Parvovirus B19 and the Kidney

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Infection with parvovirus B19 causes several clinical syndromes (fifth disease, transient aplastic crisis, pure red cell aplasia, and hydrops fetalis) and may contribute to other illnesses. B19 has been linked to renal disease in three settings: As a cause of acute glomerulopathy and as a cause of anemia in ESRD and kidney transplantation. Case reports implicate parvovirus in the pathogenesis of proliferative glomerulonephritis and collapsing glomerulopathy, but a causal relationship has not been established. A proposed role for B19 infection is based on the temporal association of renal findings with viral infection, positive serology, and identification of the viral genome in the glomerulus. Mechanisms may include cytopathic effects on glomerular epithelial cells and/or endothelial cells and glomerular deposition of immune complexes. Patients who require dialysis may have increased susceptibility to acute and chronic anemia after parvoviral infection. Factors that predispose this population to complications of B19 infection include impaired immune response, deficient erythropoietin production, and possibly decreased erythrocyte survival. The clinical burden of parvovirus B19 infection in renal transplant recipients may be underestimated; these individuals may develop persistent viremia as a result of a dysfunctional immune response. Chronic anemia and pure red blood cell aplasia are the most common complications of parvovirus infection in this population; the diagnosis should be considered in transplant recipients with unexplained anemia or pancytopenia. Allograft rejection and dysfunction have been reported in association with infection, but a cause–effect relationship has not been proved. Further investigation of the relationship between B19 and kidney disease is warranted.


Parvovirus B19 is a small, nonenveloped, single-stranded DNA virus that was discovered in 1975 (1) and first linked with human disease in 1981 (2). It is a member of the Parvoviridae family and belongs to the Erythrovirus genus, the name of which describes the virus’s pronounced tropism for erythroid precursor cells (3,4). The human parvovirus B19 is divided into three genotypes (B19, LaLi-like, and V9-like) which have 10% nucleotide divergence (5–7). Whereas these genotypes generally cross-react serologically, PCR amplification may require specific primers. Humans are the only known host for B19, and it is an autonomous virus that does not require the presence of a helper virus.

The B19 genome encodes two structural capsid proteins, viral protein 1 (VP1) and viral protein 2 (VP2), and a nonstructural protein (NS1) (8). B19 viral particles possess icosahedral symmetry (20 sided), consisting of 60 capsomers that are composed predominantly of VP2 (9). VP2 appears to facilitate viral attachment onto cells via its amino terminal end, which protrudes from the external virion surface (10). NS1 is a multifunctional protein; it has regulatory functions in the viral life cycle, allowing for replication of viral DNA and viral packaging; and it interferes with cellular signaling pathways, leading to apoptosis of host cells (11) and target cell cytotoxicity (12). NS1 transactivation of proinflammatory cytokine promoters such as IL-6 may trigger inflammation that is associated with infection (13). These data suggest that NS1 plays a critical role in B19-induced disease.

Epidemiology

Infection with parvovirus is very common and occurs worldwide. Acquisition is often during childhood and continues at lower rates throughout adulthood such that between 70 and 85% of adults show serologic evidence of past infection (14,15). Infectivity shows seasonal variation in temperate climates, being more common in winter and spring. Transmission of infection usually occurs by inhalation of virus in aerosol droplets (16). Infection also can be transmitted vertically from mother to fetus (17) and less commonly through transfusion of blood products (18), bone marrow transplants (19), and solid-organ transplants (20,21).

Pathogenesis and Immune Response

After gaining access to the human host, B19 targets the erythroid progenitors in the bone marrow by binding to the glycosphingolipid globoside (Gb4), also known as blood group P antigen (12). P antigen is expressed abundantly on erythroblasts and at lower levels in a limited number of other nonerythroid cell types (22). Although the P antigen is necessary for binding of the virus to the cell surface, it is not sufficient for entry and replicative infection in human cells (22,23). Recent studies support the existence of a cellular co-receptor, α5β1 integrin, for successful infection (24), although this remains controversial. This integrin is expressed at high levels on erythroid progenitors, whereas P antigen–positive nonerythroid cells that do not express this co-receptor are considered non-

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permissive for efficient infection. A third molecule, Ku80, has also been suggested as a possible co-receptor for B19 infection (25).

After B19 infection of erythroid progenitors, cell death ensues either by lysis (3) or by apoptosis (26) mediated by the NS1 protein. In normal infection, intense viremia lasts several days, during which time the reticulocyte count can drop to zero. Recovery is associated with production of virus-specific IgM antibodies 10 to 12 d after infection (27). This is followed by the production of IgG antibodies that are directed against both viral capsid proteins, although antibodies to the unique amino terminal region of VP1 seem most important (28). It has been a long-held belief that the development of antibodies results in rapid and complete clearance of viremia. However, emerging evidence challenges this notion. With the use of sensitive quantitative techniques such as dot blot and nested PCR assays, B19 DNA has been detected in bone marrow and in peripheral blood for months and even years in seemingly immunocompetent individuals, despite the presence of neutralizing antibody (29,30). The clinical significance of this delayed clearance and low-level viremia is unknown.

Traditionally, the humoral immune response has been considered most important for clearance of parvoviral infection and for long-term protection from re-infection. However, accumulating data suggest that humoral immunity alone may be insufficient for virus eradication. The cellular immune response is now attracting more attention, and its contribution to control of infection is gaining appreciation. Although limited data are available, studies have shown a striking CD8⁺ T cell response mounted predominantly against B19 NS1 (31). Moreover, activated CD8⁺ T cells against B19 epitopes have been detected for up to 2 yr after infection, which may suggest that T cells contribute to long-term pathogen control (32). It is interesting that Isa et al. (33) showed a discordance between the distribution of the cellular immune response in healthy seropositive individuals compared with those with B19 persistence with skewing of the CD8⁺ T cell response toward structural VP proteins in the latter. Thus, lack of B19 clearance could potentially be related to failure or perhaps “exhaustion” of the NS1 response (34). However, this remains to be proved. Less is understood about the role of B19-specific CD4⁺ T cells in acute infection, but it does seem that CD4⁺ T cell proliferative responses are directed against VP1 and VP2 (35,36). Further studies are required to clarify the role of the cellular immune response in viral clearance, in establishment of persistent infection, and in relation to clinical manifestations.

Clinical Manifestations and Complications

The clinical spectrum of disorders that are associated with B19 infection ranges from benign to life threatening depending on the age, hematologic status, and immunologic status of the host. Many immunocompetent individuals with detectable B19-specific IgG have no recollection of specific symptoms or recall only nonspecific symptoms of an upper respiratory tract illness. There are several common and well-established outcomes of B19 infection. Erythema infectiosum, also referred to as fifth disease, is the most common manifestation of infection in children (37). It is characterized by low-grade fever, malaise, a “slapped cheek” facial rash, and later by the spread of a lacy maculopapular rash involving the trunk and limbs. The rash normally disappears within 1 wk, although recrudescences can occur for several months after emotional or physical stress or exposure to sunlight or heat (38). Arthralgias and arthritis can occur in the setting of erythema infectiosum, but arthropathy is a more common manifestation of infection in adults, particularly in women (39). It typically manifests as sudden onset of symmetric polyarthralgia or polyarthritis with a rheumatoid-like distribution involving knees, wrists, ankles, and metacarpophalangeal joints. Although the joint symptoms are usually of brief duration, some do have prolonged symptoms that last weeks to years. The pathogenesis of the cutaneous eruptions and joint symptoms are presumed to be, at least in part, due to deposition of immune complexes in skin and synovial tissue because onset of manifestations coincides with appearance of B19-specific antibodies in the serum. Immunocompromised patients who cannot mount an antibody response to B19 typically do not develop these symptoms, whereas treatment of these patients with intravenous Ig (IVIG) may produce rash and/or joint pains. Nevertheless, other mechanisms besides immune complex deposition may be involved in the inflammatory response; skin biopsies from infected patients suggest that direct infection of dermal vessels and cellular infiltration may contribute to tissue injury (40,41). Moreover, because all immunocompetent individuals mount an antibody response but only some patients develop manifestations, other factors that are unique to the host likely play a role, such as elaboration of particular cytokine profiles (42,43).

Transient aplastic crisis as a result of B19 infection is of particular concern in patients with either decreased red blood cell production or increased turnover (e.g., hereditary spherocytosis, sickle cell disease) (44). In healthy individuals, temporary suppression of erythropoiesis during the viremic phase is usually well tolerated owing to the long life span of erythrocytes (120 d), and hemoglobin levels remain fairly stable. In contrast, a severe and sometimes life-threatening drop in hemoglobin can occur in those with shortened red cell lifespan (5 to 15 d), as is the case with chronic hemolytic disorders. Although supportive care with transfusion is often required, the aplastic crisis is usually self-limiting, rarely lasting for >2 wk, as a result of the production of neutralizing antivirus antibodies. Finally, B19 infection during pregnancy may lead to hydrops fetalis and intrauterine fetal death (45).

Although these are the best described clinical illnesses that are caused by B19 infection in the immunocompetent host, the virus has been implicated in an expanding spectrum of other clinical disorders (Table 1). These associations have been proposed on the basis of the temporal association of symptoms in the context of serologic documentation of recent infection or detection of B19 in peripheral blood or affected tissue. However, clear causality has been difficult to prove in many cases, and many of these associations remain controversial.
Glomerular Diseases Associated with Parvovirus

The possibility of a link between B19 infection and glomerular disease has been suggested from numerous case reports that describe onset of nephritis or nephrotic syndrome after onset of parvovirus infection. Several clinical presentations and histologic patterns have been described (46–56). Acute nephritic syndrome with hypocomplementemia often following a prodrome of fever, rash, and arthritis is most common, but nephrotic-range proteinuria is seen as well (46–49,51,52,57–60). Reported histologic features include endocapillary and/or mesangial proliferation often with subendothelial deposits together with granular deposition of C3 and IgG along capillary walls and mesangium, a pattern that is consistent with acute postinfectious glomerulonephritis. Viral genome has been detected in renal biopsies by PCR, and immunohistochemical analysis has demonstrated B19 antigen within glomeruli in some cases (48,51,52). Spontaneous recovery is common, but some have persistent renal dysfunction and/or proteinuria.

Several case reports have linked acute B19 infection to nephrotic syndrome in patients with sickle cell disease. Wirenga et al. (61) reported on seven patients who had homozygous sickle cell disease and developed glomerulonephritis and proteinuria 1 to 7 wk after aplastic crisis as a result of B19 infection. Renal biopsies showed segmental proliferative glomerulonephritis in four patients and FSGS in one patient who underwent biopsy 4 mo after onset of symptoms. Spontaneous recovery occurred in one patient, one died with chronic renal failure, and the others had impaired creatinine clearance, four with persistent proteinuria. Tolaymat et al. (55) similarly reported onset of hematuria and proteinuria 10 d after B19-associated aplastic crisis in a patient with sickle cell disease. Renal biopsy at 3 mo showed focal mesangial proliferative glomerulonephritis with mesangial deposits, extensive foot process effacement, and tubuloreticular structures, but no viral particles were observed. Viral genome was detected in renal tissue by PCR. Follow-up biopsy done 1 yr later because of persistence of the nephrotic syndrome showed FSGS, and B19 DNA remained detectable by PCR. Thrombotic microangiopathy (56), hemolytic uremic syndrome (62), and renal involvement in association with systemic vasculitides such as Henoch Schönlein purpura (54,63), polyarteritis nodosa (64) and Wegener’s granulomatosis (64) have also been associated with B19 infection.

Several investigators have attempted to characterize the potential association between B19 infection and glomerular disease. Tanawattanacharoen et al. (53) tested for B19 genome by PCR in native renal biopsies that were derived from 44 patients with various glomerular diseases (collapsing glomerulopathy and idiopathic FSGS, membranous nephropathy, minimal-change nephropathy, and controls) and found that the prevalence...
lence of parvovirus B19 was greatest among patients with collapsing glomerulopathy and FSGS compared with other renal diseases, although the difference was marginally significant. However, in situ hybridization failed to detect parvovirus B19 nucleic acid in any samples. In a similar study, Moudgil et al. (50) found a significantly higher prevalence of B19 DNA in renal biopsies from patients with collapsing glomerulopathy (78%), compared with other nephropathies (idiopathic FSGS 22%; HIV-associated collapsing glomerulopathy 16%; controls 26%). In situ hybridization detected B19 in the majority of biopsies that tested positive for virus by PCR (100% collapsing glomerulopathy; 75% idiopathic FSGS; 67% HIV-associated collapsing glomerulopathy; 0% controls). It is interesting that B19 DNA was localized to glomerular podocytes and parietal epithelial cells, both of which have been implicated in the pathogenesis of collapsing glomerulopathy. In contrast to these findings, Swaminathan et al. (65) were unable to detect parvovirus DNA sequences (by in situ hybridization) in 29 cases of FSGS and collapsing glomerulopathy that occurred after renal transplantation.

These conflicting results make it difficult to draw definitive conclusions regarding the role of parvovirus in the pathogenesis of certain glomerular disease. Nevertheless, the data are certainly provocative and are fairly convincing in the cases of proliferative glomerulonephritis that are temporally associated with primary B19 infection. Large-scale studies are warranted to help further define the potential relationship between infection and disease manifestations and to provide answers to important questions regarding the interaction of this virus with humans. For example, what is the clinical significance of the detection of viral DNA in nonerythroid cells such as in the kidney? It has been shown that B19 DNA can remain detectable by nucleic acid amplification testing in a variety of tissues (30), including bone marrow (66), synovial tissue (67), and skin (6), for extended periods without evidence of disease in some (30). As discussed, viral DNA has been detected in seemingly “normal, control” kidneys (50). The mechanisms that facilitate this persistence in human tissues are unclear. It is also not known whether this represents intact infectious virions or residual DNA from remote infection and to what extent, if any, it can be reactivated. Therefore, detection of viral DNA in tissues does not necessarily indicate active viral infection and must be interpreted with caution because the virus may be an “innocent bystander.” It is noteworthy that, to date, intact virions have not been visualized within the kidney despite that viral DNA is detected; however, this is also true for other viral nephropathies, such as HIV-associated collapsing glomerulopathy. Whether this is related to a low viral load, small size of the B19 virus (22 to 24 nm), or false-positive results is not known. Alternatively, restricted production of viral proteins may occur; indeed, isolated expression of the B19 nonstructural protein, NS1, has been demonstrated in some nonpermissive, nonerythroid cells even in the absence of complete viral propagation and has been shown to be cytotoxic (68). It is not known whether this process occurs in kidney cells, but it cannot be excluded as a possible mechanism of glomerular cell injury and deserves further study.

Even if one assumes that the virus can enter glomerular cells, the mechanism of cell entry is incompletely understood. The P antigen receptor has been found in kidney tissue (22), but its cellular localization is unknown. In addition, whether the level of expression, distribution, or accessibility of this and other co-receptors influences disease susceptibility has not been studied. Nevertheless, it is unlikely that a direct cytopathic effect on glomerular epithelial cells is the sole mechanism of viral injury. Several histologic patterns have been reported in association with infection, and this suggests that other mechanisms may play a role. Deposition of circulating immune complexes that involve viral antigens and host antiviral antibodies could lead to a pattern of injury that is consistent with postinfectious glomerulonephritis. Development of autoantibodies to cardiolipin, phospholipids, and double-stranded DNA have been reported during parvovirus infection (69), and these could also potentially contribute to preformed circulating immune complexes or in situ deposition. Direct infection of glomerular endothelial cells has been proposed as the mechanism of renal injury in cases of thrombotic microangiopathy and vasculitis. The P antigen has been demonstrated on endothelial cells (22), and B19 DNA has been localized to these cells in cases of B19-associated vasculitis (70). Thus, infection could result in endothelial cell dysfunction or cell death, leading to capillary thrombosis and glomerular ischemia. The cellular immune response to infection is not well characterized, but perhaps as we gain more insight into this area, we may find that an aberrant T cell response after infection also contributes to glomerular disease.

Given the ubiquitous nature of B19 infection, factors that are unique to the host likely increase susceptibility to glomerular disease after infection. This has not been studied specifically as it relates to glomerular diseases, but investigation of other infection-associated manifestations have revealed interesting findings that may have relevance (71). Inherent variability in cytokine expression and cytokine genetic polymorphisms may affect symptoms and outcome of infection; for example, increased levels of TNF-α and IFN-γ during acute and convalescent infection are associated with chronic fatigue, whereas lower levels of TNF and IL-6 have been detected in patients with postinfectious arthritis. A particular allele of TGF-β has been associated with development of skin rash during acute infection (42). Certain human leukocyte antigen alleles (HLA-DRB1*01, *04, *07, and B49) have been associated with symptomatic parvovirus infection (71). Single-nucleotide polymorphisms in genes that are linked to apoptosis, cell cycle and growth, and cytoskeleton were also found to associate with symptomatic B19 infection (71).

Further work is needed to better define the role of B19 in kidney disease. We need more detailed case reports that include careful longitudinal virologic analysis of serum and renal tissue. We also need well-designed epidemiologic studies with appropriate controls. If further evidence of a link can be established, then there will be a need to characterize the immune response to B19 infection in such patients and to identify genetic and other factors that increase susceptibility for renal complications.
**Parvovirus Infection in Dialysis Populations**

The impact and role of parvovirus B19 infection in patients with chronic kidney disease or ESRD is not known. Nevertheless, there are several reasons to think that parvovirus may be an important pathogen in these populations. For most patients, erythropoiesis is maintained by erythropoiesis-stimulating agents, and red blood cells may have a shortened life span in the setting of uremia. This combination of factors may predispose these patients to potentially life-threatening transient aplastic crisis associated with parvovirus infection (72). Furthermore, some believe that administration of erythropoietin during B19 infection can facilitate viral replication by providing new target cells (73), thereby prolonging viremia and its associated complications. However, this remains controversial. Nosocomial spread of infection in an enclosed dialysis unit is also a potential threat, but this is not well described in the literature (74).

In addition to the acute complications, the immunocompromised state in some dialysis patients (related to underlying diseases or medications) may prevent an effective antiviral immune response that can potentially lead to persistent viremia and chronic anemia that is resistant to erythropoietin. The frequency of this complication in chronic dialysis patients is not clear because this has not been systematically evaluated in a large cohort of anemic dialysis patients. Finally, it is possible that persistent B19 infection in these chronic dialysis patients can become clinically relevant after renal transplantation and introduction of immunosuppressants, as discussed in the next section.

**Parvovirus in Kidney Transplant Recipients**

Transplant recipients are susceptible to many primary viral infections and to reactivation of persistent viruses. Most clinically relevant infections in the posttransplantation period are caused by the Herpesviridae group, respiratory viruses, and hepatitis viruses B and C. The first report of parvovirus B19 infection in a kidney transplant recipient was published in 1986 (75). Since then, numerous cases of B19 infection after solid-organ transplantations have been reported (20,76–79). However, the clinical burden and true overall impact of B19 infection in the renal transplant population is not well characterized.

The prevalence of B19 infection in organ transplant recipients is difficult to estimate because much of the literature consists of case reports rather than carefully monitored cohorts. Furthermore, interpretation is difficult given different selection criteria, diagnostic methods with different detection sensitivities, different definitions of infection, and various (but limited) lengths of follow-up, together with confounding by concurrent viral epidemiology (80). Nevertheless, on the basis of several longitudinal studies, between 1 and 12% of unselected, mainly adult, renal transplant recipients have symptomatic B19 infection during the first year after transplantation (79–81). Given the prevalence of parvovirus in the general population, the increased susceptibility to viral infections after transplantation, and the increasing number of patients who have additional immunocompromised states (e.g., HIV infection, advanced age, diabetestes) and undergo transplantation, it is possible that this is an underestimation.

Although the mode of transmission of B19 infection in the normal host is mostly via the respiratory tract, it is less well defined in the transplant setting. Onset of symptoms has been reported to occur from a few days to >1 yr after transplantation, suggesting different paths of transmission (20,76,78,79). Certainly, the short time lapse between transplantation and onset of illness that has been reported in some has the characteristic of donor-transmitted disease, but this is often difficult to prove (56,81,82). Other possible routes of B19 infection besides airway transmission include transfusion of blood products and viral reactivation in the setting of intense immunosuppression.

The clinical picture of B19 infection in the immunocompromised host differs significantly from that of immunocompetent individuals. Because of the inability to mount an efficient humoral and/or cellular immune response, viral clearance is significantly delayed, or, in some cases, infection remains persistent, resulting in prolonged suppression of erythropoiesis. Therefore, it is not surprising that both acute anemia and chronic pure red blood cell aplasia are the most frequently reported consequences of B19 infection in organ transplant recipients (21,77,78,81,83). Several case series have evaluated the incidence of active B19 infection in renal transplant patients who present with anemia. Egbuna et al. (21) screened for anemia in 212 patients who were seen at a transplant clinic during a 3-mo period in late winter to early spring. Of eight patients selected with severe unexplained anemia (defined as hematocrit <30%) and erythropoietin resistance, three (38%) were found to be positive for B19 by PCR. Cavallo et al. (83) reported that 11 (23%) of 48 transplant recipients with anemia had B19 detected in serum by nested PCR compared with one (5%) of 21 without anemia. Similarly, Bertoni et al. (76) reported that four (44%) of nine transplant recipients with severe hypoproliferative anemia (hemoglobin <7 g/dl) were found to have parvovirus DNA in serum.

Hematologic findings consist of normochromic normocytic anemia, usually lacking reticulocytes, and the anemia is typically resistant to erythropoietin therapy (21,83). Onset of B19-associated anemia has been reported from 2 wk to 63 mo after transplantation (76–79). The diagnosis of B19-associated anemia in this population can be challenging for many reasons. There is often a lack of classical B19-associated symptoms, such as rash and arthritis, that could provide clues to the diagnosis. Anemia is relatively common after transplantation, particularly in the early posttransplantation period, and can be multifactorial. Therefore, B19 is often not considered in the very long list of causes of anemia, which include acute and chronic blood loss, generalized bone marrow suppression from immunosuppressants and antiviral medications, allograft dysfunction, iron deficiency, hyperparathyroidism, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and other, more common viral infections, such as cytomegalovirus. Furthermore, neutropenia, thrombocytopenia, or pancytopenia may occasionally accompany the anemia, further broadening the differential diagnosis (77). Other clinical complications that have been linked with B19 infection in renal transplant recipi-
ents include liver dysfunction (84), fibrosing cholestatic hepatitis (85), encephalitis (86), and cerebral vasculitis (87). However, causality has been difficult to infer in many cases.

**Allograft Dysfunction and Acute Rejection**

There are many data to support that certain viral infections such as cytomegalovirus and polyomavirus (BK) are associated with allograft rejection or dysfunction in renal transplant recipients. The evidence for a role of parvovirus in such processes is not as compelling. Isolated case reports describe elevated plasma creatinine and proteinuria at the time of acute B19 infection, but most reports lack renal biopsies and follow-up. Yango et al. (82) described a patient who presented 8 d after transplantation with fever, myalgia, polyarthralgia, and pancytopenia and 2 wk later developed graft dysfunction associated with elevated IgM and IgG titers against B19. Kidney biopsy revealed tubular cell damage, and parvovirus DNA was detected by PCR in biopsy. Zolnourian et al. (81) implicated acute parvovirus infection as a cause of acute rejection and graft loss in one pediatric patient. Several series have reported different rates of allograft dysfunction associated with infection. Ki et al. (80) found no association between allograft dysfunction and B19 infection. In contrast, Cavallo et al. (83) reported that 36% of patients with active infection had elevated serum creatinine levels but none developed rejection or glomerulopathy.

Murer et al. (56) implicated B19 infection in four cases of renal allograft dysfunction, all of which had histologic findings of thrombotic microangiopathy. Renal dysfunction was simultaneous or within days of an aplastic crisis that occurred 6 to 45 d after transplantation. Viral genome was isolated by PCR in all renal biopsies and in the peripheral blood of those tested. All patients subsequently became serologically positive for anti-B19 IgM. One patient was treated with IVIG, but the others improved spontaneously with gradual resolution of anemia (after 22 d to 12 mo) and recovery of graft function 22 to 110 d after onset. Direct viral infection of endothelial cells has been proposed as the mechanism of injury. Sensitization of glomerular endothelium as a result of other forms of injury such as acute rejection may have increased susceptibility to B19-induced damage. Collapsing glomerulopathy and subsequent graft failure (69,88) associated with parvovirus infection have been reported in renal transplant patients, but, as previously discussed, a larger series was unable to find a relationship between B19 infection and collapsing glomerulopathy in kidney transplants (65).

Given the paucity of available data, it is difficult to definitively establish a causal relationship between B19 and allograft rejection or dysfunction. Nevertheless, this does not exclude a role for this virus in such processes. It is possible that we have failed to recognize a pattern of renal injury associated with infection as a result of a lack of suspicion and inadequate testing. Large-scale studies that systematically test for parvovirus in allograft specimens would be beneficial but may not be practical.

**Screening**

There are no established guidelines for screening for B19 infection in organ transplant recipients. Although there is insufficient evidence for universal screening of all donors and recipients, there is evidence to support screening in patients who have moderate to severe anemia and for whom other causes of anemia have been excluded. In addition, the index of suspicion for this infection should be even greater during high-risk periods such as early after transplantation during the highest level of immunosuppression and after treatment for rejection. Increased vigilance is also required for pregnant transplant recipients (because of the risk of fetal complications associated with infection) and in patients with possible increased exposure related to occupation, including nurses, teachers, and child care providers.

**Diagnosis of B19 Infection**

The choice of diagnostic tests for detection of parvovirus must take into account the immunologic status of the patient (89). For most immunocompetent individuals, serologic testing for B19 virus–specific antibodies is most practical and is measured using enzyme immunoassays, which usually use recombinant capsid proteins (90). IgM antibodies directed to viral capsid antigens indicate acute infection, although, in some cases, these antibodies persist and can be detected for months. Previous infection is usually confirmed by detecting IgG antibodies toward viral capsid proteins in the absence of IgM antibody (27).

If only viral serologies are obtained, then the diagnosis of B19 infection can be missed in immunosuppressed patients who may not mount an antibody response. Furthermore, in organ transplant recipients, diagnosis by serology can be confounded by administration of blood products or Ig after transplantation, because these therapies may produce false-positive IgG antibody tests. Thus, identification of the viral DNA by PCR is preferred for diagnosis in these patients (91).

**Treatment**

Specific antiviral therapy is not available to treat B19 infection. The approach to therapy of infection depends on host factors such as immune status, underlying conditions, and manifestations of infection. Most cases of infection in immunocompetent hosts do not need treatment because the symptoms are transient, although nonsteroidal anti-inflammatory agents may be helpful in cases of arthropathy. Patients with transient aplastic crisis may need supportive therapy with blood transfusions until neutralizing antibody response can clear the virus and hematopoiesis is restored.

There are several options for the treatment of pure red cell aplasia and persistent infection in immunocompromised patients in whom B19-specific antibody response is absent or minimal. Commercial Ig (IVIG), a significant source of anti-B19 antibodies, has proved to be efficacious, although no controlled studies have been carried out (21,69,76,78–81,92,93). Various regimens have been reported with favorable outcomes, but on the basis of the pooled data, 400 mg/kg per d for 5 to 10 consecutive days seems to be clinically useful in most cases.
Although clinical response is common as evidenced by reticulocytosis, increased hemoglobin levels, and decline in serum viral DNA, complete eradication of viremia may not occur in some patients, particularly in transplant patients, who are highly immunosuppressed. Thus, relapses of anemia can occur up to several months after completion of treatment. Repeated administration of IVIG may be helpful, but some patients experience multiple relapses (79). Reduction of immunosuppressive mediation is often recommended in addition to IVIG (or without IVIG in less severe cases) to allow the patient's own immune response to mature and neutralize the virus (78,93–95).

Several reports have concluded that symptomatic B19 infection is linked specifically to the use of tacrolimus rather than the overall state of immunosuppression. This is based on observations that a switch from tacrolimus to cyclosporine was followed by viral clearance and complete resolution of anemia in some patients (78,96,97). Accordingly, some have suggested this change in drug regimen for infected recipients who fail to respond to IVIG. The mechanism for this difference, if it is real, remains unknown. Spontaneous recovery has also been reported in some patients without therapy (77,83).

Conclusions

Parvovirus B19 infection is associated with a wide spectrum of clinical manifestations, some of which are well established and some of which are controversial. The role of parvovirus infection as a trigger of glomerular disease has yet to be firmly established but deserves further attention because it may have implications in prevention strategies and treatment. The clinical significance of B19 infection in patients who have ESRD and are on hemodialysis is not clear, but this population may be vulnerable to transient aplastic crisis or chronic anemia as a result of viral infection. Although B19 infection is relatively uncommon in the renal transplant population, parvovirus B19 infection should be included in the differential diagnosis of moderate to severe unexplained anemia or pancytopenia in this population. B19 serology is of limited value for diagnosis, and PCR is better for confirmation of infection in immunocompromised patients. IVIG has been shown to be beneficial in transplant recipients with anemia associated with parvovirus infection, but relapses can occur. The combination of decreased immunosuppression and IVIG may promote viral clearance. The association of parvoviral infection with allograft rejection or dysfunction is not clearly established. Further studies are warranted to understand better the relationship between B19 infection and glomerular diseases and the impact of the disease in the ESRD and transplant populations.

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