

Pediatric Viral Exanthema: A Review Article

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Received 2016 October 25; Revised 2017 March 07; Accepted 2017 March 13.

Abstract

Context: Many diseases caused by viral agents are associated with fever and cutaneous manifestations. Viral exanthema is a widespread nonspecific skin rash, commonly characterized by generalized eruption of erythematous macules and papular lesions. Although these rashes are mostly benign and self-limited, some may be serious and life-threatening. Differentiation between severe and benign types is clinically important and life-saving.

Evidence Acquisition: In this narrative review, electronic databases, including Google Scholar, Science Direct, PubMed (including Medline), Web of Science, Scientific Information Database, and Scopus, were searched. We conducted a narrative review of papers published on pediatric viral exanthema during 2000 - 2016. The used keywords included "viral exanthema", "fever", and "skin rash". Articles on skin rash, caused by drug reactions or nonviral exanthema, were excluded.

Results: Different viral agents can cause different types of skin reactions. Cutaneous manifestations and skin rashes can be categorized, based on the form of the rash (macular, papular, vesicular, blister, petechial, and purpuric) or the general term, which denotes illnesses such as measles-like morbilliform rash, rubella or rubelliform rash, and scarlatiniform rash, a scarlet-fever like infection.

Conclusions: Based on the findings, a systematic approach relying on accurate history-taking and analysis of epidemiological cues and rash characteristics is of great significance.

Keywords: Viral Exanthema, Viral Rash, Exanthema, Viral Rash, Children, Infant

1. Context

Cutaneous manifestations, accompanied by fever, are common findings in children, presenting to emergency departments or physician office. The causes are diverse, including a large number of infectious and noninfectious diseases. Rash is a common finding in many viral infections among children. Viral exanthema is a nonspecific rash, commonly characterized by generalized eruption of erythematous papules and/or macules (1). In most cases, the rashes are benign with a self-limited course, while in some patients, treatment of exanthematous disease may be crucial to facilitate appropriate management and prevent further spread of the infection (2).

In the initial evaluation of children with cutaneous eruption, a systematic approach relying on clear history-taking, epidemiological clues, and careful physical examination (with special attention to the type and characteristics of exanthema and its association with fever and other signs and symptoms) can be helpful in differentiating the causes of exanthema. Through these measures, we can determine patients who need immediate medical intervention or those who require adequate management to prevent further transmission of the infection without per-

forming any specific laboratory tests (3).

In this narrative review, the main objective was to establish a systematic clinical approach for timely diagnosis of patients who present with cutaneous eruption and require immediate medical intervention to prevent infection transmission through proper medical history-taking, careful physical examination, and epidemiological cues, without applying any specific laboratory tests. In addition, in this paper, we conducted a short overview of a number of viral infections, which are associated with some form of cutaneous eruption and other signs and symptoms and are differentiated using epidemiological cues.

2. Evidence Acquisition

In this narrative review, electronic databases, including Google Scholar, Science Direct, PubMed (including Medline), Web of Science, Scientific Information Database, and Scopus, were searched. We conducted a review of articles published on pediatric viral exanthema during 2000-2016. The keywords included "viral exanthema", "exanthema", "fever", and "skin rash". All studies on different types of pediatric viral exanthema, with or without fever,

were included. On the other hand, articles concerning skin rashes, caused by drug reactions and nonviral exanthema, were excluded.

3. Results

3.1. Clinical Examination

Careful clinical examination is fundamental for every patient with exanthema. Therefore, special attention should be paid to the general appearance, mental status, and cardiopulmonary status to select patients at risk. Also, full examination of skin and mucus for determining rash characteristics and enanthema, along with the analysis of other signs and symptoms, is important for differential diagnosis of diseases.

3.2. Types and Characteristics of Exanthema

Various infectious and noninfectious agents can cause cutaneous eruption and/or similar clinical syndromes. In patients with febrile exanthema, special attention should be paid to the characteristics of the rash, including shape, color, initial site of eruption, distribution, progression, evolution, tenderness, and desquamation, for making a differential diagnosis.

Different viral agents can cause similar skin reactions, while one viral agent may lead to different types of rash. Dermal manifestations and rashes can be categorized based on the form of the rash (ie, macular, papular, vesicular, blistery, petechial, and purpuric) or the general term, which denotes diseases such as measles-like morbilliform rash, rubella or rubelliform infection, and scarlet fever-like scarlatiniform rash.

In addition, distribution of rash throughout the body (diffused or localized, symmetric bilateral or unilateral, and open or covered), its progression from the primary site to other parts of the body, and its distribution in the body (face, trunk, abdomen, and peripheral regions with the highest density in the extremities) can be useful in distinguishing the pathogens (4-6).

Clinical features other than mucocutaneous syndrome (alone or in combination with other diseases) can provide valuable clues for clinical diagnosis. Mucocutaneous eruption is common in many viral illnesses, whereas other signs and symptoms, such as fever, cough, hoarseness, sore throat, organomegaly, lymphadenopathy, and conjunctival involvement may narrow the differential diagnosis.

3.3. Epidemiological Cues and Agents

Information about contact between the patient and the epidemiological agent (and its environment) is important in skin exanthema. Epidemiological features such as

age, season, geographical location, exposure, incubation period, contact with animals/insects, history of immunization or prior diseases, immune system status, and medication use are more helpful in distinguishing viral infections than exanthema itself.

3.3.1. Measles or rubeola

Measles is a highly contagious disease with a worldwide distribution. It is a vaccine-preventable infection, for which highly effective vaccines have been available for more than 50 years. Immunization of children aged ≥ 12 months with 2 doses of vaccine (administered 4 weeks apart) can result in life-long immunization in the majority of cases (7, 8). Measles remains as one of the leading causes of pediatric mortality, with more than 530,000 children dying from measles each year worldwide (9).

After universal implementation of measles vaccination, the incidence of this disease has markedly decreased worldwide. With the use of vaccines over the past 30 years, the incidence of measles has markedly decreased, compared with prevaccine eras. Despite high vaccination coverage, measles outbreak continues to occur in both developed and developing countries, and the disease is still regarded as a major health burden (10, 11).

Following incubation for 10 days, measles classically presents with prodromal fever, cough, nasal congestion, and rhinoconjunctivitis. In severe cases, generalized lymphadenopathy may present prominently in the cervical and occipital regions. In the late prodromal phase, pathognomonic enanthema, known as Koplik spots, develops, composed of gray-white papules with an erythematous base on the buccal mucosa, adjacent to molar teeth. Exanthema develops 2 - 4 days after the prodromal phase and consists of erythematous maculopapular lesions, which begin on the forehead, on the hairline, and behind the ears and then spread in a cephalocaudal trend.

At time of skin eruption, high fever persists for 48 hours, followed by sudden occurrence of lysis. On the fifth day, exanthema starts to fade in the same manner as it appeared, accompanied by fine desquamation. Full vaccination in children after 12 months (2 doses, 4 weeks apart) results in full immunization, meaning that exanthematous disease is probably not measles (12). Although measles is not classically confused with other diseases, in mild cases, it may be confused with rubella, infectious mononucleosis, mycoplasma infection, roseola, enteroviral infections, or Kawasaki disease. By considering other signs and symptoms of rash associated with fever, we can differentiate measles from other diseases.

3.3.2. Rubella

Rubella, also known as German measles or 3-day measles, is an epidemic disease, caused by an enveloped RNA togavirus (13). The mechanism of infection in rubella is similar to measles. It is usually a mild, self-limited disease in children and adults, although it can cause major complications, including miscarriage, stillbirth, and severe congenital malformations during early pregnancy and lead to viral transmission to the fetus. In general, rubella is a vaccine-preventable infectious disease. Administration of a single dose of vaccine in children (after 12 months) can result in full immunization in the majority of cases.

The incidence of rubella has markedly declined since the licensure of MMR vaccine in 1969, administered in children aged 12 - 15 months. In the United States, the incidence of rubella has declined by more than 98%. A seroepidemiological study among 16- to 35-year-old unvaccinated females in Mazandaran (North of Iran) showed that nearly 91% of cases were infected before marriage (14). Rubella typically presents after an incubation period of 16 - 18 days with mild prodromes, including fever, headache, and upper respiratory tract symptoms.

In children, many cases of rubella are subclinical. One to 3 days following the prodromes, eruption of erythematous macules and papules appears on the face, spreading in a cephalocaudal trend over 2 - 3 days. Erythematous petechial macules may be also present on the soft palate (Forchheimer spots). The eruption is often accompanied by tender lymphadenopathy, especially in the occipital, posterior auricular, and cervical regions. The cutaneous eruption tends to fade in 2 - 3 days in the same manner as it appeared without desquamation (in contrast to measles). The most common complication of rubella is congenital rubella syndrome.

Congenital rubella occurs when an unvaccinated pregnant woman is infected during the first few weeks of gestation and the virus is transmitted to the fetus. Birth defects occur most commonly following infection during the first 16 weeks of pregnancy. Congenital rubella syndrome is characterized by cataract, glaucoma, deafness, congenital heart disease, and central nervous system abnormalities (ie, microcephaly and hydrocephalus) (15).

3.3.3. Varicella

Varicella, also known as chickenpox, is caused by the varicella-zoster virus. It is the clinical manifestation of primary infection with varicella zoster virus and is mainly a pediatric disease (16). Studies on unvaccinated cases indicate that nearly 90% of individuals naturally become infected by 16 years of age. The disease is a vaccine-preventable infection, and 2 doses of vaccine can lead to

specific protection. However, vaccination is not dominant in many parts of the world (17). The virus usually spreads through direct contact with cutaneous lesions or respiratory droplets.

Varicella viruses are highly contagious and are transmittable within 1 to 2 days prior to the onset of symptoms. Varicella is contagious as long as active lesions are present in immunocompetent patients (until about 5 days after the onset of exanthema). The average incubation period is 2 weeks (10 - 28 days) (2). In children, the disease begins after an incubation period of 12 - 18 days, and the prodromal stage is milder in children than adults.

Varicella is characterized by elevated body temperature and mild fatigue. Exanthema typically begins at the hairline and spreads in a cranial to caudal direction, with involvement of the scalp and oral mucosa; the lesions are mostly distributed in the center. Initially, erupted lesions are red macules, which progress to papules, umbilicated vesicles, and pustules and then crust within 48 hours. The most important characteristics of varicella include central distribution, umbilication, and presence of different highly pruritic skin rashes in the anatomic area (Figure 1).



Figure 1. Varicella, Characterized by Papules, Umbilicated Vesicles, and Pustules on the Trunk

Primary infection with varicella zoster virus persists in the body for a lifetime. Reactivation of the virus, as a result of diminished T-cell immunity (due to advanced age, immunosuppressant therapy, malignancy, and sometimes no obvious cause), leads to herpes zoster. Herpes zoster begins with prodromal pruritus, tingling, tenderness, hyperesthesia, and/or intense pain in more than 90% of patients. These symptoms occasionally occur without subsequent skin lesions, a phenomenon referred to as “zoster sine herpete”. However, most patients develop painful eruption of grouped vesicles on an erythematous base with a dermatomal distribution.

Herpes zoster usually resolves without sequelae in children and young adults with intact immune systems. However, pain, cutaneous lesions, and complications associated with herpes zoster become more severe with advancing age and compromised immunity. The most common

complication is postherpetic neuralgia, which is characterized by dysesthetic pain (a burning or stabbing sensation and allodynia) and persists after skin lesions have healed. This condition affects 10% - 20% of all herpes zoster patients, and its incidence and severity increase with age (18).

3.3.4. Hand-Foot-Mouth Disease (HFMD)

HFMD typically occurs in young children during summer and fall. It is highly contagious, and the most common pathogen is coxsackievirus A16. Less common causative agents include coxsackieviruses A2, A5, A9, A10, B2, B3, and B5, as well as enterovirus 71 (19). Transmission is predominantly through the fecal-oral route. Exanthema is preceded by a prodromal stage (lasting 2 - 4 days) and is associated with fever, loss of appetite, sore throat, and abdominal pain. It is characterized by large (2 - 8 mm), oval, and gray blisters on the dorsal surface of the fingers and the palmoplantar surface.

Painful aphthous-like erosions on the oral mucous membranes (palate, tongue, and cheeks) characterize enanthema (Figure 2). It should be noted that exanthema is not always present at all sites of predilection (incomplete forms) and can also affect other regions, such as the thighs. Recovery may be expected after 5 - 10 days (20-22). The rash distribution in classical cases helps distinguish it from other vesiculobullous diseases, such as herpetic infection, herpes zoster, and chickenpox.



Figure 2. Hand-Foot-Mouth Disease Characterized by Oval, Gray Blisters with Painful Aphthous-Like Erosions

3.3.5. Parvovirus B19 Infection

This type of infection is most often known as erythema infectiosum or fifth disease. In infants and children, it is characterized by a distinctive rash, which may be preceded by mild systemic or upper respiratory tract symptoms, including mild fever, malaise, headache, myalgia, and arthralgia (7 - 10 days before exanthema eruption). In older children, adolescents, and adults, especially women, arthritis is more common, while skin rash is less prominent and distinctive.

Arthropathy is symmetric and polyarticular, involving the knees, fingers, and other joints. The characteristic rash in children is deep facial erythema (slapped cheek syndrome) with perioral pallor. The symmetric red macular skin rash extends from the trunk (proximal end of the extremities), is clear in the center, and progresses peripherally, with a lace-like reticulated appearance involving the trunk, arms, buttocks, and thighs. The rash can wax and wane with environmental changes, such as low and high temperature for weeks to months.

In addition, other types of skin rash, such as rubelliform rash, scarlatiniform rash, and papular-purpuric glove-and-sock syndrome with pruritus may occur. Erythema infectiosum is characteristic in children, while in adults, the disease should be confirmed by specific IgM antibodies. When diagnostic confirmation of B19 infection is indicated, detection of serum anti-B19 IgM antibody is the preferred method; in fact, its presence indicates infection over the past 2 - 4 months. Nucleic acid hybridization and polymerase chain reaction assay are especially useful for diagnosing infection in immunocompromised hosts (18).

3.3.6. Epstein-Barr Virus Infection (EBV)

Infectious mononucleosis (IM) is the most common presentation of EBV infection, which classically manifests as fever, exudative tonsillopharyngitis with petechiae, cervical lymphadenopathy, and atypical lymphocytosis. The spectrum of disease is wide, ranging from asymptomatic infection, unrecognized upper respiratory tract infection in infants and young children, classic IM, IM with generalized lymphadenopathy, hepatosplenomegaly, and even complicated fatal infections.

In 3% -15% of IM cases, a red maculopapular rash can develop centrally within 3 - 5 days following the onset of the disease. However, in more than 90% of patients with IM, an erythematous maculopapular skin rash may develop on the face, trunk, and extremities 5 - 10 days after treatment with penicillin (eg, penicillin and amoxicillin); the rash may be pruritic mostly in adults rather than children. Infection can be diagnosed serologically by positive IgM antibody against viral-capsid antigen (23). It may be even confused with streptococcal pharyngitis or scarlet fever.

3.3.7. Molluscum Contagiosum (MC)

MC is the only remaining poxvirus infection to specifically afflict humans. This disorder is caused by the MC virus (MCV), a member of the Molluscipox genus of Poxviridae viruses. Two molecular subtypes of the virus, ie, MCVI and MCVII, can result in indistinguishable skin lesions. In general, MC is a common, self-limited condition in children.

MC lesions are firm and umbilicated with pearly papules and a waxy surface. They can occur anywhere on

the skin surface but are most common in skin folds (eg, axillae and neck) on the lateral trunk, thighs, and genital region. Facial lesions can also occur and are often distressing for the patients. Also, widespread, large, and occasionally deforming lesions may be seen in the setting of immunosuppression, particularly AIDS. The associated molluscum dermatitis is common, especially in children with atopic dermatitis (24).

3.3.8. Human Papillomavirus (HPV) Infection

HPV infects epithelial cells in the skin and mucous membranes. The most common clinical manifestation of this virus is wart (verrucae). There are more than 150 different HPV subtypes, each with a tendency to a particular part of the body. For instance, the most common warts on the hands and feet are caused by HPV types 1, 2, 4, 27, and 57.

Warts have various forms, including common warts (*verruca vulgaris*), flat warts, myrmecia, plantar warts, coalesced mosaic warts, filiform warts, periungual warts, anogenital warts (venereal or *condyloma acuminata*), oral warts, and respiratory papillomas. Palmar and plantar warts are lesions described as rough papules on the palms, soles, and lateral sides of the hands and feet with slight central depression.

Cutaneous warts are caused by a small group of specific HPV types, with an overall prevalence of 20% in school children and a decline with increasing age. Patients residing in larger households often report an infected cohabitant, supporting person-to-person transmission. The majority of warts regress spontaneously within 1 - 2 years. Reinfection with the same HPV type is uncommon after clearance, suggesting the development of protective type-specific immunity.

Common warts not only can cause inconvenience, anxiety and reduced quality of life among patients (due to persistence and pain), but also can be a therapeutic challenge for clinicians; therefore, analysis of treatment options seems necessary. Although warts are self-limited in nature and can disappear after a few months, they may remain for years and have recurrences (25, 26).

A subset of HPVs, designated as high-risk (most often HPV 16 - 18), is now recognized as the primary etiological agent for cervical cancer and the associated precursor lesions (a subset of malignancies in other anogenital sites or upper aerodigestive tract and squamous cell cancer of the digits in rare cases). In contrast, infection with common cutaneous HPV types (eg, types 1, 2, 4, and 27) is not thought to have an oncogenic potential. In immunocompromised patients, HPV infection tends to persist and result in an increased risk of anogenital neoplasia.

3.3.9. Crimean-Congo Haemorrhagic Fever (CCHF)

CCHF is a serious and potentially fatal viral disease, which often has hemorrhagic manifestations. This disease is a tick-borne viral infection, reported in many parts of the world including Iran. The virus is maintained through a tick-vertebrate-tick transmission cycle. The typical zoonotic hosts seem to be small mammals, including sheep and goats.

The overt symptomatic disease is known to occur only in humans. Humans are infected through tick bites or contact with tissue, blood, or milk of infected animals or humans. Since infected animals are asymptomatic, most human cases are reported among farmers. Also, several outbreaks of CCHF have been reported among healthcare workers, hospital staff, and laboratory technicians.

The incubation period seems to be 3 - 7 days. The pre-hemorrhagic phase suddenly begins with high fever, general toxicity, flushing, myalgia, nausea, vomiting, and diarrhea, associated with conjunctival injection. After few days (mostly 3 days), the hemorrhagic phase begins and continues for 2 - 3 days. In this phase, petechia, large hematoma, nasal bleeding, hematuria, and bleeding of the gingiva, gastrointestinal tract, vagina, and lung may occur. If the patient survives the hemorrhagic phase, a slow convalescent phase begins. Fatality is high, but early treatment with ribavirin may improve the outcomes (27).

3.3.10. Other Exanthematous Diseases

There are a number of viruses which cause exanthema and are associated with respiratory or intestinal infections. They primarily include nonpolio enteroviruses (coxsackie, ECHO, and new types of enterovirus) in the summer, as well as rhinovirus, adenovirus, parainfluenza virus, respiratory syncytial virus, and influenza virus in cold months. Nonspecific exanthema is usually maculopapular. Also, enterovirus-associated exanthema tends towards the formation of papulovesicles resembling varicella, but lack the classic polymorphic appearance and rarely affect the scalp or oral mucosa; the specific exanthema in HFMD is an exception. The main characteristics of some viral infections, accompanied by cutaneous manifestations, are presented in Table 1.

4. Conclusions

Fever is a common symptom among patients with viral exanthema. In the initial evaluation of febrile children with rash, proper history-taking and careful clinical examination are preferred to the sole use of laboratory tests, the results of which may not be immediately available. Certain exanthema rashes have distinct patterns and prodromal

Table 1. The Main Characteristics, Clinical Presentations, and Types of Rash in Some Viral Infections

Viruses	Incubation Period, d	Season	Clinical Manifestations	Exanthema	Distribution	Duration, d
Adenovirus (ADV)	6 - 9	Winter and spring	Fever, acute respiratory infections, pharyngitis with or without red conjunctivitis, and occasional rash after fever	Most commonly erythematous papular rash, discrete rubelliform rash, and rarely EM and SJS	Commonly extending from the face and spreading downward towards the trunk and extremities	3 - 5
Enterovirus	4 - 7	Summer and fall	Fever and mild pharyngitis, herpangina, HFMD, and other manifestations of systemic disease	Exanthema in 5-50% of infections, most commonly maculopapular and discrete, and rarely petechial, vesicular, or urticarial	- Commonly extending from the face and spreading downward to the trunk and extremities - Possible peripheral distribution similar to HFMD	3 - 7
Herpes simplex virus (HSV-1 & HSV-2)	2 - 12	Non-seasonal	Primary disease including fever and systemic symptoms and recurrent disease caused by exogenous stimuli	Single or grouped vesicles (2 - 10 mm) on a mild erythematous base and occasionally associated with EM, SJS, and erythema nodosum	- Primary infection: lesion around the mouth - Recurrent infection: anogenital in the mouth	7 - 14
Human herpes simplex (HSV-6)	3 - 7	Non-seasonal	Fever for 2-6 days, sudden rash after disappearance of fever, and posterior-auricular, occipital lymphadenopathy	Red macules or M papules	Prominent on the neck, trunk, and some extremities	1 - 2
Mumps	14 - 21	Fall, winter, and spring	Fever, headache, salivary swelling, meningoencephalitis, and postpubertal orchitis	Discrete erythematous M papular lesions	Mostly on the trunk	2 - 5
Molluscum contagiosum	-	Winter and spring	Umbilicated nodular lesions (single or in clusters)	Umbilicated nodular lesion and skin color changes	Most commonly on the face, inner sides of the thighs, breasts, and genitals	+100
Papilloma (wart)	-	Non-seasonal	Localized disease	Papular, nodular, and isolated lesions	Most commonly on the extremities	+100
Varicella (chickenpox)	2 - 20	Winter and spring	Malaise, fever, and headache for 5 - 6 days	Basic vesicular lesion evolving in different stages, macular to papular, vesicular, and pustular rashes, crusting within 48 hours in crops	Most prominently on the face, trunk, and proximal extremities	6 - 7
Zoster			Pain and paresthesia with dermatome distribution	Basic lesion as chickenpox	Localized in the skin, innervated by a single sensory ganglion	10 - 28
Rhinovirus	2 - 4	Fall, winter, and spring	Mild fever, nasal congestion, and exanthema in 5% of cases	Discrete and red maculopapular rash	Extending from the face and spreading downward towards the trunk and extremities	1 - 4
Reovirus	4 - 7	Summer	Fever, pharyngitis, and cervical lymphadenopathy	Erythematous maculopapular rash, discrete or confluent in some vesicles	Extending from the face and spreading down towards the trunk and extremities	3 - 9

Abbreviations: EM, Erythema multiforme; HFMD, Hand-foot-mouth disease; SJS, Steven-Johnson syndrome (4, 18, 19).

symptoms (before rash eruption), which aid in incriminating the causative virus. However, in many cases, an accurate diagnosis cannot be established on the basis of clinical findings alone. History-taking, including the disease transmission route, immunization records, previous exanthematous diseases, and the associated prodromal symptoms, may be helpful when evaluating these patients. In this regard, careful physical examination, clear history-taking, and analysis of epidemiological cues are of great importance.

Footnotes

Financial Disclosure: None.

Funding/Support: None.

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