Clinical Presentations of Parvovirus B19 Infection

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Although most persons with parvovirus B19 infection are asymptomatic or have mild, nonspecific, cold-like symptoms, several clinical conditions have been linked to the virus. Parvovirus B19 usually infects children and causes the classic "slapped-cheek" rash of erythema infectiosum (fifth disease). The virus is highly infectious and spreads mainly through respiratory droplets. By the time the rash appears, the virus is no longer infectious. The virus also may cause acute or persistent arthropathy and papular, purpuric eruptions on the hands and feet ("gloves and socks" syndrome) in adults. Parvovirus B19 infection can trigger an acute cessation of red blood cell production, causing transient aplastic crisis, chronic red cell aplasia, hydrops fetalis, or congenital anemia. This is even more likely in patients with illnesses that have already shortened the lifespan of erythrocytes (e.g., iron deficiency anemia, human immunodeficiency virus, sickle cell disease, thalassemia, spherocytosis). A clinical diagnosis can be made without laboratory confirmation if erythema infectiosum is present. If laboratory confirmation is needed, serum immunoglobulin M testing is recommended for immunocompetent patients; viral DNA testing is recommended for patients in aplastic crisis and for those who are immunocompromised. Treatment is usually supportive, although some patients may require transfusions or intravenous immune globulin therapy. Most patients recover completely. (Am Fam Physician 2007;75:373-6, 377. Copyright © 2007 American Academy of Family Physicians.)

▶ **Patient information:** A handout on parvovirus B19, written by the authors of this article, is provided on page 377.

Parvovirus B19 infection is common worldwide, and most persons who contract the virus are infected by 15 years of age. Infection is most common in late winter or early spring.[1] The virus is transmitted through exposure to infected respiratory droplets or blood products and vertically from mother to fetus.[1] Exposure to respiratory droplets is the most common means of transmission. The transmission rate is about 50 percent for those living with infected persons and about 20 to 30 percent for susceptible teachers and day care workers who are exposed to infected children.[1] Nosocomial transmission also has been documented.[2] The incubation period of the infection ranges from four to 14 days but can last as long as 21 days.[1]

Virology

Parvovirus is a small, single-stranded DNA virus. The lack of a lipid envelope makes it resistant to physical inactivation with heat or detergents.[3] The virus targets rapidly growing erythroid progenitor cells, which are found in human bone marrow, fetal liver, human umbilical cord, and peripheral blood.[4,5] To become infective, the parvovirus attaches to a P antigen receptor. Persons with parvovirus B19 infection are no longer contagious when the rash appears because viremia has cleared by this point. Most symptoms occur secondary to immune complex formation.

Clinical Conditions Associated with Parvovirus B19

Most persons with parvovirus B19 infection are asymptomatic or exhibit mild, nonspecific, cold-like symptoms that are never linked to the virus.[6] However, clinical conditions associated with the infection include erythema infectiosum; arthropathy; transient aplastic crisis; chronic red cell aplasia; papular, purpuric eruptions on the hands and feet ("gloves and socks" syndrome); and hydrops fetalis. Conditions postulated to have a link to parvovirus B19 infection include encephalopathy, epilepsy, meningitis, myocarditis, dilated cardiomyopathy, and autoimmune hepatitis.[6]

ERYTHEMA INFECTIOSUM (FIFTH DISEASE)

Erythema infectiosum is the most recognizable presentation of parvovirus B19 infection. The disease generally affects children

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Patients with persistent parvovirus B19 infection may benefit from intravenous immune globulin therapy.	C	13
Pregnant women who are diagnosed with parvovirus B19 infection should receive serial ultrasonography (weekly or biweekly) for 10 to 12 weeks.	C	19
Patients presenting with typical erythema infectiosum (fifth disease) do not need laboratory testing to confirm parvovirus B19 infection.	C	1, 3, 7

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 295 or http://www.aafp.org/afpsort.xml.

four to 10 years of age,[7] although a less-pronounced rash can occur in adults. Prodromal symptoms are mild and include fever, coryza, headache, and nausea. The first stage of the rash *(Figure 1A[8])* presents as erythema of the cheeks ("slapped-cheek" rash) with circumoral pallor. After one to four days, the second stage *(Figures 1B and 1C[8])* appears as a maculopapular rash of the extremities and trunk. Central clearing of the rash is possible, giving it a lacy, reticular pattern.[3] The second-stage rash usually lasts one to six weeks. The third stage may continue for the next one to three weeks. The rash persists but varies with exposure to heat or sunlight,[6] resolving spontaneously with no permanent sequelae.

ARTHROPATHY

Arthropathy may be a complication of erythema infectiosum or a primary presentation of parvovirus B19 infection. Approximately 8 percent of children infected with the virus have arthralgia. However, arthralgia is more common in adolescents and adults with parvovirus B19 infection, affecting up to 60 percent of these persons. Arthropathy affects women twice as often as men.[9]

The pattern of arthropathy differs between adults and children. In adults, the pattern is symmetric and polyarticular and usually involves the proximal interphalangeal and metacarpophalangeal joints. It affects the knees, wrists, and ankles less often. Arthropathy generally resolves within three weeks but can last for months to years, especially in women. In children, the pattern can be symmetric or asymmetric and usually involves the knees (82 percent of patients) and ankles.[9] Some patients may test positive for rheumatoid factor and antinuclear antibodies.

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There is a significant overlap in symptoms of parvovirus-related arthropathy and those of other diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus). Patients with parvovirus B19 infections do not have articular erosion.[3,10]

TRANSIENT APLASTIC CRISIS

Persons with decreased erythrocytes caused by conditions such as iron deficiency anemia, human immunodeficiency virus (HIV), sickle cell disease, spherocytosis, or thalassemia are at risk of transient aplastic crisis if infected with parvovirus B19. The virus causes a cessation of erythrocyte production. This can be life threatening, although most patients make a full recovery within two weeks. Multiple blood transfusions may be necessary initially.

The precipitous drop in hemoglobin also may cause congestive heart failure, a cerebrovascular accident, or acute splenic sequestration. White blood cell and platelet counts also may fall.[11] Patients are highly contagious during aplastic crisis and should be isolated to prevent transmission of the virus.[11]

CHRONIC RED CELL APLASIA

Parvovirus B19 infection may persist in immunocompromised persons without antibodies. Rashes and arthropathy do not develop because they occur secondary to antibody complex deposition in the skin and joints.[12] Patients present with fatigue and pallor caused by anemia, which can be severe, prolonged, or recurrent. Reticulocytes may be absent and transfusions may be required. If severe anemia continues, intravenous immune globulin treatment may be necessary.[13] The rash and arthropathy may develop secondary to the infusion of antibodies and the formation of immune complexes. Cessation of immunosuppressant or antiretroviral treatment may ameliorate symptoms in patients with HIV.[12]

GLOVES AND SOCKS SYNDROME

Parvovirus B19 has been associated with papular, purpuric gloves and socks syndrome, although a causative relationship has not been proven. The syndrome typically occurs in young adults and presents as symmetric, painful erythema and edema of the feet and hands. The condition gradually progresses to petechiae and purpura and may develop into vesicles and bullae with skin sloughing.[14] A hallmark of the syndrome is a sharp demarcation of the rash at the wrists and ankles, although other areas (e.g., cheeks, elbows, knees, inner thighs, glans penis,

buttocks, or vulva) may be involved.[15] Patients may generally appear well but may experience arthralgia, fever, or both. Symptoms usually resolve within one to three weeks without scarring. Gloves and socks syndrome also has been associated with hepatitis B, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, measles, coxsackievirus B, and drug reactions.[16]

HYDROPS FETALIS

Pregnancy does not alter parvovirus B19 infection in the mother,[17] although the fetal liver and heart may become infected. The infant may develop severe anemia, caused by an already shortened red cell lifespan, or may develop myocarditis from direct infection of the heart. The combination of severe anemia and myocarditis can cause congestive heart failure and hydrops fetalis.[18] The estimated risk of transplacental infection is 30 percent. Many fetuses are born without symptoms, but there is a 2 to 6 percent risk of fetal loss.[1] Second-trimester pregnancies are the most vulnerable because of increased hematopoiesis in the liver. Although the placenta has an abundance of P antigen receptors for the virus, first-trimester pregnancies have the lowest risk because of the fetal inability to produce immunoglobulin M (IgM) and the difficulty of antibody transfer across the placenta.[18]

If a pregnant woman is exposed to parvovirus B19, acute infection should be confirmed by testing for the presence of IgM antibodies or by seroconversion of IgG antibodies.[19] If acute infection is confirmed, serial ultrasonography (weekly or biweekly) should be performed for 10 to 12 weeks after initial infection to prevent hydrops fetalis.[19] The risk virtually disappears after 12 weeks. If hydrops occurs, fetal blood sampling and possible transfusion are necessary.[19] Routine testing for parvovirus is not indicated in pregnant women.[20]

Figure 1. Erythema infectiosum (fifth disease). *(A)* Stage one presents as erythema of the cheek ("slapped-cheek" rash) with circumoral pallor. Stage two presents as *(B)* maculopapular erythema of the extremities and *(C)* trunk that commonly has a lacy, reticular pattern.

Diagnosis

If erythema infectiosum is present, a clinical diagnosis can be made without laboratory testing.[1,3,7] If laboratory testing is needed, there are two types of diagnostic tests to confirm parvovirus B19 infection: B19-specific antibody testing and viral DNA testing. Giant pronormoblasts on a peripheral blood smear or in a bone marrow aspirate are suggestive of parvovirus B19 infection but are not diagnostic.[21]

Serum IgM testing is recommended to diagnose acute viral infection in immunocompetent patients, with 89 percent sensitivity and 99 percent specificity.[22] Elevated IgM antibodies will remain detectable for two to three months after acute infection. IgG testing is less useful because it only indicates previous infection and immunity.[1] Viral DNA testing is crucial for the diagnosis of

parvovirus B19 infection in patients in transient aplastic crisis or in immunocompromised patients with chronic infection. These patients do not test positive for IgM or IgG and remain contagious.[11] Polymerase chain reaction (PCR) assays are preferred over less sensitive nucleic acid hybridization assays. The sensitivity and specificity of PCR assays vary widely among laboratories, and, overall, PCR does not appear to be more sensitive than IgM antibody assays for the diagnosis of acute parvovirus infection.

Treatment

Generally, erythema infectiosum is self-limited and does not require treatment. Patients with arthralgia may require nonsteroidal anti-inflammatory drug treatment.[6] Patients in transient aplastic crisis may require erythrocyte transfusions while the marrow recovers.[12] Chronic red cell aplasia, if severe, may require intravenous immune globulin therapy.[13] This treatment may improve anemia symptoms, but it may precipitate a rash or arthropathy. Intravenous immune globulin also has been used in several case reports of severe illness.[13] A vaccine has been developed but is not yet available.[23]

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department or the Air Force service at large.

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Author disclosure: Nothing to disclose.

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