CHAPTER 31

Parvoviruses

Parvoviruses are the simplest DNA animal viruses. Because of the small coding capacity of their genome, viral replication is dependent on functions supplied by replicating host cells or by coinfecting helper viruses. Parvovirus B19 is pathogenic for humans and has a tropism for erythroid progenitor cells. It is the cause of erythema infectiosum ("fifth disease"), a common childhood exanthem; of a polyarthralgia-arthritis syndrome in normal adults; of aplastic crisis in patients with hemolytic disorders; of chronic anemia in immunocompromised individuals; and of fetal death. The human bocaviruses have been detected in respiratory specimens from children with acute respiratory disease and in stool samples, but a role in disease is unproven.

PROPERTIES OF PARVOVIRUSES

Important properties of parvoviruses are listed in Table 31-1. It is noteworthy that there are both autonomously replicating and defective parvoviruses.

Structure and Composition

The icosahedral, nonenveloped particles are 18–26 nm in diameter (Figure 31-1). The particles have a molecular weight of 5.5–6.2 × 10^6 and a heavy buoyant density of 1.39–1.42 g/cm^3. Virions are extremely resistant to inactivation. They are stable between a pH of 3 and 9 and withstand heating at 56°C for 60 minutes, but they can be inactivated by formalin, β-propiolactone, and oxidizing agents.

Virions contain two coat proteins that are encoded by an overlapping, in-frame DNA sequence, so that VP2 is identical in sequence to the carboxy portion of VP1. The major capsid protein, VP2, represents about 90% of virion protein. The genome is about 5 kb, linear, single-stranded DNA. Whereas an autonomous virus, B19, contains 5596 nucleotides, a defective parvovirus, AAV-2, contains 4680 bases. Autonomous parvoviruses usually encapsidate primarily DNA strands complementary to viral mRNA; defective viruses tend to encapsidate DNA strands of both polarities with equal frequency into separate virions.

TABLE 31-1 Important Properties of Parvoviruses

Virion: Icosahedral, 18–26 nm in diameter, 32 capsomeres
Composition: DNA (20%), protein (80%)
Genome: Single-stranded DNA, linear, 5.6 kb, MW 1.5–2.0 million
Proteins: One major (VP2) and one minor (VP1)
Envelope: None
Replication: Nucleus, dependent on functions of dividing host cells
Outstanding characteristics: Very simple viruses Human pathogen, B19, has tropism for red blood cell progenitors One genus contains viruses that are replication-defective and require a helper virus

MW, molecular weight.

Classification

There are two subfamilies of Parvoviridae: the **Parvovirinae,** which infect vertebrates, and the **Densovirinae,** which infect insects. The Parvovirinae comprise five genera. Human parvovirus B19 is the most common member of the *Erythrovirus* genus. There are three human genotypes in this genus. The three human bocaviruses are in the *Bocavirus* genus. Feline panleukopenia virus and canine parvovirus, both serious causes of veterinary diseases, are classified as members of the *Parvovirus* genus, as are isolates from many other animals. The genus *Dependovirus* contains members that are defective and depend on a helper virus (an adenovirus or herpesvirus) for replication. Human "adeno-associated viruses" have not been linked with any disease.

Parvovirus Replication

It is difficult to culture human B19 parvovirus. Only primary erythroid progenitors are known to be permissive for B19 infection. The cellular receptor for B19 is blood group P antigen (globoside). P antigen is expressed on mature erythrocytes, erythroid progenitors, megakaryocytes, endothelial cells, placenta, and fetal liver and heart, which helps explain

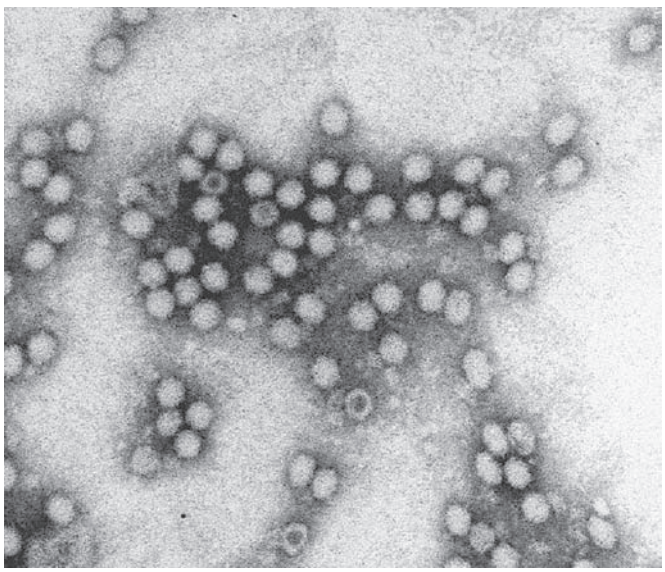

FIGURE 31-1 Electron micrograph of parvovirus particles. (Courtesy of FA Murphy and EL Palmer.)

the narrow tissue tropism of B19 virus. The α5β1 integrin is believed to be a coreceptor for B19 entry.

The parvoviruses are highly dependent on cellular functions for replication. Viral DNA replication occurs in the nucleus. The parvoviruses do not have the ability to stimulate resting cells to initiate DNA synthesis, so they must infect dividing cells. One or more cellular DNA polymerases are involved. The nonstructural protein, NS1, is required for virus replication. There are two capsid proteins. Viral replication results in cell death.

PARVOVIRUS INFECTIONS IN HUMANS

Pathogenesis and Pathology

A typical course of human parvovirus B19 infection in adults is illustrated in Figure 31-2. B19 has been implicated as the causative agent of several diseases (Table 31-2). Immature cells in the erythroid lineage are principal targets for human B19 parvovirus. Hence, the major sites of virus replication in patients are assumed to be the adult marrow, some blood cells, and the fetal liver. Viral replication causes cell death, interrupting red blood cell production. In immunocompromised patients, persistent B19 infections occur, resulting in chronic anemia. In cases of fetal death, chronic infections may have caused severe anemia in the fetus.

Because nondefective parvoviruses require dividing host cells to replicate, known parvovirus diseases reflect that target specificity (Figure 31-3).

Both virus-specific immunoglobulin M (IgM) and IgG antibodies are made after B19 infections. Persistent parvovirus infections occur in patients with immune

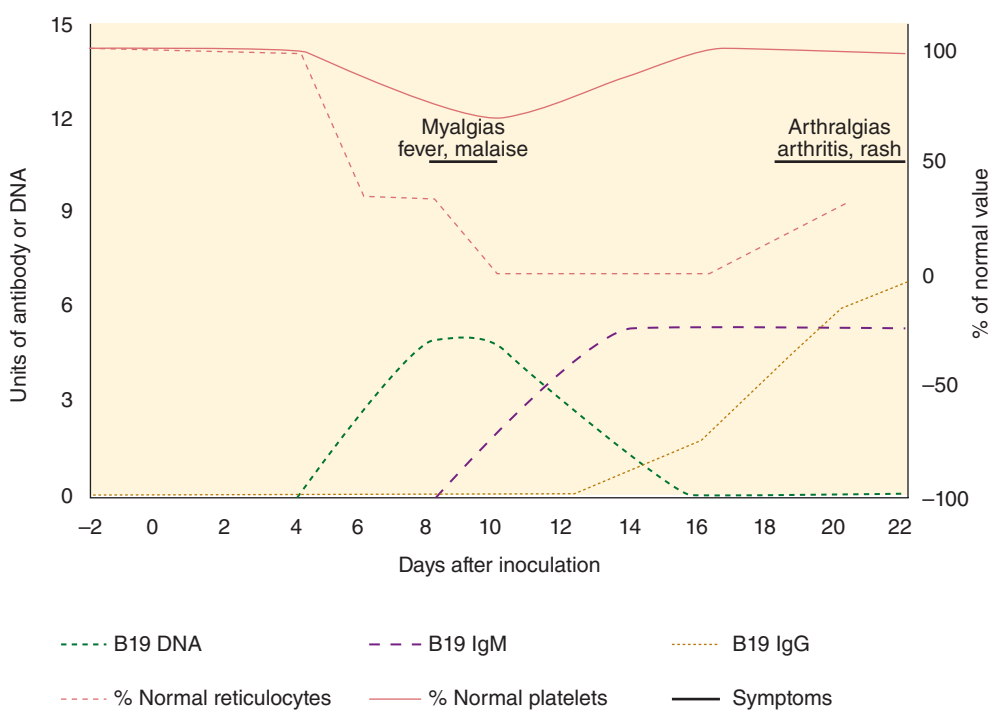

FIGURE 31-2 Clinical and laboratory findings during the course of human parvovirus B19 infection in adult volunteers. The first phase of illness with flu-like symptoms coincides with viremia (days 6–12); the second phase of illness with rash appears on about day 18. (Reproduced with permission from Anderson LJ: Human parvovirus B19. In Richman DD, Whitley RJ, Hayden FG [editors]. *Clinical Virology,* 3rd ed. Washington DC: ASM Press, 2009; data taken from Anderson MJ, Higgins PG, Davis LR, et al: Experimental parvoviral infection in humans. *J Infect Dis* 1985;152:257–265.)

TABLE 31-2 Human Diseases Associated with B19 Parvovirus

Syndrome	Host or Condition	Clinical Features
Erythema infectiosum	Children (fifth disease) Adults	Cutaneous rash Arthralgia-arthritis
Transient aplastic crisis	Underlying hemolysis	Severe acute anemia
Pure red cell aplasia	Immunodeficiencies	Chronic anemia
Hydrops fetalis	Fetus	Fatal anemia

Modified with permission from Young NS: Parvoviruses. In Fields BN, Knipe DM, Howley PM (editors-in-chief). *Fields Virology,* 3rd ed. Lippincott-Raven, 1996.

deficiencies who fail to make virus-neutralizing antibodies, resulting in anemia. Persistence of low levels of B19 DNA, and to a lesser extent virus type 2 DNA, has also been detected in blood, skin, tonsil, liver, and synovial tissues of immunocompetent volunteers. The rash associated with erythema infectiosum is at least partly immune complex mediated.

B19 can be found in blood and respiratory secretions of infected patients. Transmission is presumably by the respiratory route. There is no evidence of virus excretion in feces or urine. The virus can be transmitted parenterally by blood transfusions or by infected blood products (clotting and immunoglobulin concentrates) and vertically from mother to fetus. Because B19 is resistant to harsh treatments that inactivate enveloped viruses, some clotting factor concentrates end up contaminated. The prevalence of antibodies to B19 is

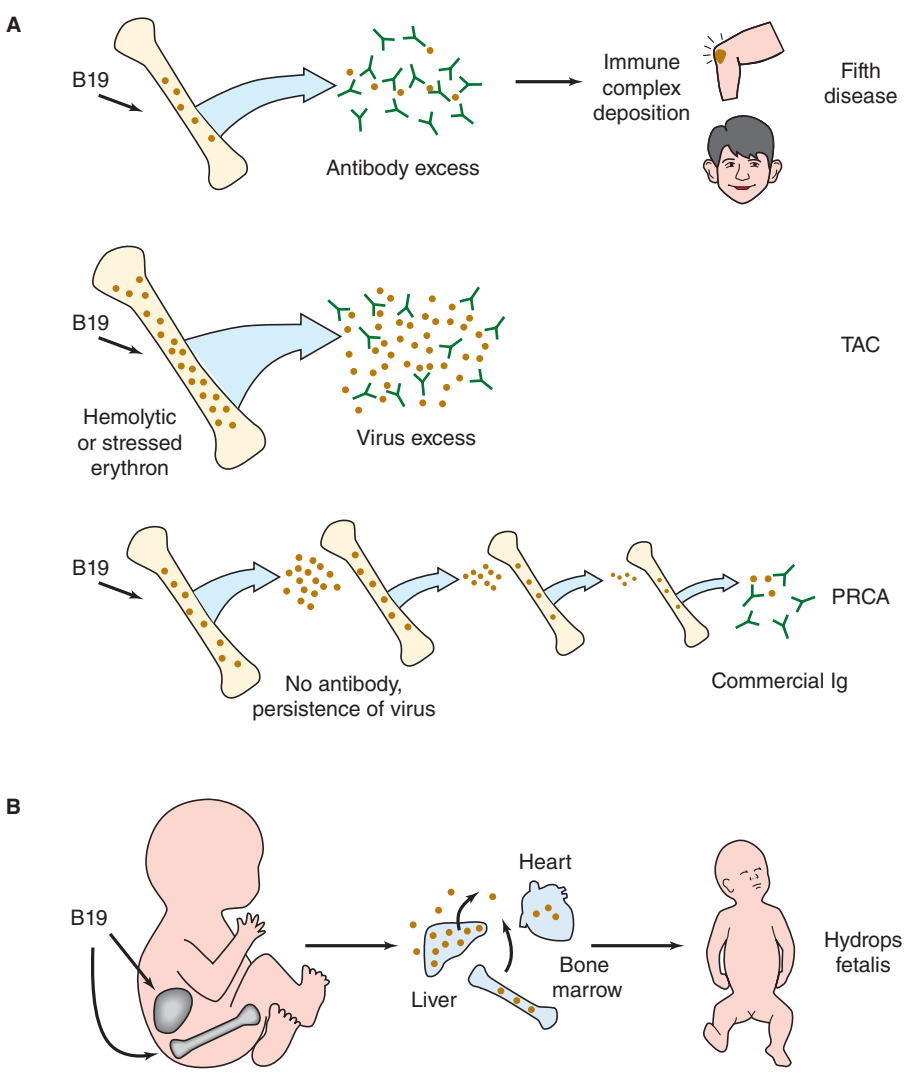

FIGURE 31-3 Pathogenesis of diseases caused by B19 parvovirus. **A:** In children and adults. (TAC, transient aplastic crisis; PRCA, pure red cell aplasia.) **B:** In fetal infections. (Modified with permission from Brown KE, Young NS: Parvovirus B19 infection and hematopoiesis. *Blood Rev* 1995;9:176. Copyright Elsevier.)

higher among people with hemophilia than the general population; however, the minimal level of virus in blood products able to cause infections is not known.

The pathogenesis of human bocavirus infection is not yet known. Because it has been found in respiratory specimens, it is presumed to infect the respiratory tract and be transmitted by the respiratory route. It has also been detected in stool and serum samples.

Several pathogenic parvoviruses of animals replicate in intestinal mucosal cells and cause enteritis.

Clinical Findings

A. Erythema Infectiosum (Fifth Disease)

The most common manifestation of human parvovirus B19 infection is erythema infectiosum, or fifth disease. This erythematous illness is most common in children of early school age and occasionally affects adults. Mild constitutional symptoms may accompany the rash, which has a typical "slapped cheek" appearance (Figure 31-4). Both sporadic cases and epidemics have been described. Joint involvement is a prominent feature in adult cases; joints in the hands and the knees are most frequently affected. The symptoms mimic rheumatoid arthritis, and the arthropathy may persist for weeks, months, or years.

The incubation period is usually 1–2 weeks but may extend to 3 weeks. Viremia occurs 1 week after infection and persists for about 5 days. During the period of viremia, virus is present in nasal washes and gargle specimens, identifying the upper respiratory tract—most probably the pharynx—as the site of viral shedding. The first phase of illness occurs at the end of the first week; symptoms are flu-like, including fever, malaise, myalgia, chills, and itching. The first episode of illness coincides in time with viremia and reticulocytopenia and with detection of circulating IgM–parvovirus immune complexes. After an incubation period of about 17 days, a second phase of illness begins. The appearance of an erythematous facial rash and a lacelike rash on the limbs or trunk may be accompanied by joint symptoms, especially in adults. The illness is short-lived, with the rash fading after 2–4 days, although the joint symptoms may persist longer. Specific IgG antibodies appear about 15 days postinfection.

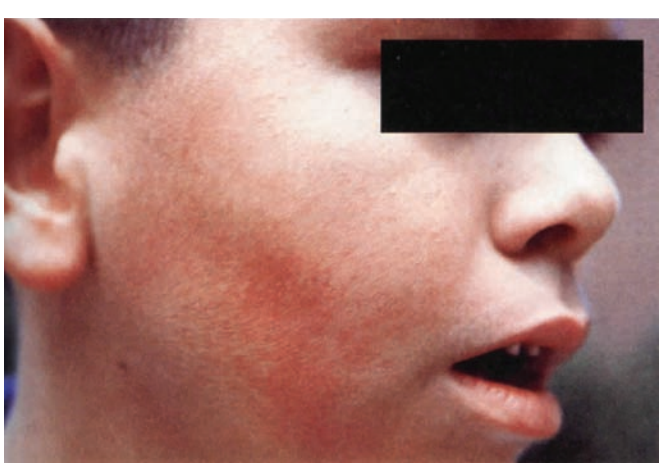

FIGURE 31-4 Erythema infectiosum (fifth disease). Typical "slapped cheek" appearance of the rash on the face. (Source: CDC Public Health Image Library.)

B. Transient Aplastic Crisis

Parvovirus B19 is the cause of transient aplastic crisis that may complicate chronic hemolytic anemia, such as in patients with sickle cell disease, thalassemias, and acquired hemolytic anemias in adults. Transient aplastic crisis may also occur after bone marrow transplantation. The syndrome is an abrupt cessation of red blood cell synthesis in the bone marrow and is reflected in the absence of erythroid precursors in the marrow, accompanied by a rapid worsening of anemia. The infection lowers production of erythrocytes, causing a reduction in the hemoglobin level of peripheral blood. The temporary arrest of production of red blood cells becomes apparent only in patients with chronic hemolytic anemia because of the short life span of their erythrocytes; a 7-day interruption in erythropoiesis would not be expected to cause detectable anemia in a normal person. Few anemia patients have a rash. Symptoms of transient aplastic crisis occur during the viremic phase of infection.

C. 19 Infection in Immunodeficient Patients

B19 may establish persistent infections and cause chronic suppression of bone marrow and chronic anemia in immunocompromised patients. The disease is called pure red cell aplasia. The anemia is severe, and patients are dependent on blood transfusions. It has been observed in patient populations with congenital immunodeficiency, malignancies, AIDS, and organ transplants.

D. B19 Infection During Pregnancy

Maternal infection with B19 virus may pose a serious risk to the fetus, resulting in hydrops fetalis and fetal death due to severe anemia. The overall risk of human parvovirus infection during pregnancy is low; fetal loss occurs in fewer than 10% of primary maternal infections. Fetal death occurs most commonly before the 20th week of pregnancy. Although there is frequent intrauterine transmission of human parvovirus (with estimates of vertical transmission rates of 30% or higher), there is no evidence that B19 infection causes physical abnormalities. Maternal–fetal transmission may occur most commonly in pregnant women with high plasma viral loads.

E. Human Bocavirus Respiratory and Gastrointestinal Infections

Human bocavirus has been detected in 1.5% to 11.3% of respiratory tract samples from young children with respiratory infections. It is prevalent among children with acute

wheezing. However, bocavirus is often found in mixed infections with other viruses, so it remains unclear if bocavirus is the cause of acute respiratory disease in children. The virus has been detected in about 3% of stool samples from children with acute gastroenteritis. Coinfection rates with other enteric pathogens were high, so any causative role of bocavirus in gastroenteritis is unknown.

Laboratory Diagnosis

The most sensitive tests detect viral DNA. Available tests are polymerase chain reaction (PCR), probe hybridization of serum or tissue extracts, and in situ hybridization of fixed tissue. PCR is the most sensitive assay. B19 DNA has been detected in serum, blood cells, tissue samples, and respiratory secretions. During acute infections, viral loads in the blood can reach approximately 10^{11} genome copies/mL. PCR assays based on B19 may miss non-B19 strains because of sequence differences. The only assay currently available for human bocavirus is PCR. Bocavirus DNA has been found in serum, saliva, stool samples, and respiratory specimens.

Serologic assays based on recombinant parvovirus B19 antigens produced in vitro using bacterial or baculovirus expression systems are used to measure antibodies. VP2 virus-like particles appear to be optimal as antigen for antibody detection. Detection of B19 IgM antibody is indicative of recent infection; it is present for 2–3 months after infection. B19 IgG antibody against conformational epitopes on VP1 and VP2 persists for years, although antibody responses against linear epitopes decline within months postinfection. Antibody may not be found in immunodeficient patients with chronic B19 infections. In those patients, chronic infection is diagnosed by detecting viral DNA.

Antigen detection assays can identify high-titered B19 virus in clinical samples. Immunohistochemistry has been used to detect B19 antigens in fetal tissues and bone marrow.

Human B19 and human bocaviruses are difficult to grow. Virus isolation is not used to detect infection.

Epidemiology

The B19 virus is widespread. Infections can occur throughout the year in all age groups and as outbreaks or as sporadic cases. Infections are most commonly seen as outbreaks in schools. Parvovirus infection is common in childhood; antibody most often develops between the ages of 5 and 19 years. Up to 60% of all adults and 90% of elderly people are seropositive.

B19 infection seems to be transmitted via the respiratory tract. The viruses are stable in the environment, and contaminated surfaces may also be involved in transmission. Transfer among siblings and children in schools and daycare centers is the main path of transmission. The source of maternal infection during pregnancy is often the mother's older child. Many infections are subclinical. Estimates of attack rates in susceptible contacts range from 20% to 50%.

Transmission of B19 from patients with aplastic crisis to members of the hospital staff has been documented. Whereas patients with aplastic crisis are likely to be infectious during the course of their illness, patients with fifth disease are probably no longer infectious by the time of onset of rash.

The epidemiology of human bocavirus is not known. It has been found in young children and appears to be global in distribution.

Treatment

Fifth disease and transient aplastic crisis are treated symptomatically. The latter may require transfusion therapy.

Commercial immunoglobulin preparations contain neutralizing antibodies to human parvovirus. They can sometimes ameliorate persistent B19 infections in immunocompromised patients and in those with anemia.

There is no treatment for human bocavirus infections.

Prevention and Control

There is no vaccine against human parvovirus, although prospects are good that a vaccine can be developed. There are effective vaccines against animal parvoviruses for use in cats, dogs, and pigs. There is no antiviral drug therapy.

Good hygienic practices, such as hand washing and not sharing drinks, should help prevent the spread of B19 through respiratory secretions, aerosols, and fomites. Standard infection control practices should be followed to prevent transmission of B19 to health care workers from patients with aplastic crisis and from immunodeficient patients with chronic B19 infection.

CHAPTER SUMMARY

- Parvoviruses are small, very simple viruses with single-stranded DNA genomes.
- Human B19 virus targets erythroid progenitor cells.
- B19 is associated with erythema infectiosum (fifth disease), transient aplastic crisis, pure red cell aplasia, and hydrops fetalis (most commonly in early pregnancy).
- Human bocaviruses have been linked with acute respiratory disease and gastroenteritis in children, but causation has not been proven.
- Human B19 and bocaviruses are difficult to grow; laboratory diagnosis depends on molecular assays.

REVIEW QUESTIONS

1. Which one of the following best describes a physicochemical property of parvoviruses?
   (A) Enveloped virus particle
   (B) Single-stranded DNA genome
   (C) Infectivity is inactivated by ether treatment
   (D) Virion exhibits helical symmetry
   (E) Virion is about the same size as herpesviruses

2. An 8-year-old child recently had erythema infectiosum. Her 33-year-old mother subsequently developed arthralgia followed by painful arthritis with swelling in the small joints of both hands. In addition to the apparent tropism for joints, human parvovirus B19 is highly tropic for which cell type?
   (A) CD4 T lymphocytes
   (B) Renal tubule cells
   (C) Erythroid cells
   (D) Glial cells
   (E) Peyer patches
3. The 8-year-old child in Question 2 had an illness with more than one phase. Which symptoms coincide with the second phase of the illness?
   (A) Sore throat
   (B) Skin rash
   (C) Headache
   (D) Diarrhea
   (E) Cough
4. A 42-year-old man with HIV/AIDS presented with aplastic anemia. Using the polymerase chain reaction, parvovirus B19 was detected in his serum. The patient presumably acquired his parvovirus B19 infection from another person. The most likely route of transmission is
   (A) By contact with respiratory secretions or droplets
   (B) By contact with a skin rash
   (C) Through sexual activity
   (D) Through a recent blood transfusion
5. Which one of the following is a disease in which the role of parvovirus B19 has not been established?
   (A) Erythema infectiosum (fifth disease)
   (B) Transient aplastic crisis
   (C) Hydrops fetalis
   (D) Fulminant hepatitis
6. Which one of the following best describes the replication of human parvovirus B19?
   (A) Stimulates resting cells to proliferate
   (B) Uses blood group antigen P as cellular receptor
   (C) Readily establishes persistent infections
   (D) Entire replication cycle occurs in cytoplasm
   (E) Production of infectious progeny requires the presence of a helper virus
7. Which one of the following statements is most accurate concerning human infections by parvovirus B19?
   (A) Parvovirus B19 is transmitted readily by sexual intercourse.
   (B) Patients with disseminated disease caused by parvovirus B19 should be treated with acyclovir.
   (C) Parvovirus B19 does not cause any human disease.
   (D) There is no vaccine for human parvovirus.
8. Human bocavirus is a newly discovered parvovirus. It has been detected most frequently in which type of sample?
   (A) Urine
   (B) Cord blood
   (C) Respiratory secretions
   (D) Fetal liver
   (E) Bone marrow
9. Which of the following is available as a treatment or preventative for parvovirus B19 infections?
   (A) Commercial immunoglobulin
   (B) Vaccine containing recombinant VP2 viral antigen
   (C) Bone marrow transplantation
   (D) Antiviral drug that blocks virus–receptor interaction
10. Human erythroviruses and bocaviruses share the following properties except for which one?
    (A) Small, nonenveloped virus particles
    (B) Difficult to culture
    (C) Cause anemia
    (D) Global distribution
    (E) No vaccine exists

Answers

1. B	4. A	7. D	10. C
2. C	5. D	8. C	
3. B	6. B	9. A	

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