

PEDIATRIC EXANTHEMS

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Pediatric rashes generate a large amount of clinical work and a great deal of parental concern. As a result of waning maternal antibodies and increasing exposure in childcare and school settings, children are particularly susceptible to infections. Although many childhood rashes are caused by viruses (Table 1), multiple other etiologies must be considered, and some common conditions remain idiopathic. An interesting paradox complicates the diagnosis of these exanthems: Although there is a limited range of skin responses to a large number of causative agents, there can also be significant morphologic variability in response to the same agent. This article focuses on common and historically important maculopapular erythematous rashes of childhood, including some that have been greatly affected by aggressive immunization programs over the past four decades and one that has resurfaced recently as a possible bioterrorism weapon. The emphasis is on the defining characteristics of these conditions with the goal of helping clinicians with the daunting diagnostic challenge they often present. We include the latest available evidence regarding the pathophysiology, diagnosis, and management of these exanthems.

ROSEOLA INFANTUM

History

Roseola infantum is a common childhood febrile exanthem caused by herpes viruses 6 or 7 (HHV-6 or HHV-7) [1]. Other common names for this

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TABLE 1.
Common Exanthem Associated with Viral Infections

Virus/ Syndrome	Demographics	Prodrome	Rash and Disease	Diagnosis	Treatment	Complications	Prevention
Varicella (Chicken pox)	Late fall to spring 1-14 yr, 50% before 5 yr 10- to 21-d incubation	1-2 days. Low-grade fever, malaise, headache, anorexia, abdominal pain.	Starts central; spreads to extremities. Papules to vesicles (dewdrop on rose petal) to pustules to crusts. Different stages seen at same time. Pruritic. With or without enanthem. Photoexaggeration seen.	Viral Cx, direct IF antibody testing, Tzanck smear for multinucleated giant cells.	Symptomatic. Antihistamines, bland shake or menthol lotions, acyclovir in severe disease. No ASA.	Hypopigmentation, post-excoriation impetigo, invasive GABHS; rarely severe neurologic, cardiac, renal, liver sequelae.	Vaccinate all at 12-18 mo. Two doses for 13 years and older. Post-exposure vaccine if immuno compromised; VZIG if pregnant, premature, or immuno compromised.
Rubeola (Measles)	Winter or spring Infancy to young adulthood 8- to 12-day incubation Epidemics until 96% immunized	2-4 days. High fever, cough, coryza, conjunctivitis, photophobia, Koplik spots, lethargy, sneezing.	Enanthem: Koplik spots = gray pinheads, ring of erythema, buccal mucosa. 0.5-2d. Exanthem: erythematous blanching macules. Starts forehead, spreads downward, confluent by 72 hr Spare's palms, and soles, 4-6 days. Toxic appearance, LAD.	Leukopenia, IgG and IgM serologies, acute and convalescent titers	Symptomatic. Antipyretics. In severe disease, vitamin A.	Otitis media, diarrhea, pneumonia (common in atypical rubeola). Rarely, laryngo- tracheobron- chitis, myocarditis, encephalitis. Subacute sclerosing panencephalitis.	Vaccine at 12-15 mo. and 4-6 yr. Catch-up is 2 doses 1 month apart. Reportable.

<p>Rubivirus (Rubella)</p>	<p>5–14 yr before vaccines; now teens and young adults 2- to 3-wk incubation</p>	<p>Mild catarrhal symptoms, often overlooked. Marked tender lymphadenop- athy seen 24 hr before rash.</p>	<p>Exanthem: Starts face, spreads by 24 hr to trunk, extremities. Day 1: 1- to 4-mm macules, usually distinct, sometimes reticular. Day 2: pinpoint papules. Day 3: clears. Sometimes mild desquamation. Low-grade fever, pruritus possible.</p>	<p>Acute and convalescent titers, rubella IgM antibody (esp. for exposed pregnant women)</p>	<p>Symptomatic. NSAIDs for arthritis.</p>	<p>Self-limiting polyarthrits in girls, young women. Hands and wrists, large joint effusions. Fetuses of nonimmune women infected may have deafness, eye, cardiac and endocrine anomalies, and retardation.</p>	<p>Vaccine at 12–15 mo, second dose at 11–12 yr. Immune globulin not indicated.</p>
<p>Parvovirus B19 (Fifth disease)</p>	<p>Spring 5–17 yr 4- to 21-d incubation</p>	<p>Low-grade fever, headache, malaise.</p>	<p>“Slapped cheeks” facial erythema with abrupt onset, circumoral and perioral pallor, sparing of nasal bridge. Body develops pale maculopapular exanthem; may involve palms and soles. Lasts 3–5 d. Atypically, Papular-Purpuric Gloves and Socks syndrome (only hands and feet affected).</p>	<p>IgM and IgG serologies, acute and convalescent antibody titers, DNA hybridization</p>	<p>Symptomatic. IVGG and transfusions if hematologic complications.</p>	<p>In anyone: Henoch- Schonlein purpura, polyarteritis nodosa, infectious mononucleosis. In HIV+ or those with hemolytic anemia: aplastic anemia. In pregnancy: fetal hydrops or stillbirth.</p>	<p>No vaccine. No isolation once symptomatic (not contagious); pregnant women should avoid outbreak sites for 3 wk and get serologic testing.</p>

(continued on next page)

TABLE 1. (continued)

Virus/ Syndrome	Demographics	Prodrome	Rash and Disease	Diagnosis	Treatment	Complications	Prevention
HHV-6 / HHV-7 (Roseola)	0-3 yr	None	3-5 d intermittent fever to 40.5°C. Child appears well. Exanthem: 0-2 d after defervescence, 1- to 5-mm rose macules with pale areola densest on neck and trunk. Can get confluent. Lasts 1-3 d. Enanthem: pinpoint papules or streaks on uvula, soft palate. LAD, periorbital edema, cough, headache, coryza, abdominal pain.	Clinical. Specific IgM and IgG for acute and convalescent titers not widely available.	Symptomatic. Antipyretics for fever.	Febrile seizures. More rarely, mononucleosis, neonatal hepatitis, fatal hemophagocytic syndrome, encephalitis, thrombotic thrombocytopenic purpura.	None

HHV-7- Pityriasis rosea (controversial, causation not proven)	10-35 yr but usually adolescents and teens	None	Exanthem: annular herald patch, then 2-21 d later, oval pink papules in fir tree distribution on trunk. Fine collarlette of scale. 25% are pruritic. Usually lasts 2-12 wk, but can go up to 5 mo.	Clinical. Rarely, skin biopsy.	Topical steroids for itch, systemic steroids if pigment changes feared. Erythromycin gaining popularity. UVB may reduce severity	None	None
Enteroviruses (Hand, Foot, and Mouth disease)	Summer (less pronounced in tropics) 6 mo to 13 yr	Brief. Sore throat, anorexia, malaise, low-grade fever.	Exanthem: oral mucosal vesicles that erode to form ulcers 2 mm to 2 cm in diameter. Painful. Exanthem: 3- to 7- mm vesicles on dorsal hands, feet, and sometimes palms, sole. Tender, pruritic, or asymptomatic.	Clinical. Specific serotype testing should clinician suspect a particular enterovirus.	Symptomatic. Analgesia to help child with oral intake, steroids for itch.	Rare with Coxsackie A. and B. CNS or pulmonary complications possible with enterovirus-71.	

Courtesy of Mike Purdon, MD, University of Washington.

illness include exanthem subitum, roseola subitum, roseola infantalis, and sixth disease. The name sixth disease comes from the 19th century practice of numbering childhood rashes. The first description of the illness probably dates to 1870, when it was called roseola aestiva [2]. Although it is a benign, self-limiting condition, its presentation can mimic other more serious diseases.

Etiology

In 1988, Yamanishi et al [1] discovered HHV-6 as the causal agent for roseola. HHV-6 is a double-stranded DNA virus in the Roseolovirus genus of the herpesvirus subfamily. The infection is common throughout the world, with seroprevalence in adults approaching 100%. Although HHV-6B is thought to be the primary causal agent for roseola, HHV-7 produces a similar syndrome in the 24- to 36-month age range. HHV-6, like other herpesviruses, exhibits latency after the primary blood infection, with the potential for reactivation. It is thought that the virus establishes a latent state in the macrophages and a persistent infection in the salivary glands. Reactivation in tissue other than salivary glands is rare in the immunocompetent adult [2]. Asymptomatic shedding in the saliva and secretions of the caregivers is the presumed source of infection in children. There is some evidence to suggest that perinatal and congenital infections occur. Cervical shedding of virus has been demonstrated in a small percentage of pregnant women [3].

Presentation

The abrupt onset of fever in a child aged 6 months to 36 months is the most prominent feature of the disease. Although maternal antibodies were thought to prevent infection before this age, HHV-6 infection has been confirmed serologically in infants as young as 2 weeks of age, suggesting that maternal antibody is not universally protective [4,5]. Infants under 6 months of age with acute infection tend to have lower fevers. In infants older than 6 months of age, fever can be as high as 40.6°C and can last 1 to 8 days, averaging 4 days in duration. Throughout the illness the child displays only mild lethargy and irritability in spite of the height of the fever. On physical examination the child may have infection of the tonsils, pharynx, and tympanic membranes [4]. Mild upper respiratory symptoms may be present. Adenopathy is commonly found in the head and neck area, favoring the posterior cervical and occipital nodes. One third of those affected have concomitant diarrhea and vomiting. Neurologic signs may be present, including a bulging anterior fontanel in infants, aseptic meningitis, and encephalopathy. Febrile seizures are associated with HHV-6 infection, accounting for about one third of first-time febrile seizures in children presenting to the emergency department under 2 years of age [4]. The seizures originally were thought to be secondary to the

abrupt onset of high fever. However, viral DNA has been found in the cerebrovascular fluid (CSF) from some of the patients, indicating the possibility of true central nervous system infection [5].

The rash associated with roseola infantum is maculopapular, usually beginning on the trunk and spreading to the neck, face, and extremities. The rose-colored macules and papules are 2 to 3 mm in size, blanch on pressure, rarely coalesce, and are nonpruritic (Fig. 1). A white halo surrounds the typical lesion. There is no desquamation upon resolution. The rash classically appears coincident with the precipitous resolution of the fever but has also been documented concomitantly with fever. Recent investigation has demonstrated the absence of rash in serologically documented HHV-6 febrile illness. Only 20% to 30% of those affected are thought to have rash as part of the infection [4]. The exanthem, if present, may last only a few hours or may be present up to 2 days.

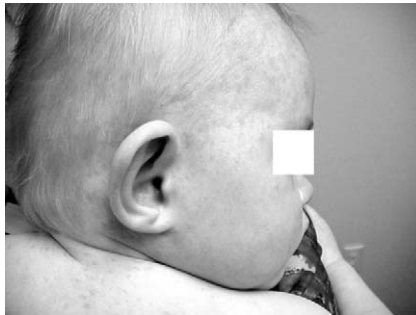
Diagnosis

The diagnosis of roseola is based on recognition of the clinical findings. A CBC, if obtained as part of the febrile work up, may show leukopenia. Laboratory evaluation of the CSF in children with neurologic findings is usually normal. To make a definitive diagnosis, isolation of the HHV-6 from peripheral blood mononuclear cells and subsequent seroconversion are required. This is neither timely nor cost-effective for the routine cases of this self-limited illness.

Treatment

Because the disease is self-limited, no specific treatment is needed for HHV-6 infection in healthy children. There are no antiviral agents

FIGURE 1.
Maculopapular rash of roseola. (Courtesy of D. Stulberg, MD, Provo, UT.) (See also Color Plate 14.)



recommended for this infection. The child should be offered symptomatic treatment, primarily directed at fever control.

VARICELLA

Cause

Varicella, or chickenpox, arises from infection with the varicella-zoster virus. Varicella-zoster is a member of the Herpes virus family of double-stranded DNA viruses [6].

Pathology

Humans represent the only known host for the varicella-zoster virus. A susceptible individual can acquire virus from an infected person via direct contact with respiratory secretions or lesion fluid from the infected individual or through airborne spread. Patients are most contagious from 2 days before rash onset through the time of lesion crusting. They can also be contagious during recurrent infection, which is known as herpes zoster. New infection occurs when the virus contacts the mucosa of the upper respiratory tract or conjunctiva of the susceptible person. Transmission can also occur transplacentally from a mother to her fetus. Within the new host, the virus replicates in the respiratory tract and then disseminates via the bloodstream to cause widespread manifestations. The incubation period generally lasts 2 weeks but can range from 10 to 21 days [6].

Presentation

Patients often experience a 1- to 2-day prodrome of low-grade fever and malaise before beginning to develop pruritic, erythematous macules on the face and scalp. These initial lesions vesiculate, umbilicate, and finally crust over, and new macules form and evolve in these areas and on the trunk and extremities. The presence of lesions in various stages of development characterizes the chickenpox infection (Fig. 2). The cumulative number of lesions ranges from fewer than 10 to more than 1500, averaging 300 lesions over the course of infection. Illness tends to be more severe in newborns, older children, adults, patients with chronic skin or respiratory diseases, patients on steroids or salicylates, and patients with infection due to secondary household spread [7].

Cases involving atypical verrucous lesions and prolonged periods of new lesion formation have been noted in HIV patients. Patients with HIV have also been found to have disseminated varicella infection without any skin manifestations [8].

Exposure early in gestation can rarely cause the congenital varicella syndrome, rather than typical chickenpox. The syndrome is characterized by limb atrophy, skin scarring, and CNS and eye findings [7].

FIGURE 2.
Varicella. (Courtesy of D. Mulvaney, MD, Phoenix, AZ.)



Diagnosis

In general, chickenpox is diagnosed by history and physical examination. Recent exposure to an infected individual suggests the illness, as does the typical presentation of a pruritic vesicular rash with characteristic lesions in different stages of evolution.

Laboratory evaluation is generally unnecessary in healthy children. When confirmation is needed, polymerase chain reaction amplification testing can be conducted on fluid or tissue specimens, or lesions can be scraped for direct fluorescent antigen staining. These tests are sensitive and provide rapid and specific results. Tzanck smears are less useful due to their low specificity. Culture of lesion scrapings is less sensitive and takes several days to provide results. Serum testing for IgG, which is produced late in infection, aids in retrospective analysis [8].

Treatment

Treatment of chickenpox is supportive in most immunocompetent children. Antiviral medications have not greatly affected the disease

course in healthy young children, and their use is not recommended in these patients. Oral acyclovir may be useful in patients in whom the disease course is expected to be more significant, such as older children or patients with infection due to household spread. Intravenous acyclovir should be administered to immunocompromised children and patients with severe manifestations. Therapy is most effective if started within 24 hours of onset of the rash [9].

In most otherwise healthy children, chickenpox resolves without complication. Temporary hypopigmentation or hyperpigmentation may result, but scarring is uncommon. After primary infection, the varicella-zoster virus establishes itself permanently in sensory ganglion neurons and may later reactivate to cause herpes zoster. Immunity to chickenpox after initial infection is thought to be lifelong in healthy patients [7].

Bacterial superinfection of skin lesions may follow chickenpox, as can mild hepatitis and mild thrombocytopenia. Unlikely complications include meningitis, encephalitis, cerebellar ataxia, pneumonia, pericarditis, myocarditis, pancreatitis, glomerulonephritis, arthritis, necrotizing fasciitis, invasive group A strep infection, and toxic shock syndrome. Progressive varicella, which involves continued new lesion development, hemorrhage, and visceral organ damage, occurs rarely in immunocompetent patients. Reye syndrome has also become a rare complication since the decrease in use of salicylates for fever in children [6].

Prevention

Routine vaccination with the live-attenuated varicella-zoster virus vaccine is recommended for most susceptible children starting at 1 year of age. The vaccine is estimated to be 85% effective in the prevention of the disease, and, in the patients who do develop chickenpox, the course is generally mild. Side effects associated with vaccination are uncommon but can include site reactions and rash [10]. Vaccine should not be administered to the majority of children with impaired cellular immunity, with the exception of certain patients with HIV [11].

Varicella-zoster immune globulin can be administered as prophylaxis to immunocompromised children and neonates exposed in utero within 96 hours after exposure to chickenpox or herpes zoster. It has not proven helpful, however, once disease has been established in these patients. Administration of immune globulin is not recommended in susceptible healthy children, although they should receive the vaccine if they have not previously been immunized [11].

SMALLPOX

Because of a successful worldwide vaccination campaign, smallpox no longer exists in the natural state. The last naturally occurring case in the United States was in 1949, and the last known naturally occurring case

in the world was in 1977 in Somalia. Beginning in 1971, the Center for Disease Control no longer recommended routine vaccination in the United States [12]. After recent events, including the distribution of anthrax in the US mail, there is increasing concern that smallpox may be used as a weapon of bioterrorism.

Presentation and Progression

Smallpox, or variola, is caused by the variola virus, a member of the genus Orthopoxvirus. There are at least two strains of the double-stranded DNA virus: variola major and variola minor [13]. Variola major, which was generally the more severe form of the disease (with a case fatality rate of about 30%) was also the most common form seen clinically. Variola minor was less severe, with fatality rates around 1%. Other forms of small pox include modified small pox, which occurred in previously immunized people, and hemorrhagic small pox, which was a rare but usually fatal form of the disease.

Humans are the only known hosts of smallpox. The virus was usually transmitted when infective droplets made contact with mucosal surfaces during face-to-face contact with an infected individual. Less commonly, smallpox was spread through direct contact with infected bodily fluids or through finely aerosolized droplets.

The incubation period averages 7 to 14 days, during which the individual is not contagious. The prodromal phase, which is characterized by fever of 102°F to 104°F, malaise, and body aches, lasts 2 to 4 days. Most infected persons are not contagious during this period.

Smallpox lesions typically begin on the oral mucosa, spreading to the face, followed by the arms and legs and finally the feet and hands (Fig. 3). The lesions begin as macules and papules, and over a period of days the lesions become vesicular, then pustular, and finally crust, often healing with pitted scars. Smallpox is most contagious during the first few days of the rash; however, transmission can occur until all crusts are gone.

FIGURE 3.

Small pox. (Courtesy of Centers for Disease Control, Atlanta, GA.)



Diagnosis

Diagnosis is based upon a high level of suspicion and recognition of the typical skin lesions. There are several important characteristics of small pox that can be used to distinguish it from varicella (chickenpox). The lesions of smallpox tend to concentrate on the face and extremities, often occurring on the palms and the hands. Varicella lesions are most dense on the trunk, rarely occurring on the palms and soles. Smallpox lesions are generally at the same stage of development throughout the body, whereas varicella lesions come in crops of new lesions every few days. Finally, whereas the lesions of varicella tend to be relatively superficial, those of smallpox are embedded deeply into the dermis.

Treatment

Aside from supportive care and treatment of secondary bacterial infections, there is no proven treatment for smallpox. Administration of the vaccine within a few days of exposure can prevent the disease or lessen symptoms.

Prevention

The vaccine for smallpox licensed in the United States is a live-virus preparation of the vaccinia virus. The efficacy of the vaccine is unknown. High levels of antibodies are thought to persist for less than 5 years after vaccination and lower antibody levels for 10 or more years. A second immunization is thought to boost antibody levels. The antibody level required to prevent smallpox is unknown. Minor reactions to the vaccinia virus are common. After inoculation, a lesion forms at the site that begins as a papule and evolves into a vesicle, pustule, and finally a scab. The lesion sheds viral particles, which can be spread to other body parts or other individuals. Fever $>100^{\circ}\text{F}$ occurs in 70% of children receiving their primary immunization. More serious reactions are rare. Death, usually from encephalitis or progressive vaccinia, occurs after about 1 in 1 million primary vaccinations [14].

RUBELLA AND RUBEOLA

Etiology

Rubella (German measles) and rubeola (measles) are two of the classic viral exanthems of childhood. Rubella is an enveloped RNA Togavirus in the Rubivirus genus, which was first isolated from army recruits in 1962 [15]. Rubeola is in the Paramyxovirus family. Both are transmitted via

direct contact or, less commonly, airborne droplets, and humans are their only known reservoir. In the pre-vaccine era, rubella and rubeola were common exanthems predominantly of school-aged children. Before vaccines were developed, at least 90% of children would acquire measles by age 15 [16]. The illnesses have a seasonal pattern with outbreaks most common in late winter and early spring in temperate regions and are highly contagious.

History

Rubella and rubeola have been successfully targeted in developed countries for elimination by aggressive vaccine campaigns. The first effective vaccines for measles and rubella were developed in the United States in 1963 and 1969, respectively. These vaccines, which contain live attenuated viruses, have greatly reduced the incidence of measles and rubella and their complications in the United States. Aggressive vaccination has also changed the epidemiology of rubella and measles in the United States from a common disease acquired during childhood to a disease primarily of unvaccinated foreign-born adults. From 1990 to 1999, the incidence of rubella in children younger than 15 years of age decreased from 0.63 to 0.06 per 100,000, but the incidence of rubella in adults 15 to 44 years of age increased from 0.13 to 0.24 per 100,000 [17]. The incidence of measles has similarly decreased to less than 0.5 cases per 1,000,000 from 1997 to 1999 in the United States [18]. Universal vaccination and the elimination of rubella and measles continue to be goals in developing nations.

Presentation

The majority of postnatally acquired rubella is asymptomatic. In symptomatic cases of rubella, the rash is usually preceded by low-grade fever and lymphadenopathy, commonly involving the cervical and occipital regions. This mild prodromal phase can usually be easily differentiated from the prodrome of measles, which presents acutely with high-grade fevers (up to 40°C), malaise, and anorexia. These symptoms are followed by the three Cs of measles: cough, coryza, and conjunctivitis. The prodromal phase in both infections typically lasts for 2 to 3 days before the appearance of rash.

Close examination of the buccal mucosa should also be performed when rubella or rubeola are suspected to look for Koplick spots, which are pathognomonic for measles. Koplick spots are 1- to 3-mm whitish, grayish or bluish elevations with an erythematous base (ie, “grains of salt on a red background”) commonly seen opposite the molars. They are seen 48 hours before presentation of the rash and may begin to slough when the exanthem appears. Koplick spots should be differentiated from Fordyce spots, which are tiny yellow-white granules that form on the buccal

or lip mucosa, representing benign ectopic sebaceous glands. Fordyce spots do not have an erythematous base.

After the prodromal phase of rubella and measles, a maculopapular erythematous rash can be seen starting on the face and spreading in a cranial to caudal direction. The early erythematous rash is blanchable and is described as morbilliform, or measles-like (Figs. 4 and 5). The rash may be confluent, particularly in areas that are first involved, such as the face and neck; the palms and soles are rarely involved. The rash of rubeola typically peaks in intensity within 3 days, coinciding with the peak intensity of fever, cough, and conjunctivitis. This rash is not pathognomonic (Box 1) but may be differentiated from rubella according to the appearance and severity of the prodromal symptoms.

The rash of rubella also tends to be less vivid than the rash of measles, which has a dark red to purplish color. The rash then fades, in the order of its appearance, to a nonblanchable brownish color after 3 to 4 days, followed by fine desquamation. The immunocompromised or previously vaccinated patients with partial immunity exposed to wild-type virus may develop atypical rash and symptoms.

The symptoms and complications of rubella infection are typically milder than those of measles, except for the devastating effects of in utero rubella infection. Complications of postnatal rubella infection can include arthritis, thrombocytopenia, encephalitis, and progressive rubella panencephalitis. Arthritis is the most common postnatal complication and occurs, coinciding with the appearance of the rash, in up to one third of infected adult women [19]. When acquired congenitally, rubella causes a group of symptoms described as the Congenital Rubella Syndrome (CRS). CRS was first described in 1941 [20] and typically causes hearing loss, developmental delay, growth retardation, cardiac defects, and ophthalmic defects (eg, cataracts) in infants. The risk of fetal defects is highest if infection is acquired by the mother in the first trimester, and infection

FIGURE 4.

Early rash associated with rubeola. (Courtesy of Centers for Disease Control, Atlanta, GA.) (See also Color Plate 15.)



FIGURE 5.

Maculopapular rash of rubella. (Courtesy of Centers for Disease Control, Atlanta, GA.) (See also Color Plate 16.)



is associated with an increased risk of spontaneous abortion and still-birth. Most rubella vaccination programs have been aimed at reducing the incidence of CRS, which is still a significant problem in the developing world. In the United States, an average of six infants with CRS were born yearly from 1992 to 1999, occurring predominantly in young, Hispanic, and foreign-born mothers [17].

Measles is a more significant cause of worldwide morbidity and mortality when acquired postnatally. Complications of measles may include generalized lymphadenopathy and splenomegaly, laryngotracheobronchitis (ie, croup), secondary otitis media, pneumonia, corneal ulceration, myocarditis, pericarditis, hepatitis, mesenteric lymphadenitis, diarrhea, and neurologic sequelae. Neurologic involvement can result in postinfectious encephalomyelitis, a demyelinating process, or subacute sclerosing panencephalitis, which is a rare degenerative disease of the central nervous system that develops years after the original infection due to persistent measles virus. In the United States, death occurs in 1 to 3 per 1000 cases of measles infection [21], most commonly due to respiratory or neurologic involvement. Patients that are immunocompromised, at extremes of age, vitamin A deficient, or live in developing nations are at higher risk

Box 1. Differential Diagnosis of an Erythematous Maculopapular Rash

Rubella
Rubeola
Scarlet fever
Kawasaki disease
Secondary syphilis
Drug eruption
Coxsackie virus
ECHO virus
Adenovirus
Infectious mononucleosis
Parvovirus
Meningococemia
Toxoplasmosis
Serum sickness
Rickettsial disease (eg, Rocky Mountain Spotted fever)
Roseola

for morbidity and mortality. Worldwide, measles was the eighth leading cause of death in 1990 [22].

Diagnosis

In suspected cases or outbreaks, the diagnosis of rubella and measles can be confirmed serologically or via viral culture. A high index of suspicion should be entertained in areas where an outbreak has occurred or where immunity is thought to be inadequate, and all suspected cases should be immediately reported to the appropriate local public health agency. Acute and convalescent phase (ie, 2 to 4 weeks after appearance of rash) serum is typically obtained for IgM and IgG titers. IgM is usually detectable in cases of measles from 3 to 30 days after the onset of rash, and IgG can be diagnostic if a fourfold increase in IgG titers is shown 2 to 4 weeks apart. Characteristic multinucleated giant cells with inclusions can also be seen in conjunctival, nasopharyngeal, or buccal epithelial cells and urine in patients with measles. Rubella-specific IgM can be detected from 4 days to 8 weeks after the onset of rash in postnatally acquired infections and can be used during the first 6 months of life to diagnose CRS. IgG can be diagnostic if CRS is suspected after 6 months of age. Diagnosis during pregnancy is crucial for management and can be confirmed by measuring IgM, demonstrating a fourfold rise in IgG, or PCR detection.

Treatment

Treatment for both illnesses is primarily supportive; therefore, vaccination is instrumental in the prevention of CRS and the morbidity and

mortality associated with measles. Prevention in the United States is implemented by vaccinating children after 1 year of age with two doses of the MMR vaccine separated by at least 28 days. Pregnant women are then screened for rubella. Possible additional therapies for the treatment of measles include IgG, Ribavirin, and vitamin A. According to the World Health Organization and UNICEF guidelines, vitamin A should be considered in areas where vitamin A deficiency is prevalent or measles mortality exceeds 1% [21].

FIFTH DISEASE

Etiology

Fifth disease (erythema infectiosum) arises as a result of infection with Human Parvovirus B19 [23]. It is primarily an illness of childhood that is characterized by a facial “slapped-cheek” rash followed by a lacy erythematous eruption on the extremities and trunk.

Human Parvovirus B19 infections were first designated as Fifth Disease in the early 1900s. Descriptions of the illness were published in the early 1800s, and the first known clinical picture was in 1808. The B19 viral particle was identified in 1975 and was the first Parvovirus found to infect humans [24]. B19 is the smallest DNA-containing virus known to infect humans and contains a single strand of DNA. It is the only current member of its genus Erythrovirus in the family Parvoviridae [24]. Parvovirus B19 is distributed worldwide, and the only known hosts are humans. Transmission is by contact with respiratory secretions, percutaneous exposure to blood products, and vertical transmission from mother to fetus [25]. Studies on the timing of the presence of B19 DNA in serum and respiratory secretions show that persons with the infection are most infectious before the illness and during the mild prodrome. Patients are not considered infectious after the appearance of the rash. The incubation period is usually 4 to 14 days but can last as long as 21 days [25]. Transmission is effective, with secondary spread to susceptible close household contacts of about 50% [24]. Approximately 20% of infections are believed to be asymptomatic. Epidemic outbreaks can occur that affect up to 35% of school-age children.

Presentation

Parvovirus B19 tends to have a different manifestation in children and adults. It is most common in children between 5 and 15 years of age. The classic presentation is of nonspecific mild symptoms for 2 to 3 days before the rash that includes headache, coryza, malaise, and low-grade fever. Children may have pharyngitis, fever, myalgias, nausea, diarrhea, cough, coryza, and conjunctivitis with the rash. Arthralgias and arthritis develop in approximately 10% of children and tend to involve large joints more than small joints [26]. Chronic joint complaints may mimic juvenile rheumatoid arthritis (JRA).

FIGURE 6.

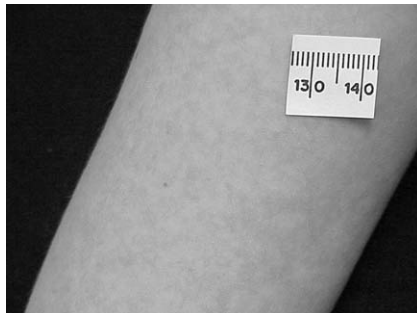
Classic “slapped cheeks” appearance of erythema infectiosum (Fifth disease). (Courtesy of D. Stulberg, MD, Provo, UT) (See also Color Plate 17.)



The fiery red macular erythema or slightly raised edematous plaques, so-called “slapped-cheeks” (Fig. 6), fade over 1 to 4 days as a more generalized rash develops. Erythematous macules and papules appear on the neck, trunk, and extremities that tend to evolve into a lacy reticular pattern most prominent on the extremities (Fig. 7) [23]. Temperature changes, exercise, sunlight, and emotional factors can cause the rash to wax and wane for several weeks or up to several months. A typical eruption lasts 5 to 10 days. Pruritus is sometimes prominent in an outbreak. In patients with hemolytic anemias, hemoglobinopathies, or immunodeficient patients, B19 infection can lead to transient aplastic crisis due to destruction of reticulocytes and erythroblasts [24].

FIGURE 7.

Lacy reticular pattern of erythema infectiosum (Fifth disease). (Courtesy of D. Stulberg, MD, Provo, UT.) (See also Color Plate 18.)



In adults, the primary manifestation is often acute arthropathy, which usually affects the small joints of the hands, knees, wrists, ankles, and feet. This is a symmetric polyarthrititis of sudden onset and is usually self-limited. In some cases, the arthritis can persist for months [24]. The fever, adenopathy, and constitutional symptoms tend to be worse in adults than children. Men typically have a flu-like illness, and women are more likely to have joint complaints [26]. The rash in adults is often absent, and when it does occur, it is usually macular or lacy and mostly on the extremities [24].

Diagnosis

Diagnosis tends to be clinical in most cases. Parvovirus infections should be considered in all patients with acute arthritis or viral exanthems with a consistent history and physical examination (Box 2).

Laboratory testing for the virus or antibody is only done at limited laboratories and is usually only done in patients with aplastic crisis, immunodeficiency, chronic anemia, and cases of infection in pregnancy or fetal hydrops where infection is suspected. IgM can be detected up to 6 months to determine a recent infection, whereas IgG develops after 7 days and persists for years [24].

Natural History and Treatment

The typical clinical course for Fifth Disease is self-limited and requires only minimal supportive care. An increasing number of complications have been recognized or suggested, but only a few are common. There is no specific antiviral therapy. A vaccine has been in development but is not available.

In patients with chronic hemolytic anemias, Parvovirus B19 commonly causes a transient aplastic crisis that may require transfusions. Most cases tend to resolve in about 1 week. During this time, these patients are infectious and tend to be placed in isolation. A transient red

Box 2. Differential Diagnosis for Fifth Disease

- Rubella
- Measles
- Roseola
- Scarlet fever
- Drug hypersensitivity reaction
- Enteroviral infection
- Erysipelas on the cheek

cell aplasia that is asymptomatic can occur in healthy patients without a chronic anemia [24].

A chronic anemia can develop in immunodeficient patients. This usually requires and responds well to intravenous gammaglobulin [25]. These patients also tend to have persistent infectivity for a much longer period.

Infection in pregnancy is a major concern for the 50% of women who are not already immune from previous infection. Fetal infection is greatest in the first 20 weeks of pregnancy. Parvovirus B19 is not teratogenic but can cause a nonimmune fetal hydrops [24]. Most fetuses are not infected or harmed, but the fetal death rate with maternal infection is somewhere between 3% and 10% [23]. IgM blood testing should be offered to exposed pregnant women and, if infected, frequent ultrasounds may be warranted.

There is no known effective preventive measure at this time. Because most patients with clinical Fifth Disease are no longer infectious, control measures directed toward these individuals are not effective. Children with the rash do not have to be kept out of school.

COXSACKIE INFECTIONS

Hand, foot, and mouth disease (HFMD) is a self-limited nonpolio enterovirus caused by coxsackie A and B. HFMD is highly contagious and occurs in a bimodal pattern in spring and summer. HFMD is spread via aerosol and nasal inoculation and most often afflicts children younger than 5 years of age. The incubation period is 4 days, with subsequent onset of constitutional malaise, fever, lymphadenopathy, and oral vesicles that rapidly ulcerate. The oral lesions often involve the palate, tongue, and buccal mucosa while sparing the gingiva. Subsequent multiple maculopapular cutaneous lesions appear on the hands and feet (occasionally elsewhere) that progress to vesicles, ulcerate, and then crust (Fig. 8) [27–29]. The differential diagnosis for coxsackie infections includes several other viral exanthems (Box 3). Although the vast majority of HFMD requires only palliative care and is characterized by spontaneous resolution within 2 weeks, HFMD outbreaks can also be associated with enterovirus-71 and progress to CNS and pulmonary complications that may lead to death [30]. Thus, although the diagnosis is generally clinical, with a progression of systemic symptoms, virus culture and circulating antibody titers may be indicated to confirm a diagnosis.

Herpangina is another manifestation of coxsackie A and B occurring in the summer and late fall. As with HFMD, it is highly contagious and has a short incubation period. Herpangina is characterized by headache, abdominal pain, fever, and malaise, with oral lesions that appear on the anterior pillars of the tonsillar fauces, soft palate, and uvula. The oral lesions are characterized by small gray vesicles that coalesce to form larger fibrin-covered ulcerations. Treatment remains palliative because the symptoms are usually mild and resolve in 3 to 5 days. Serologic markers

FIGURE 8.
Coxsackie lesions of hand, foot, and mouth disease. (Courtesy of D. Stulberg, MD, Provo, UT.)



and disease characteristics can distinguish herpangina from other vesiculo-ulcerative diseases [27–29].

PITYRIASIS ROSEA

History

Pityriasis rosea (PR) is a relatively common, self-limited skin condition that usually affects children and young adults. It has been described in the medical literature for over 200 years but was given its current name by Camille Gilbert in 1860. The name reflects the typical scaly, rose-colored appearance. Numerous synonyms have been used, including pityriasis circine, roseola annulata, roseola squamosa, and erythema annulatum. PR is thought to have a viral etiology and shares many features with the viral exanthemas of childhood. Cases tend to cluster in the fall

Box 3. Differential Diagnoses for Coxsackie Infections

- Herpes simplex virus
- Varicella-zoster virus
- Epstein Barr virus
- Cytomegalovirus
- Smallpox
- Syphilis

and winter. Some research has implicated human herpesvirus-7 as a causative agent, but later studies have failed to confirm this hypothesis [31,32]. Numerous drugs have also been implicated in a severe, prolonged exanthem that resembles PR (Box 4).

PR most commonly affects adolescents, with a concentration of cases in the 10- to 35-year age range. There seems to be a slight female preponderance, with a prevalence of 0.14% for females and 0.13% for males. The pathologic picture is characterized by patchy parakeratosis. There is cytolytic degeneration of keratinocytes adjacent to Langerhans cells [33].

Presentation

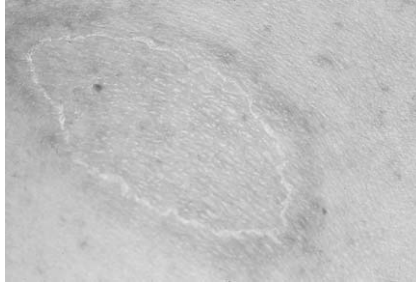
Eighty percent of cases follow a typical clinical pattern. Five percent of these patients report a viral-like prodrome of fever, headache, malaise, and arthralgias. Over half manifest the primary plaque or “herald patch,” which is 2 to 6 cm in diameter, oval to round, and salmon colored centrally with a darker red rim. The border is separated from the center by a “collette” of delicate scale (Fig. 9). The herald patch usually appears on the trunk or proximal extremity. Days to weeks later a secondary rash appears, usually peaking at 10 days. These lesions may be smaller, 5- to 10-mm versions of the herald patch that align along skin cleavage lines or punctate, nonscaly papules (Fig. 10). Pruritus is variable but is prominent in 25% of cases. The typical duration of PR is 2 to 6 weeks but can extend beyond 3 months.

Atypical cases make up 20% of the total and occur more commonly in children. Lesions can exhibit urticarial, vesicular, pustular, or purpuric characteristics. There may be associated ulcerative oral lesions. PR inversa is an atypical pattern in which the secondary rash involves more

Box 4. Drugs Associated with a PR-Type Rash

- Arsenic
- Barbiturates
- Bismuth
- BCG vaccine
- Captopril
- Clonidine
- Diphtheria toxoid
- D-penicillamine
- Gold
- Isotretinoin
- Ketotifen
- Levamisole
- Metronidazole
- Omeprazole
- Terbinafine

FIGURE 9.
Herald patch of pityriasis rosea. (Courtesy of D. Mulvaney, MD, Phoenix, AZ.)
(See also Color Plate 19.)



peripheral sites, including the pelvis and face. In the gigantea form, secondary lesions are larger and less numerous, often clustered near the herald patch. In pityriasis circinate et marginata of Vidal, large, confluent, circinate lesions may persist for months. Pigmentation changes can occur at the sites of PR involvement, with dark-skinned individuals being especially at risk for hyperpigmentation.

The differential diagnosis for PR includes other erythematous, scaly, or papular eruptions and other conditions that involve the trunk in a “Christmas tree” pattern (Box 5). Microscopy with KOH prep may be needed to distinguish a herald patch from a tinea infection. Secondary syphilis can mimic PR, often with involvement of palms and soles. Serologic testing should be strongly considered when considering a diagnosis of PR.

FIGURE 10.
Pityriasis rosea, secondary rash on trunk. (Courtesy of D. Mulvaney, MD, Phoenix, AZ.)



Box 5. Differential Diagnosis for Pityriasis Rosea

- Tinea infection
- Secondary syphilis
- Guttate psoriasis
- Nummular eczema
- Parapsoriasis
- Lichen planus
- Pityriasis lichenoides
- Kaposi sarcoma
- Drug reaction

Treatment

PR is a self-limited condition and treatment is primarily symptomatic. Antihistamines, oatmeal soaks, and topical steroids are useful for pruritus. Rarely, a brief course of systemic steroids is needed for severe itching. UVB therapy has been advocated for years, but a controlled clinical trial indicated no significant impact on pruritus or disease course [34]. A recent study showed an apparent benefit of oral erythromycin in reducing the severity and duration of disease [35]. Because of the dramatic appearance of the rash, patients should be reassured about the usual resolution within weeks to months and should be advised to report duration beyond 14 weeks or the emergence of new manifestations.

Antibiotic Drug Reactions

Antibiotics can cause many minor and serious, life-threatening skin eruptions. Antibiotic drug eruptions occur in 7.3% of children treated orally, with penicillins, cephalosporins, and sulfonamides being the most common offending agents [36]. The most common types of cutaneous reactions are exanthems and urticaria.

Exanthems are divided into morbilliform (measles-like) (Fig. 11) and scarlatiniform reactions and can easily be confused with viral rashes. The lesions usually begin within 2 to 3 weeks of treatment and can last about 1 week after treatment is discontinued [37]. After the erythema resolves, superficial desquamation frequently occurs [38]. Treatment includes removal of the offending agent, oral antihistamines, and topical or oral corticosteroids.

Urticaria denotes edematous, transitory plaques or wheals that involve the dermis. The eruption can be localized or generalized as plaques coalesce. Acute urticarial reactions develop within a few hours to days after drug exposure and may last up to 6 weeks. It can be misdiagnosed as erythema multiforme or Kawasaki disease given its various manifestations (ie, annular, hemorrhagic, serpiginous) [39]. Urticaria may progress

FIGURE 11.

Morbilliform rash associated with amoxicillin therapy. (Courtesy of J. Alexander, MD, Tucson, AZ.) (See also Color Plate 20.)



to angioedema (diffuse subcutaneous or submucosal edema) or anaphylaxis, indicating a more severe reaction.

Among the many causes of urticaria, antibiotics, especially sulfonamides and tetracyclines, are among the most common [40]. Diagnosis is usually based on history and physical examination. Treatment is similar to that of exanthems, unless angioedema or anaphylaxis occurs. In this case, the use of epinephrine and supportive care may be required. Desensitization, although difficult, can be performed if a certain antibiotic is required, but the effects are not long lasting.

ERYTHEMA MULTIFORME/STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are hypersensitivity reactions to various agents, such as drugs and infections. They may represent variants of the same disease process and are characterized by mucosal erosions, target lesions, and epidermal necrosis. Because there is clinical and histopathologic overlap among the entities, the exact incidence is unknown [41].

EM and SJS may occur at any age, but as many as 20% of cases are in children and adolescents [42]. TEN usually affects older children and adults and is rarely seen in young children [43].

EM

EM is divided into EM major and EM minor. EM minor is benign and self-limited, whereas EM major is equivalent to SJS in most classification schemes.

Presentation

EM is characterized by acute, fixed erythematous macules that develop into papules and target lesions and may coalesce to form plaques. A prodrome of fever, headache, sore throat, and cough usually precedes the rash by 1 week. The initial surrounding blanching erythema resembles urticaria or insect bites. Lesions in different stages can be seen at the same time [43], and scaling, desquamation, hyperpigmentation or hypopigmentation can occur as the lesions resolve [44].

EM is usually symmetric, involving the hands and face, dorsum, and palms, soles, and extensor surfaces of the extremities (Fig. 12). The mouth is the most common mucous membrane involved; lesions in the mouth can appear at any time. The conjunctiva, genital, or upper airway tract can also be affected [44].

Etiology

The most common cause of EM minor is herpes simplex virus infection or reactivation [45]; however, in 50% of cases there is no identifiable cause [46]. Drugs and other infections (eg, *Mycoplasma pneumoniae*) can also precipitate EM minor. The most common drugs are anticonvulsants (phenobarbital, phenytoin, carbamazepine) and antibiotics (sulfonamides, penicillin, amoxicillin, erythromycin, ampicillin) [47].

Treatment

EM minor is generally mild and resolves in 1 to 2 weeks. Avoidance of the causative agent is recommended, but rechallenge is not advised because a more serious reaction can occur. Oral antihistamine and topical steroids may provide symptomatic relief.

SJS

Presentation

SJS, or EM major, is characterized by high fever, constitutional symptoms and diffuse blistering on two or more mucosal surfaces. Prodromal symptoms precede the rash by 1 to 14 days [43], and mucosal involvement precedes the rash by 1 to 2 days. New lesions may erupt over a 6-week period.

FIGURE 12.
Symmetric distribution of erythema multiforme. (Courtesy of J. Alexander, MD, Tucson, AZ.)



Extensive blistering with hemorrhagic crust usually occurs, with lip involvement being characteristic (Fig. 12). Almost all patients with SJS have stomatitis and conjunctivitis, and the genital, urethral, and upper airway mucosa can be involved [44]. Serious complications can occur, including keratitis and conjunctival scarring.

Most patients recover after several weeks. Skin re-epithelialization usually occurs after 2 weeks, but postinflammatory hyperpigmentation can remain for months.

Etiology

Causative agents are the same as for EM minor [45], and treatment is aimed at providing adequate wound care, hydration, and nutritional support.

Treatment

Treatment includes removal of the offending agent, fluid replacement, and treating underlying infections. ICU or burn unit admission is usually recommended. Physical therapy is required to limit contractures, and ophthalmologic consultation is required to prevent ocular complications.

Corticosteroid use for SJS and TEN is controversial. Steroids may limit necrolysis but increase susceptibility to infection and delay wound healing [48]. Plasmapheresis, intravenous immunoglobulin, and thalidomide have been used in severe cases of SJS and TEN with variable results [44].

TEN

Skin lesions of TEN develop within 24 hours of prodromal symptoms (malaise, anorexia, and fever). The rash appears as erythema of the face and extremities, rapidly becoming generalized. Bullae develop in the areas of erythema, progressing to rupture of the blisters, leaving denuded skin. Exfoliation begins after 3 to 4 days of the rash onset and lasts 7 to 14 days [44]. Mucosal involvement typically involves the mouth, anogenital region, and conjunctiva. Pulmonary and hematologic abnormalities can complicate the disease course [49,50].

The mortality rate ranges from 25% to 50%, primarily from fluid and electrolyte disturbance and secondary bacterial infection [51]. Diffuse disease and mucosal involvement indicate a poor prognosis [43].

Etiology

The cause of TEN is found in only 50% of cases. As with EM and SJS, antibiotics and anticonvulsants are the most common causes, but NSAIDs have also been implicated [49]. Patients with TEN typically have a disease course of 2 to 4 weeks. Patients can have permanent pigmentation changes, scarring, or loss of hair and nails [47].

EM, SJS, and TEN are frequently misdiagnosed as urticaria, exanthemous drug reactions, and Kawasaki disease [44]. TEN resembles staphylococcal scaled skin syndrome, but those patients have milder constitutional symptoms and recover quickly with antibiotic therapy.

Diagnosis

The diagnosis of TEN and SJS is based on presentation but can be differentiated by skin biopsy.

Treatment

See SJS treatment section.

FIXED DRUG ERUPTIONS

Fixed drug eruptions (FDEs) are the second most common type of cutaneous drug reactions in children, after drug exanthems [52]. FDEs occurred in 22% of children with cutaneous drug reactions in one study [53].

Presentation

FDE is evident as well demarcated, 2- to 10-cm, oval, erythematous plaques, appearing 30 minutes to 8 hours after exposure to the drug. The acute inflammation usually fades after several days, leaving areas of hyperpigmentation that can last from months to years [54]. They characteristically reappear in the exact location after reexposure [55]. The most common locations for FDEs are the trunk, limbs, lips, and genitalia [54,56]. FDE can mimic urticaria, insect bites, or erythema multiforme [54].

Etiology

The most common offending drug is TMP-SMX [54]. Other drugs causing FDE include ASA, NSAIDs, ampicillin, metronidazole, tetracycline, barbiturates, anticonvulsants, phenolphthalein, and oral contraceptives [44]. The mechanism of FDE is unknown.

Treatment

FDEs are usually asymptomatic. Management includes removal of the offending agent. Rechallenge is safe and, if positive, is diagnostic. More severe reactions can be rechallenged using half dose of the drug. Patch testing can also be performed but is less sensitive [57]. Skin biopsy may be helpful in the inflammatory or pigmentation phase but is usually not necessary for the diagnosis.

PHOTOSENSITIVITY REACTIONS

Presentation

Photosensitivity reactions occur after drug ingestion and exposure to the sun. The reaction occurs in sun-exposed areas, primarily on the face, arms, and chest, resembles sunburn and is usually not pruritic.

Reactions are divided into phototoxic and photoallergic. Phototoxic reactions are more common and are not truly allergic because previous exposure is not necessary. The severity of the reaction is drug and UVA dose dependent and usually occurs within hours [44].

Etiology

Doxycycline, tetracycline, and minocycline are the most common offending phototoxic agents [44]. Less commonly, diuretics (including thiazides and furosemide), griseofulvin, and NSAIDs can cause photosensitivity.

Photoallergic reactions represent delayed-type hypersensitivity and require previous exposure to a drug plus UVA exposure. This reaction is typically pruritic and eczematous and occurs within 1 to 2 days of exposure. Thiazides, griseofulvin, quinidine, sulfonamides, sulfonyleureas, and vitamin B6 are commonly involved [44]. Topical antibacterial agents (pHisoHex and Hibiclens) may cause photoallergy [44].

Diagnosis and Treatment

Diagnosis is made through a careful history and physical examination. Treatment includes elimination of the offending agent. Antihistamines and topical corticosteroids can provide symptomatic relief. Oral steroids are reserved for severe cases.

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Key Points

- Abrupt onset of fever is the most prominent feature of Roseola; the child may appear only mildly ill despite high fever.
- Varicella is characterized by fever and pruritic vesicular rash, with lesions in various stages of evolution.
- Smallpox, caused by the variola virus, is characterized by fever and rash, lesions of which progress simultaneously from papules to vesicles to pustules before crusting.
- Vaccination is the key to prevention of the Congenital Rubella Syndrome and the morbidity and mortality associated with measles.
- Fifth Disease is caused by infection with Human Parvovirus B19, and pregnant patients should be monitored for fetal hydrops.
- In Coxsackie infections, there is a bimodal occurrence involving spring and summer or late fall.
- A 2- to 6-cm "herald patch" is usually the initial lesion in Pityriasis Rosea; the rash may persist for 2 to 3 months.

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