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(e.g., research laboratorians) to orthopoxviruses via either ACAM2000 or JYNNEOS. Booster doses for these persons at sustained risk for occupational exposure to orthopoxviruses should be administered either 2 years, 3 years, or 10 years after primary vaccination depending on the vaccine administered and reason for vaccination. JYNNEOS is also recommended for persons at risk of mpox during mpox outbreaks and on the routine immunization schedule for persons with specific risk factors defined by CDC’s Advisory Committee on Immunization Practices (ACIP). There is currently no recommendation for booster doses for these persons at risk or for persons to whom JYNNEOS was recommended during the mpox outbreak that started in 2022. Effec tiveness of ACAM2000 is inferred from use of similar live, replicating vaccines during the smallpox eradication era when administration of a qualified vaccine 3–5 years earlier was viewed as 100% protective against variola virus. During mpox surveillance efforts in Democratic Republic of the Congo in the 1980s, smallpox vaccination 3–19 years earlier was 85% protective against disease among household contacts of people with mpox. The duration of efficacy is unclear. JYNNEOS was widely used during the global mpox outbreak, and effectiveness against mpox ranged from 36% to 75% for one-dose vaccination and 66% to 89% for two-dose vaccination. The duration of immunity following JYNNEOS vaccination compared with live, replicating vaccinia virus vaccines is unclear.

Acknowledgment Inger K. Damon contributed to this chapter in the last edition and some material from that chapter has been retained here. ■ ■FURTHER READING Chen X et al: Molluscum contagiosum virus infection. Lancet Infect PART 5 Infectious Diseases Dis 13:877, 2013. Rao AK et al: Interim clinical treatment considerations for severe manifestations of mpox — United States, February. MMWR Morb Mortal Wkly Rep 72:232, 2023. Thornhill JP et al: Monkeypox virus infection in humans across 16 countries — April–June 2022. N Engl J Med 387:679, 2022. Maria Söderlund-Venermo

Parvovirus Infections Parvoviruses, members of the large family Parvoviridae, are small (diameter, ~22 nm), nonenveloped, icosahedral viruses with a lin ear single-stranded DNA genome of ~5000 nucleotides. The family includes viruses infecting many different animal hosts, from mammals to insects. Five main groups of parvoviruses infect humans: parvovirus B19 (B19V), adeno-associated viruses (AAVs), parvovirus 4 (parv4), human bocaviruses (HBoVs), and human protoparvoviruses (bufavirus and cutavirus). PARVOVIRUS B19 ■ ■DEFINITION B19V belongs to the genus Erythroparvovirus, so named due to its narrow tropism of erythrocyte precursors in the bone marrow. B19V is divided into three genotypes (1, 2, and 3), with similar antigenic, pathogenic, and

biological properties. ■ ■EPIDEMIOLOGY B19V exclusively infects humans, and infection is common in virtually all parts of the world. Genotype 1 is currently predominant world wide, whereas genotype 2 nowadays rarely causes active infections but

remains persistent in tissues of older individuals. Genotype 3 is the most diverse and appears to be more common in the western parts of Africa. Outbreaks of B19V infection, causing childhood rash (erythema infectiosum), are most common in schools and day-care centers and occur as epidemics a few years apart, in temperate climates, mostly in winter and spring. Within households, schools, and day-care centers, the infection rates approach 50%. The risk of infection increases in pro portion to the number of children. Transmission occurs primarily via the respiratory route and occurs before the onset of rash or arthralgia. By the age of 15 years, ~50% of children have detectable IgG antibody to B19V; this seroprevalence may rise to 80% among the elderly. Especially in patients with a hemolytic disorder or compromised immune system, the viral load of B19V in blood can be extremely high (up to 1014 particles/mL), which increases the risk of transmission to hospital staff and family. Transmission can also occur via transfusion, particularly of pooled blood products. However, plasma pools are nowadays screened for B19V DNA, and high-titer pools are discarded. B19V is quite resistant to both heat and solvent-detergent inactivation. ■ ■PATHOGENESIS B19V replicates in erythroid progenitors. This specificity may be due in part to a limited tissue distribution of the yet unknown primary B19V receptor that is recognized by the N-terminal unique region of B19-virus protein 1 (VP1u). Another important receptor, the blood group P antigen (globoside), recognized by the common VP region, VP2, is needed at a later intracellular step. Individuals who lack this P antigen are naturally resistant to B19V infection. Infection leads to high-titer viremia, with 104-12 virus particles/mL detectable in the blood at the apex (Fig. 202-1), and virus-induced cytotoxicity results in cessation of red cell production. The viral load will, however, quickly drop, leaving very low-level B19V DNA in the blood for months and even years after the acute infection. B19V DNAemia in nonacute infections has, however, also been shown to be due to nonencapsidated naked DNA being released from injured tissues. In immunocompetent individuals with normal hemopoiesis, the arrest of erythropoiesis is transient, with only a minimal drop in hemoglobin levels, which resolves as the immune response is mounted. However, in individuals with increased erythropoiesis (especially with hemolytic anemia), the cessation of red cell production can induce a transient crisis with severe anemia (Fig. 202-1). Similarly, if an individual (or a fetus) does not induce neutralizing antibodies to halt the lytic infection, erythroid production is compromised, and chronic anemia develops (Fig. 202-1). In immunocompetent individuals, the immune-mediated phase of illness, which begins 2–3 weeks after acute infection as the IgM response peaks, manifests as the rash of erythema infectiosum or fifth disease alone or together with arthralgia and/or frank arthritis (see “Clinical Manifestations”). If immunocompromised patients with chronic B19V-induced anemia are given immunoglobulins, they may also present with a rash, which is due to antigen-antibody complexes in skin. Even if B19V requires erythroid precursor cells for its replication, it can also enter nonpermissive cells, such as B cells, monocytes, and endothelial cells, by antibody-dependent enhancement (ADE), and remain presumably dormant for life in multiple tissues, such as the heart, liver, kidneys, synovia, brain, and even bones. This persistent presence of B19V DNA in our tissues does not generally seem to com plicate normal health but may nevertheless be responsible for some disease presentations in predisposed individuals, as has been suggested in myocarditis, for example. ■ ■CLINICAL MANIFESTATIONS Erythema Infectiosum Most B19V infections are asymptomatic or exhibit only a mild nonspecific illness. The main manifestation of symptomatic B19V infection is erythema

infectiosum, also known as fifth disease or slapped-cheek disease (Figs. 202-2 and A1-1A). Infection may begin with a minor febrile prodrome ~7–10 days after exposure, but it is often absent, and the classic facial rash develops

B19 Virus B19 Antibodies Hemoglobin (g%) Clinical manifestations B19 Virus B19 Antibodies Hemoglobin (g%) Clinical manifestations

IgM

IgG

1.0

Reticulocytes (g%) 0.2

Rash, arthralgia Fever, chills, headache, myalgia 2 6 10

Days Inoculation or infection 2 6 10

Days Infection Normals A B FIGURE 202-1 Schematic of the time course of parvovirus B19 infection in (A) normals (erythema infectiosum), (B) transient aplastic crisis (TAC), and (C) chronic anemia/ pure red cell aplasia (PRCA). (From The New England Journal of Medicine, Parvovirus B19, NS Young, KE Brown: 350:586. Copyright @2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) FIGURE 202-2 Young child with erythema infectiosum, or fifth disease, showing typical “slapped-cheek” appearance.

B19 Virus B19 Antibodies Hemoglobin (g%) Clinical manifestations

IgM

IgG IgM and IgG

Reticulocytes (g%) Reticulocytes (g%)

Symptoms of anemia CHAPTER 202 Symptoms of anemia 2 6 10

Days Infection PRCA TAC Parvovirus Infections C suddenly several days later. After 2–3 days, the erythematous maculo papular rash may spread to the trunk and extremities in a lacy reticular pattern. However, its pattern, intensity, and distribution vary, and B19V-induced rash is difficult to clinically distinguish from other viral exanthems, so a laboratory test should be used when a definite diagnosis is necessary, such as in pregnant women. Typically, the rash may recur for weeks when exercising or sunbathing, but the child is no longer infectious and can go to school. Adults typically do not exhibit the “slapped-cheek” appearance but present with arthralgia, with or without a macular rash. In children, arthritis and encephalitis are rare complications. Polyarthropathy Syndrome Although uncommon among children, arthropathy occurs in ~50% of adults and is more common among women than among men. The distribution of the affected joints is often symmetrical, with arthralgia affecting the small joints of the hands and occasionally the

ankles, knees, and wrists. Resolution usually occurs within a few weeks, but recurring symptoms can continue for months. The illness may mimic rheumatoid arthritis, and rheumatoid factor can often be detected in serum. However, the mere presence of B19V DNA in synovia is not enough to prove a causative relation, since healthy individuals also may exhibit viral DNA in their synovia. Transient Aplastic Crisis Asymptomatic transient reticulocy topenia occurs in most individuals with B19V infection. However, in patients who depend on continual rapid production of red cells, infection can cause a transient aplastic crisis (TAC). B19V is the pre dominant cause of TAC in individuals with hemolytic disorders, hemo globinopathies, red cell enzymopathies, and autoimmune hemolytic anemias. Patients present with severe to life-threatening anemia and a

low reticulocyte count, and bone marrow examination reveals charac teristic giant pronormoblasts and an absence of erythroid precursors. However, reticulocytopenia in sickle-cell patients with acute worsening of anemia is diagnostic without bone marrow examination. Patients are often febrile and very ill, often including other complications. As its name indicates, the illness is transient, and anemia resolves with the cessation of cytopathic infection in the erythroid progenitors, and lifelong immunity follows.

Pure Red Cell Aplasia (PRCA)/Chronic Anemia Chronic B19V infection has been reported in a wide range of immunocom promised patients who are unable to mount a neutralizing immune response, including those with certain congenital immunodeficien cies, AIDS (Chap. 208), lymphoproliferative disorders (especially acute lymphocytic leukemia), and transplantation (Chap. 148). PRCA patients have persistent anemia with reticulocytopenia, absent or low levels of B19V IgG, extremely high titers of B19V DNA in serum, and typically scattered giant pronormoblasts on bone marrow examina tion. Nonerythroid hematologic lineages are rarely affected, but tran sient neutropenia, lymphopenia, and thrombocytopenia (including idiopathic thrombocytopenic purpura) have been observed. B19V occasionally causes a hemophagocytic syndrome. The suspicion of B19V infection in such cases is often difficult due to the lack of normal B19V-related symptoms like rash or arthralgia, which are immune mediated. Diagnosis is, however, important due to the existence of effective therapy in form of repeated immunoglobulin administrations. Co-infection with Plasmodium and B19V has been suggested to play a role in the development of severe anemia in young children with malaria. B19V-infected immunocompetent individuals seldom show PRCA or chronic anemia. PART 5 Infectious Diseases Hydrops Fetalis B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss, due to either miscarriage (before 22 weeks of gestation) or fetal death (after 22 weeks of gestation). B19V probably causes 10–20% of all cases of nonimmune hydrops, which is character ized by gross edema and severe anemia. The risk of transplacental fetal infection is ~30%, and the excess risk of fetal loss (when the mother is infected before gestational week 20) is ~9%, but very low thereafter. Although B19V does not appear to be teratogenic, rare cases of eye damage, central nervous system (CNS) abnormalities, and congenital anemia have been reported. B19V infection may not cause any symp toms in the pregnant mother, so exposed seronegative mothers should undergo tests for B19V infection, and if found positive, they should be monitored regularly throughout pregnancy. Most fetal infections resolve themselves, but sometimes intrauterine red cell transfusions are needed. Unusual Manifestations B19V infection may rarely cause hepati tis, vasculitis, myocarditis, glomerulosclerosis, or meningoencephalitis. A variety of other cardiac manifestations, CNS diseases, and autoim mune diseases have also been reported in conjunction with B19V infection. However, B19V DNA can be detected by polymerase chain reaction (PCR) for life in many tissues;

therefore, this finding is of no known clinical significance, but its interpretation may cause confusion regarding B19V disease association. TABLE 202-1 Diseases Associated with Human Parvovirus B19 Infection and Methods of Diagnosis DISEASE HOSTS IgM IgG PCR QUANTITATIVE PCR Fifth disease Healthy children Positive Positive Positive

> 104 IU/mL Polyarthropathy syndrome Healthy adults (more often women) Positive within 3 months of onset Transient aplastic crisis Patients with increased Negative/positive Negative/positive Positive Often >1012 IU/mL, but rapidly decreases erythropoiesis Persistent anemia/pure red cell aplasia Immunodeficient or immunosuppressed patients Negative/weakly positive Hydrops fetalis/ congenital anemia Fetuses (of mothers infected <20 weeks) Negative/positive Positive Positive amniotic fluid or tissue Abbreviations: IU, international units (1 IU equals ~1 genome); n/a, not applicable; PCR, polymerase chain reaction.

■ ■DIAGNOSIS Diagnosis of B19V infection in immunocompetent individuals is gen erally based on detection of B19V antibodies (Table 202-1). IgM can be detected by indirect enzyme immunoassay (EIA) at the time of the rash in erythema infectiosum and by the third day of TAC in patients with hematologic disorders, and may remain detectable for ~3 months or longer. B19V IgG is detectable by the seventh day of illness and persists throughout life, whereby IgG positivity marks immunity. However, serum samples taken 2 weeks apart that show seroconversion or a four fold or greater increase in IgG titer are considered diagnostic for acute infection. Modern serology can further measure the quality of IgG; as the immune response matures with time, the initially low avidity of IgG gradually increases within 6 months and can be measured with a dena turing EIA. Another way of timing the B19V infection is by comparing the IgG responses toward linear versus conformational B19V VP2 epitopes using epitope-type-specific (ETS) EIA. Both avidity and ETS EIAs differentiate between acute and past infection and thus increase the specificity of the diagnosis. Detection of B19V DNA in serum (or amniotic fluid) by PCR provides further help, especially in pregnancy, TAC, or chronic anemia. In acute infection at the height of viremia,

> 1012 B19V DNA IU/mL of serum can be detected; nevertheless, the viral load falls rapidly within a few days but can remain detectable by PCR for months or even years after acute infection, even in healthy individuals, necessitating a quantitative (q)PCR. Of note, in tissue material, PCR alone should not be used to establish a B19V etiology because viral DNA remains in healthy bodies for decades. TREATMENT Parvovirus B19 Infection No antiviral drugs against B19V are available for patient use, and treatment of B19V infection often targets symptoms only. However, cidofovir, and its lipid conjugate brincidofovir, as well as hydroxy urea, seem to inhibit B19V replication in vitro. TAC caused by B19V infection frequently necessitates treatment with repeated blood transfusions. In patients receiving chemotherapy, temporary ces sation of treatment may result in an immune response and resolu tion. If this approach is unsuccessful or not

applicable, commercial immunoglobulin can cure or ameliorate chronic B19V infection in immunosuppressed or otherwise immunocompromised patients. Generally, the intravenous IgG (IVIG) dose is 400 mg/kg daily for 5–10 days and the patient should be monitored for relapses. Administration of IVIG is not beneficial for the immune-mediated erythema infectiosum or B19V-associated arthropathies, which generally are self-limited. Intrauterine blood transfusion can pre vent fetal loss in some cases of fetal hydrops; however, the risks need to be evaluated. ■ ■PREVENTION No vaccine has been approved for the prevention of B19V infection, although vaccines based on B19V virus–like particles expressed in insect cells are known to be highly immunogenic. Phase 1 trials of a putative vaccine were discontinued because of adverse side effects, but others are under development. Positive Positive 104 IU/mL Negative/weakly positive Positive Often >1012 IU/mL, but should be >106 in the absence of treatment n/a

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