

Donor-Derived West Nile Virus Infection in Solid Organ Transplant Recipients: Report of Four Additional Cases and Review of Clinical, Diagnostic, and Therapeutic Features

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We describe four solid-organ transplant recipients with donor-derived West Nile virus (WNV) infection (encephalitis 3, asymptomatic 1) from a common donor residing in a region of increased WNV activity. All four transplant recipients had molecular evidence of WNV infection in their serum and/or cerebrospinal fluid (CSF) by reverse transcription polymerase chain reaction (RT-PCR) testing. Serum from the organ donor was positive for WNV IgM but negative for WNV RNA, whereas his lymph node and spleen tissues tested positive for WNV by RT-PCR. Combination therapy included intravenous immunoglobulin (4 cases), interferon (3 cases), fresh frozen plasma with WNV IgG (2 cases), and ribavirin (1 case). Two of the four transplant recipients survived.

Review of the 20 published cases of organ-derived WNV infection found that this infection is associated with a high incidence of neuroinvasive disease (70%) and severe morbidity and mortality (30%). Median time to onset of symptomatic WNV infection was 13 days after transplantation (range 5–37 days). Initial unexplained fever unresponsive to antibiotic therapy followed by rapid onset of neurologic deficits was the most common clinical presentation. Confirmation of infection was made by testing serum and CSF for both WNV RNA by RT-PCR and WNV IgM by serological assays. Treatment usually included supportive care, reduction of immunosuppression, and frequent intravenous immunoglobulin. The often negative results for WNV by current RT-PCR and serological assays and the absence of clinical signs of acute infection in donors contribute to the sporadic occurrence of donor-derived WNV infection. Potential organ donors should be assessed for unexplained fever and neurological symptoms, particularly if they reside in areas of increased WNV activity.

Keywords: West Nile virus, Donor-derived infection.

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West Nile virus (WNV) is an arthropod-borne, single-stranded RNA flavivirus first observed in the United States in 1999 (1). Since 1999, WNV has emerged as the

most common cause of neuroinvasive arboviral disease in the continental United States (2). West Nile virus infection is usually transmitted by mosquitoes that acquire the virus from infected wild birds and then spread the virus to

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humans (3). Approximately 75% of WNV infections in humans are asymptomatic (4). However, 25% of humans develop a self-limiting febrile illness (West Nile fever), whereas less than 1% experience neuroinvasive disease manifested by encephalitis, meningitis, or acute flaccid paralysis (5, 6).

Transmission of WNV infection has also occurred through blood transfusion, breast-feeding, transplacental exposure, percutaneous injury in the laboratory, and conjunctival exposure to infected avian brain and body fluids (7–11). Transmission of WNV by organ transplantation was first reported in 2002 and appears to be associated with a high incidence of severe neuroinvasive disease (12, 13). Nonetheless, proven organ-derived WNV infection has generally been an uncommon, sporadic occurrence and can easily be overlooked in susceptible patients and their organ donors (14). Thus, we report four additional cases of organ-derived WNV infection. In addition, we summarize the clinical, diagnostic, and therapeutic features of organ-derived WNV infection based on these 4 cases and previously published cases of transplant recipients acquiring infection from a WNV-infected donor.

CASE REPORTS AND INVESTIGATION OF WNV TRANSMISSION

Organ Donor

In the early fall of 2011, a 56-year-old man with a history of cerebral palsy, developmental cognitive delay, blindness, and seizures, developed fever, muscle weakness, and an altered level of consciousness. He was seen in the emergency room of a local hospital, where he was noted to be confused and uncooperative. He was started on an oral antibiotic for a possible urinary tract infection and sent home. Final urine and blood cultures were negative. Three days later, he became progressively more lethargic and developed a severe cough and choking spells. Paramedics were called to his home and found him unresponsive and in cardiopulmonary arrest. After intubation and cardiopulmonary resuscitation, he was transported to another different local hospital. He was admitted to the intensive care unit, placed on a ventilator, and given broad-spectrum antibiotics for possible sepsis. Neurologic exam revealed unresponsiveness, absent corneal reflexes, and no spontaneous movements. Blood and urine cultures were negative. Computed tomography (CT) scan of the brain showed decrease in gray matter and mild cortical edema. Electroencephalogram showed no cortical activity consistent with brain death. A lumbar puncture or other studies for central nervous system infection were not performed. On hospital day 7, after permission from the patient's mother was obtained, organ procurement occurred.

Patient 1 (Left Kidney Recipient)

A 59-year-old man, with end-stage renal disease due to diabetic nephropathy and requiring chronic hemodialysis, received the left donor kidney in hospital A. Baseline immunosuppressive therapy consisted of alemtuzumab and corticosteroids, followed by tacrolimus plus mycophenolate. After initial slow recovery of kidney graft function requiring posttransplantation hemodialysis, the patient was discharged

home on day+5 after transplantation. On day+10, the patient was readmitted to the hospital for fever, myalgias, and diarrhea. Cultures were negative, and the fevers persisted despite treatment with antibiotics. On day+13, the patient developed lethargy, encephalopathy, tachypnea, and hypotension. He was transferred to the intensive care unit and given additional broad-spectrum antibiotics for possible sepsis. On day+14, tests of cerebrospinal fluid (CSF) revealed 698 RBC/mm³, 38 WBC/mm³ with 69% neutrophils, protein of 92 mg/dL, and glucose of 44 mg/dL. He was treated with high-dose intravenous acyclovir, ampicillin, and doxycycline. On day+15, patient experienced new left-sided weakness followed by coma. Magnetic resonance imaging (MRI) of the brain showed evidence of a subacute stroke in the left pons. On day+16, when CSF WNV polymerase chain reaction (PCR) was reported positive for WNV, the dosages of immunosuppressive drugs were reduced. Other CSF viral tests were negative. The United Network for Organ Sharing (UNOS) and Donor Network were immediately contacted on day+16 regarding possible donor-derived encephalitis. Retrospective testing of CSF for WNV IgM was negative, whereas the serum WNV PCR was positive (Table 1). The patient was treated with polyvalent intravenous immunoglobulin (500 mg/kg per day from day+15 to day+19) plus subcutaneous interferon alfa-2b (3 million units per day from day+19 to day+22). However, the patient remained in a coma and developed status epilepticus. On day+23, care was withdrawn. Autopsy was declined.

Patient 2 (Right Kidney Recipient)

A 51-year-old man on hemodialysis for end-stage renal disease due to hypertension received the right donor kidney in hospital A. Baseline immunosuppressive therapy consisted of thymoglobulin and corticosteroids followed by tacrolimus plus mycophenolate. He was discharged home on day+5 after transplantation but required posttransplantation dialysis because of delayed kidney graft function. On day+17, he was readmitted to the hospital for fever. Because of the awareness of WNV encephalitis in the other kidney recipient, lumbar puncture was performed. Tests of the CSF revealed 355 RBC/mm³, 11 WBC/mm³ with 79% neutrophils, and protein of 29 mg/dL. On day+19, he developed headaches and disorientation in addition to persistent fever. When both the CSF and serum WNV PCR were reported positive (Table 1), his tacrolimus was discontinued. Testing for WNV IgM was negative for the CSF but positive for the serum (Table 1). He was treated with polyvalent intravenous immunoglobulin (500 mg/kg per day from day+18 to day+21) plus subcutaneous interferon alfa-2b (3 million units per day from day+18 day+28). He also received infusions of fresh frozen plasma containing WNV IgG on 3 consecutive days. His fever resolved, and his mental status returned to normal. On day+30, tacrolimus was restarted, and the patient was discharged home. He had no residual neurologic deficits. He subsequently developed chronic rejection and is being evaluated for repeat kidney transplantation.

Patient 3 (Bilateral Lung Recipient)

A 59-year-old man with interstitial pneumonitis received both donor lungs in hospital B. Baseline immunosuppression consisted of basiliximab, corticosteroids, and

TABLE 1. WNV testing in organ donor and transplant recipients in our cluster. Arizona and California, 2011

Patient	Day posttransplant	Serum results			CSF results			Other results
		PCR	IgM	IgG	PCR	IgM	IgG	
Donor		Negative	Positive	Positive				Lymph node-PCR positive spleen-PCR positive
Left kidney recipient	Pre	Negative	Negative	Negative				
	+14				Positive	Negative		
	+18	Positive						
Right kidney recipient	Pre	Negative	Negative	Negative				
	+16	Negative	Positive	Negative	Positive			
	+17				Positive	Negative		
	+18	Positive						
Bilateral lung recipient	Pre		Negative	Positive				
	+20	Negative	Negative	Negative				
	+21	Positive	Negative	Negative				
	+23				Positive	Negative		
	+24					Negative	Negative	
	+28	Positive				Positive	Positive	
Liver recipient	Pre	Negative	Negative					
	+17 ^a	Negative	Negative	Positive				
	+21				Positive	Negative		
	+29							Liver tissue-PCR negative

^a Plasma.

WNV, West Nile virus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction with NAAT or TaqMan; IgM and IgG by enzyme-linked immunosorbent assay or microsphere-based immunoassay.

mycophenolate, followed by tacrolimus, corticosteroids, and mycophenolate. His initial posttransplantation course was uncomplicated, and he was discharged home on day+10 after transplantation. On day+13, he was readmitted to the hospital for dyspnea and hypoxemia. He was given diuretics for fluid overload and high-dose corticosteroids for presumed acute cellular rejection. There was partial improvement in his clinical condition. On day+20, the patient developed encephalopathy, right upper-extremity weakness, and respiratory distress requiring intubation. When the transplant physicians were notified of the WNV infections in the two kidney recipients from the same donor, the dosages of immunosuppressive drugs were reduced. On day+22, tests of CSF revealed 7 RBC/mm³, 1 WBC/mm³, protein of 48 mg/dL, and glucose of 67 mg/dL. CSF was positive for WNV RNA by PCR and WNV IgM by enzyme-linked immunosorbent assay (ELISA) (Table 1). Serum WNV PCR was also positive. MRI of the brain and spine showed diffuse leptomeningeal and cauda equina enhancement. The patient was treated with polyvalent intravenous immunoglobulin (500 mg/kg per day on days 20, 22, 23, 25, 26, and 31 posttransplantation; Privigen, CSL Behring, King of Prussia, PA or Gamunex, Grifols Therapeutics, Clayton, NC) plus subcutaneous interferon alpha-2b (6 million units on day 20 posttransplantation, 3 million units per day on days 21, 22, 23, 31, and 32 posttransplantation, and then 1 million units per day on days 33, 34, and 35 posttransplantation). Despite these therapies, the patient developed complete flaccid paralysis and multiple seizures. He expired on day+38. Autopsy revealed severe encephalomyelitis.

Patient 4 (Liver Recipient)

A 63-year-old man with end-stage liver disease due to alcoholic cirrhosis and hepatocellular carcinoma received the donor liver in hospital C. The patient was feeling well before transplantation and had a model for end-stage liver disease (MELD) score of 33. Baseline immunosuppression was tacrolimus, corticosteroids, and mycophenolate. The liver transplant surgery was complicated because of multiple adhesions, postperfusion coagulopathy, and severe hemorrhage requiring multiple transfusions (50 units of packed red blood cells, 50 units of fresh frozen plasma). The initial posttransplantation course was further complicated by delayed graft function, renal failure, and pulmonary edema. On day+18, the patient developed fever and transient confusion associated with an *E. coli* urinary tract infection treated successfully with piperacillin-tazobactam. However, when the transplant physicians were notified of WNV infection in the two kidney recipients from the same donor, an investigation for WNV infection was initiated. Plasma from day+17 was positive for WNV IgG but negative for WNV IgM by ELISA and WNV RNA by PCR (Table 1). On day+19, tests of CSF showed 11 RBC/mm³, 1 WBC/mm³, protein of 43 mg/dL, and glucose of 74 mg/dL. Cerebrospinal fluid WNV PCR was positive, but the CSF WNV IgM was negative (Table 1). Computed tomographic scan of the brain showed mild generalized cerebral atrophy. Patient was subsequently treated with oral ribavirin (600 mg every 12 hours) plus polyvalent intravenous immunoglobulin (500 mg/kg daily for 4 doses and then 500 mg/kg every other day from day+18 to day+40; Privigen). On day+27, patient underwent

a second liver transplant surgery for delayed nonfunction of the first graft. WNV RT-PCR testing on tissue from the first liver graft was negative. During the next 8 weeks, patient had a prolonged hospital course with slow recovery of liver graft function and ongoing need for hemodialysis. He never developed any clinical symptoms or signs of encephalitis or meningitis. He was finally discharged to a rehabilitation facility and then returned home. The patient's renal function improved, and he is doing well with excellent liver graft function.

Investigation and Reporting of WNV Transmission

When physicians in hospital A notified UNOS and the Donor Network of possible donor-derived encephalitis in the left kidney transplant recipient, the health-care providers for the other recipients of organs from the same donor were immediately informed on the same day of this likely donor-derived central nervous system infection. A public health investigation was also initiated to coordinate WNV testing of these other recipients, to review the donor's history for WNV risk factors, and to test stored serum and tissues for WNV (15).

By late summer 2011, the donor's county of residence had the highest number of confirmed cases of human WNV infection as well as the greatest amount of WNV nonhuman surveillance activity within the state. The organ donor had no history of receipt of blood products before his hospitalization. The donor's mother did not recall any definite mosquito bites but stated that the doors and windows of their non-air conditioned home were frequently left open and were not fitted with screens. The donor occasionally spent time sitting in a nearby park.

Testing of the organ donor for WNV infection was not performed as part of the organ donor screening process. However, retrospective postdonation testing of the donor's serum by the CDC was positive for both WNV IgM by microsphere-based immunoassay (MIA) and WNV IgG by ELISA (Table 1) (16, 17). The donor's serum WNV plaque reduction neutralization antibody titer was positive at 1:160 (18). Taqman reverse transcriptase-PCR testing of stored donor's serum obtained at time of donation was negative for WNV, but similar PCR testing on the donor's lymph nodes and spleen homogenate by the CDC was positive for WNV RNA (19).

None of the four transplant recipients had a recent febrile illness before transplantation. Retrospective testing by WNV TaqMan reverse transcriptase-PCR of stored pretransplantation serum by the CDC was negative for the two kidney recipients and the liver recipient (Table 1). The lung recipient's pretransplantation serum was not available for PCR testing. Tests of pretransplantation serum for WNV IgM in the two kidney recipients and the liver recipient by the CDC (by MIA) and in the lung recipient by a local laboratory (by ELISA) were all negative.

REVIEW OF CLINICAL, DIAGNOSTIC, AND THERAPEUTIC FEATURES OF DONOR-DERIVED WNV INFECTION

There have been seven other published reports of WNV infection transmitted by solid-organ transplantation

(13, 20–26). One unpublished report of a donor-derived cluster of WNV infection among solid-organ transplant recipients has also been noted, but no data are provided for analysis (27). The characteristics of the eight published organ donors transmitting WNV infection are summarized in Table 2. All the organ donors were adults. Six donors resided in areas of increased WNV activity and most likely acquired their infection by a mosquito bite. Two donors had WNV infection from a previous blood transfusion. Except for the organ donor with cerebral palsy and a recent febrile illness described in the present report, none of the organ donors had any symptoms or signs of infection at the time of donation. Testing for WNV infection before organ donation was done in only one of the eight donors. Because of a high level of WNV infection in northeastern Italy, the Italian National Transplant Network instituted a surveillance program in 2008 to detect WNV in organ donors in northeastern Italy (24, 25). However, the blood of this tested organ donor was negative for WNV by nucleic acid amplification (NAT). In contrast, WNV testing of deceased organ donors in the United States is currently not required (28) and, therefore, was not done in the other six donors who

TABLE 2. Characteristics of published organ donors transmitting WNV infection

Characteristic	
No. of donors	8
Age	
Mean (range), yr	46 (18–78)
Median (range), yr	43 (18–78)
Sex	
Male	4
Female	3
Not reported	1
Mode of WNV acquisition	
Mosquito	6
Blood transfusion	2
Residence in area of increased WNV activity	
Yes	6
No	2
Medical condition leading to organ donation	
Trauma	4
Cerebral hemorrhage	2
Gunshot wound	1
Cerebral palsy, febrile illness	1
WNV testing before donation	
No	7
Yes ^a	1
Retrospective WNV testing ^b	
Positive serum PCR	4/8
Positive serum IgM	3/8
Positive serum IgG	4/6
Positive tissue PCR (lymph node, spleen)	1/1

^a Tested negative by NAT, nucleic acid amplification.

^b No. of donors positive/No. of donors tested.

WNV, West Nile virus; PCR, polymerase chain reaction.

lived in the United States or in another Italian donor before organ procurement (22). Retrospectively, only four (50%) of the eight donors tested positive for WNV by serum PCR, and only three of the eight donors (38%) tested positive for serum WNV IgM.

A total of 23 transplant recipients receiving organs from donors infected with WNV have been published (13, 20–26). Twenty of these transplant recipients (87%) became infected with WNV. One kidney recipient, one liver recipient, and one heart recipient each tested negative for WNV after transplantation by either serum PCR or serologic tests and remained asymptomatic. The clinical characteristics of the 20 published cases of transplant recipients with donor-derived WNV infection are summarized in Table 3. The median age was 52 years. Fifteen of the 20 recipients had received either donor kidney, or liver, organs. Baseline immunosuppressive agents usually included tacrolimus and corticosteroids. Seven recipients had received antilymphocyte antibodies (antithymocyte globulin, thymoglobulin, basiliximab, or alemtuzumab). The median time from transplantation to onset of symptoms was 13 days. Fourteen of the 20 transplant recipients (70%) developed encephalitis, one had WNV fever, and 5 remained asymptomatic. The most common initial presentation of infection was fever and constitutional symptoms (myalgias, arthralgias, fatigue, or diarrhea) usually unresponsive to empiric antibiotic therapy and associated with negative bacterial cultures. Only five patients had neurological symptoms (encephalopathy, altered mental status, or seizure) as part of the initial presentation of their WNV infection. On the other hand, patients developing encephalitis subsequently experienced altered mental status and frequent rapid onset of neurological deficits causing dysarthria, flaccid paralysis, seizures, and coma. The diagnosis of WNV infection was usually confirmed by testing of both serum and CSF for WNV RNA and/or WNV IgM. WNV RNA was detected in the serum of 10 (83%) of 12 tested patients, whereas serologic testing of serum for WNV IgM was positive in 15 (83%) of 18 tested patients.

Cerebrospinal fluid findings in the published cases of donor-derived WNV central nervous system infection in transplant recipients are summarized in Table 4. The mean CSF WBC was minimally elevated (86 WBC/mm³), with a predilection toward polymorphonuclear pleocytosis (mean % of polymorphonuclear cells of 62%). The CSF protein was slightly increased (mean protein of 88 mg/dL), whereas the CSF glucose was usually in the normal range (mean glucose of 65 mg/dL, range of 44–105 mg/dL). The CSF WNV PCR was positive in 6 (75%) of 8 tested patients, whereas serological testing of CSF for WNV IgM was positive in 10 of 14 tested patients (71%).

Results of MRI of the brain were reported in six transplant recipients with WNV encephalitis and were abnormal in four patients. Abnormalities reported were diffuse restriction of the internal capsule; increased signal in the thalamus, basal ganglia, white matter, and brain stem; subacute stroke involving the pons; and diffuse leptomeningeal enhancement. Results of CT scan of the brain in 3 transplant recipients with asymptomatic WNV infection were unremarkable.

TABLE 3. Clinical characteristics of published transplant recipients with donor-derived WNV infection

Characteristic (No. of recipients with data)	
No. of transplant recipients	20
Age (14)	
Mean (range), yr	52 (25–73)
Median (range), yr	52 (25–73)
Sex (20)	
Male	10
Female	4
Not reported	6
Type of transplant (20)	
Kidney	9
Liver	6
Lung	3
Heart	2
Immunosuppressive agents (13)	
Tacrolimus	12
Corticosteroids	11
Mycophenolate	10
Antilymphocyte antibodies	7
Cyclosporine	1
Sirolimus	1
Days from transplant to symptoms (15)	
Mean (range), d	14 (5–37)
Median (range), d	13 (5–37)
Clinical WNV diagnosis (20)	
Encephalitis	14
WNV fever	1
Asymptomatic	5
Initial symptoms (15)	
Fever, constitutional symptoms	10
Fever, dyspnea	1
Fever, altered mental status	1
Altered mental status	1
Encephalopathy	2
Seizures	1
Neurological symptoms in patients with WNV encephalitis (11)	
Altered mental status	11
Dysarthria	4
Lower extremity weakness	4
Flaccid paralysis	5
Hemiparesis	2
Facial nerve palsy	1
Seizures	4
Coma	8
WNV testing of serum	
Positive serum PCR	10/12 ^a
Positive serum IgM	15/18
Positive serum IgG	5/8
Positive tissue PCR (brain)	2/2

^a No. of transplant recipients positive/no. of transplant recipients tested. WNV, West Nile virus; PCR, polymerase chain reaction.

TABLE 4. Cerebrospinal fluid findings in published transplant recipients with donor-derived WNV infection of central nervous system

Parameter	No. of patients tested	Result
Mean RBC count/mm ³ (range)	5	227 (2–698)
Mean WBC count/mm ³ (range)	11	86 (0–675)
Mean % of PMN (range)	7	62% (24%–92%)
Mean protein, mg/dl (range)	11	88 (29–149)
Mean glucose, mg/dl (range)	7	65 (44–105)
Positive WNV PCR, No. positive/No. tested (%)	8	6/8 (75%)
Positive WNV IgM No. positive/No. tested (%)	14	10/14 (71%)
Positive WNV IgG No. positive/No. tested (%)	6	3/6 (50%)

WNV, West Nile virus; RBC, red blood cell count; WBC, white blood cell count; PMN, polymorphonuclear neutrophil; PCR, polymerase chain reaction.

The treatment regimens used in the published cases of donor-derived WNV infections are summarized in Table 5. Six (30%) of the 20 patients expired or were reported in coma. The most common treatment was intravenous immunoglobulin. Both polyvalent intravenous immunoglobulin (Privigen, Gamunex, and other products) and a hyperimmune intravenous immunoglobulin with high antibody-titers against WNV (Omr-IgG-am, Omrix Biopharmaceutical Ltd, Kiryat-Ono, Israel) were used. Three (43%) of seven transplant recipients with WNV encephalitis treated with an intravenous immunoglobulin alone or in combination with interferon or fresh frozen plasma containing WNV IgG improved. On the other hand, five (71%) of seven transplant recipients with encephalitis and receiving only supportive care also improved. All four transplant recipients receiving intravenous immunoglobulin for asymptomatic WNV infection remained asymptomatic and never developed neuroinvasive disease. Only one of three transplant recipients treated with interferon survived.

DISCUSSION

This report describes the transmission of WNV infection through organ transplantation to a cluster of four solid-organ transplant recipients from a common organ donor, who probably recently acquired the infection by a mosquito bite in a geographic area of increased WNV activity. Both the organ donor and all four organ transplant recipients had molecular evidence of WNV infection in various clinical samples (Table 1). WNV RNA was not detectable in the donor's pretransplant serum but was found in the donor's lymph nodes and spleen. The organ donor had also experienced a recent acute febrile illness. In contrast, all four transplant recipients had been afebrile and clinically stable before transplantation. The two kidney recipients and the lung recipient subsequently developed WNV encephalitis within the first 3 weeks after transplantation, whereas the liver recipient had detectable asymptomatic WNV central nervous system infection very early after transplantation.

Encephalitis and other central nervous system infections within the first month after solid-organ transplantation are very uncommon (29). The early occurrence of encephalitis in the left kidney transplant recipient in this report alerted the transplant physicians of possible donor-derived infection. Immediate reporting of this index case to public health authorities and the Organ Procurement and Transplantation Network (OPTN) facilitated the prompt initiation of diagnostic and therapeutic procedures in the other patients.

Overall, in published reports, 87% of persons receiving organs from WNV-infected donors became infected with WNV. Seventy percent of the infected transplant recipients developed encephalitis, whereas only 25% remained asymptomatic. This high incidence of neuroinvasive disease is much greater than the less than 1% incidence of neuroinvasive disease in immunocompetent people infected with WNV by a mosquito bite (5, 6). Furthermore, 30% of the patients with organ-derived WNV infection either expired or were reported in coma. This high morbidity and mortality rate is similar to the 18% mortality rate among transplant patients with naturally acquired WNV encephalomyelitis (30). Among nonimmunocompromised persons with WNV infection, the mortality rate is less than 1% (2).

The most common initial clinical presentation of symptomatic donor-derived WNV infection in transplant recipients is fever plus constitutional symptoms associated with negative routine cultures and unresponsive to antibiotic therapy within the first month after transplantation. Although 70% of patients eventually develop encephalitis, only 33% have neurologic symptoms at the time of their initial clinical presentation (Table 3). Studies of the CSF in those patients with neuroinvasive WNV disease usually show only a modest

TABLE 5. Treatment regimens for donor-derived WNV infection in transplant recipients^a

	No. improved/No. treated
Encephalitis (N=14 patients)	
Supportive care	5/7
IV immunoglobulin alone	1/3
IV immunoglobulin, fresh frozen immune plasma	1/1
IV immunoglobulin, fresh frozen immune plasma, interferon	1/1
IV immunoglobulin, interferon	0/2
WNV fever (N=1 patient)	
Supportive care	1/1
Asymptomatic (N=5 patients)	
IV immunoglobulin alone	2/2
IV immunoglobulin, fresh frozen immune plasma	1/1
IV immunoglobulin, ribavirin	1/1
Supportive care	1/1

^a IV immunoglobulin (polyvalent=6, Omr-IgG-am with high titer WNV antibodies=5).

Fresh frozen immune plasma with WNV IgG antibodies.

Interferon (interferon alfa-2b, subcutaneous).

WNV, West Nile virus.

pleocytosis with a predominance of polymorphonuclear cells, a mild elevation of CSF protein, and a normal CSF glucose. The CSF WBC counts in these transplant patients with donor-derived WNV encephalitis (mean CSF WBC of 86 cells/mm³) are minimally elevated compared with the CSF cell counts in immunocompetent patients with WNV encephalitis (mean CSF WBC of 227 cells/mm³) but are similar to the CSF WBC counts in transplant patients with naturally acquired WNV encephalitis (mean CSF WBC of 89 cells/mm³) (30, 31). On the other hand, there seems to be no significant difference in the CSF protein and glucose concentrations between transplant patients with encephalitis and immunocompetent patients with encephalitis (31).

The diagnosis of donor-derived WNV infection in solid-organ transplant patients requires a high index of clinical suspicion in any patient who develops unexplained fever followed by neurologic symptoms during the early posttransplantation period. Confirmation of the diagnosis of WNV infection is usually made by testing both serum and CSF for WNV IgM antibodies by serological assays and for WNV RNA by nucleic acid amplification (NAT) assays (Table 3). Various NAT tests have been developed for WNV, including RT-PCR and nucleic acid sequence-based amplification (19, 32). Although these NAT assays can be useful for acute infection, their results can become negative later in the course of symptomatic disease when viral-specific antibodies are detectable (33, 34). The production of WNV IgM antibodies commonly follows the decline in WNV viremia but may be blunted in patients with defective humoral immunity (35). Some WNV serologic tests may also cross react with other flavivirus antigens. A positive IgM result by ELISA or microsphere assay can be confirmed by a plaque reduction neutralization test specific for WNV (18).

There is no treatment of proven benefit for WNV infection. Supportive care and temporary reduction in immunosuppressive agents have been common approaches. Recently, favorable results with intravenous immunoglobulin or pooled immune plasma containing WNV antibodies have been described in animal models and in some cases of human infection (22, 23, 36–42). Efficacy appears greatest when an immunoglobulin preparation or pooled immune plasma containing very high titers of anti-WNV antibodies is administered early in the course of infection before severe neuroinvasive disease develops. In our review of transplant recipients with donor-derived WNV infection, three (43%) of seven patients with encephalitis treated with intravenous immunoglobulin alone or with fresh frozen plasma containing WNV IgG improved, whereas all four patients with asymptomatic WNV infection treated with intravenous immunoglobulin or plasma survived. However, there are no results available from controlled trials to determine what proportion of infected patients would have developed disease had they not received antibody therapy. Furthermore, five of seven transplant recipients (71%) with encephalitis and receiving only supportive care also improved. Of note, the liver transplant recipient with asymptomatic CNS WNV infection in this report received massive amounts of fresh frozen plasma during the transplant surgery and was seropositive for WNV IgG after transplantation (Table 1). Thus, it is possible that he may have received WNV IgG antibodies

in the fresh frozen plasma transfusions which ameliorated his WNV infection (43).

Both interferon and ribavirin have *in vitro* antiviral activity for WNV (44). Several case reports of the successful treatment of WNV meningoencephalitis with interferon in nontransplant patients have been published (45–47). In a small randomized unblinded trial of alpha interferon therapy (3 million units subcutaneously each day for 14 days) for WNV encephalitis in immunocompetent patients, interferon treated patients had greater neurologic improvement compared with untreated patients but also more toxicity (neutropenia, hepatitis) (48). Only one of the three transplant patients in this report with organ-derived WNV encephalitis treated with interferon survived (Table 5), but there was no apparent toxicity. Ribavirin, which shows *in vitro* activity for WNV only at very high concentrations and has limited penetration into the CSF, had no significant benefits in either animal models or in normal hosts with WNV infection (49, 50). The liver transplant recipient in this report received oral ribavirin for 3 weeks plus intravenous immunoglobulin and survived. The use of ribavirin and interferon for WNV infection requires further study.

To avoid the potential morbidity and mortality associated with donor-derived WNV infection, identification of potentially infected organ donors is necessary. For living organ donors, HRSA and OPTN recommend screening for WNV as close to the time of donation as possible (28, 51). On the other hand, because of concerns about false-positive screening results using NAT and potential loss of organs, routine screening of deceased organ donors for WNV is not recommended (27, 28, 51). Furthermore, it is not known if WNV screening would necessarily decrease transmission of WNV infection. Indeed, only four of the eight organ donors associated with published cases of organ-derived WNV infection tested positive for WNV infection in their serum by NAT (Table 2). In the one case in Italy where the organ donor was screened for WNV at time of organ donation, the patient's serum tested negative for WNV by NAT (24). The organ donor described in this report had WNV RNA in his lymph nodes and spleen, although retrospective testing of his serum for WNV by NAT and reverse transcription PCR was negative. Thus, current laboratory methods for WNV screening of organ donors appear inadequate. Seven of the eight organ donors associated with published cases of organ-derived WNV infections had no clinical features of WNV disease; however, one donor had a recent febrile illness and mental status changes (Table 2). Potential organ donors with unexplained fever and neurologic symptoms should be thoroughly evaluated for meningoencephalitis, including testing of CSF for WNV and other potential pathogens (52, 53). Deferring donors with fever and neurologic symptoms of uncertain etiology should be considered (53). The risk of transmission of a donor-derived infection must be balanced with the risk of a poor recipient outcome if the donor is not used. Potential organ recipients also need to be advised of the possible risk of donor-derived WNV infection even when a high-risk donor tests negative for WNV.

In summary, organ-derived WNV infection is associated with a high incidence of neuroinvasive disease. Diagnosis requires a high index of clinical suspicion in a

transplant recipient with fever and neurologic symptoms within the first month after transplantation. WNV infection is confirmed by testing both serum and CSF for WNV RNA and IgM antibody. As there is no specific antiviral treatment available, treatment remains supportive; reduction in immunosuppressive agents and the use of IV IgG and interferon have been reported in the literature, but there is no proven efficacy. Prompt reporting of cases of donor-derived WNV infection to public authorities can facilitate the diagnosis and treatment in other transplant recipients at risk for infection. Data are lacking regarding the sensitivity and specificity of available WNV tests when used to screen deceased organ donors, and screening of deceased organ donors for WNV is currently not required in the United States. However, considering deferral of organ donors with recent fever and unexplained neurologic symptoms, especially in areas with known WNV activity, may decrease the risk of WNV transmission from an infected organ donor.

REFERENCES

- Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001; 344: 1807.
- Lindsey NP, Staples JE, Lehman JA, et al. Surveillance for human West Nile virus disease - United States, 1999–2008. *MMWR Surveill Summ* 2010; 59: 1.
- Colpitts TM, Conway MJ, Montgomery RR, et al. West Nile Virus: biology, transmission, and human infection. *Clin Microbiol Rev* 2012; 25: 635.
- Zou S, Foster GA, Dodd RY, et al. West Nile fever characteristics among viremic persons identified through blood donor screening. *J Infect Dis* 2010; 202: 1354.
- Mostashari F, Bunning ML, Kitsutani PT, et al. Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey. *Lancet* 2001; 358: 261.
- Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection. *JAMA* 2003; 290: 511.
- Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med* 2003; 349: 1236.
- Centers for Disease C, Prevention. Possible West Nile virus transmission to an infant through breast-feeding—Michigan, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51: 877.
- Centers for Disease C, Prevention. Interim guidelines for the evaluation of infants born to mothers infected with West Nile virus during pregnancy. *MMWR Morb Mortal Wkly Rep* 2004; 53: 154.
- From the Centers for Disease Control and Prevention. Laboratory-acquired West Nile virus infections—United States, 2002. *JAMA* 2003; 289: 414.
- Fonseca K, Prince GD, Bratvold J, et al. West Nile virus infection and conjunctival exposure. *Emerg Infect Dis* 2005; 11: 1648.
- Centers for Disease C, Prevention. Update: Investigations of West Nile virus infections in recipients of organ transplantation and blood transfusion—Michigan, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51: 879.
- Iwamoto M, Jernigan DB, Guasch A, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003; 348: 2196.
- Singh N, Levi ME, Practice ASTIDCo. Arenavirus and West Nile virus in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4): 361.
- Blau DM, Rabe IR, Bhatnagar J, et al. West Nile virus RNA in tissues from donor associated with transmission to organ transplant recipients. *Emerging Infectious Diseases* 2013; 19: 1518.
- Hogrefe WR, Moore R, Lape-Nixon M, et al. Performance of immunoglobulin G (IgG) and IgM enzyme-linked immunosorbent assays using a West Nile virus recombinant antigen (preM/E) for detection of West Nile virus- and other flavivirus-specific antibodies. *J Clin Microbiol* 2004; 42: 4641.
- Johnson AJ, Cheshier RC, Cosentino G, et al. Validation of a microsphere-based immunoassay for detection of anti-West Nile virus and anti-St. Louis encephalitis virus immunoglobulin m antibodies. *Clin Vaccine Immunol* 2007; 14: 1084.
- Lindsey HS, Calisher CH, Mathews JH. Serum dilution neutralization test for California group virus identification and serology. *J Clin Microbiol* 1976; 4: 503.
- Lanciotti RS, Kerst AJ, Nasci RS, et al. Rapid detection of west nile virus from human clinical specimens, field-collected mosquitoes, and avian samples by a TaqMan reverse transcriptase-PCR assay. *J Clin Microbiol* 2000; 38: 4066.
- Centers for Disease C, Prevention. West Nile virus infections in organ transplant recipients—New York and Pennsylvania, August–September, 2005. *MMWR Morb Mortal Wkly Rep* 2005; 54: 1021.
- Centers for Disease C, Prevention. West Nile virus transmission via organ transplantation and blood transfusion - Louisiana, 2008. *MMWR Morb Mortal Wkly Rep* 2009; 58: 1263.
- Morelli MC, Sambri V, Grazi GL, et al. Absence of neuroinvasive disease in a liver transplant recipient who acquired West Nile virus (WNV) infection from the organ donor and who received WNV antibodies prophylactically. *Clin Infect Dis* 2010; 51: e34.
- Rhee C, Eaton EF, Concepcion W, et al. West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature. *Transpl Infect Dis* 2011; 13: 312.
- Costa AN, Capobianchi MR, Ippolito G, et al. West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011. *Euro Surveill* 2011; 16.
- Inojosa WO, Scotton PG, Fuser R, et al. West Nile virus transmission through organ transplantation in north-eastern Italy: a case report and implications for pre-procurement screening. *Infection* 2012; 40: 557.
- Rabe IB, Schwartz BS, Farnon EC, et al. Fatal transplant-associated west nile virus encephalitis and public health investigation-california, 2010. *Transplantation* 2013; 96: 463.
- Nett RJ, Kuehnert MJ, Ison MG, et al. Current practices and evaluation of screening solid organ donors for West Nile virus. *Transpl Infect Dis* 2012; 14: 268.
- HRSA. A special announcement from HRSA regarding West Nile virus. Available at: <http://optn.transplant.hrsa.gov/news/newsDetail.asp?id=303>. Accessed January 9, 2004.
- Fishman JA. Introduction: infection in solid organ transplant recipients. *Am J Transplant* 2009; 9(Suppl 4): S3.
- Kleinschmidt-DeMasters BK, Marder BA, Levi ME, et al. Naturally acquired West Nile virus encephalomyelitis in transplant recipients: clinical, laboratory, diagnostic, and neuropathological features. *Arch Neurol* 2004; 61: 1210.
- Tyler KL, Pape J, Goody RJ, et al. CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. *Neurology* 2006; 66: 361.
- Lanciotti RS, Kerst AJ. Nucleic acid sequence-based amplification assays for rapid detection of West Nile and St. Louis encephalitis viruses. *J Clin Microbiol* 2001; 39: 4506.
- Zhang W, Wu J, Li Y, et al. Rapid and accurate in vitro assays for detection of West Nile virus in blood and tissues. *Trans Med Rev* 2009; 23: 146.
- Busch MP, Kleinman SH, Tobler LH, et al. Virus and antibody dynamics in acute west nile virus infection. *J Infect Dis* 2008; 198: 984.
- Levi ME, Quan D, Ho JT, et al. Impact of rituximab-associated B-cell defects on West Nile virus meningoencephalitis in solid organ transplant recipients. *Clin Transplant* 2010; 24: 223.
- Engle MJ, Diamond MS. Antibody prophylaxis and therapy against West Nile virus infection in wild-type and immunodeficient mice. *J Virol* 2003; 77: 12941.
- Ben-Nathan D, Gershoni-Yahalom O, Samina I, et al. Using high titer West Nile intravenous immunoglobulin from selected Israeli donors for treatment of West Nile virus infection. *BMC Infect Dis* 2009; 9: 18.
- Ben-Nathan D, Lustig S, Tam G, et al. Prophylactic and therapeutic efficacy of human intravenous immunoglobulin in treating West Nile virus infection in mice. *J Infect Dis* 2003; 188: 5.
- Shimoni Z, Niven MJ, Pitlick S, et al. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. *Emerg Infect Dis* 2001; 7: 759.
- Saquist R, Randall H, Chandrakantan A, et al. West Nile virus encephalitis in a renal transplant recipient: the role of intravenous immunoglobulin. *Am J Kidney Dis* 2008; 52: e19.

41. Makhoul B, Braun E, Herskovitz M, et al. Hyperimmune gammaglobulin for the treatment of West Nile virus encephalitis. *Israel Med Assoc J* 2009; 11: 151.
42. Camenga DL, Nathanson N, Cole GA. Cyclophosphamide-potentiated West Nile viral encephalitis: relative influence of cellular and humoral factors. *J Infect Dis* 1974; 130: 634.
43. Planitzer CB, Modrof J, Yu MY, et al. West Nile virus infection in plasma of blood and plasma donors, United States. *Emerg Infect Dis* 2009; 15: 1668.
44. Anderson JF, Rahal JJ. Efficacy of interferon alpha-2b and ribavirin against West Nile virus in vitro. *Emerg Infect Dis* 2002; 8: 107.
45. Sayao AL, Suchowersky O, Al-Khathaami A, et al. Calgary experience with West Nile virus neurological syndrome during the late summer of 2003. *Can J Neurol Sci* 2004; 31: 194.
46. Kalil AC, Devetten MP, Singh S, et al. Use of interferon-alpha in patients with West Nile encephalitis: report of 2 cases. *Clin Infect Dis* 2005; 40: 764.
47. Lewis M, Amsden JR. Successful treatment of West Nile virus infection after approximately 3 weeks into the disease course. *Pharmacotherapy* 2007; 27: 455.
48. Gea-Banacloche J, Johnson RT, Bagic A, et al. West Nile virus: pathogenesis and therapeutic options. *Ann Intern Med* 2004; 140: 545.
49. Morrey JD, Smee DF, Sidwell RW, et al. Identification of active antiviral compounds against a New York isolate of West Nile virus. *Antiviral Res* 2002; 55: 107.
50. Chowers MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* 2001; 7: 675.
51. Kiberd BA, Forward K. Screening for West Nile virus in organ transplantation: a medical decision analysis. *Am J Transplant* 2004; 4: 1296.
52. OPTN. Identifying risk factors for West Nile virus (WNV) during evaluation of potential living donors. Available at: http://optn.transplant.hrsa.gov/SharedContentDocuments/West_Nile_Virus_Living_Donors.pdf. Accessed June 25, 2013.
53. OPTN. Guidance for recognizing central nervous system infections in potential deceased organ donors: what to consider during donor evaluation and organ offers. Available at: http://optn.transplant.hrsa.gov/ContentDocuments/Guidance_DTAC_CNS_Infections_07-2012.pdf. Accessed June 25, 2013.