; in the United States, the association with hepatitis B is rare.
ition of the eruption, patients often are referred to the dermatologist for evaluation of possible contact dermatitis.

The lesions themselves can be macules or papules; the papules can be morbilliform or scarlatiniform, and sometimes they actually appear eczematous. Although it starts unilaterally, it is quite common for this eruption to spread to the contralateral side; however, the side of origin always predominates. Approximately 60% of patients complain of pruritus. The condition has not been linked to any specific viral agent, and, in fact, several viral agents have been implicated according to serologic evaluation. This condition usually resolves spontaneously, but the course is often prolonged—typically, 4 to 6 weeks. As with PAC, parents can be reassured but should be told about the expected duration of this process.

**Pityriasis Rosea**

Pityriasis rosea is a condition that is commonly considered to be a viral exanthem, and the fact that it persists for 6 to 8 weeks in many patients certainly supports such a classification.

The classic American medical school discussion of pityriasis rosea may provide an inaccurate view of the spectrum of this condition. Medical students in this country are taught that a herald patch and truncal eruption are characteristic. However, many patients present with lesions centered around the groin, the axillae, and the neck areas—the so-called inverse version of pityriasis rosea. As a result, the diagnosis may be missed, despite the fact that the lesions themselves are typical: oval, with an outward scale at the border. In addition, it is important to remember that lesions may have more pigmentation in patients of color.

If patients are seen early in the course of their disease, the use of oral erythromycin may shorten the course, according to some recent evidence. In addition, one or two sessions with natural or artificial ultraviolet light, as may be delivered in a dermatologist’s office, may be helpful to hasten resolution of the condition. Applications of topical corticosteroids may decrease pruritus, if present, but does not affect the presence of the eruption.

**Discussion**

**DR. ORLOW:** We are seeing quite a number of cases of asymmetric periflexural exanthem at our center, and I wonder whether that reflects an increased incidence of this condition or increased recognition of it.

**DR. PALLER:** In fact, this disorder has been around for decades—reports were found dating as far back as 1962—but it’s not yet clear whether the incidence is really increasing. Now that we’re aware of this condition and we’re able to group these patients, it certainly becomes a diagnosis that we’ll start to see more of.

**DR. ORLOW:** Once a clinician is alert to the characteristics of this eruption, it certainly is an easy diagnosis to make. It should be considered in any child of the appropriate age who presents with an asymmetric exanthem and in any child in whom the diagnosis of axillary unilateral eczema or contact dermatitis is being considered.

**References**


Viral Skin Diseases in the Pediatric Practice:
Update on Management, Immune Response Modifiers, and Other Therapies
CME Test and Post-Test Evaluation

INSTRUCTIONS: Please circle the most appropriate response. Seven of ten correct responses are required for credit.

1. The 1991 American Academy of Pediatrics Committee on Child Abuse and Neglect suggested that any case of anogenital warts in a child resulted from probable abuse and needed reporting. The 1999 Guidelines:
   a. made this statement even stronger
   b. reaffirmed this view
   c. stated that anogenital warts should raise suspicion and advised close follow-up
   d. stated that anogenital warts should be reported based on the age of the patient, history, and other physical findings

2. The treatment specifically approved for common warts in children is:
   a. cantharidin
   b. imiquimod
   c. squaric acid dibutylester
   d. none of the above

3. The gold standard for diagnosing a herpesvirus infection is:
   a. direct fluorescent antibody antigen test
   b. serologic test
   c. Tzanck smear
   d. viral culture

4. Filiform warts occur most commonly on the:
   a. hands
   b. face
   c. feet
   d. genitals

5. Which one of the following statements concerning HSV is not true?
   a. Anatomic location is an excellent indication of the causative HSV type.
   b. HSV-1 increasingly is a cause of genital herpes.
   c. HSV-2 infection incidence in teenagers down to age 12 has increased by 30% over the past 2 decades.
   d. Infection with genital HSV is associated with a fivefold increase in HIV infection.

6. In individuals with a history of a primary genital herpes lesion from HSV-1, the risk of recurrence is approximately:
   a. 30%
   b. 50%
   c. 70%
   d. 90%

7. The only antiviral drug available in elixir form is:
   a. acyclovir
   b. famciclovir
   c. penciclovir
   d. valacyclovir

8. The varicella vaccine is ___ effective in preventing chickenpox of any severity.
   a. 100%
   b. almost 100%
   c. 90% to 95%
   d. 85% to 90%

9. Scarring after resolution of molluscum contagiosum lesions may occur:
   a. with any intervention or with no treatment
   b. with cryosurgery only
   c. with curettage only
   d. with immunotherapy only

10. The so-called slapped-cheek appearance is a cutaneous manifestation of:
    a. cytomegalovirus
    b. echoviruses
    c. HHV-6
    d. parvovirus B19

CME ACTIVITY EVALUATION

1. Were you able to meet the objectives of this CME activity? (circle one)
   YES      NO

   If no, please note which objectives you were not able to meet:

2. Will the information presented in this issue be useful in your practice setting?
   YES      NO

   Comments:

3. Did you find the information presented in this publication to be objective, balanced, and free of commercial bias?
   YES      NO

   Comments:

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