

ORIGINAL ARTICLE

Transmission of West Nile Virus from an Organ Donor to Four Transplant Recipients

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ABSTRACT

BACKGROUND

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In August 2002, fever and mental-status changes developed in recipients of organs from a common donor. Transmission of West Nile virus through organ transplantation was suspected.

METHODS

We reviewed medical records, conducted interviews, and collected blood and tissue samples for testing with a variety of assays. Persons who donated blood to the organ donor and associated blood components were identified and tested for West Nile virus.

RESULTS

We identified West Nile virus infection in the organ donor and in all four organ recipients. Encephalitis developed in three of the organ recipients, and febrile illness developed in one. Three recipients became seropositive for West Nile virus IgM antibody; the fourth recipient had brain tissue that was positive for West Nile virus by isolation and nucleic acid and antigen assays. Serum specimens obtained from the organ donor before and immediately after blood transfusions showed no evidence of West Nile virus; however, serum and plasma samples obtained at the time of organ recovery were positive on viral nucleic acid testing and viral culture. The organ donor had received blood transfusions from 63 donors. A review of blood donors and follow-up testing identified one donor who had viremia at the time of donation and who became seropositive for West Nile virus IgM antibodies during the next two months.

CONCLUSIONS

Our investigation of this cluster documents the transmission of West Nile virus by organ transplantation. Organ recipients receiving immunosuppressive drugs may be at high risk for severe disease after West Nile virus infection. Blood transfusion was the probable source of the West Nile virus viremia in the organ donor.

WEST NILE VIRUS INFECTS BIRDS and mosquitoes; humans and horses are incidental hosts. As of April 15, 2003, in the United States, 4156 cases had been reported in 39 states and the District of Columbia (Centers for Disease Control and Prevention [CDC]; unpublished data). Although transmission of West Nile virus through blood or organs has not previously been documented, such transmission has been postulated.¹ The virus may be transiently present in the blood or organs of infected persons, many of whom probably have no symptoms. The widespread epidemic of West Nile virus infections in 2002 in the United States has increased concern about such transmission.

In August 2002, two recipients of cadaveric kidneys from a single donor were readmitted to a Georgia hospital with headache and fever. Encephalitis subsequently developed in both, and clinicians suspected West Nile virus infection. Two Florida recipients of organs from the same donor also had an unexplained febrile illness while hospitalized, with encephalitis developing in one. We report on the investigation of these cases, which demonstrated the transmission of West Nile virus through transplanted organs and transfused blood.

METHODS

INVESTIGATION OF THE ORGAN DONOR AND TRANSPLANT RECIPIENTS

Organ-procurement agencies and clinicians were contacted to identify all organs and tissues recovered from the organ donor. To characterize the clinical course of the illness caused by West Nile virus and to identify potential sources of exposure to the virus for the organ donor and organ recipients, we reviewed medical records using a standardized form and interviewed patients and family members. Cerebrospinal fluid, serum, tissue, and autopsy specimens obtained from patients were tested for West Nile virus.

Formalin-fixed tissues were tested by immunohistochemical staining with the use of polyclonal and monoclonal antibodies against West Nile virus and other flaviviruses. Selected samples of serum, plasma, cerebrospinal fluid, and nonfixed tissue were tested by quantitative real-time polymerase chain reaction (PCR) with the use of TaqMan (Applied Biosystems), IgM antibody-capture enzyme-linked immunosorbent assay (ELISA), and viral iso-

lation on Vero cells and by intracerebral inoculation of suckling mice.²⁻⁵

Laboratory criteria for a confirmed recent West Nile virus infection, based on national case definitions, were isolation of the virus from tissue, blood, or cerebrospinal fluid; detection of the West Nile virus antigen by immunohistochemical staining or by the identification of West Nile virus genomic sequences in tissue, blood, or cerebrospinal fluid; detection by IgM antibody-capture ELISA of West Nile virus IgM antibodies in a cerebrospinal fluid sample obtained during the acute phase of the illness; or recent seroconversion, with the detection of West Nile virus IgM by IgM antibody-capture ELISA.^{6,7}

INVESTIGATION OF BLOOD DONORS

We reviewed the blood-transfusion histories of the organ donor and the transplant recipients and notified the implicated blood-collection agencies. Donations associated with blood components given to the organ donor, other blood components manufactured from these donations (co-components), and recipients of these co-components were identified. All co-components that were not transfused or expired were retrieved. Retrieved co-components and available blood samples from tubing from the blood container obtained at the time of blood donation or manufacturing of the components ("retention tubing") from implicated donations were collected and tested for West Nile virus nucleic acid and IgM antibody. Because quantitative DNA PCR with the use of TaqMan may be more sensitive than viral culture,⁵ we tested specimens for West Nile virus nucleic acid sequences and submitted positive specimens for viral culture. The quantitative sensitivity of PCR with the use of TaqMan is 0.8 plaque-forming unit per milliliter, with a 100 percent rate of detection (CDC; unpublished data). The blood-collection agency attempted to contact all donors of blood components transfused to the organ donor. Personal identifying information for blood donors was retained by the blood-collection agency. Those contacted were queried about symptoms compatible with West Nile virus illness and invited to undergo testing for West Nile virus antibody.

RESULTS

CLINICAL INVESTIGATION

Four organs — the heart, liver, and two kidneys — recovered from a single organ donor on August 1,

2002, were transplanted into four recipients one day later. No other organs or tissues from this donor were transplanted or stored. The donor and all four recipients met the laboratory criteria for confirmed recent West Nile virus infection (Table 1). Encephalitis developed in three organ recipients, and one had a febrile illness without encephalitis; the organ donor had had West Nile virus viremia (Fig. 1). Serum collected from all organ recipients on August 1, before transplantation, showed no evidence of West Nile virus infection.

ORGAN DONOR

A previously healthy woman was hospitalized in Georgia from July 30 to August 1 for injuries from unintentional trauma. On July 30 and July 31, she received 53 units of blood components and 1 pool

of cryoprecipitated antihemophilic factor. She was declared brain dead July 31, and her organs were recovered August 1. Screening of the organ donor by the procurement agency revealed no symptoms or laboratory findings suggestive of infection before the fatal injury. Medical records and interviews with family members indicated potential exposure to mosquitoes, but no symptoms of infection were noted before the injury. The donor lived in and traveled through areas of Georgia that had epizootic West Nile virus activity in 2002. Two serum samples collected at the time of admission on July 30, before blood transfusion, had no detectable West Nile virus IgM antibody or nucleic acid. Although a serum sample obtained July 31, after the receipt of all transfusions, had no detectable levels of West Nile virus nucleic acid, serum and plasma samples collected

Table 1. Clinical Characteristics and Selected West Nile Virus Test Results in Transplant Recipients and an Organ Donor.*

Patient	Age (yr)/ Sex	Days from Transplan- tation to Onset of Illness	Date Specimen Collected	Specimen Tested	Test Facility	WNV Test Results†	Clinical Diagnosis	Vital Status
Organ donor	~20/F	—	7/30/02	Pre-transfusion serum	CDC	Negative PCR and WNV IgM	WNV viremia	Died; death not related to West Nile virus
			7/31/02	Post-transfusion serum	CDC	Negative PCR and WNV IgM		
			8/1/02	Post-transfusion serum	CDC	Positive PCR and viral culture		
Patient 1	31/F	14	8/22/02	Post-transplantation CSF	CDC	Positive WNV IgM	WNV encephalitis	Alive
			8/22/02	Post-transplantation CSF	Commercial laboratory	Negative WNV IgM		
			8/23/02	Post-transplantation serum	Commercial laboratory	Equivocal WNV IgM		
Patient 2	38/M	17	8/23/02	Post-transplantation CSF	CDC	Negative WNV IgM	WNV encephalitis	Died of West Nile virus infection
			8/23/02	Post-transplantation serum and CSF	Commercial laboratory	Negative WNV IgM		
			8/29/02	Brain at autopsy	CDC	Positive PCR, IHC, and viral culture		
Patient 3	63/M	10	8/14/02– 8/25/02	Post-transplantation serum‡	CDC	Positive PCR	WNV encephalitis	Alive
			8/24/02	Post-transplantation CSF and serum	FL DOH	Positive WNV IgM		
Patient 4	71/F	7	8/29/02	Post-transplantation serum	FL DOH	Positive WNV IgM	WNV fever	Alive

* WNV denotes West Nile virus, CDC Centers for Disease Control and Prevention, CSF cerebrospinal fluid, and FL DOH Florida Department of Health Bureau of Laboratories.

† The tests consisted of West Nile virus–specific IgM antibody-capture enzyme-linked immunosorbent assay, quantitative real-time polymerase chain reaction (PCR) with TaqMan, viral culture, and flavivirus-specific immunohistochemical staining (IHC).

‡ Twelve serum samples were collected from August 14 through August 25 that were each positive for nucleic acid by PCR.

August 1 at organ recovery yielded West Nile virus nucleic acid on quantitative PCR (13 and 5 plaque-forming units per milliliter, respectively) and West Nile virus on culture.

PATIENT 1

Patient 1 was a 31-year-old woman with hypertension-induced end-stage renal disease who received one donor kidney. Her immunosuppressive medications after transplantation included tacrolimus, mycophenolate mofetil, and corticosteroids. She was discharged on August 6 to her Georgia home. West Nile virus activity in humans, birds, and horses had been reported in her county. She was readmitted August 18 with a two-day history of fever (maximal

temperature, 39.4°C), four to five days of rash on the upper chest and neck, six days of upper respiratory tract symptoms, and one day of backache and diarrhea. Hematologic tests showed leukocytosis (Table 2).

The patient remained febrile despite antibiotic therapy, and meningismus developed, followed by a progressive decline in mental status, and she became unresponsive and required mechanical ventilation on August 22. Tests of cerebrospinal fluid revealed pleocytosis (Table 2). Commercial-laboratory testing of serum collected August 23 for West Nile virus IgG and IgM antibody with the use of the indirect fluorescent antibody method was equivocal, with a neutralizing antibody titer of 1:16 (a titer of

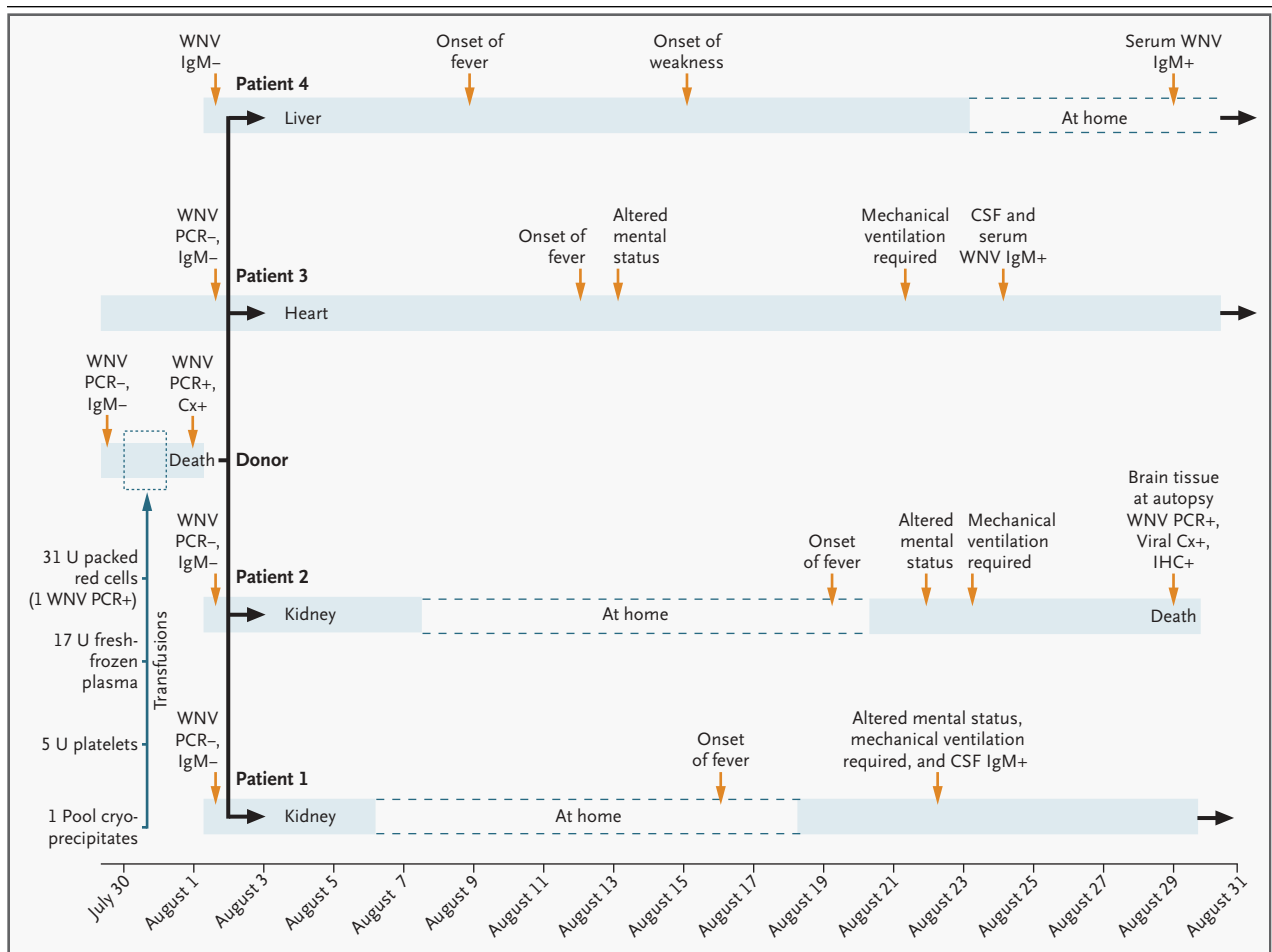


Figure 1. Clinical and Laboratory Findings in Four Organ-Transplant Recipients with West Nile Virus Infection Associated with an Organ Donor with West Nile Virus Viremia.

The shaded areas show the dates of hospitalization. Tests for West Nile virus (WNV) consisted of quantitative real-time polymerase chain reaction (PCR) with TaqMan, IgM antibody-capture enzyme-linked immunosorbent assay, viral culture (Cx), and flavivirus-specific immunohistochemical staining (IHC). Minus signs indicate negative results, and plus signs positive results. CSF denotes cerebrospinal fluid.

Table 2. Selected Laboratory Results for Organ Recipients during Acute West Nile Virus Illness.

Variable	Patient 1	Patient 2	Patient 3	Patient 4*
Blood†				
Hemoglobin (g/dl)	10.0	10.9	12.7	9.1
White-cell count ($10^{-3}/\text{mm}^3$)	15.8	4.8	8.0	4.1
Neutrophils (%)	90	73	94	84
Lymphocytes (%)	8	19	4	7
Other (%)	2	8	2	9
Platelet count ($10^{-3}/\text{mm}^3$)	237	121	140	46
Tacrolimus level (ng/ml)	6.7	12.0	17.5	3.4
Cerebrospinal fluid‡				
Protein (mg/dl)	87	71	75	—
White-cell count (per mm^3)	675	10	1	—
Neutrophils (%)	92	43	24	—
Lymphocytes (%)	6	48	16	—
Other (%)	2	9	60	—
Glucose (mg/dl)§	67	56	74	—

* Cerebrospinal fluid was not obtained from Patient 4.

† Blood samples were obtained at the time of the onset of symptoms or readmission to the hospital.

‡ Cerebrospinal fluid samples were obtained while patients were having symptoms of febrile encephalopathy.

§ To convert values for glucose to millimoles per liter, multiply by 0.05551.

less than 1:16 was considered to indicate that no antibody was detected); similar testing of the patient's cerebrospinal fluid showed no evidence of West Nile virus antibody. However, cerebrospinal fluid specimens collected August 22 and 29 were positive for West Nile virus IgM antibody on IgM antibody capture ELISA at the CDC laboratories. Serum collected September 11 was positive for West Nile virus IgM and had a neutralizing antibody titer of 1:5120. The patient's clinical condition improved, and she was discharged to a rehabilitation center September 11.

PATIENT 2

Patient 2 was a 38-year-old man with hypertension-induced end-stage renal disease who received the other donor kidney. His immunosuppressive medications after transplantation included tacrolimus, mycophenolate mofetil, and corticosteroids. The patient was discharged to his Georgia home August 7. West Nile virus activity in humans, horses, and birds had been reported in his county. On August 19, he began to have fever (temperature, 39°C), head-

ache, myalgias, arthralgias, anorexia, and diarrhea, and he was readmitted the next day. Tests at the time of readmission showed thrombocytopenia (Table 2). Over the following two days, he remained febrile despite antimicrobial therapy and became tremulous, confused, and dysarthric. On August 23, he became unresponsive and required mechanical ventilation. Cerebrospinal fluid obtained August 23 revealed mild pleocytosis (Table 2); cerebrospinal fluid and serum samples tested with use of the indirect fluorescent antibody method at a commercial laboratory were reported as negative for West Nile virus IgG and IgM. The cerebrospinal fluid sample also tested negative on IgM antibody-capture ELISA at the CDC.

The patient subsequently died from brain-stem herniation on August 29. Immunohistochemical staining of brain tissues obtained at autopsy showed abundant flavivirus antigens with the use of both polyclonal flavivirus antibodies (Fig. 2) and monoclonal West Nile virus antibodies. These tissues were strongly positive for West Nile virus on quantitative PCR (1 million plaque-forming units per milliliter), and the virus was isolated from both cell culture and suckling mice.

PATIENT 3

Patient 3 was a 63-year-old man with congestive heart failure who received the donor heart. He had been hospitalized for one month before transplantation, with limited physical activity because of his cardiac disease. His immunosuppressive medications after transplantation included antithymocyte globulin, tacrolimus, sirolimus, and corticosteroids. No recent West Nile virus activity had been reported in the Florida county where the patient resided and had been hospitalized. While he was hospitalized on August 12, he had a low-grade fever (temperature, 38.2°C), and on the following day confusion, diarrhea, incontinence, and leg weakness developed; laboratory tests were performed (Table 2).

The patient remained febrile (maximal temperature, 39.2°C) for the next three days, and dysarthria and tremors developed. Cerebrospinal fluid collected August 18 did not show pleocytosis (Table 2). On August 21, he became unresponsive and required mechanical ventilation. PCR tests of serial samples of serum revealed a prolonged viremia, with West Nile virus nucleic acid present in samples obtained August 14 (the first available post-transplantation sample) through August 25, 23 days after transplan-

tation. Cerebrospinal fluid and serum samples obtained August 24 and tested at the Florida Department of Health Bureau of Laboratories were positive for West Nile virus IgM antibody on IgM antibody-capture ELISA. The patient's symptoms improved, and he was discharged home September 25.

PATIENT 4

Patient 4 was a 71-year-old woman with chronic hepatitis C virus infection and hepatocellular carcinoma who received the donor liver. Her immunosuppressive medications after transplantation included tacrolimus and corticosteroids; she received mycophenolate mofetil from August 2 to August 6. No West Nile virus activity had been reported in the Florida counties where she resided or had been hospitalized. Fever developed (temperature, 38.5°C) while she was hospitalized on August 9; hematologic tests showed thrombocytopenia (Table 2). On August 10, she began to have diarrhea, which lasted five days, and on August 15, generalized weakness developed with low back pain. The following day, tremors of the hand and mouth area developed that were attributed to an elevated serum tacrolimus level (19.8 ng per milliliter). She remained febrile despite antimicrobial therapy. Mild cognitive impairment was apparent during the fever, but specific signs of meningoencephalitis or other neurologic changes were not noted. Fever resolved August 17, and constitutional symptoms resolved by August 23, allowing her to be discharged from the hospital. Serum collected August 29 and tested at the Florida Department of Health Bureau of Laboratories was positive for West Nile virus IgM antibody on IgM antibody-capture ELISA.

REVIEW OF BLOOD PRODUCTS

The organ donor received 31 units of packed red cells, 17 units of fresh-frozen plasma, 5 units of apheresis platelets, and 1 pool of cryoprecipitated antihemophilic factor containing 10 individual units. The components originated from 63 blood donors residing in eight states; all states had reported West Nile virus activity. From these 63 donations, 140 components were identified. Of these 140 components, 64 were transfused into the organ donor, 35 were transfused into other persons, 27 were retrieved for West Nile virus testing, 12 were discarded owing to expiration or breakage, and 2 were pooled for plasma fractionation.

Specimens collected at the time of blood donation (i.e., retention tubing or retrieved cocompo-

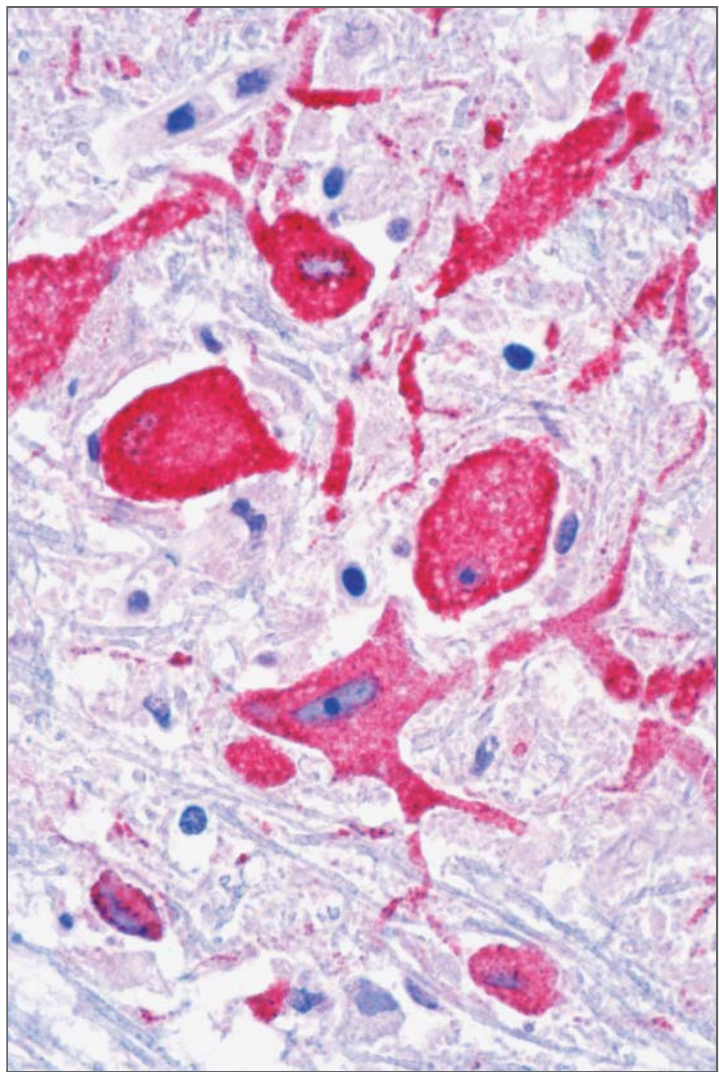


Figure 2. Immunostaining of Flaviviral Antigens in Neurons and Neuronal Processes in Central Nervous System Tissue from Patient 2 (Flavivirus–Hyperimmune Mouse Ascitic Fluid, Naphthol Fast Red Substrate with Hematoxylin Counterstain, $\times 158$).

ment) were available for 41 (65 percent) of the donors; 1, a retrieved unit of plasma, was positive for West Nile virus nucleic acid on quantitative PCR (20 plaque-forming units per milliliter), and all were negative for IgM antibody. Of the 63 blood donors, 57 (90 percent) have undergone follow-up testing. Only the donor with a positive PCR result on testing of the initial donation samples had IgM antibody at follow-up testing in mid-September. This donor reported symptoms compatible with West Nile virus illness (fever, headache, rash, eye

pain, generalized weakness, and abdominal pain) during the two to three weeks before blood donation in July but reported no symptoms at the time of blood donation. On July 31, the last transfusion given to the organ donor had originated from this blood donor with viremia. No other persons received co-components from this blood donor.

DISCUSSION

Our investigation demonstrates the transmission of West Nile virus through transplanted organs and transfused blood. All four patients received organs from an organ donor with viremia and became ill in the weeks after transplantation as a result of West Nile virus infection. The organ donor had received blood from a blood donor with viremia.

Most persons infected with West Nile virus are asymptomatic or have only mild symptoms.^{8,9} Meningitis or encephalitis develops in approximately 1 in 150 infected persons.⁸⁻¹⁰ There are no data regarding immunosuppressive drugs as a risk factor for severe West Nile virus disease; however, limited data suggest that immunocompromised patients may be at high risk for death after West Nile virus infection.^{11,12} All four organ recipients became ill, and encephalitis developed in three, indicating that organ recipients who are taking immunosuppressive drugs may be at substantial risk for severe disease after infection with West Nile virus.

West Nile virus infection should be considered in patients in whom fever and encephalitis develop after transplantation; however, the clinical presentation of the illness in immunosuppressed organ recipients may differ from that in other patients. The incubation period is generally thought to range from 2 to 14 days.⁷ Among the organ recipients we studied, symptoms began 7 to 17 days after transplantation. Although pleocytosis is common in patients with West Nile virus meningoencephalitis,¹¹⁻¹⁴ it was not observed in the heart-transplant recipient, and only mild pleocytosis was found in one kidney-transplant recipient despite the finding at autopsy of substantial viral involvement of brain tissue. Further study is needed of the role of immunosuppression in the pathophysiology, clinical presentation, and clinical management of West Nile virus infection.

The organ donor probably acquired the infection through the transfusion of blood from a blood donor with viremia. The identification of West Nile virus and viral nucleic acid in specimens from the organ donor that were collected at the time of organ

recovery, but not in serum samples obtained before transfusion or in the initial post-transfusion sample, is consistent with an infection occurring at the time of blood transfusion. Follow-up testing of 57 of 63 blood donors revealed 1 with seroconversion to West Nile virus. Quantitative PCR indicated that this donor had viremia at the time of donation. Although the organ donor could have been infected by a mosquito bite, the timing of the organ donor's viremia and the presence of a blood donor with viremia make transmission by blood more likely.

The long period between the blood donor's symptoms and blood donation is noteworthy; however, inaccurate recall of the date of onset of symptoms was possible. Since West Nile virus IgM antibody almost always develops within eight days after the onset of symptoms, the absence of IgM antibody at the time of donation suggests that symptoms may have occurred closer to donation.¹⁵ Finally, we were not able to exclude the possibility of transfusion-associated transmission of West Nile virus in the case of the six blood donors who did not undergo follow-up testing.

Prevention of the transmission of West Nile virus through organ transplantation or transfused blood relies on the exclusion of donors with viremia. Our findings suggest that screening donors of organs and blood may be beneficial, although the sensitivity, feasibility, timeliness, and cost benefit of screening need to be assessed. Because the risk of transmission of West Nile virus is related to the incidence of infection in the donor population, the public health benefits associated with screening will probably vary according to the year, season, and location. Since most persons infected with West Nile virus are asymptomatic, exclusion criteria that are based on a donor's history of recent illness would have limited effectiveness. Although tests to detect West Nile virus antibody are useful for clinical diagnosis, antibodies usually develop after the period of highest viremia.¹⁶ Therefore, potential screening will need to rely on other methods of detection, such as testing for viral nucleic acid, which we found to be more useful if performed on specimens collected close to the time of organ recovery. In addition, it is not known whether donor organs remain infected after the apparent resolution of viremia.¹⁶

Findings from this and concurrent investigations^{17,18} have prompted the Food and Drug Administration (FDA) to issue "Guidance for Industry" in order to reduce the risk of transmitting West Nile virus infection through transfusions.¹⁹ The guide-

lines include information on determining the suitability of blood donors, reporting illnesses suggestive of West Nile virus infection in donors, and withdrawing and quarantining blood products from these donors. In addition, the FDA is working with the blood and medical diagnostics industry to speed development of screening tests for West Nile virus. Clinicians are strongly encouraged to report to public health authorities patients infected with West Nile virus who have symptoms within four weeks after receiving an organ or tissue transplant or blood transfusions or within two weeks after donating blood, an organ, or tissue. Prompt reporting of these cases will assist in the withdrawal and retrieval

of potentially infected tissues and blood products and will help define the epidemiology and clinical significance of the transmission of West Nile virus through transplanted organs and transfused blood.¹⁷

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APPENDIX

The members of the West Nile Virus in Transplant Recipients Investigation Team are as follows: P. Blake, W. Bower, L. Dowdy, J. Fleming, J. Guarner, J. Jimenez, M. Kuehnert, F. Leguen, T. Luu, S. Mallon, R. Moseley, A. Nejman, P. Page, L. Pealer, X.-S. Qi, E. Rico, J. Roehrig, P. Rollin, M. Salameh, W.-J. Shieh, P. Tso, and D. Withum.

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