Human Parvovirus B19

Disease Agent:

- Human parvovirus B19 (B19V)

Disease Agent Characteristics:

- Family: *Parvoviridae*; Genus: *Erythrovirus*; Species: human parvovirus B19
- Virion morphology and size: Nonenveloped, icosahedral nucleocapsid symmetry, spherical particles, 23-26 nm in diameter
- Nucleic acid: Linear, negative and positive single-stranded DNA, ~5.6 kb in length. The genome comprises two large open reading frames encoding the non-structural proteins and capsid proteins.
- Physicochemical properties: In general resistant to dry heat, freezing and lipid solvents. Inactivated by formalin, β-propiolactone and gamma irradiation. B19V genotypes 1 and 3 were inactivated below the limit of detection at 56˚C for 30 minutes, pH 4 at 37˚C and at pH 4.5 at 23˚C.

Disease Name:

- Erythema infectiosum (fifth disease) in children
- Associated with arthropathy, aplastic anemia/crisis, fetal hydrops

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Very low/Low since all pooled plasma and fractionated products in the US, Canada and Europe are tested for B19V by NAT. A higher level of concern for immunocompromised patients, patients with chronic anemia (sickle cell, thalassemia), and bone marrow transplant patients exists.
- Public perception and/or regulatory concern regarding blood safety: Very low in the US; similarly very low in patients with hemophilia since all pooled plasma and fractionated products in the US, Canada and Europe are tested for B19V by NAT. However, concern exists for immunocompromised individuals, patients with chronic anemia (sickle cell, thalassemia), and bone marrow transplant patients.
- Public concern regarding disease agent: Low

Background:

- Virus discovered in 1974
- Three genotypes: 1, 2 and 3. Genotype 1 is responsible for the majority of human infections worldwide; genotypes 2 and 3 appear to have some geographic and temporal variation in distribution. B19V, in contrast to other DNA viruses, has an inherent rate of genetic drift similar to that of RNA viruses. The nucleotide divergence among the three genotypes is approximately 10%-20% when compared to reference B19V strains. Currently, regulatory authorities expect approved tests to detect all three genotypes as all three have been recovered from clotting factor concentrates.
    - Genotype 2 has been identified at very low frequencies in viremic individuals in Europe, Brazil, and Vietnam. It has also been found sporadically in donations from plasma donors in North America.
    - In Central and Northern Europe, genotype 2 is typically found at higher frequencies in individuals older than 40 years of age.
    - To date, genotype 3 has been shown to be endemic in West Africa (Ghana), and sporadically identified in Brazil, France, the UK and Asia. Plasma donations containing high titers of genotype 3 were recently identified from a US blood donor.
    - In one study in South Africa, 75% of diagnostic samples submitted to a reference laboratory were identified as genotype 1, 6% as genotype 2 and 19% as genotype 3 by genotype-specific PCR or consensus NS1 PCR.
- Clinical associations discovered in the early 1980s (arthropathy, aplastic anemia/crisis, fetal hydrops)
- Global and endemic infection
- Seasonal, with greater occurrence in late winter and spring
- Periodic focal outbreaks occurring at intervals of several years are typical in temperate climates.

Common Human Exposure Routes:

- Respiratory (droplet infection)
- *In utero* (transplacental) from acutely infected mother

Likelihood of Secondary Transmission:

- High in day-care centers, schools, and household contacts through the respiratory route

At-Risk Populations:

- Children (because of lack of immunity)
- Populations at most risk for serious complications by transfusion route include patients who have shortened RBC survivals, patients who are immunocompromised, and women who are pregnant (because of transmission of infection to the fetus).

Vector Involved:

- None

Blood Phase:

- Virus is tropic for erythroid progenitor cells.
- Extremely high-titer viremia (up to 10^{14} IU/mL, where an IU is roughly equivalent to one copy) occurs approximately 1 week following infection and persists for approximately 5 days.
- IgM antibody develops 10-14 days post-infection followed by the development of IgG antibodies directed toward viral capsid components. Low-level DNA (less than 10^{3} IU/mL) has been reported frequently in the blood of donors with greater than 6 months follow-up, but the clinical relevance of this finding is unknown. Viremia subsequently

declines rapidly, usually disappearing within weeks of IgM development.
- IgM antibody becomes undetectable after several months, but IgG persists long term and is thought to convey immunity to reinfection.
- Infrequently, low-level B19V nucleic acid in association with IgG may persist for months or years.

Survival/Persistence in Blood Products:

- Survives in blood components and frozen plasma products

Transmission by Blood Transfusion:

- Transmitted by blood components (at least 12 clinical cases documented in the literature); actual frequency of transmission not reliably assessed prospectively.
  - 8 cases from Japan recognized by clinical outcomes including red cell aplasia and one case of pancytopenia; all cases resolved spontaneously
    - Transfusion transmission was reported from donors with virus-specific IgM antibodies, with or without IgG. Genetic identity between donor and recipient was used to confirm transfusion transmission. Transmission from antibody-positive units has otherwise not been reported.
    - One of the cases in this report involved transmission resulting in clinical disease from a red cell concentrate with a B19V titer of 5×10^3 IU/mL.
  - German lookback studies on 18 donors with greater than 10^5 IU/mL B19V identified 9 transmissions (asymptomatic); in contrast, none of 16 recipients of components with less than 10^5 IU/mL were infected.
  - One US study found no transmission to 24 susceptible recipients of components with B19V titers less than 10^3 IU/mL.
  - Solvent-detergent (SD) treated plasma lots in the US with B19V DNA titers of $> 10^7$ IU per mL transmitted to patients and to seronegative volunteers; units with $<10^4$ IU per mL of virus did not transmit.
- Commonly transmitted from Factor VIII and Factor IX concentrates prior to B19V DNA testing

Cases/Frequency in Population:

- Half of the population has been infected by late adolescence, with 70-80% infected by adult life.
- Annual incidence in women of childbearing age is 1-1.5% (may be higher in periodic outbreaks).
- Seasonal epidemics generally occur in the late spring.

Incubation Period:

- Approximately 5-6 days to viremia, peaking at days 8-9; slightly longer time interval to disease symptoms

Likelihood of Clinical Disease:

- Most cases asymptomatic
- Erythema infectiosum (fifth disease) common in children
- Arthropathy (acute and chronic; more common in adult females)
- Transient aplastic crisis in patients with shortened RBC survival or hemolytic anemias
- Pure RBC aplasia or pancytopenia in immunocompromised patients
- Myocarditis rarely reported
- Fetal hydrops common

Primary Disease Symptoms:

- Acute biphasic illness with fever, chills, headache, and myalgia, followed subsequently by classic fifth disease symptoms associated with the appearance of IgM antibodies (generalized erythematous eruption and joint inflammation) indicative of immune complex formation.

Severity of Clinical Disease:

- Transient aplastic crisis can cause significant morbidity and occasionally be fatal.
- Seronegative pregnant women are at risk for adverse outcomes of pregnancy including giving birth to infants with congenital anemia or for fetal demise due to fetal hydrops (vertical transmission rate of 33%).

Mortality:

- 5-9% risk of fetal mortality in transplacental infection

Chronic Carriage:

- Chronicity is presumably rare in immunocompetent patients, but low concentrations of virus-specific nucleic acid have been detected by sensitive NAT assays in plasma for a year or longer; more common in immunocompromised patients who cannot make antibody.
- After primary infection, B19V DNA persists for decades as a full-length molecule in solid tissues of both symptomatic and non-symptomatic subjects.

Treatment Available/Efficacious:

- Pure RBC aplasia is often effectively treated by IVIG.
- Fetal hydrops may respond to high dose IVIG.
- Other clinical syndromes are treated with supportive care.

Agent-Specific Screening Question(s):

- No specific question is in use.
- Not indicated because of the rarity of transfusion transmission resulting in clinical disease
- No sensitive or specific question is feasible.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
  - NAT is available, either as an in-house or as an unlicensed commercial real-time duplex test for B19V DNA (and HAV RNA) on fully-automated platforms from two manufacturers for in-process plasma screening.
  - NAT assays are used in-process to test large sample pools of plasma for further manufacture into plasma derivatives. Such testing is recommended by the FDA

with the objective of assuring the concentration of B19V in manufacturing pools does not exceed 10^4 IU/mL. Primers and probes are selected to ensure detection of all B19V genotypes. The first international parvovirus B19V genotype panel is available.
    - In-date blood components associated with high-titer B19V plasma units are quarantined and destroyed when possible. However, in-process screening may occur after red cell units have been transfused; in such cases, routine consignee notification of units with positive test results is not required.
    - More sensitive testing (detection limit at ~10^3 IU/mL) is used in Germany to make available, upon request, B19V-safe blood components for categories of patients susceptible to severe clinical outcomes of infection.
- B19V antigen tests are available but are not sensitive enough for donor screening.
- IgG and IgM antibody tests are commercially available and licensed in the US for diagnostic testing. In the Netherlands, donors with two positive IgG tests at an interval of > 6 months are considered B19V-safe, and their components are available for particular categories of susceptible patients upon request.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- At minimum, prudent practice would be to defer a donor with signs and symptoms of B19V disease until they resolve. Longer deferral periods may be necessary to ensure clearance of B19V DNA.

Impact on Blood Availability:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Impact could be relatively high if sensitive NAT were used (donor DNA positivity rates of 0.2%-0.9%) and perhaps higher in communities experiencing epidemics; low if insensitive NAT is used as currently recommended (donor DNA positivity rates of 0.03%-0.1%)

Impact on Blood Safety:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: NAT screening could decrease transmission rate by removal of viremic units capable of transmitting disease. However, the extent of clinical disease because of transfusion transmission is unknown but reported infrequently; therefore, the benefits of screening may be minimal. Conversely, outcomes could theoretically be severe in particular populations of transfused recipients (e.g., patients with hemolytic anemias, pregnant women and immunosuppressed patients). These recipients might benefit from B19V-safe components.

Leukoreduction Efficacy:

- None, because virus has tropism for RBCs and RBC precursors.

Pathogen Reduction Efficacy for Plasma Derivatives:

- Only partially inactivated by heat and solvent-detergent treatment
- Inactivation appears to be effective if titer of plasma pool is below 10^4-10^5 IU per mL.

Other Prevention Measures:

- None

Suggested Reading:

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