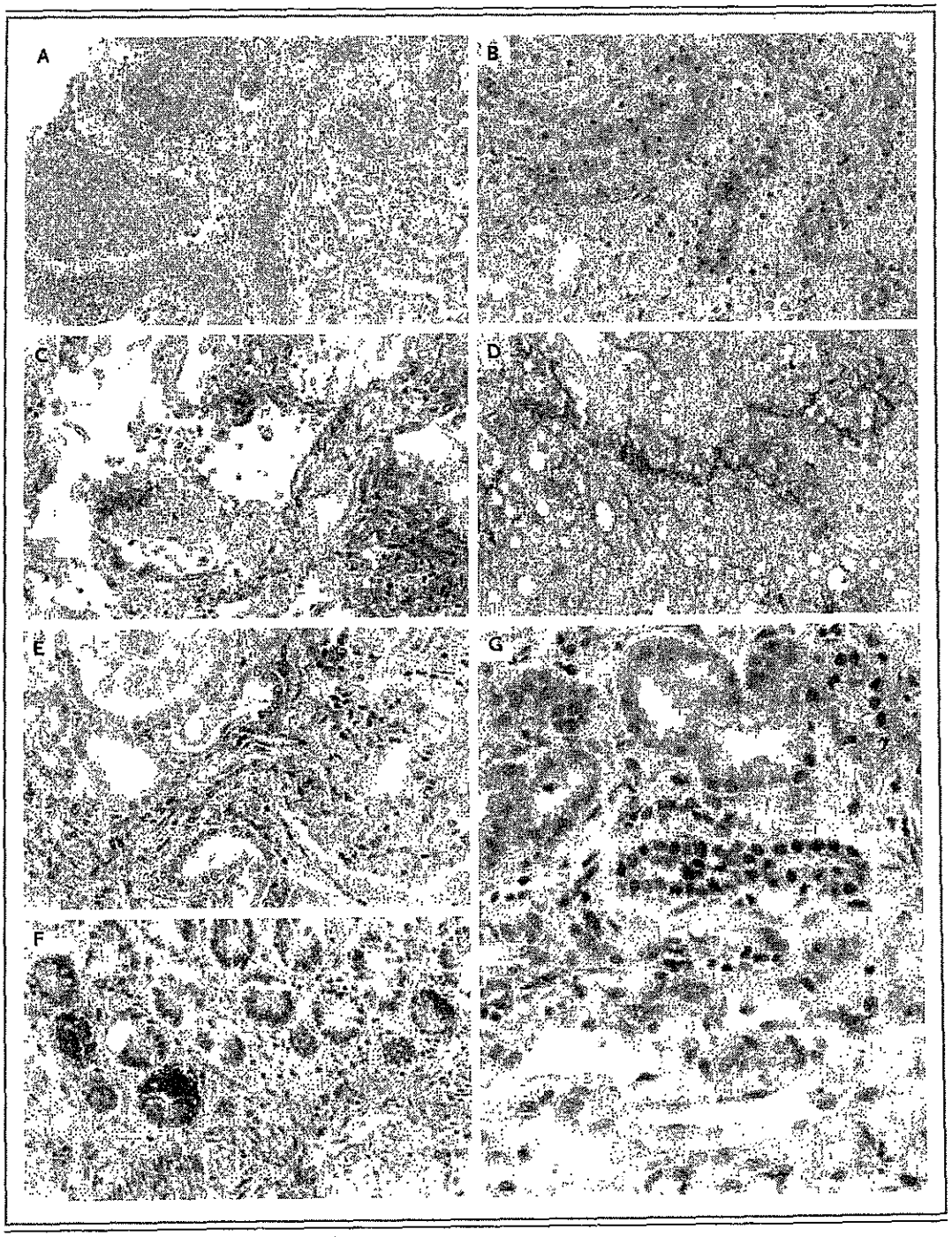

cal or laboratory evidence of infection. In the 2003 cluster, no rodent exposures could be identified, whereas the 2005 cluster was associated with recent donor exposure to an LCMV-infected pet hamster. The isolation of identical virus strains from the two kidney recipients in the 2003 cluster and from all the organ recipients and the donor household's pet hamster in the 2005 cluster indicates that in both clusters, LCMV was transmitted through organ transplantation.[15]

LCMV infection in humans is sporadic, is generally benign, and can be asymptomatic.[4,16,17] Serologic surveys suggest that up to 5 percent of adults in the United States have been infected with LCMV.[18,19] Humans become infected with LCMV by direct contact with rodents or through

Table 2. Summary of Laboratory Evaluations for Lymphocytic Choriomeningitis Virus Infection in the 2005 Cluster.*

Patient or Source of Specimen	Outcome or Status	Immunohistochemical Staining	Quantitative Real-Time RT-PCR†	Blood and Serum Testing		Culture
				IgM	IgG	
Donor‡	No reported disease	–	–	–	–	–
Liver recipient§	Death 26 days after transplantation	+	+	–	–	+
Lung recipient¶	Death 23 days after transplantation	+	+	–	–	+
Kidney Recipient B‖	Death 23 days after transplantation	+	+	+	–	+
Kidney Recipient A**	Survival	+	+	+	–	+
Hamster in donor's household††	No reported disease	+	+	NT	–	+
Hamster's caregiver‡‡	No reported symptoms	NA	–	+	+	–

* RT-PCR denotes reverse-transcriptase polymerase chain reaction, NT not tested, and NA not applicable.
† Quantitative real-time RT-PCR (TaqMan) assays were carried out as follows: complementary DNA was synthesized with a High Capacity cDNA Archive Kit (Applied Biosystems) and used as a template in a second reaction involving TaqMan Universal PCR Master Mix (Applied Biosystems), forward primer 5′TGGGACTCCATTCGCTATGG3′ at 1 μM per reaction, reverse primer 5′TTAAGTGCAAGGAACCACATCAA at 1 μM per reaction, and probe FAM 5′TGGTCAGCAATCGTGTCTATTGTTTCACAAA at 0.1 μM per reaction. Samples with a cycle-threshold value below 40 were considered positive.
‡ Autopsy specimens that tested negative by one or more tests included central nervous system tissue, heart, spleen, liver, pancreas, uterus, thyroid, gastrointestinal tract, muscle, skin, kidney, blood, and serum.
§ Autopsy specimens that tested positive by one or more tests included central nervous system tissue, lung, heart, kidney, skin, liver, spleen, gastrointestinal tract, adrenal gland, pancreas, testis, blood, and serum. Liver- and colon-biopsy specimens obtained on days 16 and 19, respectively, were also positive by immunohistochemical analysis.
¶ Autopsy specimens that tested positive by one or more tests included central nervous system tissue, lung, heart, kidney, skin, liver, spleen, gastrointestinal tract, blood, and serum.
‖ Autopsy specimens that tested positive by one or more tests included spleen, heart, lung, kidney, gastrointestinal tract, pancreas, liver, blood, and serum. Blood and serum samples obtained on day 17 were positive by PCR, serologic testing for IgM, and culture.
** A colon-biopsy specimen obtained on day 26 was positive, a kidney-biopsy specimen on day 31 was positive, and a kidney-biopsy specimen on day 56 was negative by immunohistochemical analysis. Serial blood or serum samples obtained on days 16 to 50 were positive, blood and serum obtained on days 52 and 85 were negative, urine obtained on days 24 and 37 was positive, urine obtained on day 85 was negative, and a kidney-biopsy specimen obtained on day 55 was negative by PCR and culture. Serial blood and serum samples obtained on days 16 to 39 were IgM negative, on days 52 and 85 IgM positive, and on days 16 to 85 IgG negative by serologic testing.
†† Necropsy specimens that were positive on one or more tests included urinary bladder, skin, muscle, testis, central nervous system tissue, heart, lung, kidney, adrenal gland, salivary gland, pancreas, liver, and spleen.
‡‡ Blood and serum specimens were evaluated.

aerosolized droplets from rodent secretions and excretions, including urine or feces.[20,21] Reports of sporadic infection have most frequently implicated the common house mouse, although outbreaks of infection have been reported after exposure to infected pet hamsters and laboratory rodents.[17,20-28]

In clinically apparent infection, the incubation period is 5 to 13 days, with subsequent fever, headache, and myalgias. Abdominal pain, diarrhea, and rash have been described.[16,20,22,26,29] A second phase of illness may be seen five to nine days after convalescence, with meningitis or, rarely, encephalomyelitis, orchitis, parotitis, pneumonitis, arthritis, myocarditis, or alopecia.[16,22,30] Recognized LCMV infection carries a mortality rate of less than 1 percent.[3]

The marked severity of LCMV-related illness in transplant recipients is probably the result of intensive immunosuppression, including T-cell depletion, coincident with direct viral inoculation by way of the transplanted organs. There are few data on the clinical behavior and outcomes of LCMV infection in immunocompromised patients. However, three patients with advanced lymphoma experimentally inoculated with the virus in a trial investigating its antitumor effect died with disseminated infection within 14 to 45 days after inoculation[31] — a pattern similar to that seen in the current clusters after solid-organ transplantation.

The clinical presentation of LCMV infection in the recipients was variable and included fever, diarrhea, peri-incisional erythema and tenderness, altered mental status, and respiratory insufficiency (as noted in the table of the Supplementary Appendix). Leukopenia or leukocytosis, thrombocytopenia, coagulopathy, renal insuf-

ficiency, and progressive liver dysfunction dominated the laboratory findings. Histopathological findings in all the recipients were characterized by necrotic and occasionally hemorrhagic foci in multiple tissues, with a notable absence of inflammatory infiltrates and viral inclusions. LCMV antigens present in some tissues (e.g., the gastrointestinal tract and skin) correlated with clinical symptoms (e.g., diarrhea and erythema or pustular rash, respectively). Antigens were identified in the leptomeninges of some patients in both clusters. However, signs of meningeal inflammation, though prominent in the 2003 cluster, were generally absent in the 2005 cluster. Clinical manifestations and pathological findings in all the cases were probably altered by immunosuppression.

To our knowledge, there have been no trials of antiviral agents in human LCMV disease. Ribavirin has demonstrated efficacy in the treatment of Lassa fever and possesses in vitro activity against LCMV infection, which prompted its use in the renal-transplant recipient who survived.[14,32] The role of ribavirin in this patient's improvement is unclear, since the level of immunosuppression was also considerably reduced, as it was for all four kidney recipients in the two clusters.

Rapid evaluation of organ-donor suitability is essential in transplantation to minimize the duration of ischemia and to preserve allograft function. Therefore, assays used to screen potential donors for transmissible infections must be rapid, sensitive, reproducible, and readily available to OPOs. The Food and Drug Administration has not approved any diagnostic tests for LCMV infection. Furthermore, the sensitivity of currently available assays is not adequate for routine donor screening, as demonstrated by the negative results of tests on a wide array of clinical specimens from the donors in both clusters. The use of information pertaining to recent rodent exposure for donor-suitability screening may exclude healthy donors from an already limited organ-donor pool. However, the collection of additional epidemiologic information on donors' exposures may be useful, notably for the investigation of unusual outcomes after transplantation. Zoonotic-disease transmission after transplantation is also a concern; immunosuppressed persons should take special care and limit exposure to some animals, including certain pets (additional information is available from the CDC at www.cdc.gov/healthypets).

Transplant recipients are susceptible to infection with a variety of donor-derived pathogens, including West Nile virus, *Trypanosoma cruzi*, rabies virus, and now LCMV.[33-36] Although such infections are probably uncommon, outcomes can be fatal, and diagnosis is feasible with specialized laboratory testing. Diagnosis of LCMV infection is usually made by serologic testing, isolation of the virus from the blood or cerebrospinal fluid, or PCR testing.[37-39] Because immunohistochemical staining revealed LCMV in multiple biopsy specimens obtained to evaluate unexplained post-transplantation symptoms in the clusters described in the current report, such testing might be beneficial in the early diagnosis of LCMV infection.

Each year, approximately 25,000 organ transplantations are performed at more than 250 transplantation centers throughout the United States.[40] Allocation policies commonly result in the distribution of organs from a single donor to multiple transplantation centers. It is unlikely that either LCMV-illness cluster would have been identified without the allocation of kidneys to two recipients in whom similar symptoms simultaneously developed after undergoing transplantation at the same hospital. Similar chance clinical observations have been critical in the recognition of recent transplant-associated outbreaks of rabies and West Nile virus infection.[33,35]

The Organ Procurement and Transplantation Network (OPTN), which is operated by the United Network for Organ Sharing, requires transplantation centers to report certain outcomes, including allograft failure and the death of transplant recipients, in a timely manner. In April 2005, the OPTN revised its policies to require the reporting of suspected donor-transmitted medical conditions (including cancers and infections) to the procuring OPO, which is then responsible for investigating and communicating with the transplantation centers caring for the recipients of other transplants from the donor and the involved tissue and eye banks.[41]

Investigation of potential donor-transmitted infection requires rapid communication among physicians in multiple transplantation centers, OPOs, and public health authorities. An immediate system for tracking and disseminating pertinent patient data is needed. Until such a system can be established, clinicians must recognize that the presence of an unusual constellation of

symptoms, particularly during the first few weeks after transplantation, should raise the possibility of donor-transmitted infection. Prompt notification of the OPO and public health authorities can help facilitate rapid investigation and discovery of these events.

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APPENDIX

The members of the LCMV in Transplant Recipients Investigation Team are as follows: *Brigham and Women's Hospital:* D.A. Milner and M. Wilck; *Centers for Disease Control and Prevention:* C. Albarino, B. Amman, M. Bell, B. Bird, B. Holloway, J. Mills, and J. Towner; *Massachusetts Department of Public Health:* C. Daniel, S. Fleming, P. Kludt, and B.T. Matyas; *Massachusetts General Hospital:* R. Chung, A.B. Cosimi, N. Elias, N. Goes, M. Hertl, A. Reid, E.S. Rosenberg, and R.N. Smith; *Medical College of Wisconsin:* C.P. Johnson, S.C. Kehl, and C. Schultzenberg; *New England Organ Bank:* R.S. Luskin and K.J. O'Connor; *Rhode Island Department of Health:* C. Hannafin and C. Vanner; and *Rhode Island Hospital:* R. DeLellis, A. Gautam, R. Gohh, K. Kurek, P. Morrissey, and A. Yango.

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