Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation and the title of the report in the subject line of e-mail. This report* was developed to assist physicians, public health officials, and other health-care professionals respond to public concerns about recently recognized, serious complications of human parvovirus B19 (B19) infection, including transient aplastic crisis (TAC), chronic anemia, and fetal death. It includes background information about the virus, clinical manifestations, pathogenesis, epidemiology, and diagnostic testing. In addition, interim guidelines are presented for preventing B19 infection, managing persons exposed to persons with B19 infection, and managing patients infected with B19. These guidelines reflect both the current limited information about the extent to which B19 infection leads to severe complications and the limited availability of diagnostic testing. Priorities for future research are identified.

GENERAL INFORMATION B19 was discovered in England in 1975 in serum specimens from healthy blood donors (1). Since its discovery, B19 has been shown to be the

causative agent of erythema infectiosum (EI) (also known as fifth disease) and is the primary etiologic agent of TAC in patients with chronic hemolytic anemias (2-4). B19 has also been associated with fetal death (both spontaneous abortions and stillbirths), acute arthralgias and arthritis, and chronic anemia in immunodeficient patients (5-14). The virus belongs to the family Parvoviridae, which includes two genera of vertebrate viruses: genus parvovirus (autonomously replicating parvoviruses) and genus dependovirus (parvoviruses that require a helper virus, such as adenovirus or herpes virus, for replication); and one genus of invertebrate viruses, the genus densovirus (15). B19 is in the genus parvovirus, which includes a number of animal parvoviruses such as the canine parvovirus and feline panleukopenia virus. The parvoviruses tend to be species-specific; only the adeno-associated parvoviruses (members of the dependovirus genus) and B19 are known to infect humans. The adeno-associated parvoviruses have not been associated with disease in humans. Fecal parvoviruses and the RA1 virus have been reported but not confirmed to be human pathogens (16,17). B19 is a heat-stable virus and can survive at 60 C

(140 F) for up to 12 hours.

CLINICAL FEATURES OF B19 INFECTION

Erythema Infectiosum (Fifth Disease) The most commonly recognized illness associated with B19 infection is EI. EI is a mild childhood illness characterized by a facial rash ("slapped cheek" appearance), and a reticulated or lacelike rash on the trunk and extremities (18). Reappearance of the rash may occur for several weeks following nonspecific stimuli such as change in temperature, sunlight, and emotional stress. Typically, the patient is otherwise well at rash onset but often gives a history of mild systemic symptoms 1-4 days before rash onset. In some EI outbreaks, pruritis has been a common clinical feature. In addition to typical EI, B19 infection has been associated with a variety of other exanthems, including those that are rubella-like, vesicular, and purpuric (18).

Asymptomatic Infection In outbreak investigations, asymptomatic infection has been reported in approximately 20% of children and adults (19,20).

Arthropathy In some outbreaks of EI, arthralgias and arthritis have been commonly reported (7,8,21). Infection may produce a symmetrical peripheral polyarthropathy. Joints in the hands are most frequently affected,

followed by the knees and wrists. Symptoms are usually self-limited but may persist for several months. Joint symptoms, more common in adults, may occur as the sole manifestation of infection.

Transient Aplastic Crisis and Severe Anemia B19 is the primary etiologic agent causing TAC in patients with chronic hemolytic anemias (e.g., sickle cell disease, hemoglobin SC disease, hereditary spherocytosis, alpha-thalassemia, and autoimmune hemolytic anemia) (22,23). It can also cause TAC in other conditions in which increased red cell production is necessary to maintain stable red cell indices, as may occur in anemia due to blood loss. Patients with TAC typically present with pallor, weakness, and lethargy and may report a nonspecific prodromal illness in the preceding 1-7 days. Few patients with TAC report a rash. In the acute phase of the illness, patients usually have a moderate to severe anemia with absence f reticulocytes, and bone marrow examination shows a hypoplastic or an aplastic erythroid series with a normal myeloid series. Recovery is

indicated by a return of reticulocytes in the peripheral smear approximately 7-10 days after their disappearance. TAC may require transfusion and hospitalization and can be fatal if not treated promptly.

B19 Infection in Immunodeficient Patients A B19-related severe chronic anemia associated with red cell aplasia has been described in patients on maintenance chemotherapy for acute lymphocytic leukemia, patients with congenital immunodeficiencies, and patients with human immunodeficiency virus (HIV)-related immunodeficiency (9-14). It is not yet known how often B19 causes chronic anemia in immunodeficient patients or which patients are most susceptible to this complication of infection. Chronic B19 infection should, however, be included in the differential diagnosis of chronic anemia in the immunodeficient patient.

Infection in the Pregnant Woman

Intrauterine infection and fetal death In most of the reported B19 infections occurring during pregnancy, the fetus has not been adversely affected (5,6,24-30). However, in some

cases B19 infection has been associated with fetal death. The risk of fetal death attributable to parvovirus infection following documented maternal infection (B19 IgM-antibody-positive) is not known, but preliminary results of one study from the United Kingdom suggest that it is less than 10% (30; SM Hall, unpublished data). In that study, 174 pregnant women with IgM antibody to B19 were followed prospectively to delivery. Fetal loss occurred in 30 (17.2%): 21 (19.1%) of 110 women infected during the first 12 weeks of pregnancy, seven (15.2%) of 46 women infected during weeks 13-20, one (6.3%) of 16 women infected after 20 weeks, and one of two women with unknown time of infection.

Fetal death most commonly occurred from the 10th through the 20th weeks of pregnancy. Not all fetal deaths directly resulted from B19 infection. Since this study did not include a control group, the number of deaths attributable to B19 infection cannot be calculated directly.

In other studies, rates of recognized pregnancies ending in spontaneous

abortions from all causes by 28 weeks' gestation range from 10% to 25%
(31). In the British study, the number of fetal deaths linked to B19
infection can be estimated by determining whether fetal tissues contain
B19 DNA. Tissues from 14 fetuses were tested for B19 DNA: six were
positive, two were equivocal, and six were negative. The cause of death
is likely to have been B19 infection for the DNA-positive fetuses;
thus, at least six (3.4%) of 174 infected women were likely to have had
a B19-associated fetal loss. When the results of the 14 tested were

extrapolated to all 30 fetal deaths, an estimated 17 fetuses would be
B19 DNA-positive or equivocal, suggesting that less than or equal to17
(less than or equal to9.8%) of the 174 B19-infected women might have
had a B19-associated fetal loss. Antibody studies of liveborn infants
and hybridization studies of fetal tissues indicate that less than one
third of maternal infections are associated with fetal infection in

this study. Results from an ongoing study in the United States also suggest

that
B19- attributable fetal deaths are infrequent (CDC, unpublished
data).
In this study, 95 pregnant women with IgM antibody to B19 are being

followed prospectively. Fetal loss has so far occurred in two
(4.1%) of
49 women followed to term. It is not known whether the two fetal
deaths
were caused by B19 infection. One fetus was hydropic; the other was
not
described. No tissues from either fetus were available for B19
hybridization studies. When the antibody status of the woman is unknown, estimates of
the

risk of fetal death after exposure must take into account the rate
of
susceptibility in the population and the risk of infection after
the
exposure. For example, by taking these factors into account, the
upper
limit estimate of the risk of fetal death would be less than 2.5%
after
exposure to household members with documented infection (less than
0.1
risk of fetal death x 0.5 rate of susceptibility x 0.5 rate of
infection x 100; see sections on Epidemiologic Features of B19

Infection: Prevalence and Transmission) and less than 1.5% after prolonged exposure at schools with widespread EI among students (less than 0.1 risk of fetal death x 0.5 rate of susceptibility x 0.3 rate of infection x 100). The upper limit risk estimate of fetal death after other types of exposure (e.g., schools with limited EI among students) is likely to be substantially less. A study of 96 women who had stillbirths, 96 women who had spontaneous abortions, and controls matched by age, duration of pregnancy, and location suggests that B19 is not responsible for a substantial proportion of fetal deaths in the general population (32). In this study, the rate of serologically confirmed B19 infection was the same (1%) in cases and controls. In a survey of 50 fetuses with nonimmunologic hydrops fetalis, an uncommonly diagnosed cause of fetal death, four (8%) were positive for B19 DNA (25).

Congenital anomalies Since some of the animal parvoviruses are teratogens (33), the possibility that infection may also be associated with congenital anomalies in humans is a concern. However, there is no evidence that

the rate of congenital anomalies following B19 infection exceeds background rates. B19-associated congenital anomalies have not been reported among several hundred liveborn infants of B19-infected mothers. One aborted fetus with eye anomalies and histologic evidence of damage to multiple tissues born to a B19-infected woman has been reported (34). An anencephalic fetus was reported in a B19-infected woman, but the timing of infection made it unlikely that B19 contributed to the defect (35).

ATHOGENESIS The pathogenesis of the rash in EI is unknown, but the rash may be immune- complex-mediated. The other, more serious manifestations of B19 infection are related to the propensity of the virus to infect and lyse erythroid precursor cells and interrupt normal red cell production (36). In a person with normal hematopoiesis, B19 infection produces a self-limited red cell aplasia that is clinically inapparent. Transient leukopenia, lymphocytopenia, and thrombocytopenia have also been reported with B19 infection in the normal host (37,38). In patients who have increased rates of red cell destruction or loss

and who depend on compensatory increases in red cell production to maintain stable red cell indices, B19 infection may lead to TAC. Patients at risk for TAC include those with chronic hemolytic anemias and those with anemias associated with acute or chronic blood loss. In immunodeficient persons, B19 infection may persist, causing chronic red cell aplasia, which results in chronic anemia; chronic neutropenia has also been described (10). B19 DNA-positive tissues have been reported in 20 fetal deaths; in all 17 cases in which pathologic findings were described, the fetuses had nonimmunologic hydrops fetalis (6,25-27,30,35,39-44). The precise pathogenesis of fetal death remains unclear. Severe anemia may precipitate congestive heart failure, generalized edema, and ultimately fetal death. The fetus may be particularly vulnerable to B19 infection because red cell survival is short, and the red cell volume is rapidly expanding. Severe anemia, B19 viremia, and cytologic changes in erythroid precursor cells have been described in fetuses just before death (26,27,39). Chronic infection may occur in the fetus (one

fetus
was viremic for at least 4 weeks) (26). In one case report,
infection
of myocardial cells was noted, suggesting that direct damage to
myocardial tissue may also contribute to the disease process in the

fetus (29).

EPIDEMIOLOGIC FEATURES OF B19 INFECTION

Prevalence B19 infection occurs worldwide (45,46). Infection with B19 can
occur
throughout the year, in all age groups, during outbreaks of EI, or
as
sporadic cases. B19 infection is most frequently recognized during
outbreaks of EI in schools. These outbreaks often begin in late
winter
or early spring and may continue until school recesses for the
summer.

The level of EI activity in a community varies from year to year;
periods of increased activity lasting several years are generally
followed by several years of decreased activity (47-50). The
reported
seroprevalence ranges from 2% to 15% in children 1-5 years old, 15%
to
60% in children 5-19 years old, and 30% to 60% in adults
(18,40,51,52).

Incubation Period Studies of secondary illness in households suggest that the
incubation

period for clinical EI and TAC is usually 4-14 days but can be as long as 20 days (18). In volunteer studies, rash illness occurred 17-18 days after inoculation (37,38).

Transmission B19 DNA has been found in respiratory secretions in viremic patients, which suggests that these secretions are involved in transmission (19,20,37). In studies of human volunteers, serum and respiratory secretions became positive for B19 DNA 5-10 days after intranasal inoculation (during the prodromal illness) (37,38). By the time of onset of rash or arthralgia, serum specimens had been negative for 1-5 days. B19 has not been detected in the respiratory secretions and only rarely in the serum of patients after onset of EI (37). In contrast, acute serum specimens are often positive for B19 DNA in patients when they present with TAC; serum specimens are usually negative by 7 days after onset of illness (53). The presence of B19 DNA in serum or respiratory secretions presumably correlates with infectiousness; thus, patients with EI are probably past the period of greatest infectiousness, while patients with TAC are likely to be

infectious during the course of their illness. The presence of IgG antibody correlates with a lower risk of infection. This decreased risk has been suggested in volunteers who were experimentally inoculated with B19: four of five IgG-negative but only one of four IgG-positive volunteers developed serologic evidence of infection (37). The IgG-positive volunteer who became infected had low levels of IgG antibody before challenge and had a lower titer and shorter duration of viremia than had the four infected volunteers who were IgG-negative. The virus is transmitted effectively after close contact exposures. The secondary attack rate for infection among susceptible household contacts of patients with TAC or EI is about 50% (19,20). In school outbreaks, 10%-60% of students may develop EI. In outbreaks in which student involvement is widespread, preliminary data suggest 20%-30% of susceptible (IgG-antibody-negative) staff may develop serologic evidence of B19 infection during the course of the outbreak (CDC, unpublished data). In outbreak settings, it is not known whether the primary mode of

transmission involves direct person-to-person contact, fomites, large-particle droplets, or small- particle droplets. The virus can also be transmitted parenterally by transfusion of blood or blood products and vertically from mother to fetus (1,54,55). Transmission rarely occurs during transfusion with single-donor blood products but is common during treatment with clotting-factor concentrates even after steam- or dry-heat treatment of the clotting factor concentrate (1,54,55). Tattooing was suspected as the source of B19 transmission in two instances (56).

DIAGNOSIS

B19 Antibody Assays The most sensitive test to detect recent infection is the IgM-antibody assay. B19 IgM antibody can be detected by capture-antibody radioimmunoassay or enzyme immunoassay in approximately 90% of cases by the third day after symptoms of TAC or EI begin (57,58). The titer and the percentage of positives begin to decline 30-60 days after onset.

B19 IgG antibody is usually present by the seventh day of illness and persists for years. B19 antibody may not be detectable in

immunodeficient patients with chronic B19 infection, and additional testing for B19 DNA or viral antigens may be necessary to document infection. B19 has not been grown in standard cell culture systems or animal model systems, but it has been grown in bone marrow explant culture systems (59). The inability to grow the virus in sufficient quantity to produce antigen for diagnostic assays has precluded widespread availability of B19 testing (36,60,61). Recently parvovirus B19 DNA has been incorporated into the genome of a Chinese hamster ovary cell line (62). This cell line expresses B19 capsid proteins as noninfectious virionlike particles that can be used as antigen for antibody assays; this source of antigen should lead to increased availability of diagnostic tests.

Assays for B19 DNA The most sensitive test for detecting the virus is nucleic acid hybridization (63,64). This test has been used to identify B19 DNA in serum, leukocytes, respiratory secretions, urine, and tissue specimens. One group reported that B19 DNA was more likely to be detected in leukocytes than in serum (65).

Histologic Features of B19 Infection Light and electron microscopy can be helpful in

diagnosing B19 infections (1,23,41) By light microscopy, eosinophilic nuclear inclusions with peripheral condensation of chromatin can be seen in erythroid precursor cells of infected patients. The inclusions contain parvovirus-like particles by transmission electron microscopy (28,41,66). B19-like particles may also be seen by electron microscopy in serum specimens of some infected patients (1,23,41). Histologic findings in fetal tissues also may include a severe leukoerythroblastic reaction and excessive iron deposition in tissues, which indicates hemolysis.

Assays to Determine Site of Infection It is not known which tissues, in addition to erythroid precursor cells, support virus replication. Several tests have been developed that distinguish virus infection of tissue or cells from deposition of virus by passive transfer in blood. In situ hybridization can demonstrate viral DNA in specific cells and has been used to show that B19 sometimes infects fetal myocardial cells (29). Replicative forms of B19 DNA and nonstructural proteins can be demonstrated by Southern and

Western blot analysis, respectively, indicating infection in the tissue (67,68).

PREVENTION OF INFECTION

Risk Groups Although B19 infection usually produces a mild, self-limited illness, three groups of persons are at risk for serious complications of infection: 1) persons with chronic hemolytic anemias, 2) persons with congenital or acquired immunodeficiencies, and 3) pregnant women. Since infection in these persons can lead to substantial morbidity and some mortality, consideration should be given to preventing or ameliorating disease.

Immunization **Active** There is no vaccine to prevent B19, but a recently developed cell line that expresses B19 capsid proteins as noninfectious viruslike particles has been proposed as a source of antigen for development of a candidate vaccine (62).

Passive No studies have been conducted to determine whether preexposure or postexposure prophylaxis with commercially available immune globulin

(IG) preparations would prevent infection or modify the course of illness during community outbreaks. Routine prophylaxis with IG cannot be recommended at this time.

Health-Care Settings Guidelines for isolation precautions in hospitals have been published for EI (69), but recent information suggests that these guidelines should be modified. Most patients with EI are past their period of infectiousness and do not present a risk for further transmission; thus isolation precautions are not indicated. However, there is risk for nosocomial transmission of B19 from patients with TAC and from immunodeficient patients with chronic B19 infection. These patients should be considered infectious and placed on isolation precautions for the duration of their illness or until the infection has been cleared.

Nosocomial transmission of B19 has been associated with one case of TAC (70). Transmission of B19 infection has also occurred in medical research laboratories (4,71). Patients with TAC or chronic B19 infection should be admitted to private rooms. Persons in close contact with the patients should wear masks. Gloves should be worn by persons likely to touch infective

material such as respiratory secretions, and gowns should be worn when soiling is anticipated (contact isolation) (69). Hands should be washed after the patient or potentially contaminated articles are touched and before care is provided to another patient. B19-infected patients may share a room with another B19-infected patient unless sharing is contraindicated by another infection or condition. Health-care workers should be advised that they are at risk of B19

infection after exposure in the hospital or in the community and that there may be a risk for further transmission to patients. Routine infection-control practices should minimize the risk of transmission. Personnel who may be pregnant or who might become pregnant should know about potential risks to the fetus from B19 infection and about preventive measures that may reduce those risks. Homes, Schools, and Workplaces When outbreaks of B19 infection occur in situations in which prolonged, close contact exposures occur (e.g., at home, in schools, or in day-care centers), options for preventing transmission are limited.

The greatest risk of transmitting the virus occurs before symptoms

of
EI develop; therefore, transmission cannot be prevented by
identifying
and excluding persons with EI. The efficacy of decontaminating toys
and
environmental surfaces to decrease B19 transmission has not been
studied. The efficacy of handwashing to decrease B19 transmission
has
not been studied either, but handwashing is recommended as a
practical
and probably effective measure. When outbreaks occur, parents of school-aged children and
employees
should be advised about the risk of transmitting and acquiring
infection and about who is at risk for serious complications.
Persons
who wish to obtain additional information about risks and
management of
B19 exposures should be referred to their health-care provider and
state or local health officials. The decision to try to decrease any person's risk of infection by
avoiding a workplace or school evironment in which an EI outbreak
is
occurring should be made by the person after discussions with
family
members, health-care providers, public health officials, and
employers

or school officials. A policy to routinely exclude members of high-risk groups is not recommended.

PATIENT MANAGEMENT

Patients with Chronic Hemolytic Anemia The exposed patient with chronic hemolytic anemia should be managed by alerting the patient or his/her parents or guardians about the exposure, the symptoms and signs associated with TAC (pallor, weakness, and lethargy), and the need to consult a physician immediately if symptoms or signs of TAC develop. Management of the patient with TAC is based on treating symptoms of the associated anemia and may require blood transfusion. Patients with Congenital and Acquired Immunodeficiencies The exposed patient with a congenital or acquired immunodeficiency should be managed by advising the patient or his/her parents or guardians about the exposure and the possibility that B19 infection may lead to chronic anemia. The physician should consider B19 infection in the differential diagnosis of chronic anemia in this group of patients, especially if there is an outbreak of EI in the community.

In several patients with acute lymphocytic leukemia, the administration of IG resulted in disappearance of viremia and improvement in red cell indices (10). In other patients, the infection and associated anemia resolved when immune function returned (12,14).

The role of IG in the treatment of these patients needs further study.

Pregnant Women The knowledge that B19 infection during pregnancy can cause fetal death has created concern among health-care providers, public health officials, and pregnant women and their families. In managing exposed pregnant women, risks should be considered in the context of other risks to the pregnancy and the risks associated with intervention. For women with a documented infection, maternal serum œga-fetoprotein levels and diagnostic ultrasound examinations have been used to identify adversely affected fetuses, but the sensitivity and specificity of these tests, their appropriate timing, and the risks and benefits of their use in managing infected pregnant women have not yet been determined (39,41). Interpretation of the ultrasound is difficult early in pregnancy and should be supervised by a physician

experienced in diagnosing fetal abnormalities. Intrauterine blood transfusion (IBT) has been proposed as treatment for the fetus with B19-induced severe anemia. However, IBT is a high-risk, specialized procedure of unproven benefit in this situation and cannot be recommended for routine treatment of B19-related hydrops fetalis (72).

AVAILABILITY OF DIAGNOSTIC TESTING AT CDC Diagnostic testing is available at only a few sites, primarily research laboratories; increasing the availability of diagnostic testing is a public health priority. The Division of Viral Diseases, Center for Infectious Diseases, CDC, can accept a limited number of specimens for B19 diagnostic testing. At this time, CDC is accepting specimens through state health departments from patients with TAC, immunodeficient patients with chronic anemia, pregnant women exposed to B19 or with symptoms suggestive of B19 infection, and cases of nonimmune fetal hydrops possibly related to B19 infection, and not accepting specimens for routine antibody testing. Physicians can arrange testing at CDC by consulting their state health department.

PRIORITIES FOR FUTURE RESEARCH The following areas have been identified as high

priorities for future public health-related research on B19 infection:

Develop surveillance methods that distinguish outbreaks from sporadic disease.

2.Refine estimates of infection rates following exposures in the home, the workplace, and school.

3.Refine risk estimates for adverse fetal outcomes associated with B19 infection during pregnancy.

4.Evaluate methods to treat and prevent B19-related fetal hydrops.

5.Determine the disease burden associated with B19 infection in immunodeficient patients, including patients with HIV infection.

6.Determine the risk of infection and factors associated with transmission in health-care settings.

7.Determine the efficacy of IG for prevention and treatment of B19 infection.

8.Determine the potential reduction in morbidity and mortality associated with development and use of a B19 vaccine.

Reported by: Div of Reproductive Health, Center for Chronic Disease Prevention and Health Promotion; Div of Immunization, Center for Prevention Svcs; Div of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control; Div of Surveillance

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