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ONLINE EXCLUSIVE

Fifth and sixth diseases: More than a fever and a rash

While most parvovirus B19 or HHV-6 infections resolve without sequelae, rheumatologic and hemolytic complications and seizures can develop.

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PRACTICE RECOMMENDATIONS

› *Reserve serologic testing for parvovirus B19 for pregnant women with known exposure to the virus, immunocompromised individuals, or patients with chronic hemolytic conditions or severe or persistent arthropathy* (B)

› *Keep in mind that up to 15% of children infected with human herpesvirus 6 can experience febrile seizures. Treat with an antiepileptic drug, as you would for any febrile seizure that lasts >5 minutes.* (C)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Fifth and sixth diseases are frequently encountered viral exanthems in family medicine. This article delineates the unique clinical characteristics of these disorders, describes rare but serious sequelae of each, and offers recommendations to guide your practice.

Fifth disease

Parvovirus B19, an infectious agent found worldwide, is the cause of fifth disease, also known as slapped cheek syndrome or erythema infectiosum. It is transmitted via respiratory droplets, most commonly in late winter and early spring. The peak incidence of parvovirus B19 infection is in children ages 5 to 15 years.[1] Approximately 20% of parvovirus B19 infections remain subclinical.[1,2] An observational study of children in the United Kingdom who were 6 months to 16 years of age and had been immunized for measles and rubella revealed that parvovirus B19 was the number one identifiable cause of febrile rash, responsible for 17% of cases.[3] Seroprevalence increases with age, and 40% to 60% of adults test positive for prior infection.[1]

Clinical presentation: Not necessarily limited to fever and rash

Parvovirus B19 has an incubation period of 4 to 21 days before the classic symptoms of malaise, fever, and red "slapped" cheeks appear (**FIGURE 1**). Four to 14 days after the onset of symptoms, a pruritic lacy rash covers the entire body, preferentially on the extensor surfaces (sparing the palms and soles), and may wax and wane for up to 3 weeks, with flaring triggered by stress, exercise, heat, or exposure to sunlight.[1,4] Rarely, and usually among young adults, parvovirus B19 can cause papular-purpuric "gloves and stocking" syndrome, with fever, painful edema, erythema, and pruritus of the distal extremities.[5]

Associated arthritis. Parvovirus B19 may also cause a symmetric polyarthritis of the hands, wrists, knees, or ankles,

particularly in adult females. The course of arthritis usually lasts 1 to 3 weeks, but up to 20% may evolve into a chronic arthritis.[6] In addition, numerous case studies suggest that parvovirus B19 may, in rare cases, cause a viral myocarditis in infants and children.[7]

Hemolytic complications. The target of parvovirus B19 is the erythroid blood cell line.[1] Consequently, immunocompromised patients and those with chronic hemolytic conditions (eg, sickle cell disease, thalassemia, spherocytosis, or pyruvate kinase deficiency) may develop hematologic complications such as aplastic crisis, chronic anemia, thrombocytopenia, neutropenia, or pancytopenia. Patients with hemolytic complications can be quite ill, presenting with fever, malaise, tachycardia, tachypnea, and profound anemia.

Perinatal perils. Approximately one-third of pregnant mothers are at risk for parvovirus B19 infection, and having children at home, a severe medical condition, or stressful employment have been shown to increase their risk of active infection.[8] The annual incidence of symptomatic parvovirus B19 during pregnancy is 1.5%, increasing to 13% during epidemics.[9] Such infection can cause significant morbidity and mortality for the fetus. Mothers newly infected during the first trimester have experienced a 71% increased risk of intrauterine fetal demise (fetal loss <20 weeks gestation) when compared with baseline risk of fetal loss.[9] In one prospective observational study, fetal death was only observed when mothers were infected prior to 20 weeks of gestation.[10] Intrauterine B19 infection during any trimester carries a 4% overall risk of hydrops fetalis, thought to be due to high output cardiac failure secondary to severe anemia.[10]

Parvovirus B19 may cause a symmetric polyarthritis, particularly in adult females, usually lasting one to 3 weeks. But it can evolve into a chronic arthritis.

Rely on clinical findings to diagnose; restrict serologic testing

The characteristic "slapped cheek" rash usually distinguishes fifth disease from other causes of febrile rash. Differential diagnosis includes measles, scarlet fever, roseola infantum, enterovirus, and adenovirus. A diagnostic tool (TABLE) can help differentiate fifth disease from other viral exanthems.

In most cases of suspected parvovirus B19 infection, serologic testing is not indicated. However, consider serologic testing for pregnant women with known exposure to the virus, immunocompromised patients, patients with chronic hemolytic conditions, or patients with severe or persistent arthropathy. Serum immunoglobulin M can usually be detected 10 days after infection and can persist for 3 months, while serum immunoglobulin G is produced 2 weeks after inoculation and presumably lasts for life.[11]

FIGURE 1
Classic "slapped cheek" rash of fifth disease

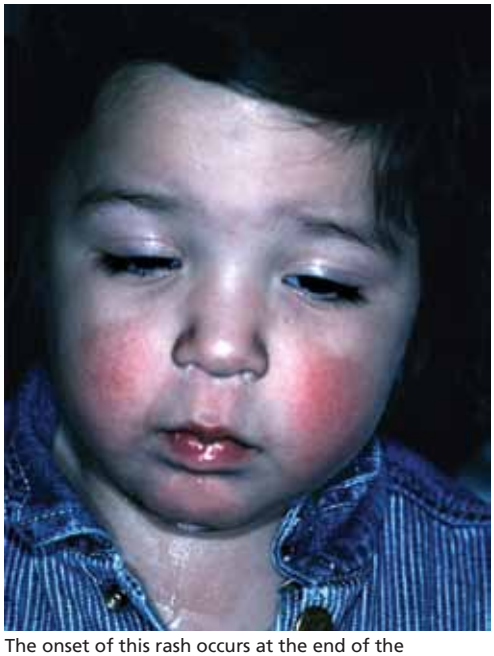


IMAGE COURTESY OF: RICHARD P. USATINE, MD

The onset of this rash occurs at the end of the prodromal period and signals that the child is no longer infectious.

Treat supportively

No specific treatment exists for parvovirus B19 infection. Management is supportive and the infection is usually mild and self-limiting. A nonsteroidal anti-inflammatory agent may be sufficient for associated arthritis; if needed, a low-dose oral corticosteroid can be used without prolonging the viral illness.[6] Refer for hematologic consultation any immunocompromised patient with confirmed parvovirus who develops a hematologic complication, which may require intravenous immunoglobulin treatment or, in severe cases, bone marrow transplantation.

TABLE

Diagnostic aid for distinguishing among pediatric exanthems

	First disease (rubeola)	Second disease (scarlet fever)	Third disease (German measles)	Fifth disease (erythema infectiosum)	Sixth disease (roseola infantum)
Causative agent	Measles virus	Pyrogenic exotoxin-producing group A *Streptococcus*	Rubella virus	Parvovirus B19	Human herpesvirus 6 (HHV-6)
Mode of transmission	Respiratory droplets	Respiratory droplets	Respiratory droplets	Respiratory droplets	Saliva via mucosal surfaces
Incubation period	8-12 days	2-5 days	14-21 days	4-21 days	10-15 days
Symptoms			Fever, sore throat, red eyes, headache, malaise, coalescing pink macules starting on the head and neck and spreading to the trunk and extremities, Forchheimer spots, petechial hemorrhage on soft palate		
1st stage	Mild fever, conjunctivitis, cough, coryza, Koplik spots	Fever, sore throat		Malaise, fever, red "slapped" cheeks	Mild rhinorrhea, sore throat, conjunctival redness, high fever
2nd stage	Red maculopapular rash beginning on the forehead and neck, spreading to trunk, arms, and legs. (Involves palms and soles 50% of the time)	Fine, papular erythematous eruption around the neck, trunk, and extremities (face is usually spared), followed by desquamation		Pruritic lacy body rash that spares the palms and soles	After fever abates, tiny erythematous papules develop on the trunk and spread to neck and extremities
Treatment	Supportive	Antibiotics (penicillin or cephalosporins)	Supportive	Supportive	Supportive
Duration of illness					
1st stage	2-4 days	1-2 days	3 days	4-14 days	3-5 days
2nd stage	7-10 days	3-4 days		Up to 3 weeks	1-3 days
Sequelae	Diarrhea, encephalitis, pneumonia, otitis media, death	Peritonsillar abscess, otitis media, sinusitis, pneumonia, rheumatic fever, poststreptococcal glomerulonephritis, reactive arthritis	Congenital rubella syndrome, thrombocytopenia, arthritis, encephalitis	Polyarthritis, aplastic crisis, chronic anemia, pancytopenia, intrauterine fetal demise, hydrops fetalis	Febrile seizures, meningoencephalitis, acute disseminated demyelination, hepatitis, myocarditis
Vaccine preventable	Yes	No	Yes	No	No

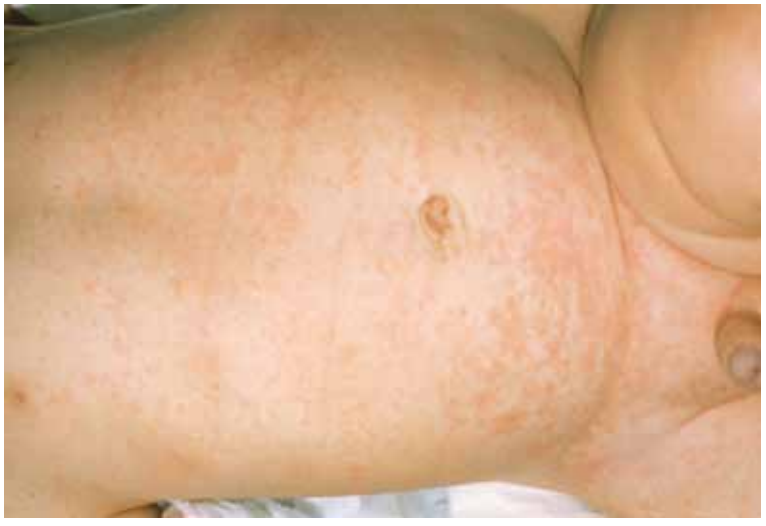
Clinical recommendations

Parvovirus B19 is communicable only during the nonspecific prodromal period—the 4 to 21 days of incubation in which the patient seems to have a common cold, with coryza, sore throat, and headache. With the appearance of the "slapped cheek" rash (an immune-mediated, postinfectious sequela), a child with erythema infectiosum is no longer infectious. At this stage, exclusion from school or child care is unnecessary.[1]

Perform serologic testing to determine immunity for all pregnant women with documented exposure to parvovirus B19.[12] Retest women who are initially nonimmune after 3 to 4 weeks. Patients who seroconvert should un-

FIGURE 2

Sixth disease: The rash



This rash occurs in just 20% of infected patients and appears as tiny, erythematous, raised papules on the trunk and spreads to the neck and extremities.

dergo serial ultrasounds for 10 weeks to evaluate for hydrops fetalis or growth restriction. Repeat testing is unwarranted for those who do not seroconvert. There is no evidence to suggest that seronegative pregnant women should avoid work environments during endemic periods of infection.[13]

Sixth disease

Human herpesvirus 6 (HHV-6) causes sixth disease, also known as roseola infantum or exanthem subitum. Ninety percent of children have been infected by 2 years of age, with peak incidence occurring between 9 and 21 months of age.[14] HHV-6 is most likely transmitted via the saliva of healthy individuals and enters the body via a mucosal surface. One percent of HHV-6 infection is acquired congenitally without known sequelae, similar to the transmission rate of cytomegalovirus.[15]

Clinical presentation: Only 20% may exhibit a rash

After an incubation period of 10 to 15 days, sixth disease is characterized by a prodrome of mild rhinorrhea, sore throat, and conjunctival redness, followed by a high fever (100.4º F to 104º F).[16] Cervical, postauricular, or occipital lymphadenopathy usually develops. Other symptoms are usually absent but may include abdominal pain, vomiting, or diarrhea. After 3 to 5 days, the fever abates and the rash of roseola may begin—if at all—as tiny, erythematous, raised papules on the trunk that spread to the neck and extremities (**FIGURE 2**), lasting 1 to 3 days. Interestingly, while 93% of those infected are symptomatic (fevers, fussiness, rhinorrhea), only 20% of those infected exhibit the rash of roseola.[1] Nagayama spots (ulcers at the uvulopalatoglassal junction) can be seen in Asian infants.

Complications. Fifteen percent of infected children have febrile seizures.[1] Based on several case reports, HHV-6 infection has been associated with meningoencephalitis, acute disseminated demyelination, hepatitis, and myocarditis.[17] It is unknown whether seizures increase the risk of these complications. Long-term sequelae from these manifestations of HHV-6 infection include developmental disorders and autism-spectrum disorders.[18,19]

Treat supportively

Patients with primary HHV-6 infection usually require antipyretics and frequent hydration. Reserve antivirals such as ganciclovir, foscarnet, and cidofovir for immunocompromised patients or those with HHV-6 encephalitis.[20]

Clinical recommendations

Treat seizures associated with HHV-6 infection as you would any other febrile seizure, giving an antiepileptic (diazepam, lorazepam, or midazolam) if the seizure lasts >5 minutes. Risk of seizure recurrence with HHV-6 is equivalent to that seen with other causes of febrile seizure.[1]

Because of the ubiquitous prevalence of HHV-6 infection, there are no effective preventive measures. Little is known about the effect of HHV-6 exposure during pregnancy because most pregnant mothers are immune to the virus.[21] Exclusion from school or child care is not recommended because of the prolonged shedding of the virus.[16,22] JFP

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Most patients infected with HHV-6 have fever and rhinorrhea, and are fussy. Only 20% exhibit the rash of roseola.