

## Special Article

# Human Parvovirus B19 in Solid Organ Transplantation

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**Abbreviations:** IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; SOT, solid organ transplantation.

## Epidemiology

### Virology

The *Parvoviridae* family includes the genus erythrovirus with human parvovirus B19 being the classic type member. The virus is 25 nm in diameter, nonenveloped and consists of a single-strand linear DNA that is approximately 5 kb in length. The viral genome encodes three main proteins, a nonstructural protein (NS1) and two structural proteins (VP1 and VP2; Ref. 1). The nonstructural protein is cytotoxic to host cells (2,3). Parvovirus B19 is classified into three different genotypes (genotype 1, 2, 3), but there is no definitive association of genotypes with specific clinical manifestations.

Parvovirus B19 was first detected in a healthy blood donor's serum in 1974 (4). It was subsequently linked to disease in children with sickle cell anemia experiencing transient aplastic crisis (5) and then in children with a contagious exanthem, called erythema infectiosum, or fifth disease (6). Parvovirus B19 has particular tropism for human erythroid progenitor cells, which is the natural host cell (7,8). The cellular receptor is globoside (also called erythrocyte P antigen; Ref. 9), which is found on erythroid cells, erythroid precursors and red cells of the placenta and fetal myocardium, fetal liver and some megakaryocytes and endothelial cells. Viral replication induces a distinctive cytopathic effect by light microscopy, represented by giant pronormoblasts (10), and productive infection has only been described in erythroid precursors (11). Although P antigen receptors are found on nonerythroid cells, there is evidence that a region of the viral genome is

responsible for inhibiting viral replication in nonpermissive cells (12).

### Transmission

Parvovirus B19 is ubiquitous and a common illness of childhood so that half of the population have detectable IgG antibody by 15 years of age (13,14). Most infections occur in the spring in temperate climates with small epidemics regularly occurring several years apart (15). The incidence of parvovirus infection in solid organ transplant patients is unknown because of the lack of surveillance studies. Based on detection of parvovirus DNA in peripheral blood, one study reported a single institution incidence of 12% in kidney transplant patients who had anemia (16).

Transmission of parvovirus B19 appears to be via respiratory secretions (6,17). Direct intranasal inoculation of parvovirus B19 into healthy volunteers resulted in viremia and clinical manifestations (18). Transmission can also occur to the fetus via transplacental infection and rarely through blood products (19,20). No FDA approved test is available for parvovirus B19 screening in blood donors. However, nucleic acid testing (NAT) is available for plasma units in process of being fractionated (21). There is evidence that transmission of parvovirus B19 infection may occur at the time of transplantation (22–24). Barzon et al. showed that in the majority of 10 pediatric kidney transplant patients (pretransplant parvovirus serology D+/R–), positive detection of parvovirus B19 DNA in the allograft kidney biopsy sample, preservation solution or washing solution (which contain circulating donor cells and resident kidney cells) was associated with post-transplant detection of parvovirus DNA in the blood of the recipient (22).

The incubation period ranges from 4–14 days, and individuals with erythema infectiosum are contagious before onset of rash but rarely afterwards. Individuals with aplastic crisis can be contagious before symptoms until about one week after onset of symptoms (25). Secondary infection rates are 50% for susceptible household members (26) and 20% for school and childcare personnel (27). Transmission to hospital personnel can occur.

### Clinical disease

The clinical manifestations of parvovirus B19 infection in immunocompromised patients are atypical (Table 1). Among SOT recipients, fever, arthralgia and rash were observed in 25%, 7% and 6% of patients with parvovirus B19 infection, respectively. Anemia, however,

**Table 1:** Clinical manifestations of parvovirus B19 in immunocompromised hosts

Persistent anemia
Severe anemia
<ul style="list-style-type: none"> <li>• Lack of reticulocyte response</li> <li>• Lack of response to erythropoietin</li> </ul>
Fever
<ul style="list-style-type: none"> <li>• Observed in 25% of solid organ transplant patients.</li> </ul>
Lacy skin rash
<ul style="list-style-type: none"> <li>• Not always present because of lack of antigen-antibody complexes (30,33)</li> </ul>
Arthropathy
<ul style="list-style-type: none"> <li>• Not always present because of lack of antigen-antibody complexes (30,33)</li> </ul>
Pancytopenia
<ul style="list-style-type: none"> <li>• A subset of patients will manifest concomitant leukopenia or thrombocytopenia with the anemia (8,18,51).</li> <li>• The pathogenesis is speculated to be non-specific cytopathic effects in the bone marrow (8) or restricted non-structural protein expression in megakaryocytes, which leads to cytotoxicity but not viral progeny (52).</li> </ul>

was present in 99% of the patients (28). Therefore, parvovirus B19 infection should be suspected in SOT recipients with erythropoietin-resistant anemia since the reported incidence in this group of patients is relatively high (29).

Many clinical manifestations have been associated with parvovirus B19 (30). However, the association with parvovirus is predominantly based on finding DNA in tissue, which may not be proof of causation. Parvovirus DNA has been found persistently in a number of tissues including bone marrow, synovium, heart tissue and skin from individuals who are asymptomatic (31). The reason for the persistence is unclear but may be related to inhibition of viral replication in nonpermissive cells. Furthermore, normal healthy blood donors have been found to have circulating parvovirus B19 DNA in peripheral blood (32).

### Immunity

Antibody response to parvovirus B19 appears to confer life-long protective immunity for the individual. Lack of an antibody response is observed in patients with persistent infection (33). "Recurrences" of parvovirus B19 infection may be more related to poor initial neutralizing antibody production in immunocompetent and immunocompromised hosts.

T cell responses to parvovirus B19 have been detected (34) but their role in protective immunity is not clear (35).

### Diagnosis

Parvovirus B19 infection can be diagnosed by serology or direct viral detection in clinical specimen such as blood, bone marrow and other organs (i.e. liver, lung, kidney). In highly viremic patients following acute parvovirus B19 infection, serology might be falsely negative because

antibodies could be complexed by viral particles (36). In addition, parvovirus B19 serology is not reliable in immunocompromised patients due to inadequate or delayed antibody-mediated immune response (37,38). Parvovirus B19 IgM antibody was present in only 75% of SOT recipients at the time of disease onset. The detection of parvovirus B19 IgG antibody alone is suggestive of remote infection and is uncommonly seen (7% of patients) among transplant recipients with parvovirus B19 infection (28). The current use of polymerase chain reaction (PCR) assays significantly improved the detection of viral DNA (39). However, one should keep in mind that some PCR assays are unable to detect non-B19 strains (genotypes 2 and 3; Refs. 40–42), and real-time PCR can be falsely negative in case of high-level viremia (43). Furthermore, parvovirus B19 DNA can be detected by PCR in the serum of some patients for long time after the acute phase of infection (44). Thus, a positive PCR for parvovirus B19 does not necessarily indicate acute infection. However, the positive predictive value of positive PCR in an immunocompromised host with red cell aplasia is high. Bone marrow examination associated with *in situ* hybridization or immunohistochemical staining could be very helpful in establishing the diagnosis when the clinical presentation is strongly suggestive of parvovirus B19 infection but the PCR and serology are negative (28). Typical bone marrow findings include overall hypercellularity and the presence of giant pronormoblasts with finely granulated cytoplasm and glassy intranuclear inclusions with a clear central halo (lantern cells), and absent late normoblasts.

### Recommendations:

- (1) Parvovirus B19 infection should be suspected in SOT recipients with:
  - (a) Erythropoietin-resistant anemia or anemia with inappropriate reticulocyte response with or without:
    - (i) Fever, arthralgia or rash
    - (ii) Organ-invasive disease such as hepatitis, myocarditis, pneumonitis, neurological disease or vasculitis (III).
  - (b) Pancytopenia
- (2) The initial work-up for suspected parvovirus B19 infection should include serology (IgG and IgM) and serum/whole blood PCR for parvovirus B19 (III).
- (3) If not done earlier, bone marrow examination should be performed when parvovirus B19 infection is strongly suspected and the serology and serum PCR are negative. In addition, *in situ* hybridization or immunohistochemical staining should be performed (III).

### Treatment

Antiviral drugs are not available for the treatment of parvovirus B19 infection. However, intravenous immunoglobulin (IVIG) has appeared to be beneficial in a large number of SOT recipients with parvovirus B19 infection (28,45,46). The optimal dosing regimen and duration of IVIG

therapy for parvovirus B19 infection has not been established and some patients have been reported to have long-lasting resolution of the infection without IVIG therapy (28). Most patients are treated with 400 mg/kg/day for 5 days, although higher doses have been used for shorter periods of time. In one review, the rate of relapse was not different among transplant recipients who received a total dose of  $\leq 2$  g/kg or  $> 2$  g/kg (28). Unfortunately, in the same case series up to 28% of SOT recipients experienced relapse after receiving IVIG. The value of PCR use to monitor the response to therapy is not known, especially that persistent low grade viremia for months despite adequate clinical response to therapy is not uncommon (47). Therefore, it would be reasonable to simply follow serial hemoglobin measurement and consider obtaining parvovirus B19 PCR in case of recurrence of anemia. Patients with recurrence of parvovirus B19 infection have been successfully treated with additional courses of IVIG (47). Yet, there is a wide variation in the clinical practice in terms of dose and duration of therapy. The side effects of IVIG treatment include fever, chills, headache, myalgia, nausea, hypertension, chest pain and renal failure.

The reduction of immunosuppression is believed to contribute to the resolution of infection; however, the timing of such an intervention (i.e. before or after IVIG therapy) is a subject of debate.

#### Recommendations:

- (1) Patients with parvovirus B19 infection may be treated with 400 mg/kg/day of IVIG for 5 consecutive days (III).
- (2) Reduction of immunosuppression should be attempted if at all possible at the time of diagnosis (III).
- (3) In case of nonresponse to the first IVIG course or in case of relapse another course of IVIG (400 mg/kg/day for 5 days) may be given (III).

## Prevention

In the SOT population, no proven specific preventive strategy against parvovirus B19 infection is available. Routine screening of donor and recipient serostatus for parvovirus B19 is not recommended. In one study, donor and recipient serostatus and more importantly the detection of viral DNA in renal allograft tissue, preservation solution or washing solution were useful to predict the risk of posttransplant viremia (22). However, only a few patients developed clinically significant disease in this study, which raises the question of cost-effectiveness of such method. Furthermore, strategies to prevent symptomatic parvovirus B19 infection are yet to be defined. Recommendations aimed at avoiding exposure of transplant recipients to children or adults with parvovirus B19 have not been offered by any advisory group because symptomatic patients are usually no longer contagious. In addition, the relative rarity of this diagnosis in transplant recipients, particularly among

pediatric transplant recipients, does not support the introduction of such a policy. To avoid nosocomial transmission, standard and droplet precautions should be implemented when a patient has an active disease. Anecdotal data in bone marrow transplant recipients have demonstrated the absence of parvovirus B19 disease in cohorts of patients who received prophylactic IVIG for other reasons (48). However, studies comparing the incidence of parvovirus infection among bone marrow transplant recipients who received IVIG and those who did not are not available. Furthermore, the lack of evidence of efficacy in the SOT population, the relative low incidence of symptomatic parvovirus B19 infection and the high cost and potential toxicity associated with IVIG therapy do not favor its prophylactic use. Finally, the development of recombinant human parvovirus B19 vaccine composed of VP1 and VP2 capsid proteins is underway. All 24 volunteers who received either 2.5 or 25  $\mu$ g of parvovirus B19 recombinant vaccine (MEDI-491) formulated with the adjuvant MF59C.1 at 0, 1 and 6 months developed neutralizing antibody titers that peaked after the third immunization and were sustained through study day 364 (49). A phase I/II randomized, placebo-controlled, double-blind clinical trial of the immunogenicity and safety of 2 dose levels of a recombinant human parvovirus B19 vaccine (VAI-VP705) conducted by the National Institute of Allergy and Infectious Diseases was halted because of three unexplained cutaneous events. After the second dose of the vaccine, most vaccine recipients developed ELISA and neutralizing antibody to parvovirus B19 (50). Hopefully a vaccine will be available in the near future for clinical use in high-risk populations. However, studies will be required to specifically define its use in the SOT population.

#### Recommendations:

- (1) To avoid nosocomial transmission, standard and droplet precautions should be implemented when a patient has an active disease.

## Future Studies

Future studies should further evaluate the utility of parvovirus B19 monitoring in SOT recipients. The significance of parvovirus B19 DNA detection in the blood or tissue samples obtained from immunocompetent patients and SOT recipients should be determined. Large, prospective, multicenter studies are needed in order to investigate current and novel therapeutic options for parvovirus B19 disease. Finally, future studies are needed to investigate new parvovirus B19 vaccines and the benefit of their use among SOT candidates and recipients.

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## Disclosure

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