Parvovirus B19 Infection

David J Cennimo, MD, FAAP, AAHIVS, Fellow in Infectious Diseases, Department of Pediatrics, University of Medicine and Dentistry of New Jersey-New Jersey Medical School
Arry Dieudonne, MD, Associate Professor of Pediatrics, Division of Pulmonology, Allergy, Immunology and Infectious Diseases, University of Medicine and Dentistry of New Jersey-New Jersey Medical School; Clinical Director, Francois-Xavier Bagnold Center for Children, University Hospital

Updated: Aug 4, 2009

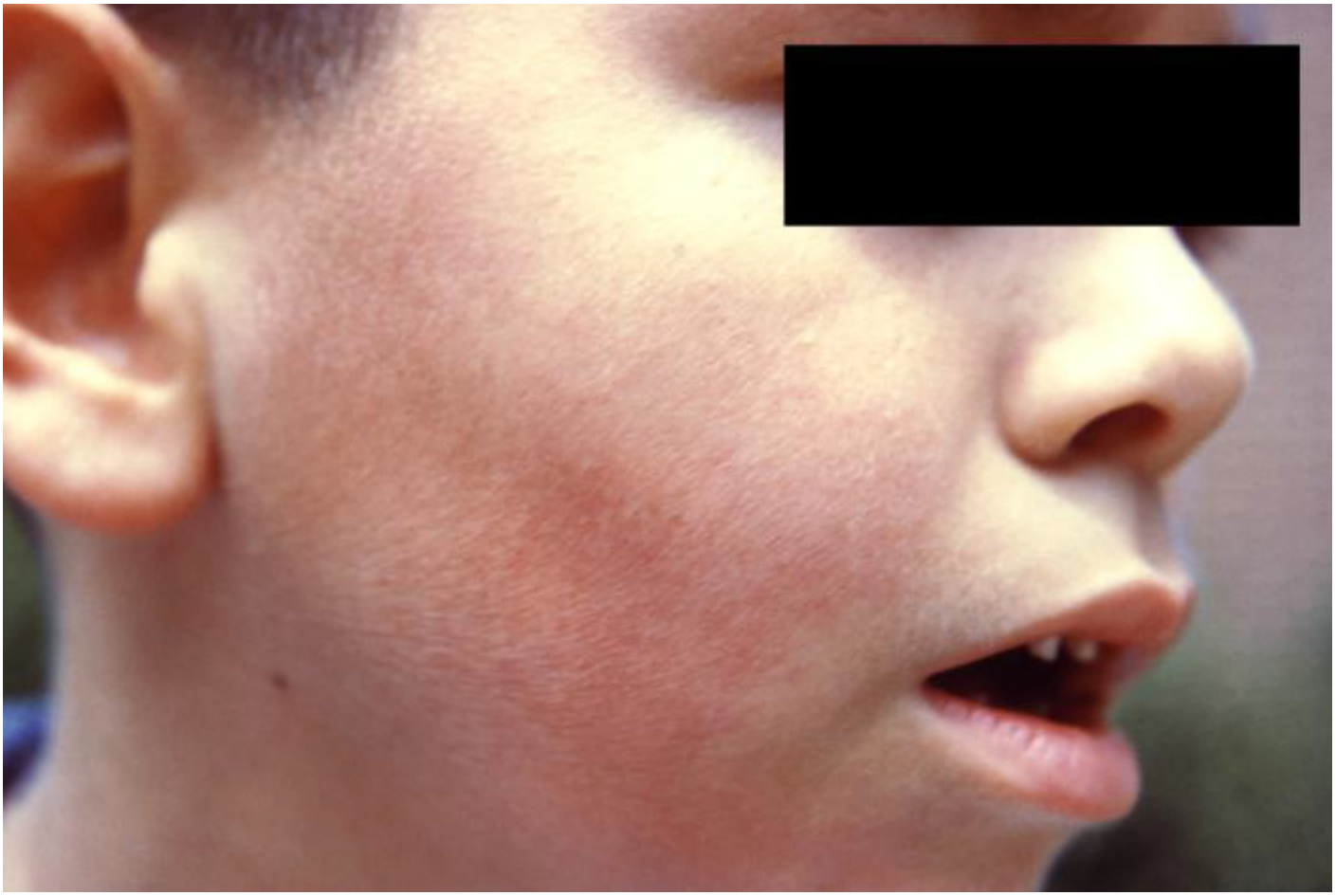
Introduction

Background

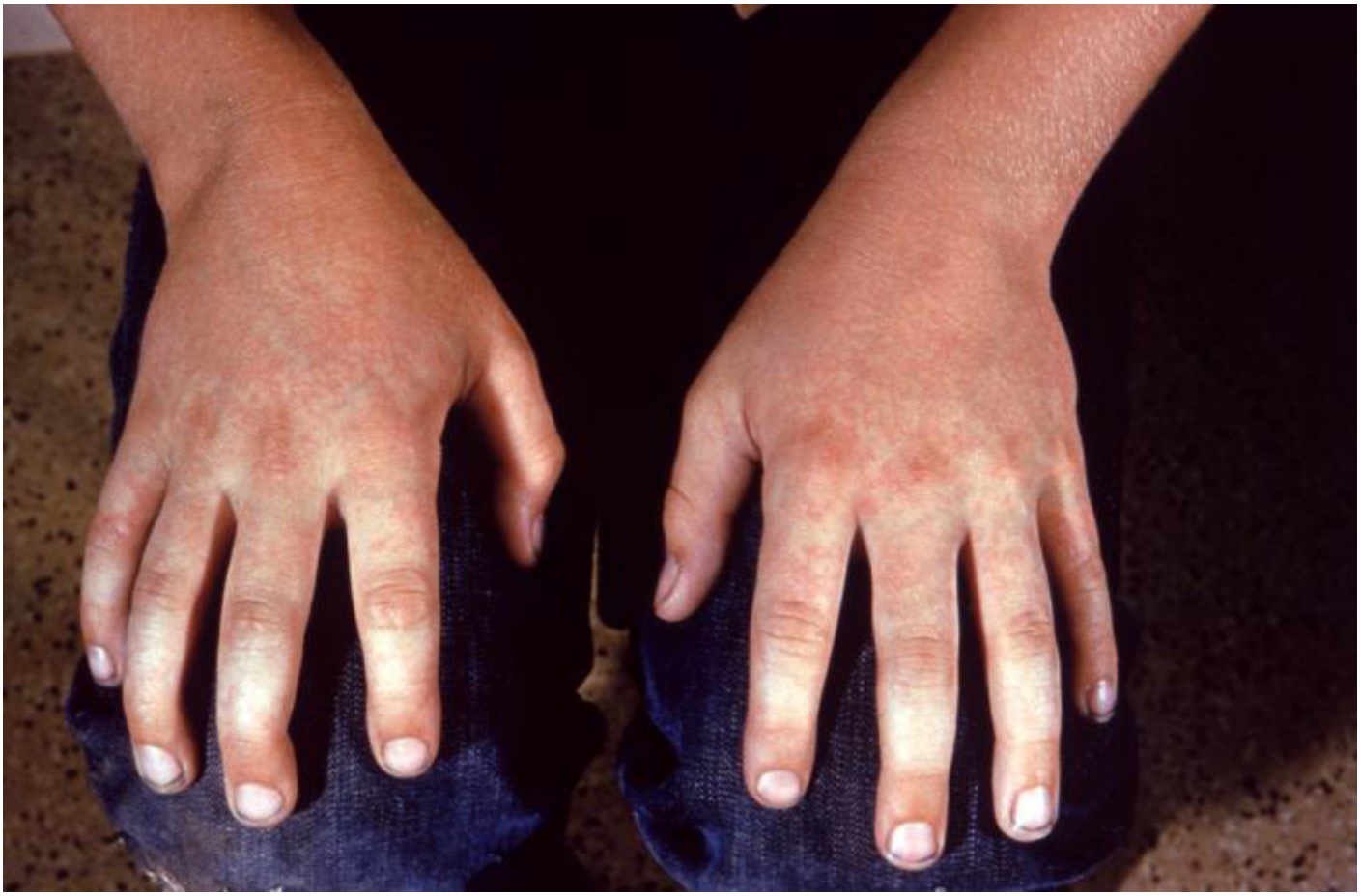
Parvovirus B19 (B19V) is a single-stranded DNA virus of the family Parvoviridae and genus Erythrovirus. Although parvoviruses commonly cause disease in animals, it was only in 1975 that the first human pathogen of this family was discovered by Cossart and colleagues while screening normal blood bank donors' sera for the hepatitis antigen (one of the donors' serum samples was coded B19).[1,2]

The presence of immunoglobulin antibodies to this virus in the serum of half of the adult population was established by epidemiological surveys, suggesting acquisition of immunity during childhood. Evidence of recent infection (viral antigen, immunoglobulin M [IgM]-specific antibodies to the virus) was first found in the blood of Jamaican children living in London, England, all of whom presented with transient aplastic crisis (TAC) of sickle cell disease.[3]

Later, Serjeant et al confirmed the close association of parvovirus and aplastic crisis in a large retrospective study of sera from sickle cell disease patients with this complication.[4]Later, human parvovirus B19 was shown to be the etiologic agent of erythema infectiosum in hematologically normal persons.[5,6] Erythema infectiosum was originally named Fifth disease because it was the fifth of 6 classic exanthematous diseases of childhood to be described. Later, cases of nonimmune hydrops fetalis were reported when infection in a woman occurred during pregnancy[7]. Parvovirus B19 has also been associated with multiple other conditions.[8,2,5,9]



Note the right side of this boy's face displaying signs of erythema infectiosum, or Fifth disease. Image courtesy of CDC



Elementary school child with Fifth Disease. Image courtesy of CDC.

Pathophysiology

The incubation period from infection to initial, nonspecific symptoms ranges from 4-14 days. Cases have been reported as long as 21 days after exposure. The rash and joint symptoms usually occur 2-3 weeks after initial infection. Patients are most contagious in the few days preceding rash. Patients with aplastic anemia are considered contagious before the onset of symptoms and for at least 1 week.[5,9,8,10]

Parvovirus B19 has a unique tropism for human erythroid progenitor cells. The virus requires the P blood antigen receptor (also known as globoside) to enter the cell. Rare individuals who lack the P antigen are immune to parvovirus B19 infection. Once inside the host cell, viral DNA enters the nucleus. The 3' end of the DNA strand folds back on itself, forming a hairpinlike bend that functions as a self-primer for viral DNA replication. The virus is cytotoxic to host cells.[2,11]This, coupled with the tropism for rapidly dividing erythrocyte precursors (particularly pronormoblasts and normoblasts, wherein they replicate to high titers), leads to the suppression of erythrogenesis seen during infection. No reticulocytes (immature erythrocytes) are available to replace aging or damaged erythrocytes as they are cleared by the reticuloendothelial system.[5,2]

Although decreases in hemoglobin levels of greater than 1 g/dL are rare in healthy children infected with parvovirus B19, decreases of 2-6 g/dL may be observed in patients with hemoglobinopathies or hemolytic anemias. Occasionally, the virus infects leukocytes (especially neutrophils).[12]Parvovirus B19 does not infect megakaryocytes; however, in vitro, parvovirus B19 proteins have a cytotoxic effect on megakaryocytes.

Although B19V infection may manifest with pancytopenia, it is not believed to contribute significantly to true aplastic anemia.[9,10]

Fetal myocardial cells are known to express P antigen and may become infected with parvovirus B19. This may explain some of the direct myocardial effects seen in fetal infection.[2,13]

Frequency

United States

Parvovirus B19 infection is extremely common. Seropositivity rates are 5-10% among young children (aged 2-5 years), increasing to 50% by age 15 years and 60% by age 30 years. A small percentage of adults acquire infection every year, resulting in an incidence of approximately 90% in adults older than 60 years.[8,6]The annual seroconversion rate among pregnant women without parvovirus B19 is 1.5%.[9]

Clinical cases of parvovirus B19 infection (erythema infectiosum) may be sporadic or may occur in outbreaks in the late winter through early spring. Attack rates during school outbreaks may be as high as 60%,[8]and secondary spread through nonimmune household contacts is common. Infection can be an occupational hazard in child care workers, with a rate of 20% reported in some studies.[9] A cyclic increase in the number of infections is also observed, peaking every 3-4 years.[8]

International

Parvovirus B19 infection is common worldwide. The age distribution is similar to that observed in the United States. A small number of groups, living in remote geographical locations, have not been exposed to human parvovirus.[2]

Mortality/Morbidity

Parvovirus B19 infection in otherwise healthy children and adults has an extremely low mortality rate.[5,2,10]

Morbidity is as follows:

- Erythema infectiosum (Fifth disease) is described in clinical manifestations below.
- Polyarthropathy syndrome is mostly seen in adult women with acute infection. Patients develop acute symmetric arthritis affecting the small joints of the hands and feet, typically lasting for 1-3 weeks. In a small number, the arthritis may be prolonged, lasting for months. These symptoms can be confused with rheumatoid arthritis and further complicated by transient rheumatoid factor production during parvovirus B19 infection.[14] For this reason, parvovirus B19 infection should be considered in the differential diagnosis of rheumatoid arthritis. Studies have not shown a causal link between parvovirus B19 infection and rheumatoid arthritis, and parvovirus B19 does not cause degenerative joint changes.[8]
- In patients with hemoglobinopathies or hemolytic anemias, in whom the duration of erythrocyte survival is decreased, a decrease in the reticulocyte count to less than 1% (usually to 0%) may precipitate a TAC. Such a crisis is characterized by profound anemia caused by a temporary halt in new erythrocyte production.[4]Because the reticuloendothelial system removes abnormal erythrocytes from circulating blood, abnormal erythrocytes have a significantly shortened half-life. Any interruption in new erythrocyte production may trigger a crisis. The bone marrow during TAC reveals an absence of erythroid precursors and the presence of striking giant pronormoblasts; rarely, necrosis may occur.[15] Parvovirus B19 is the only infectious cause of TAC known and has been shown to be the cause of aplastic crisis in over 80% of patients with sickle cell disease.[2,8].

- Patients who are immunocompromised (eg, receiving chemotherapy or immunosuppressive drugs or have immune defects [congenital and acquired]) may develop chronic parvovirus B19 infection that results in chronic anemia. Pure red cell aplasia (PRAC) persists until the virus is cleared and should be distinguished from the transient anemia described above.[8,5,6] Chronic parvovirus B19 infection in transplant recipients has been linked to anemia, other hematologic abnormalities, myocarditis, and pneumonitis.[16] Pediatric patients with hematologic malignancies and parvovirus B19 infection have suffered prolonged anemia that interferes with chemotherapy timing[17].
- Parvovirus B19 has been linked to other hematologic abnormalities. Thrombocytopenia, leukopenia, or both may be seen in acute infection, even in immunologically normal hosts. Cases of immune thrombocytopenic purpura, Henoch-Schönlein purpura, and the hemophagocytic syndrome have been attributed to parvovirus B19. However, transient erythroblastopenia of childhood and true aplastic anemia are not associated with infection.[8,18,10]
- Hydrops fetalis, perhaps the most serious complication of parvovirus B19 infection, may occur when a nonimmune woman is infected, usually in the first 20 weeks of pregnancy.
    - Parvovirus B19 infection is the most common cause of nonimmune hydrops fetalis and can result in fetal death in 2-6% of cases.[9]
    - As many as 50% of women of childbearing age may not be immune to parvovirus B19 and are susceptible to infection.[5] The seroconversion rate in the same group is 1.5% per year.[9] The vertical infection rate is estimated at 25-50%. The rate of fetal loss is estimated to be 1.6-9%.[5,19,20] Of fetuses infected in the first half of pregnancy, 85% develop hydrops develops within 10 weeks (mean 6-7 wk).
    - The most critical gestational age appears to be 13-16 weeks' gestation, when the fetus has the highest rates of hepatic hematopoiesis.
    - Historically, hydrops had a 30% mortality rate; however, newer data demonstrate a resolution of 94% of cases within 6-12 weeks and a mortality rate of less than 10% if the fetus can be supported by transfusion.[21]
    - Intrauterine growth retardation, myocarditis, and pleural and pericardial effusions, may also occur but parvovirus B19 is not associated with a congenital malformation.[9,8,13,20]
    - Infection in the pregnant patient is further covered below.

Race

No racial predilection is known.

Sex

In general, parvovirus B19 infection affects males and females in equal numbers. Adult females are more likely to develop postinfectious arthritis.

Age

Parvovirus B19 infection is common in school-aged and younger children who attend daycare facilities. In general, children transmit the virus to parents and siblings. In young children, the antibody seroprevalence ranges from 5-10%. This increases to 50% in adolescents and approaches 90% in the elderly.[9,2]

Clinical

History

- Common symptoms of parvovirus B19 (B19V) infection include a mild nonspecific prodromal illness that may consist of fever (15-30% of patients), malaise, headache, myalgia, nausea, and rhinorrhea;

typically beginning 5-7 days after initial infection.[8,22] These symptoms correspond to the initial viremia and dissipate in 2-3 days.[5] Approximately 1 week later, a bright red macular exanthem appears on the cheeks and is often associated with circumoral pallor.[9,5] A diffuse maculopapular rash can appear 1-4 days later and fades to a lacy erythematous rash, which may be pruritic and may spread gradually toward the distal extremities. Most seropositive patients have no history of this classic biphasic illness. The clinical symptoms widely vary, and the classic "slapped cheek" rash is much more common in young children.[8]

- The cause of parvovirus B19 rash is believed to be immunologically mediated, and the rash corresponds to the appearance of immunoglobulin M (IgM) in the serum. This signals the clearance of viremia. Recurrence of the rash (lasting for weeks or more) may be provoked by sunlight, stress, or exercise and does not indicate relapsed infection.[2,5]
- Alternatively, parvovirus B19 infection may manifest with purpuric rash, erythema multiforme, or pruritus of the soles of the feet. Parvovirus B19 may cause a papular-purpuric "gloves-and-socks" syndrome (PPGSS), which manifests as an erythematous exanthem of the hands and feet with a distinct margin at the wrist and ankle joints. It is mainly seen in young adults and initially presents with painful erythema and induration of the hands and feet. Less commonly, the penis, vulva, thighs, cheeks, and elbows may be involved. This syndrome occurs exclusively with parvovirus B19 infection and is an uncommon manifestation. The skin changes may progress to petechia, purpura, and bulla with skin sloughing. PPGSS usually resolves in 1-3 weeks without scaring.[5,6,23,24]
- Transient small joint arthropathy may be the main clinical presentation of parvovirus B19 in adults. Most have some joint pain, but few progress to frank arthritis. In general, the timing of joint symptoms coincide with the expected onset of rash in children. Arthritis usually improves in 1-3 weeks but may persist for months. Parvovirus B19 infection is not associated with chronic degenerative arthritis.[8,2,6] Less then 10% of children experience arthropathy; however, in these cases, the knees are most commonly involved.[9]
- Patients with severe anemia due to transient aplastic crisis (TAC) may present with pallor, fatigue, or signs of an aplastic crisis. Underlying hemoglobinopathies should be sought in these patients. Patients with thrombocytopenia may exhibit bruising.[8,10,2,12]
- Rarely, parvovirus B19 infection manifests as myocarditis, vasculitis, glomerulonephritis, or encephalitis. B19V infection has been reported in association with idiopathic thrombocytopenia purpura, Henoch-Schönlein purpura, and pseudoappendicitis. It has also been reported to precipitate hemophagocytic syndrome.[5,8,2,10] In rare cases, parvovirus B19 has been implicated in fatal myocarditis in transplant patients,[16] and has been implicated as a cause of endothelial dysfunction in patients with diastolic dysfunction.[25]
- Parvovirus B19 infection in pregnant women may result in hydrops fetalis, particularly when infection occurs before 20 weeks' gestation. In the United States, the most common etiology of hydrops fetalis is parvovirus B19 infection.[21,9,8,20]
- Neurologic manifestations associated with parvovirus B19 infection widely vary.[5] Peripheral nervous system involvement such as neuropathy may be seen more frequently in older immunocompetent individuals. CNS involvement, including meningitis, encephalitis, and seizure, has been demonstrated in younger children and immunocompromised patients.[26]
- Many individuals may experience asymptomatic or unrecognized infection.[5]

Physical

- Parvovirus B19 infection may be indistinguishable from other viral illnesses in the absence of the classic exanthem.
- Children are often febrile, but their appearance is nontoxic and the prodrome is nonspecific.
- Patients with aplastic crisis have pallor and tachycardia secondary to anemia. Children with aplastic crisis usually do not have a rash.[9] The absence of rash may result from prolonged viremia and lack of anti–parvovirus B19 IgM. Another hypothesis is that patients in aplastic crisis often receive blood transfusions, and any rash may be attributed to a transfusion reaction.

- A friction rub may be audible if pericarditis is present. Benign flow murmurs are common in anemic children with tachycardia. Patients with myocarditis or severe anemia may present with physical findings of heart failure.
- The small joints of the hands, feet, elbows, and knees may exhibit signs of arthritis.
- Painful pruritic papules and purpura may be present on the hands and feet as part of PPGSS.

Causes

- Classic fifth disease, aplastic crisis, and PPGSS are caused almost exclusively by parvovirus B19. This virus, distributed worldwide, infects only humans. Transmission occurs via vertical transmission (birth), large droplet respiratory secretions, transfusion of blood products, and percutaneous exposure to blood.[9,22]
- Parvovirus B19 has been spread by blood products, such as intravenous immunoglobulin (IVIG), packed RBCs, platelets, and nonrecombinant clotting factors. Because the virus lacks an outer lipid envelope and the genome is very stable, it is extremely resistant to heat, cold, and solvents. Since 2002, makers of plasma-derived products have screened for parvovirus B19.[2]

Differential Diagnoses

Rubella

Other Problems to Be Considered

Scarlet fever
Drug reaction
Collagen vascular disease
Rheumatoid arthritis
Enteroviruses

Workup

Laboratory Studies

- Most patients with parvovirus B19 (B19V) infection do not require laboratory studies because symptoms are mild and the illness resolves over 5-7 days.
- Parvovirus serology (anti– parvovirus B19 immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies) can be determined using enzyme-linked immunoassay (ELISA), radioimmunoassay, or immunofluorescence. Results of IgM testing are particularly difficult to interpret. Standardization between laboratories is lacking. Even in a single laboratory, sensitivity and specificity are partly determined by operator's skills.
- Polymerase chain reaction (PCR) testing for parvovirus B19 is routinely available with increased sensitivity level. However, contamination and false-positive results are noted risks that lead to confusing interpretation. Low levels of B19 DNA may detectable for more than 4 months in serum after acute infection and for years in other tissues.[27,28]. This test, a more useful clinical tool to diagnose chronic infection, detects viral DNA present in the blood or other tissues/fluids.[20]The interpretation, especially as it pertains to pregnant women is uncertain.[19,21]The diagnosis of acute or chronic infection should be made on the basis of standard DNA hybridization or quantitative (real-time) PCR in combination with serologic assays for B19-specific IgG, IgM, or both.[8]
- During experimental infection of volunteers, IgM antibodies were detected 10-12 days after inoculation, and IgG antibodies were detected at 2 weeks.[29] Ninety percent of patients with classic erythema

infectiosum rash had IgM antibodies detected at initial presentation and IgG antibodies by day 7.[9] IgM remains detectable for months and IgG for life.[9,8]

- In patients with evidence of clinically significant anemia or transient aplastic crisis (TAC), obtain a CBC count with reticulocyte count.
  - Patients infected with parvovirus B19 have a low reticulocyte count (0-1%).
  - In an aplastic crisis, hemoglobin levels drop below the patient's baseline by at least 2 g/dL.
  - IgM antibodies are usually present by day 3 of illness or the time of hematopoietic nadir. IgG antibodies are detectable around the time of the recovery of erythrogenesis.[8,9,22,18]
  - Parvovirus B19 PCR demonstrates high level viremia during TAC.[8]
- Immunodeficient patients with chronic B19V infection and pure red cell anemia (PRAC) also have signs of anemia. In contrast to TAC, PRAC is characterized by very low or absent antibody levels. PCR is the diagnostic test of choice to demonstrate viremia.[5,8]
- If a pregnant woman is exposed to parvovirus B19, obtain IgG and IgM serology as soon as possible.[21,20]
  - Positive IgG results and negative IgM results indicate past infection (no risk to fetus).
  - Positive IgG and IgM results indicate infection within the last 7-120 days (possible risk to fetus).
  - Negative IgG results and positive IgM results indicate acute infection (higher risk to fetus).
  - Negative IgG and IgM results indicate that the mother is not immune and that no evidence of acute infection is noted. In this case, repeat the tests in 3 weeks. Subsequent development of IgM indicates an acute infection.
  - No standards have been established to evaluate parvovirus B19 PCR on maternal blood; low levels may be detected long after clinical infection.[28] PCR may be performed on fetal serum of amniotic fluid to detect virus.[19]

Imaging Studies

- Routine imaging is not necessary.
- Fetal ultrasonography may be useful in detecting hydrops. The timing and frequency of ultrasonography surveillance for infected pregnant women have not been conclusively determined.[20]

Treatment

Medical Care

- Acetaminophen or ibuprofen is effective for treating fever in patients with parvovirus B19 (B19V) infection. Fever does not always require treatment with antipyretics; however, consider antipyretics if a patient appears clinically uncomfortable.
- Resolution of infection depends on the presence of immunoglobulins against parvovirus B19. Intravenous immunoglobulin (IVIG) has been used with good results for patients suffering pure red cell aplasia (PRCA). Patients should be monitored for relapsed viremia.[8,2,22]
- Patients in aplastic crisis require packed RBC transfusions. In some studies, more than 80% of patients with sickle cell disease in transient aplastic crisis (TAC) have required transfusion.[8] IVIG is not recommended for TAC.
- In patients receiving immunosuppressive agents, temporarily decreasing the dose of immunosuppressive agents usually enables the immune system to produce sufficient immunoglobulin G (IgG) to eradicate the infection and confer lifelong protection. In some individuals with human immunodeficiency virus (HIV) infection, highly active antiretroviral therapy restores immune function, enabling resolution of chronic parvovirus B19 infection.[22]
- Although its use is controversial and carries many risks, intrauterine blood transfusions may be helpful in cases of hydrops fetalis.[2,30,13,20,21]

Consultations

- Hematologist: Patients who present with aplastic crisis require intensive monitoring and RBC transfusions to prevent death and should be evaluated by a hematologist.
- Pediatric infectious disease specialist or immunologist: Patients with long-term or unusual parvovirus B19 infections can benefit from consultation with a pediatric subspecialist in infectious diseases or immunology. These patients may benefit from treatment with IVIG.

Diet

- No dietary restrictions are necessary.

Activity

- Patients with classic erythema infectiosum are no longer contagious after the rash has appeared.[9]
- Patients with aplastic crisis, papular-purpuric "gloves and socks" syndrome (PPGSS), or immunosuppression and chronic parvovirus B19 infection with anemia should be isolated with droplet and standard precautions due to ongoing viremia.[9]
- Patients with TAC should have precautions maintained for 7 days, whereas those with chronic infection should be isolated for the duration of their stay.[9]
- Pregnant staff should be alerted to the potential risks of parvovirus B19 infection when caring for these patients.[9]

Medication

No antiviral therapy is available to treat parvovirus B19 (B19V) infections. Children rarely require specific therapy other than acetaminophen for fever.

In patients with postinfectious arthritis, acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) usually provide symptomatic relief. Because the use of aspirin in children with other viral illnesses has been associated with Reye syndrome, aspirin use is not recommended in children with B19V infection. If children have pruritus from the parvovirus B19 rash, oral antihistamines (eg, diphenhydramine) and starch baths typically provide relief.

Antipyretic agents

These agents decrease or eliminate fever by acting at the level of the hypothalamus (acetaminophen) or by decreasing the activity of the enzyme cyclooxygenase, thereby decreasing the production of prostaglandins (NSAIDs).

Acetaminophen (Tylenol, Feverall, Tempra, Aspirin Free Anacin, Panadol)

Reduces fever by acting directly on hypothalamic heat-regulating centers, which increases dissipation of body heat via vasodilation and sweating.

Dosing

Adult

650 mg PO q4-6h or 1000 mg q6h; not to exceed 4 g/d

Pediatric

<12 years: 10-15 mg/kg/dose PO/PR q4-6h prn; not to exceed 5 doses/d and 2.6 g/d
≥12 years: Administer as in adults

Interactions

Rifampin can reduce analgesic effects of acetaminophen; coadministration with barbiturates, carbamazepine, hydantoins, and isoniazid may increase hepatotoxicity

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Hepatotoxicity is possible in chronic alcoholism following administration of various dose levels; severe or recurrent pain or high or continued fever may indicate serious illness; acetaminophen is contained in many OTC products, and combined use with these products may result in cumulative acetaminophen doses exceeding recommended maximum dose; avoid alternating acetaminophen with NSAIDs to reduce fever because no evidence exists proving greater effectiveness in reducing fever over use of acetaminophen or ibuprofen alone

Ibuprofen (Motrin, Ibuprin, Advil)

One of the few NSAIDs indicated for reduction of fever.

Dosing

Adult

Fever: 400-600 mg PO q4-6h while symptoms persist; not to exceed 3.2 g/d
Arthritis: 400 mg PO q4-6h, 600 mg q6h, or 800 mg q8h while symptoms persist; not to exceed 3.2 g/d

Pediatric

10 mg/kg/dose PO q4-6h while symptoms persist; not to exceed 2.4 g/d

Interactions

Coadministration with aspirin increases risk of inducing serious NSAID-related adverse effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril,

and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT when taking anticoagulants (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; phenytoin levels may be increased when concurrently administered

Contraindications

Documented hypersensitivity; peptic ulcer disease; recent GI tract bleeding or perforation; renal insufficiency; high risk of bleeding

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Category D in third trimester of pregnancy; caution in congestive heart failure, hypertension, and decreased renal and hepatic function; caution in coagulation abnormalities or during anticoagulant therapy; can trigger asthma in some patients with asthma (especially if patient has aspirin insensitivity)

Immunologic effectors

These agents are purified preparations of gamma globulin. Immunologic effectors are derived from large pools of human plasma and comprise 4 subclasses of antibodies, approximating the distribution of human serum.

Immunity to B19V infection appears to be purely humoral (ie, mediated via immunoglobulins). The role, if any, that cell-mediated immunity plays in providing immunity to B19V is unknown. As a result of the high seroprevalence of IgG against parvovirus among adults in the general population who have recovered from infection, the antiparvovirus IgG titer in IVIG is probably sufficient to provide passive immunity for the clearance of virus in immunocompromised hosts with chronic B19V infection.

Immune globulin, intravenous (Gammagard S/D, Carimune NF, Gammar-P)

Provides passive immunization against a broad spectrum of infectious agents. Neutralizes circulating myelin antibodies through anti-idiotypic antibodies; down-regulates proinflammatory cytokines, including INF-gamma; blocks Fc receptors on macrophages; suppresses inducer T and B cells and augments suppressor T cells; blocks complement cascade; promotes remyelination; may increase CSF IgG (10%).

Dosing

Adult

Limited data suggest using a dose of 400 mg/kg/d IV for 5 days.
Use of IVIG to treat chronic anemia resulting from B19V is off label; use should be limited to prescription by infectious disease specialists, immunologists, hematologists, or transplant surgeons

Pediatric

Administer as in adults

Interactions

Decreases immunogenicity of vaccines, especially live-attenuated vaccines

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

IgA deficiency occurs in 1 in 300-500 patients; check serum IgA before IVIG (use IgA-depleted product, eg, Gammagard S/D); infusions may increase serum viscosity and thromboembolic events; infusions may increase risk of migraine headaches, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d postinfusion); increases risk of renal tubular necrosis in elderly patients and in patients with diabetes, volume depletion, and preexisting kidney disease; laboratory result changes associated with infusions include elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increase in ESR for 2-3 wk, and apparent hyponatremia

Antihistamines

These agents decrease or prevent allergic symptoms caused by histamine receptors from mast cells.

Diphenhydramine (Benadryl)

First-generation antihistamine that binds to H1 receptors in the CNS and the body.
Competitively blocks histamine from binding to H1 receptors. As a result of CNS penetration, diphenhydramine frequently causes drowsiness. A small percentage of children paradoxically respond to diphenhydramine with agitation.

Dosing

Adult

25-50 mg PO q6-8h prn; not to exceed 400 mg/d
10-50 mg IV/IM q6-8h prn; not to exceed 400 mg/d

Pediatric

1.25 mg/kg/dose PO/IV/IM q6h as needed for pruritus; not to exceed 5 mg/kg/d or 50 mg q6h

Interactions

Potentiates effect of CNS depressants; due to alcohol content, do not administer elixir to patients taking medications causing disulfiramlike reaction

Contraindications

Documented hypersensitivity; MAOIs

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

May exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer disease, or urinary tract obstruction; xerostomia may occur

Follow-up

Further Inpatient Care

- Patients rarely require admission for parvovirus B19 (B19V) infections unless they have underlying disease.
- Consider the following factors for purposes of infection control:
    - Parvovirus B19 is spread via small respiratory droplets.
    - The attack rate in susceptible populations approaches 60%.
    - Parvovirus B19 is contagious from 24-48 hours before developing the viral prodrome and until the rash appears. The appearance of serum immunoglobulin (IgM) coincides with the appearance of the rash.[9]
    - See above for isolation precautions.

Further Outpatient Care

- Patients with a resolved aplastic crisis or with a rash are no longer infectious.
- Patients are no longer infectious after other symptoms resolve (usually by day 7 of illness). Thus, patients with a classic parvovirus B19 rash may return to school or daycare.[31,9]

Transfer

- Patients with an aplastic crisis may require transfer to centers that provide pediatric critical care and hematology services.

Deterrence/Prevention

- Phase I clinical trials are currently evaluating vaccine candidates against parvovirus B19.[2,8]
- The risk of contagion in typical erythema infectiosum in the community is the highest during the early stages of the infection when symptoms are least specific and the disease more difficult to diagnose. Little rationale warrants excluding children with Fifth disease exanthem from daycare centers and school and adults from work.[31]

- In addition to standard precautions, droplet precautions are recommended for hospitalized children with aplastic crises, children with the papular purpuric "gloves and socks" syndrome (PPGSS), and immunosuppressed patients with chronic infection and anemia for the duration of hospitalization.[9]

Complications

- Complications include hydrops fetalis, chronic anemia, aplastic crisis, and death.
- Immunocompetent individuals with a prolonged course of rash, fatigue, and arthralgias caused by persistent viremia have been reported. Symptoms in some of these patients respond to intravenous immunoglobulin (IVIG) therapy.

Prognosis

- Most patients recover without sequelae.

Patient Education

- Parvovirus B19 infects only humans. Approximately 60% of adults aged 30 years are immune to parvovirus B19, although few recall having had the infection. Symptoms include a low-grade fever, myalgias, arthralgias, headache, nausea, and rhinorrhea. As the symptoms disappear, children often develop a bright red rash on the cheeks (as if they had been slapped). The infection is contagious in children for a few days before symptoms begin and until the symptoms disappear. When the rash appears, the infection is no longer contagious. The presence of the parvovirus B19 rash is not a reason to keep children home from daycare or school.
- If a pregnant woman is not immune to parvovirus B19 becomes infected, the probability of hydrops fetalis developing in the neonate is small (2-5%). Any pregnant woman who is exposed to an individual in whom parvovirus B19 infection is suspected should immediately contact their obstetrician.
- In healthy adults and children, parvovirus B19 is not a serious infection. Exceptions include patients with cancer who are receiving chemotherapy, as well as patients with HIV infection and/or acquired immunodeficiency syndrome (AIDS), organ transplants, and other immunodeficient states.
- For excellent patient education resources, visit eMedicine's Children's Health Center. Also, see eMedicine's patient education article Fifth Disease.

Miscellaneous

Medicolegal Pitfalls

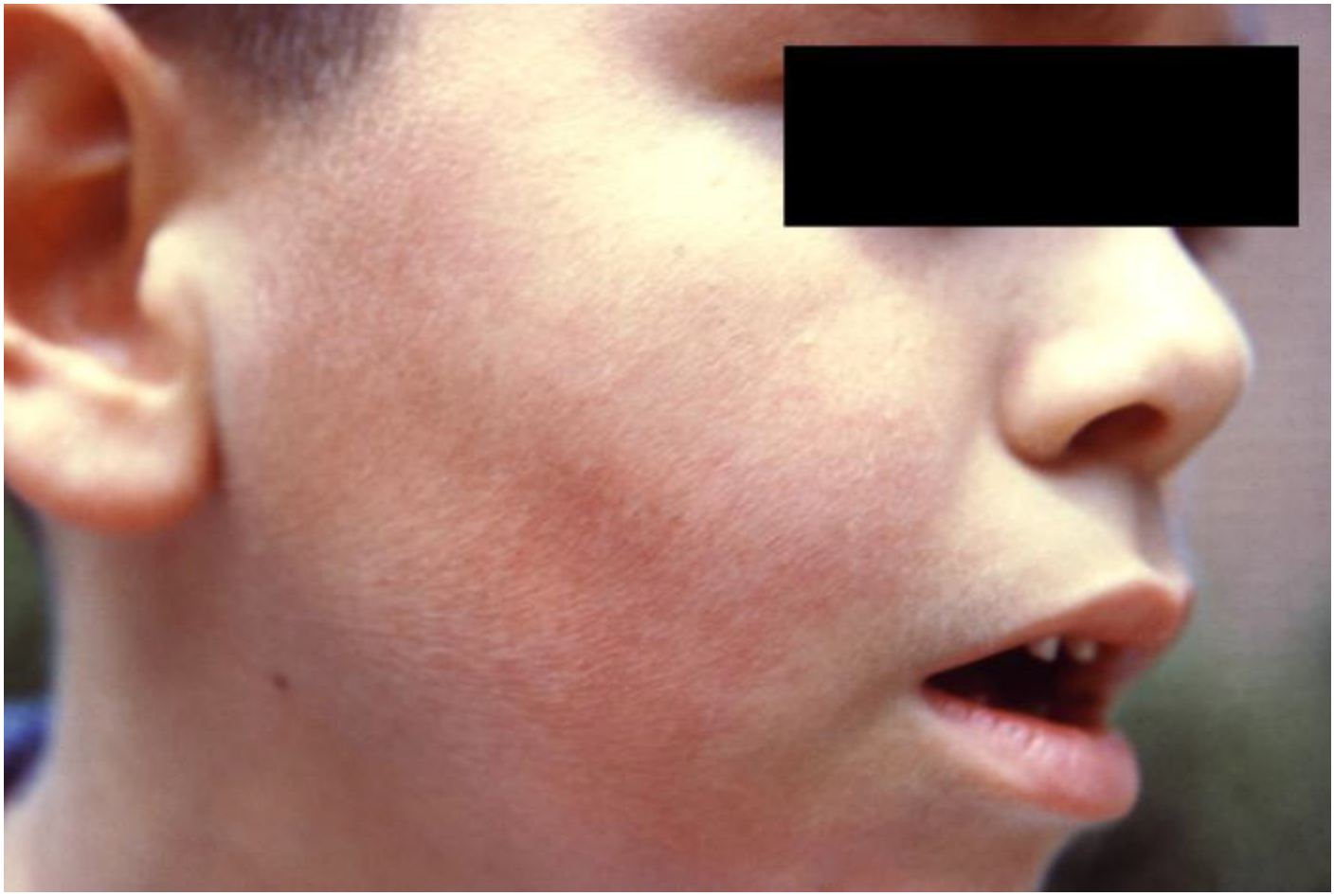
- Parvovirus B19 (B19V) infection is not a reason to terminate a pregnancy, and parvovirus B19 is not teratogenic. Less than 20% of fetuses exposed before 20 weeks' gestation have severe symptoms.
- Intrauterine RBC transfusions have been used to treat infectious and noninfectious hydrops. A minority of hydrops fetalis cases may spontaneously resolve.[8,21,20]

Special Concerns

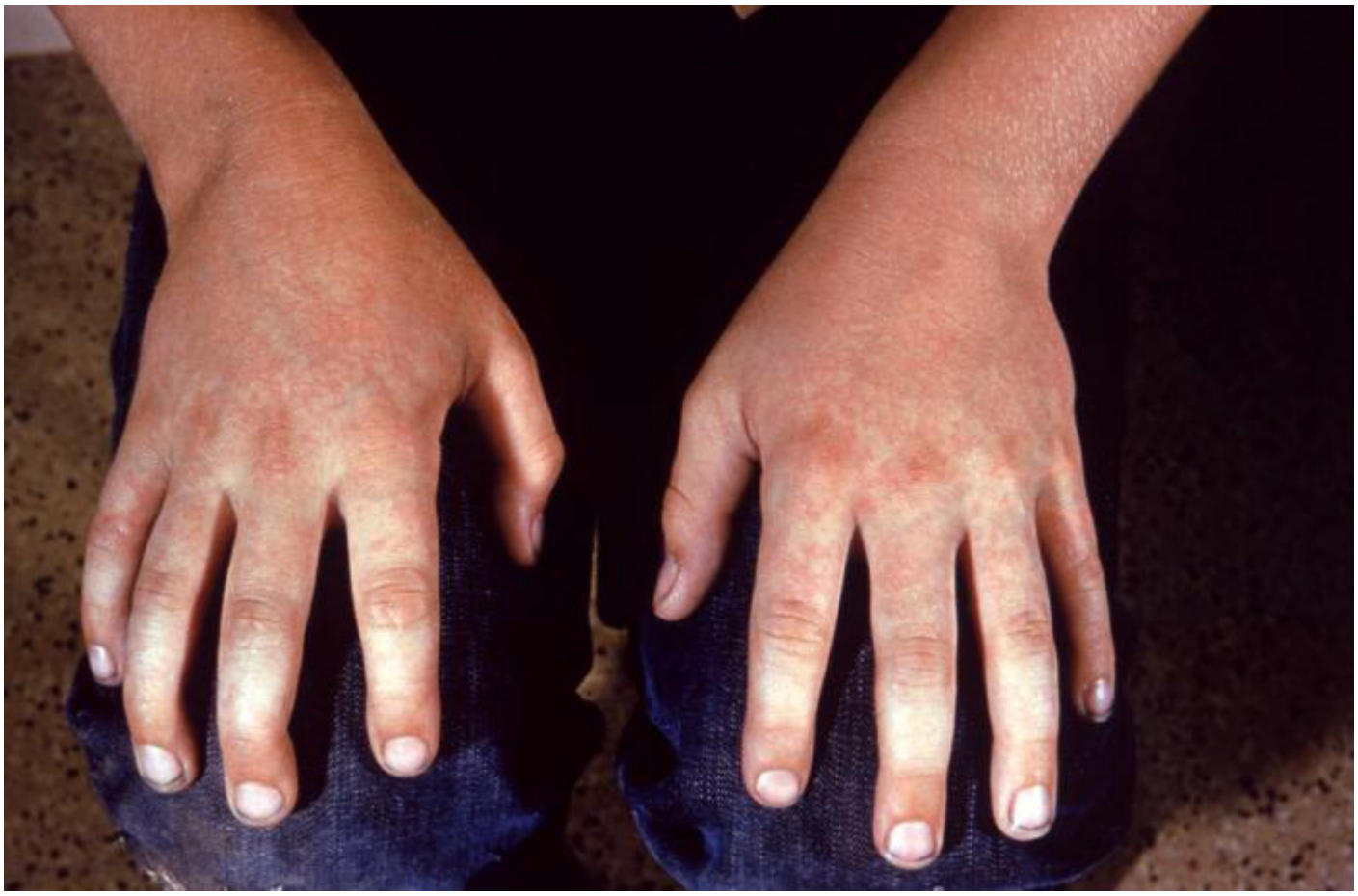
- If a pregnant woman is not immune and becomes infected with parvovirus B19, fetal infection may occur. Transplacental infection occurs in approximately 33% of pregnant women with parvovirus B19 infection. As with children, B19V infects the precursors of erythrocytes in fetuses. Because fetal RBCs have a shorter half-life of 45-60 days (compared with 90 d in normal erythrocytes), infection may cause severe anemia in the fetus. The fetus may develop signs of high-output cardiac failure (hydrops fetalis).[20,13]

- Refer women who are pregnant with acute parvovirus B19 infection to a specialist in maternal-fetal medicine for evaluation, including ultrasonography.[20]
- Routine exclusion of pregnant women from a workplace in which erythema infectiosum is present is not recommended. The relatively low potential risk of infection should be explained to them. If a pregnant woman is exposed to an individual with parvovirus B19 infection, serology to determine parvovirus B19 immunoglobulin G (IgG) and immunoglobulin M (IgM) levels is indicated.
    - A positive IgG with negative IgM result indicates past infection and reassures that no risk to the fetus is present.
    - If IgG results are negative, the woman is still at a low risk for developing parvovirus B19 infection.
    - The presence of IgM antibodies indicates acute or recent infection.
- Because the incubation period of parvovirus B19 infection is longer in the fetus than in healthy children, some experts recommend performing serial weekly ultrasonography, which is necessary to look for signs of hydrops fetalis, for 10-12 weeks.[20,13]
    - If fetal ultrasonography reveals the signs of hydrops fetalis, cordocentesis is indicated to determine the hemoglobin, hematocrit, and IgM status of the fetus' blood.
    - If IgM results are positive, the fetus has an acute infection. Severe anemia may require intrauterine transfusion of erythrocytes. Both cordocentesis and intrauterine transfusion have significant risks to the fetus and mother.
    - If ultrasound findings remain normal for 12 weeks after exposure to parvovirus B19, the prognosis is excellent.[21]

Multimedia



Media file 1: Note the right side of this boy's face displaying signs of erythema infectiosum, or Fifth disease. Image courtesy of CDC



Media file 2: Elementary school child with Fifth Disease. Image courtesy of CDC.

References

1. Cossart YE, Field AM, Cant B et al. Parvovirus-like particles in human sera. *Lancet*. 1975;1:72.
2. Young NS, Brown KE. Parvovirus B19. *N Engl J Med*. Feb 5 2004;350(6):586-97. [Medline].
3. Pattison JR,Jones SE, Hodgson J et al. Parvovirus infections and hypoplastic crisis in sickle cell anaemia. *Lancet*. 1981;1:664.
4. Serjeant GR, Topley JM, Mason K, Serjeant BE, Pattison JR, Jones SE, et al. Outbreak of aplastic crises in sickle cell anaemia associated with parvovirus-like agent. *Lancet*. Sep 19 1981;2(8247):595-7.
5. Cherry JD, Schulte DJ. Human Parvovirus B19. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, eds. *Feigin & Cherry's Textbook of Pediatric Infectious Diseases*. Vol 2. 6th ed. Philadelphia, PA: Saunders Elsevier; 2009:1902-1920.
6. Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infection. *Am Fam Physician*. Feb 1 2007;75(3):373-6. [Medline].
7. Anderson LJ, Hurwitz ES. Human parvovirus B19 and pregnancy. *Clin Perinatol*. 1988;15:273.
8. Brown KE. Parvovirus B19. In: Mandell GL, Bennet JE, Dolin R. *Mandell, Douglas and Bennett's Principals and Practice of Infectious Diseases*. Vol 2. 6th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2005:1891-1902.
9. American Academy of Pediatrics Committee on Infectious Diseases. Parvovirus B19. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *2009 Red Book: Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Peiatrics; 2009:491-493.

10. Brown KE. Human Parvoviruses. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 3rd ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2008:1072-1076.
11. Burns K, Parish CR. Parvoviridae. In: Knipe DM, Howley PM, eds. *Fields Virology*. Vol 2. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:65.
12. Mustafa MM, McClain KL. Diverse hematologic effects of parvovirus B19 infection. *Pediatr Clin North Am*. Jun 1996;43(3):809-21. [Medline].
13. Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. *Reprod Toxicol*. May 2006;21(4):421-35. [Medline].
14. Luzzi GA, Kurtz JB. Human parvovirus arthropathy and rheumatoid factor(Letter). *Lancet*. 1985;1:1218.
15. Conrad ME, Studdard H et al. Case report: aplastic crisis in sickle cell disorders: bone marrow necrosis and human parvovirus infection. *Am J Med Sci*. 1988;295:212.
16. Eid AJ, Brown RA, Patel R, Razonable RR. Parvovirus B19 infection after transplantation: a review of 98 cases. *Clin Infect Dis*. Jul 1 2006;43(1):40-8. [Medline].
17. Lindblom A, Heyman M, Gustafsson I, Norbeck O, Kaldensjo T, Vernby A. Parvovirus B19 infection in children with acute lymphoblastic leukemia is associated with cytopenia resulting in prolonged interruptions of chemotherapy. *Clin Infect Dis*. Feb 15 2008;46(4):528-36. [Medline].
18. Young NS. Hematologic and hematopoietic consequences of B19 parvovirus infection. *Semin Hematol*. 1988;25:159.
19. Mendelson E, Aboudy Y, Smetana Z, Tepperberg M, Grossman Z. Laboratory assessment and diagnosis of congenital viral infections:Rubella, cytomegalovirus (CMV), varicella-zoster virus (VZV),herpes simplex virus (HSV), parvovirus B19 andhuman immunodeficiency virus (HIV). *Reprod Toxicol*. 2006;21:350-382.
20. Adler SP, Koch WC. Human Parvovirus Infections. In: Remington JS, Klein JO, Wilson CB, Baker CJ. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2006:868-892.
21. Infections. In: Cunningham FG, Leveno KL, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD, eds. *Williams Obstetrics*. 22nd Ed. USA: McGraw-Hill; 2001:chap 58.
22. Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *Jrnl Internal Med*. 2006;260:285-304.
23. Grilli R, Izquierdo MJ, Farina MC, et al. Papular-purpuric "gloves and socks" syndrome: polymerase chain reaction demonstration of parvovirus B19 DNA in cutaneous lesions and sera. *J Am Acad Dermatol*. Nov 1999;41(5 Pt 1):793-6. [Medline].
24. Fretzayas A, Douros K, Moustaki M, Nicolaidou P. Papular-purpuric gloves and socks syndrome in children and adolescents. *Pediatr Infect Dis J*. Mar 2009;28(3):250-2. [Medline].
25. Tschope C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. *Circulation*. Feb 22 2005;111(7):879-86. [Medline].
26. Douvoyiannis M, Litman N, Goldman DL. Neurologic manifestations associated with parvovirus B19 infection. *Clin Infect Dis*. Jun 15 2009;48(12):1713-23. [Medline].
27. Soderlund-Venermo M, Hokynar K, Nieminen J et al. *Persistence of human parvovirus B 19 in human tissues*. 2002;50;:307-316.
28. Musiani M, Zerbini M et al.Gentilomi G et al. Parvovirus B19 clearance from peripheral blood after acute infection. *J Infect Dis*. 1995;172:1360-1363.
29. Anderson MJ, Higgins PG, Davis LR, Willman JS, Jones SE, Kidd IM. Experimental parvoviral infection in humans. *J Infect Dis*. Aug 1985;152(2):257-65. [Medline].
30. Failey CK, Smoleniec JS et al. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B 19 infection. *Lancet*. 1995;346:1335-1337.
31. [Guideline] Center for Disease control and Prevention. Risk associated with human parvovirus infection. *MMWR*. 1989;38:81.

Keywords

parvovirus B19 infection, erythema infectiosum, slapped cheek disease, fifth disease, B19V, aplastic crisis, postinfectious arthritis, papular purpuric "gloves and socks" syndrome, PPGSS, hydrops fetalis, hemolytic anemia, aplastic anemia, pancytopenia, polyarthropathy syndrome, arthritis, rheumatoid arthritis, transient aplastic crisis, TAC, immune thrombocytopenic purpura, Henoch-Schönlein purpura, hemophagocytic syndrome, transient erythroblastopenia of childhood, treatment, diagnosis

Contributor Information and Disclosures

Author

David J Cennimo, MD, FAAP, AAHIVS, Fellow in Infectious Diseases, Department of Pediatrics, University of Medicine and Dentistry of New Jersey-New Jersey Medical School
David J Cennimo, MD, FAAP, AAHIVS is a member of the following medical societies: American Academy of Pediatrics, American College of Physicians, American Medical Association, HIV Medicine Association of America, Infectious Diseases Society of America, Medical Society of New Jersey, and Pediatric Infectious Diseases Society
Disclosure: Nothing to disclose.

Coauthor(s)

Arry Dieudonne, MD, Associate Professor of Pediatrics, Division of Pulmonology, Allergy, Immunology and Infectious Diseases, University of Medicine and Dentistry of New Jersey-New Jersey Medical School; Clinical Director, Francois-Xavier Bagnold Center for Children, University Hospital
Arry Dieudonne, MD is a member of the following medical societies: American Academy of Pediatrics, American Medical Association, and Pediatric Infectious Diseases Society
Disclosure: Nothing to disclose.

Medical Editor

Glenn J Fennelly, MD, MPH, Director, Division of Pediatric Infectious Diseases, Jacobi Medical Center; Associate Professor, Department of Pediatrics, Albert Einstein College of Medicine
Glenn J Fennelly, MD, MPH is a member of the following medical societies: Pediatric Infectious Diseases Society
Disclosure: Nothing to disclose.

Pharmacy Editor

Mary L Windle, PharmD, Adjunct Assistant Professor, University of Nebraska Medical Center College of Pharmacy, Pharmacy Editor, eMedicine
Disclosure: Pfizer Inc Stock Investment from financial planner; Avanir Pharma Stock Investment from financial planner ; WebMD Salary and stock Employment and investment from financial planner

Managing Editor

Joseph Domachowske, MD, Professor of Pediatrics, Microbiology and Immunology, Department of Pediatrics, Division of Infectious Diseases, State University of New York-Upstate Medical University
Joseph Domachowske, MD is a member of the following medical societies: Alpha Omega Alpha, American Academy of Pediatrics, American Society for Microbiology, Infectious Diseases Society of America, Pediatric

Infectious Diseases Society, and Phi Beta Kappa
Disclosure: Nothing to disclose.

CME Editor

Robert W Tolan Jr, MD, Chief, Division of Allergy, Immunology and Infectious Diseases, The Children's Hospital at Saint Peter's University Hospital; Clinical Associate Professor of Pediatrics, Drexel University College of Medicine
Robert W Tolan Jr, MD is a member of the following medical societies: American Academy of Pediatrics, American Medical Association, American Society for Microbiology, American Society of Tropical Medicine and Hygiene, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, Phi Beta Kappa, and Physicians for Social Responsibility
Disclosure: GlaxoSmithKline Honoraria Speaking and teaching; MedImmune Honoraria Speaking and teaching; Merck Honoraria Speaking and teaching; sanofi pasteur Honoraria Speaking and teaching; Baxter Healthcare Honoraria Speaking and teaching

Chief Editor

Russell W Steele, MD, Head, Division of Pediatric Infectious Diseases, Ochsner Children's Health Center; Clinical Professor, Department of Pediatrics, Tulane University School of Medicine
Russell W Steele, MD is a member of the following medical societies: American Academy of Pediatrics, American Association of Immunologists, American Pediatric Society, American Society for Microbiology, Infectious Diseases Society of America, Louisiana State Medical Society, Pediatric Infectious Diseases Society, Society for Pediatric Research, and Southern Medical Association
Disclosure: None None None

Acknowledgments

The authors and editors of eMedicine gratefully acknowledge the contributions of previous coauthor Dennis Cunningham, MD, to the original writing and development of this article.