CDC PUBLIC HEALTH GRAND ROUNDS

Unusual Donor Derived Transplant-associated Infections: Just How Unusual?



November 18, 2014

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

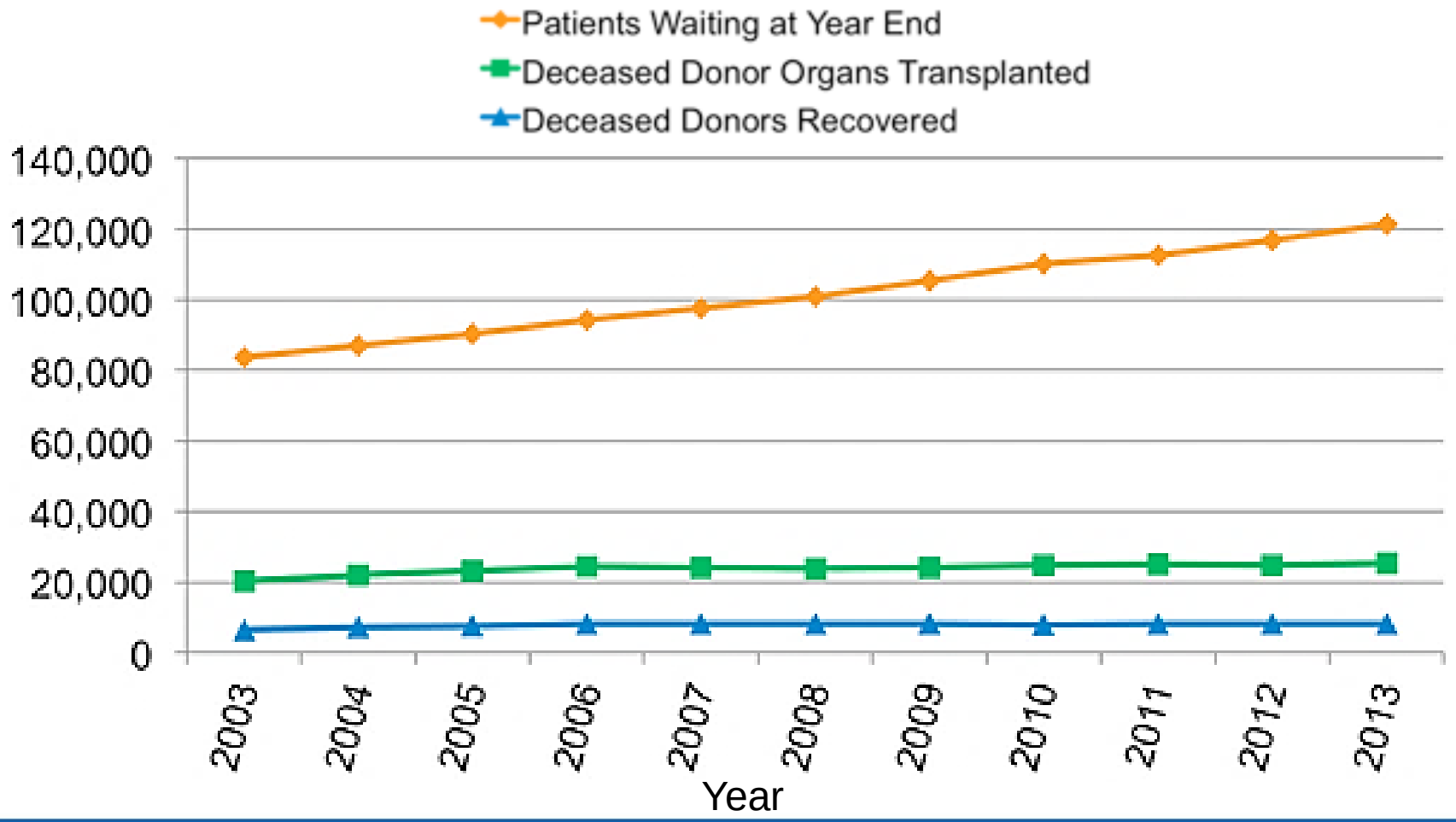
Federal Oversight of Organ Procurement and Transplantation

Robert Walsh
Director, Division of Transplantation
Health Resources and Services Administration

HRSA

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Organ Transplant Supply and Demand



http://optn.transplant.hrsa.gov

National Organ Transplant Act, 1984

- **Established the Organ Procurement and Transplantation Network (OPTN)**
  - Network to be operated by private, nonprofit organization under federal contract with HHS and HRSA
- **United Network for Organ Sharing (UNOS) operates the OPTN**
- **Created the current system of organ procurement organizations (OPOs)**
  - Currently 58 OPOs certified by Centers for Medicare and Medicaid Services

HRSA: Health Resources and Services Administration

Organ Procurement and Transplantation Network Final Rule (42 CFR, Part 121)

- **Structure, membership and oversight function**
- **Goals and requirements for policy making, particularly allocation of organs**
  - Waitlist of potential recipients
  - Matches potential recipients with organ donors
  - Donor testing
  - Organ packaging and labeling
- **Data collection and dissemination on pre-transplant and post-transplant events**
- **Advisory Committee on Organ Transplantation**

CFR: Code of Federal Regulations

HIV Organ Policy Equity (HOPE) Act

- **HOPE Act signed by US President into law November 21, 2013**

- **Stipulates that the OPTN may develop standards for use of organs from HIV–positive donors for transplant in individuals who were already infected with HIV**

Required Donor Screening Tests for Infectious Pathogens

Deceased Donors

- **Hepatitis B surface antigen and core antibody**
- **Hepatitis C serology, including**
  - Hepatitis C nucleic acid amplification testing (NAT) (all donors)*
- **HIV antibody**
- **HIV NAT or 4th generation EIA for donors with increased risk***
- **Syphilis**
- **Cytomegalovirus serology (CMV)**
- **Epstein-Barr virus serology (EBV)**
- **Blood culture**
- **Urine culture**

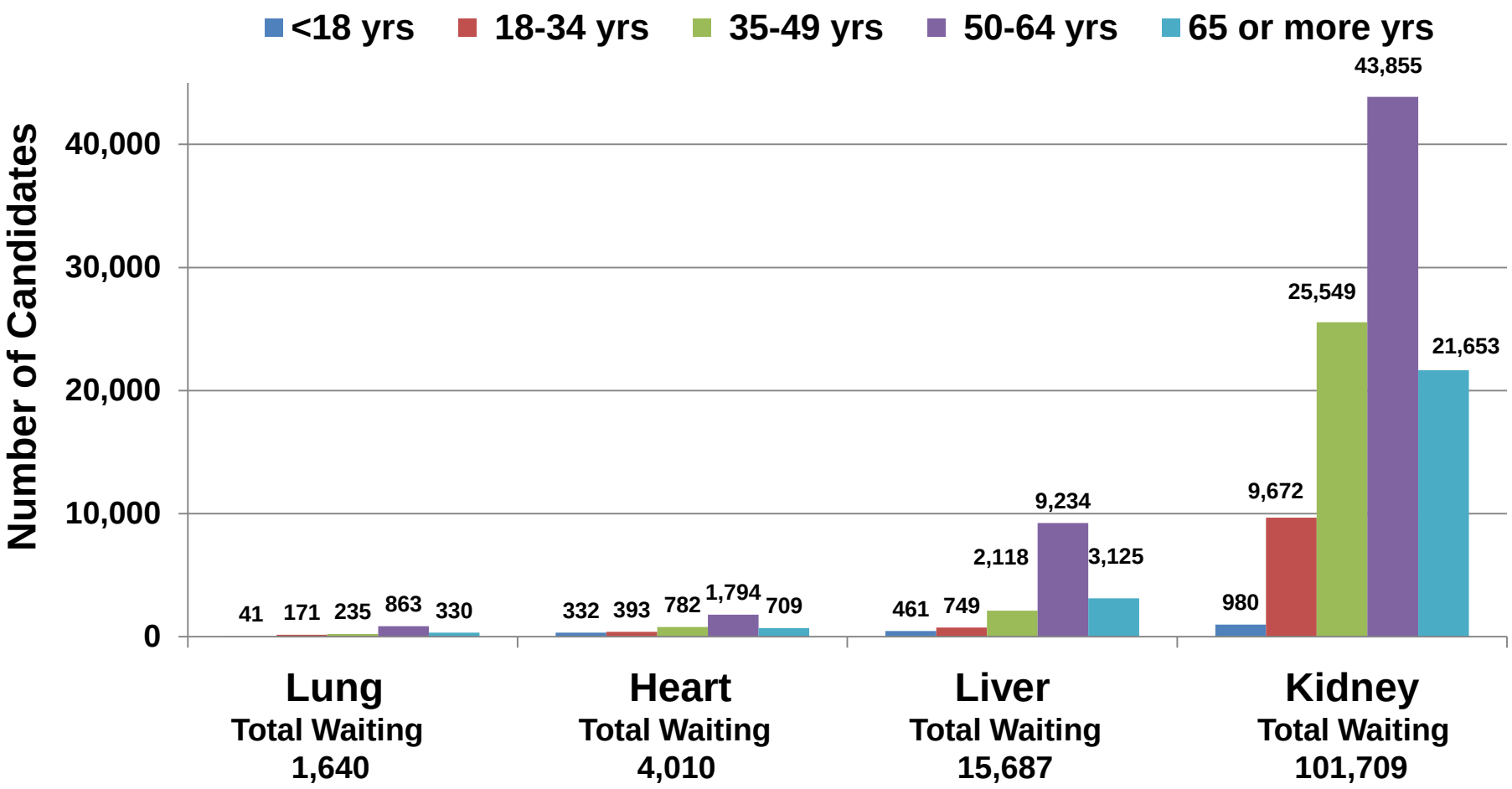
* Pending United Network for Organ Sharing (UNOS) board approval November 2014
EIA: Enzyme immunoassays.

Typical Questions in Deceased Donor Risk Assessment Interview

- **Public Health Service criteria for increased risk for incident hepatitis B, hepatitis C, and HIV**
  - Sexual exposures, drug use, hemodialysis, inmate of correctional facility, or recent sexually transmitted disease
- **Country of origin and previous residence and travel**
- **General medical history and medications**
  - Recent symptoms, including cough, fever, weight loss or headache
- **Human growth hormone exposure for CJD risk**
- **Animal exposures**
  - Screening for rabies and lymphocytic choriomeningitis virus

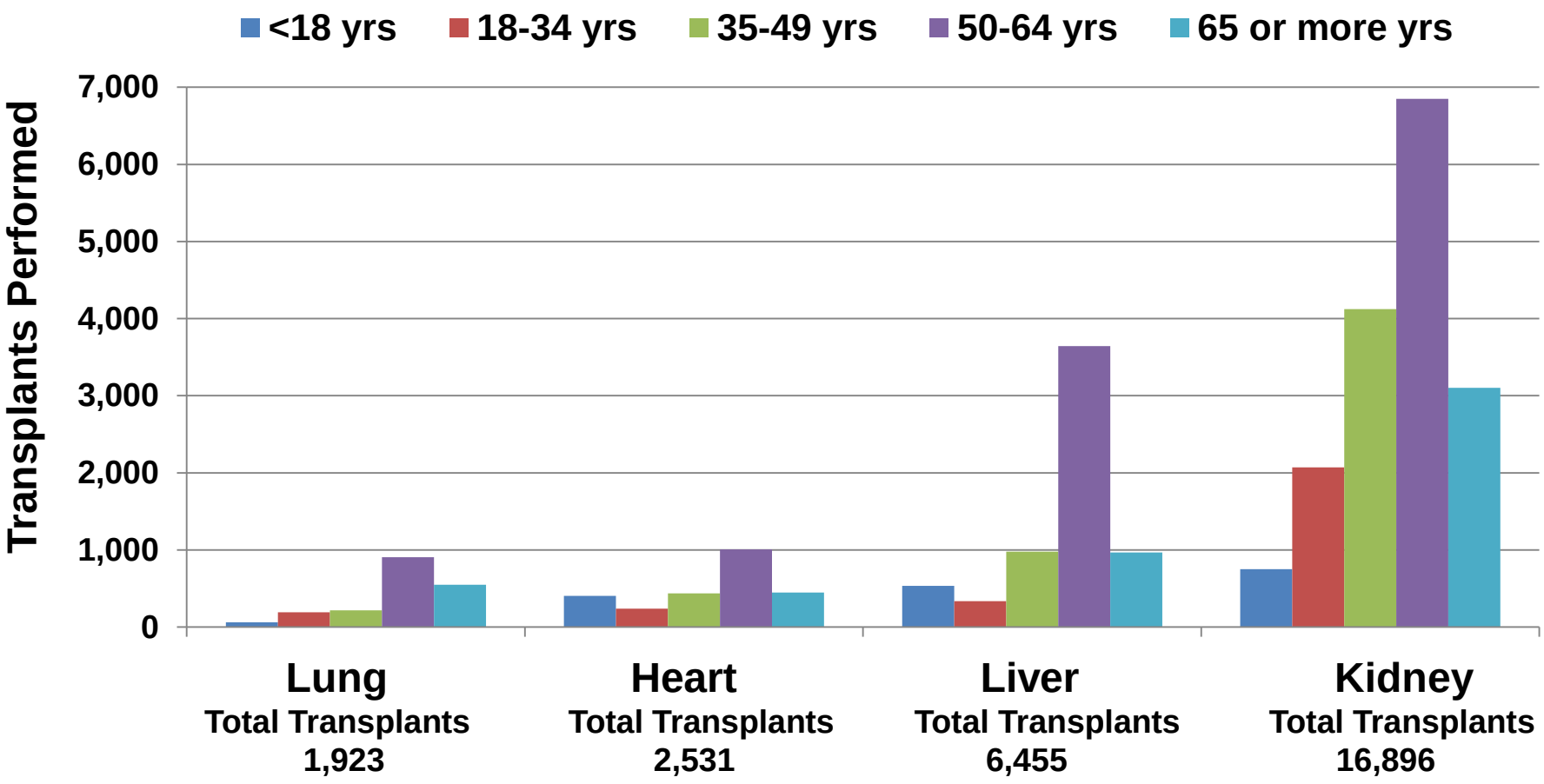
CJD: Creutzfeldt-Jakob Disease
http://www.publichealthreports.org/issueopen.cfm?articleID=2975

Current Waitlist by Organ and Age of Candidate



http://optn.transplant.hrsa.gov/converge/latestData/rptData.asp

Transplants by Organ and Age of Candidate in 2013



http://optn.transplant.hrsa.gov/converge/latestData/rptData.asp

Consequences of the Disparity Between Supply and Demand

- **Wait times vary significantly based on severity of illness and other factors**

- **Median national waiting time**
  - For kidney – nearly 4 years
  - For liver – nearly 1.5 years

- **In 2013**
  - 6,324 transplant candidates died waiting for an organ
  - 4,915 transplant candidates became too sick to transplant

http://optn.transplant.hrsa.gov/converge/latestData/rptData.asp

Current Screening of Organ Donors for Donor-derived Infections

Daniel Kaul, MD

Director, Transplant Infectious Disease Services
University of Michigan
Chair, Disease Transmission Advisory Committee (DTAC)

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

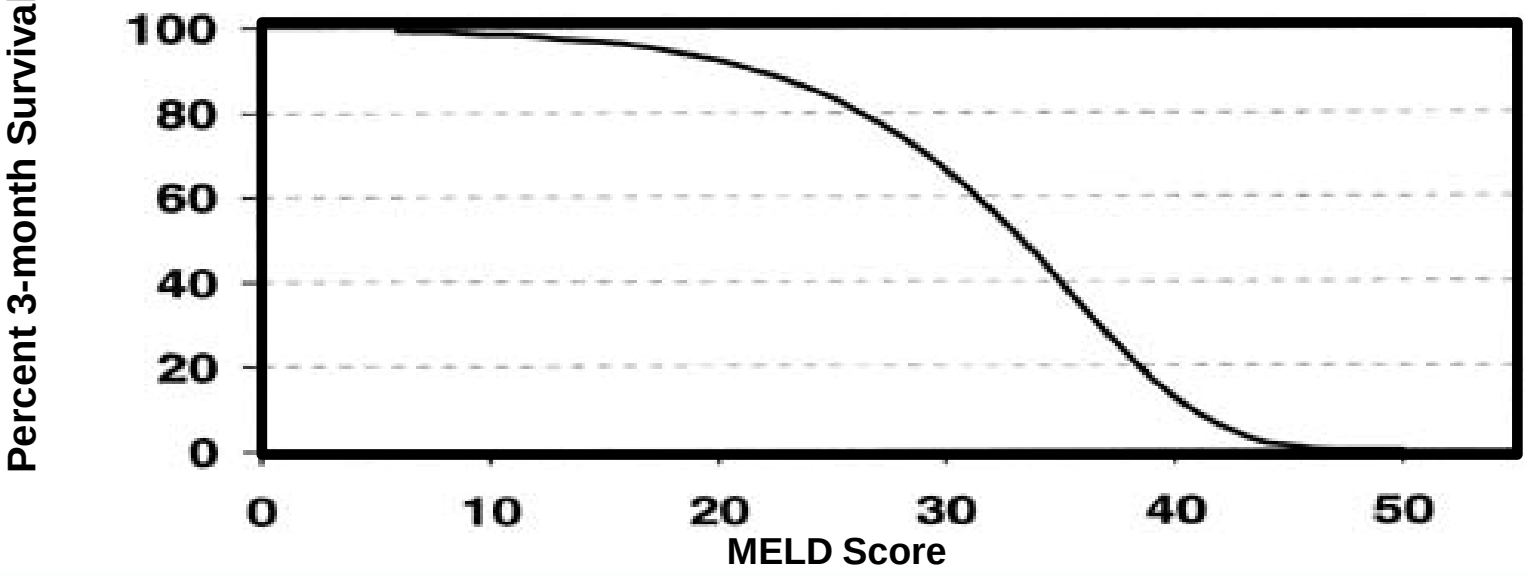
Donor Screening Tests for Selected Situations (not required)

- **Site specific protocols are used**
- **West Nile virus nucleic acid amplification testing**
  - During periods of increased mosquito activity or known outbreaks
- ***Trypansoma cruzi* (serology)**
  - At-risk donors
- **Coccidiomycosis (serology)**
  - Southwestern states
- **Strongyloides (serology)**
- **Human T-cell lymphotropic virus (HTLV-1) (serology)**
  - At-risk donors

Recipient Considerations of Accepting Organs from Donors with Possible Infection

- **Severity of disease in recipient affects urgency of need**
  - Kidney disease rarely requires urgent transplant
  - High score on MELD is an indication for urgent liver transplant

Estimated 3-month Survival As A Function of MELD Score



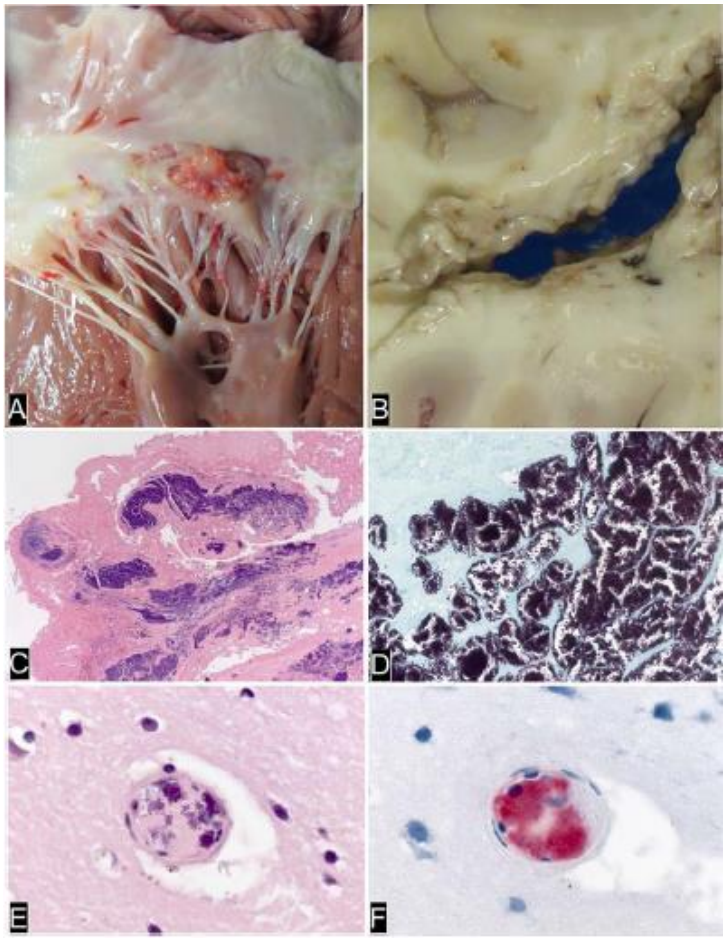
MELD: Model for End Stage Liver Disease
http://www.unos.org/docs/MELD_PELD.pdf

Other Considerations of Accepting Organs from Donors with Possible Infection

- **Has the infection been identified, and is effective treatment available?**
  - Pneumococcal meningitis
- **Is the cause of presumed infection unknown?**
  - Encephalitis of unknown cause
- **Is it a multidrug resistant organism?**
  - Toxicity and poor efficacy of available treatment options
- **What is the extent of the infection?**
  - Septic shock with multiple organ involvement

An Example of High Risk Donor
MRSA Endocarditis in Donor

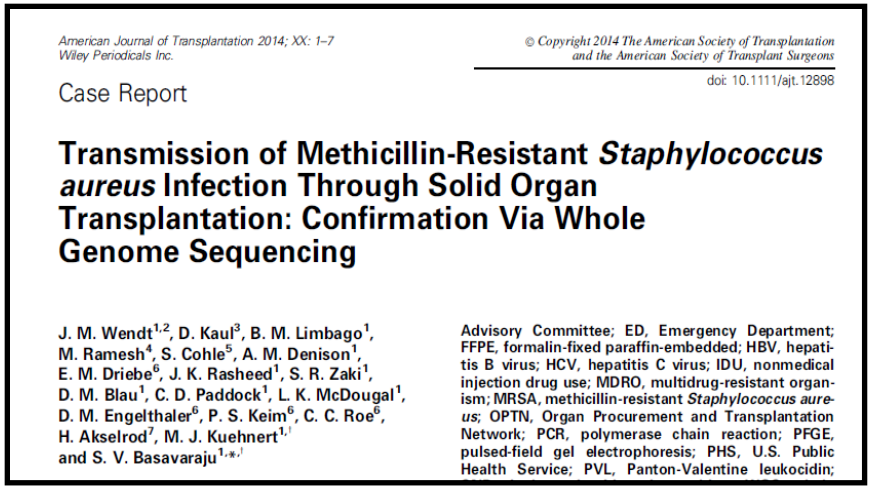
- **Potential donor: male with injection drug use**
  - MRSA bacteremia
  - Septic emboli to brain
  - Afebrile, on antibiotics for more than 48 hours
- **Recipient critically ill**
  - End stage pulmonary fibrosis
  - Mechanical ventilation in ICU
- **Should organs from this donor be transplanted?**



MRSA: Methicillin-resistant Staphylococcus aureus
ICU: Intensive care unit
Wendt JM, et al. *Am J Transplant*, 2014

Outcome of Recipients of MRSA Endocarditis Donor

- Lungs, liver, kidneys, and pancreas transplanted
- Prophylaxis given to all recipients
- Liver and lung recipient with recurrent MRSA



American Journal of Transplantation 2014; XX: 1–7
Wiley Periodicals Inc.

doi: 10.1111/ajt.12898

Case Report

Transmission of Methicillin-Resistant *Staphylococcus aureus* Infection Through Solid Organ Transplantation: Confirmation Via Whole Genome Sequencing

J. M. Wendt[1,2], D. Kaul[3], B. M. Limbago[1], M. Ramesh[4], S. Cohle[5], A. M. Denison[1], E. M. Driebe[6], J. K. Rasheed[1], S. R. Zaki[1], D. M. Blau[1], C. D. Paddock[1], L. K. McDougal[1], D. M. Engelthaler[6], P. S. Keim[6], C. C. Roe[6], H. Akselrod[7], M. J. Kuehnert[1,†] and S. V. Basavaraju[1,*,†]

Advisory Committee; ED, Emergency Department; FFPE, formalin-fixed paraffin-embedded; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, nonmedical injection drug use; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; OPTN, Organ Procurement and Transplantation Network; PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis; PHS, U.S. Public Health Service; PVL, Panton-Valentine leukocidin;

- Both doing well, without infection more than one year after transplant

MRSA: Methicillin-resistant Staphylococcus aureus

Monitoring Recipients for Post-transplant Infection and Donor-derived Disease

- **Post-transplant formal monitoring system limited to**
  - Only HIV, HBV, and HCV
- **For other diseases, high index of suspicion needed**

PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation

Figure 6. Pre- and posttransplant recipient test recommendations when a donor is at increased risk for HIV, HBV, or HCV infection; the donor's risk for HIV, HBV, and HCV infection is unknown; or the donor is infected with HCV or HBV[a]

Pre-transplant test	*Timing of pre-transplant test*	*Posttransplant test*	*Timing of posttransplant test*
No recommendation on type of assay	During hospital admission for the organ transplant, but prior to organ implantation	HIV NAT or HIV Ag/Ab combination assay HCV NAT HBV NAT and HBsAg	1–3 months
		Anti-HBs, anti-HBc, and either HBV NAT or HBsAg	At 12 months

[a]Unless transplant patient infection was documented pre-transplant

HIV: Human Immunodeficiency virus.
NAT: Nucleic acid assay testing.
PHS: Public Health Service.
Public Health Reports: July-August 2013 Volume 128

HBV: Hepatitis B virus.
HCV: Hepatitis C virus.
Ag/Ab: Antigen and antibody.

Patient Safety Initiatives to Reduce Donor-derived Disease

- **Donor centers must report:**
  - ***Relevant new post-transplant findings*** to all accepting transplant centers including cultures, pathology findings, autopsy results
  - Any "***new disease or malignancy***… that may be transmitted to transplant recipients" to the Organ Procurement and Transplant Network (OPTN)

- **Donor and recipient centers must report:**
  - ***If concern for donor-derived disease arises*** to the OPTN patient safety system including:
    - Infection or disease in both donor and recipient
    - Similar disease in multiple recipients of same donor
    - Other substantive concern for donor origin of disease

Public Health Reports: July-August 2013 Volume 128

Ad Hoc Disease Transmission Advisory Committee (DTAC)

- Part of OPTN patient safety program
- Examine and classify potential donor-derived transmission through transplantation of infection or malignancy
- Educate transplant community
- Help change policy and improve processes
- Membership includes CDC, FDA, transplant centers, transplant infectious disease, lab testing, organ procurement organizations

OPTN: Organ Procurement and Transplantation Network

Cumulative Incidence of Disease Transmission: PDDTE Reported Through 2013 Involving Donors Recovered 2008-2012

	Deceased Donors N (%)	Living Donors N (%)	Total N (%)
Donors recovered	40,223	31,278	71,501
Donors with PDDTE	763 (1.9%)	24 (0.08%)	787 (1.1%)
Donors with proven/probable PDDTE	141 (0.4%)	5 (0.02%)	146 (0.2%)
Total recipient transplants performed	110,402	31,277	141,679
Recipients with proven/probable disease	177 (0.16%)	4 (0.01%)	181 (0.13%)
Recipient deaths due to proven/probable disease	39 (0.04%)	1 (0.003%)	40 (0.03%)

33,407 individuals died between 2008-2012 while on the wait list

OPTN

PDDTE: Potential donor-disease transmission events

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

Infection Reports to the DTAC: 2005-2011

Disease	Number of Donor Reports	Number of Recipients with Confirmed Transmission	Number of DDD-Attributable Recipient Deaths
Virus[a]	166	48	16
Bacteria[b]	118	34	9
Fungus[c]	75	31	10
Mycobacteria[d]	53	10	3
Parasites[e]	35	22	7
Total Infections	**447**	**145**	**45**

In 2013: 31/284 (11%) cases reviewed by CDC

[a] **Adenovirus, HBV, HCV, HEV, HIV, HTLV, herpes simplex, influenza, LCMV, Parainfluenza (PIV)-3, Parvovirus B19, rabies, West Nile virus**

[b] ***Acinetobacter,*** **Brucella** ***Enterococcus*** **(including VRE),** ***Ehrlichia*** **spp,** ***E. coli*****, Gram Positive Bacteria,** ***Klebsiella*****, Legionella, Listeria, Lyme Disease, Nocardia,** ***Pseudomonas*****, Rocky Mountain Spotted Fever,** ***Serratia ,*** ***S. aureus*** **(MRSA), Streptococcus spp, Syphilis,** ***Veillonella*****; bacterial meningitis and bacterial emboli**

[c] ***Aspergillus*** **spp,** ***Candida*** **spp,** ***Coccidioides imitis*****,** ***Cryptococcus neoformans*****,** ***Histoplasma capsulatum*****, zygomyces**

[d] **Tuberculosis, non-TB mycobacteria**

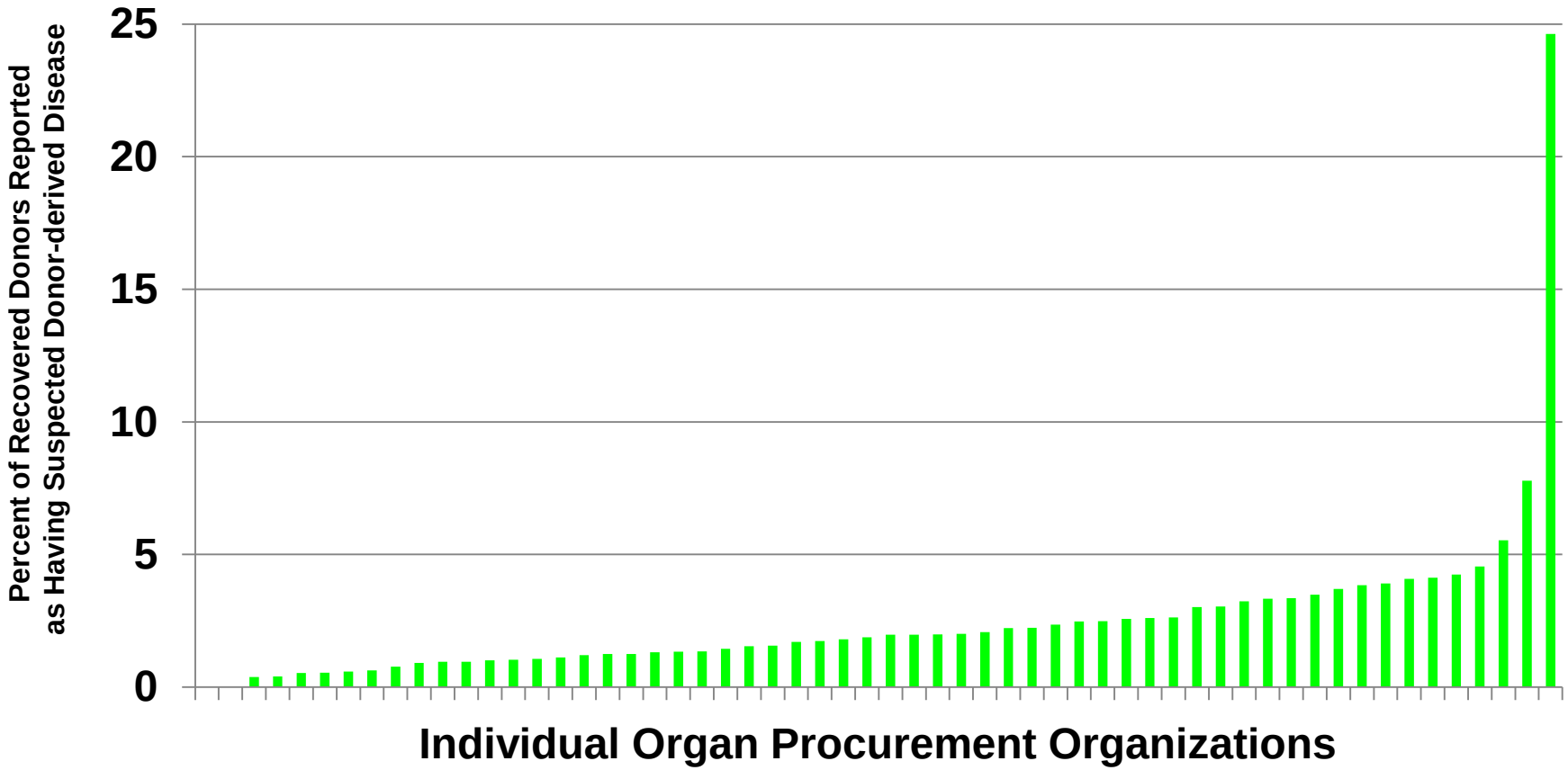
[e] **Babesia,** ***Balmuthia mandrillaris*****, Chagas (*** ***Trypanosoma cruzi*****),** ***Naegleria fowleri miasis, Strongyloides***

OPTN

DTAC: Disease Transmission Advisory Committee DDD: Donor-derived disease
Data includes cases classified as possible, probable or proven from 2005-2007 as published in AJT, and all reviewed cases from 2008-2011.

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

Variability of Reporting Suspected Donor-derived Diseases by Organ Procurement Organizations



Cases reported through 2013.

Selected DTAC Patient Safety Projects

- **Demonstrated harm associated with universal HTLV-1/2 donor testing**
- **Formal guidance documents**
  - TB risk assessment for living donors
  - Geographic and seasonally limited disease
  - West Nile virus testing
  - Central nervous system infections in deceased donors
  - Ebola virus disease screening for potential donors
- **Translation of public health service guidelines for preventing transmission of HIV, HBV, HCV into policy**
- **Process to improve communication between organ procurement organizations and transplant centers**

HTLV-1/2: Human T-cell lymphotropic virus, types 1 and 2

Kaul DR, et al. *Am J Transplant* 2010.
Nett RJ, et al. *Transpl Infect Dis* 2012.

Novel Transplant-Associated Infections

Sherif R. Zaki, MD, PhD

Chief, Infectious Diseases Pathology Branch

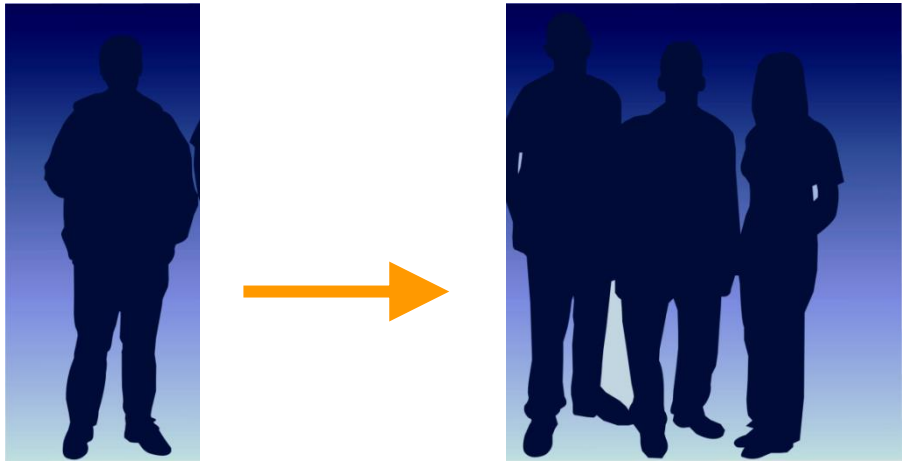
Division of High-Consequence Pathogens and Pathology

National Center for Emerging and Zoonotic Infectious Diseases

Centers for Disease Control and Prevention

Unexpected Donor-derived Infections Associated with Organ Transplantation

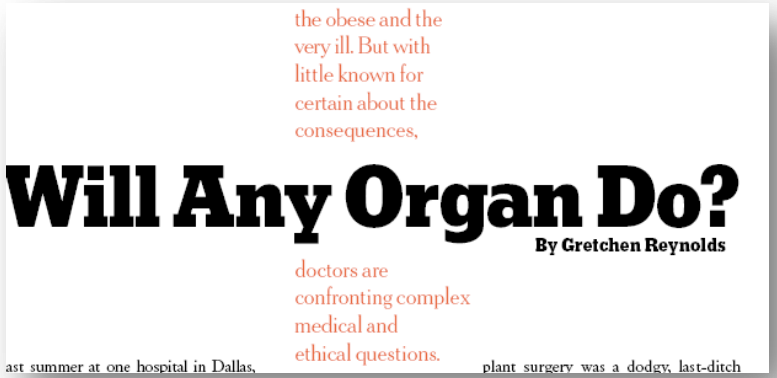
- **Multiple challenges**
  - Unexpected or unrecognized at time of death
  - Not screened for in donor
  - Unknown incidence (presumed low)
  - Associated with significant morbidity and mortality
  - High-profile events



Single donor

Multiple recipients

Unexpected Donor-derived Infections



the obese and the very ill. But with little known for certain about the consequences,

Will Any Organ Do?

By Gretchen Reynolds

doctors are confronting complex medical and ethical questions.

ast summer at one hospital in Dallas, plant surgery was a dodgy, last-ditch

NY Times, 2005 (Rabies)

The New

Transplant Patients Die of Rodent Disease

The Virus, Undetected in Organ Donors, Is Linked to 6 Cases

By KATIE ZEZIMA and DENISE GRADY

Three organ recipients in southern ew England have died in the past

lance system for organ-transplant-transmitted infections." He added, "Without a clinician reporting it, we're not going to know."

Organ donors are already tested

transmitted West Nile virus.

At the Petsmart store in Warwick, 102 small rodents were removed this past weekend, and in preliminary tests two came up positive for the vi-

NY Times, 2005 (LCMV)

Officials Re-examining Organ Transplant Rules

Brain Infection in Two Patients Raises Issue

By DENISE GRADY

The plight of two kidney transplant patients who contracted a brain infection from an organ donor is prompting health officials to re-examine their policies on using people with certain neuro-

vising in the patients' treatment.

Dr. Matthew J. Kuehnert, the director of the office of blood, organ and other tissue safety at the disease centers, said that transplant patients are sometimes an early warning system for new in-

NY Times, 2009 (Amoeba)

WEST NILE CASES RAISING QUESTIONS OVER TRANSPLANTS

NO TEST TO SCREEN BLOOD

Weeks Needed to Determine if Operation or a Transfusion Allowed Transmissions

NY Times, 2002 (WNV)

Novel and Emerging Donor-derived Transplant-transmitted Infections, 2002–2014

- **West Nile virus**
  - 6 clusters
- **Lymphocytic choriomeningitis virus**
  - 5 clusters
- **Rabies**
  - 2 clusters
- **Balamuthia**
  - 2 clusters
- **Microsporidiosis**
  - 2 clusters

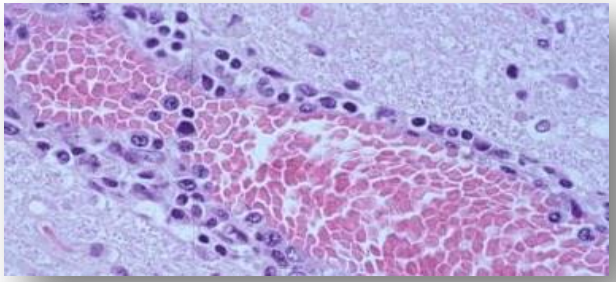
West Nile Virus (WNV) in an Organ Donor and Four Transplant Recipients, August 2002

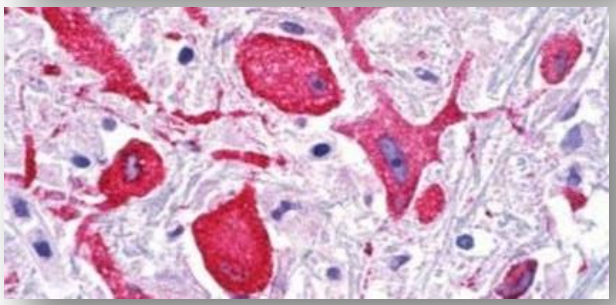
Organ DONOR
- ✓ Female victim of a car accident
- ✓ Received multiple transfusions
- ✓ Patient died

All organ RECIPIENTS became febrile (2 kidney, liver, heart)

One kidney recipient died
- ✓ Thought to have had WNV
- ✓ Seronegative for WNV

But IHC and PCR showed WNV encephalitis





Viral antigens in red, IHC

Stimulated trace back investigation

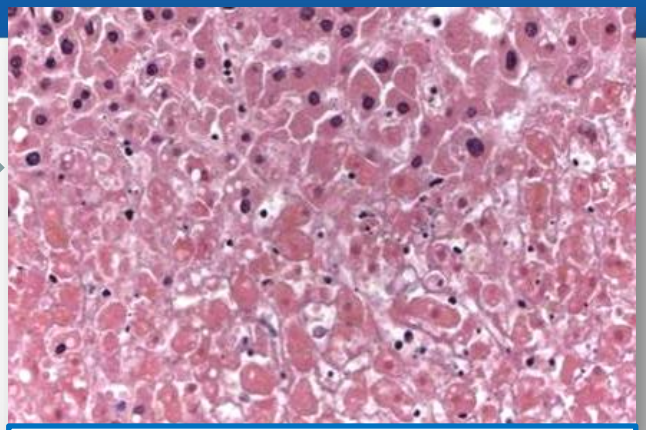
Blood components from 63 donors
- ✓ Only one component was WNV IgM positive
- ✓ Only one component was WNV PCR positive, but WNV IgM negative

IHC: Immunohistochemistry
PCR: Polymerase chain reaction
Iwamoto M, et al. *NEJM* 2003.

Single Organ Donor and Four Transplant Recipients, 2003

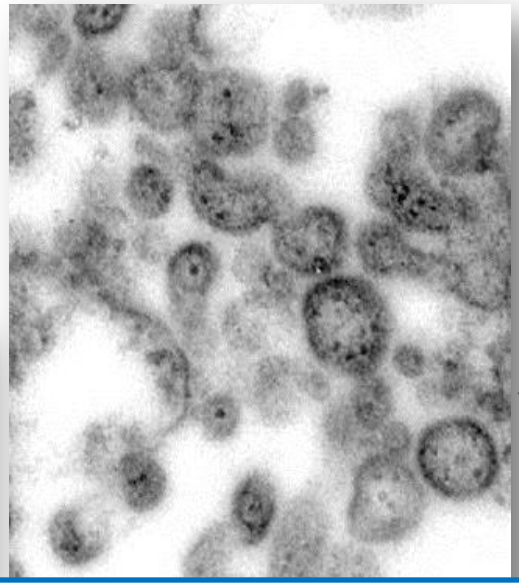
Organ DONOR
- ✓ Male who died of a head trauma

All 4 organ RECEPIENTS died 9-76 days post-transplant



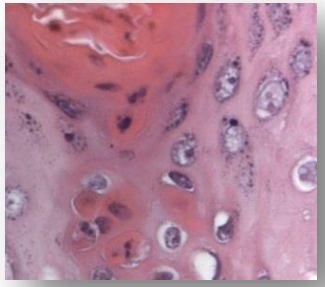
Massive hepatocellular necrosis

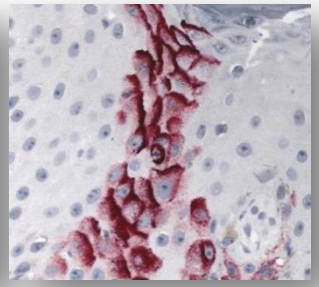
Initial IHCs for herpesviruses and adenoviruses were negative



LCMV culture results available after 6 weeks

IHC confirmed LCMV in all recipients but lack of donor tissue tracing back to donor





Viral antigens in red, IHC

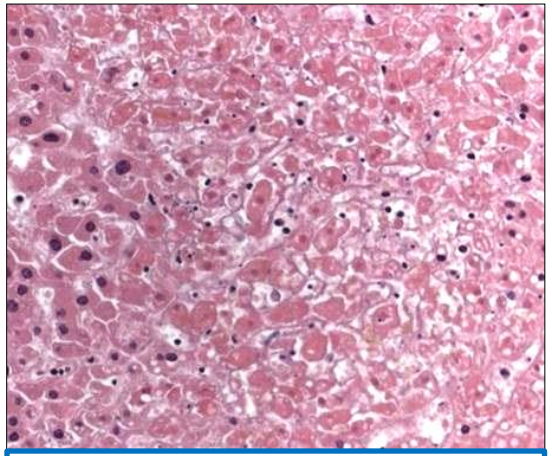
LCMV: Lymphocytic choriomeningitis virus

Fischer S, et al. *NEJM* 2006.

Second LCMV Cluster in Three Transplant Recipients, 2005

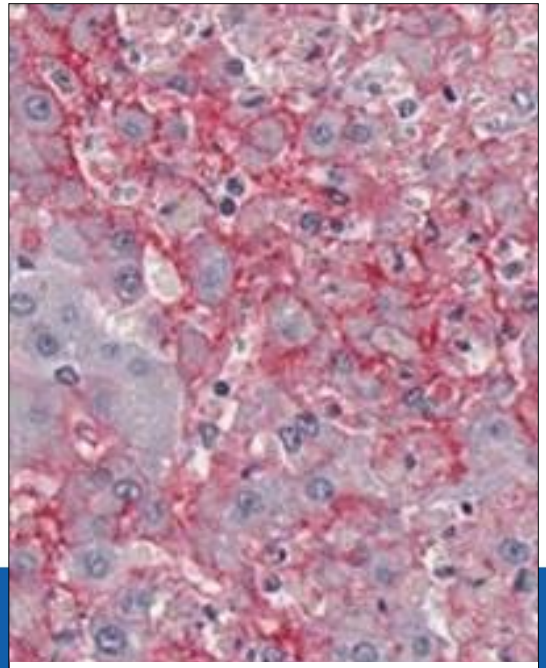
Organ DONOR
- ✓ Woman who died of a stroke.

3 of 4 organ RECIPIENTS die 23-26 days post-transplant
1 renal recipient alive



Massive hepatocellular necrosis

IHC and PCR confirmed LCMV in tissues from all 4 recipients

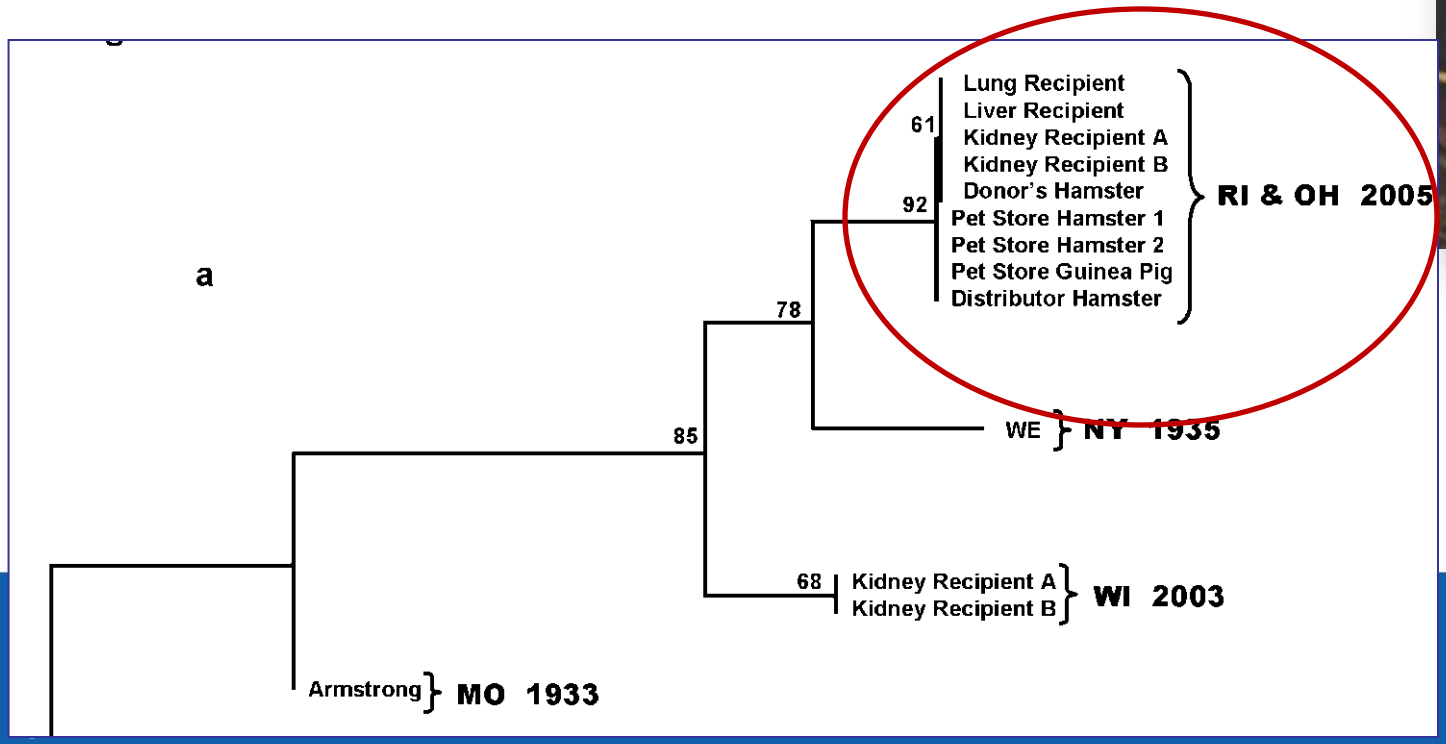


Viral antigens in red, IHC

Stimulated trace back investigations

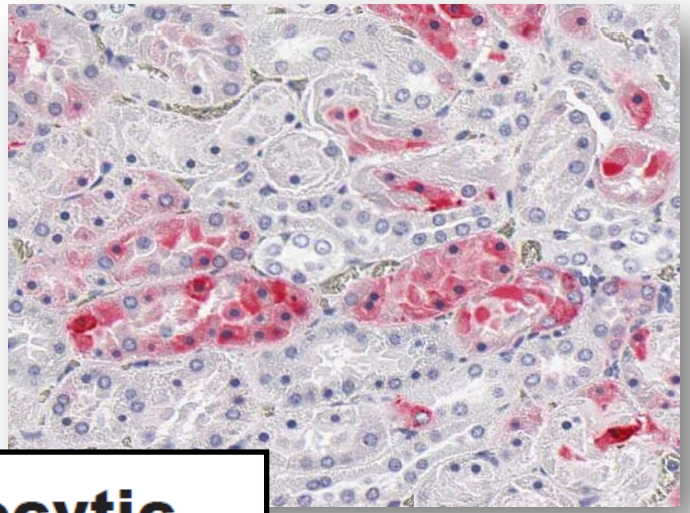
Where Did the Virus Come From?

- Donor's daughter had a pet hamster that was sick
- Donor cleaned the cage and where the hamster played



Chasing escaped mice at Ohio facility

Viral antigens in red, IHC



Pet Rodents and Fatal Lymphocytic Choriomeningitis in Transplant Patients

Brian R. Amman,[*1] Boris I. Pavlin,[*1,2] Cesar G. Albariño,[*] James A. Comer,[*] Bobbie R. Erickson,[*] Jennifer B. Oliver,[*] Tara K. Sealy,[*] Martin J. Vincent,[*] Stuart T. Nichol,[*] Christopher D. Paddock,[*] Abbigail J. Tumpey,[*] Kent D. Wagoner,[*3] R. David Glauer,[†] Kathleen A. Smith,[‡] Kim A. Winpisinger,[‡] Melody S. Parsely,[§] Phil Wyrick,[¶] Christopher H. Hannafin,[#] Utpala Bandy,[**] Sherif Zaki,[*] Pierre E. Rollin,[*] and Thomas G. Ksiazek[*]

Amman BR, et al. *Emerg Infect Dis* 2007.

As a Result, Risk Assessment and Screening Questions Improved

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	–	+	+	–

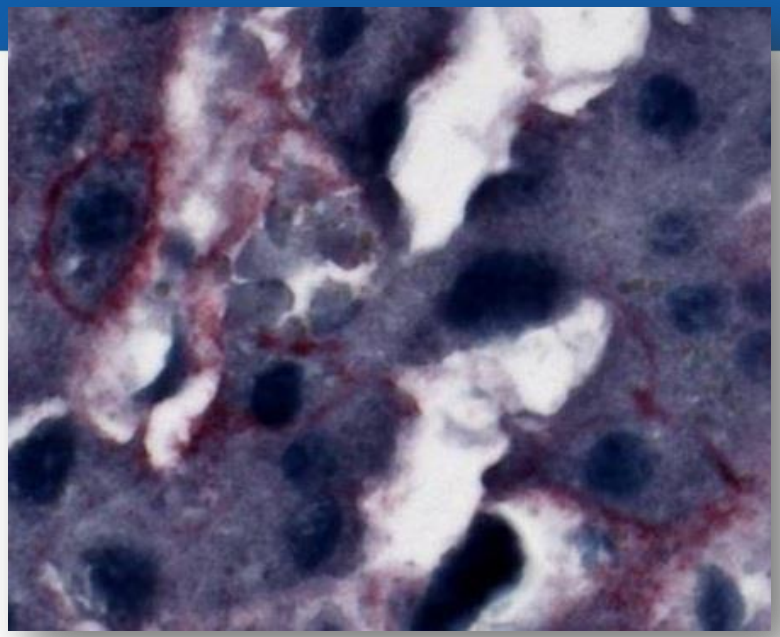
Third LCMV Cluster Detected Using Advanced Molecular Detection

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2008 VOL. 358 NO. 10

A New Arenavirus in a Cluster of Fatal Transplant-Associated Diseases

- LCMV in a cluster of fatal transplant-associated disease
- 3 recipients from single donor who died with cerebral hemorrhage
- 100 times faster than Sanger sequencing
- 25 million bases in 4 hours



Viral antigens in red, IHC

GENOMICS

Massively parallel sequencing

Yu-Hui Rogers and J. Craig Venter

A sequencing system has been developed that can read 25 million bases of genetic code — the entire genome of some fungi — within four hours. The

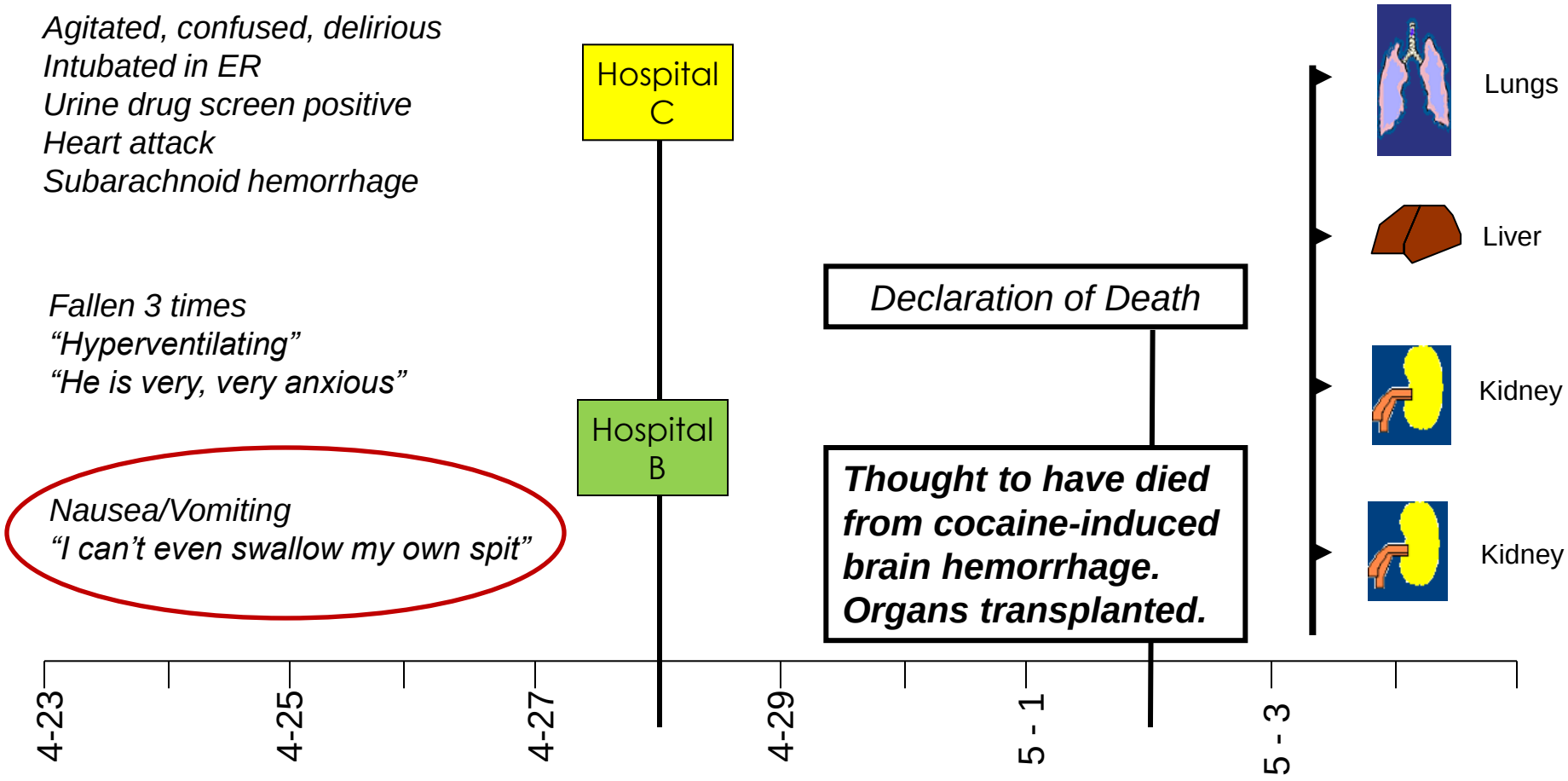
LCMV: Lymphocytic choriomeningitis virus

Another Unusual Infection Transmitted from Organ Donor to Four Transplant Recipients

- In 2004, CDC contacted by pathologist in Texas
- Two transplant recipients with unexplained deaths
- Third transplant recipient with altered mental status
- Connection of a common donor among cases was determined by families whose loved ones were in the intensive care unit

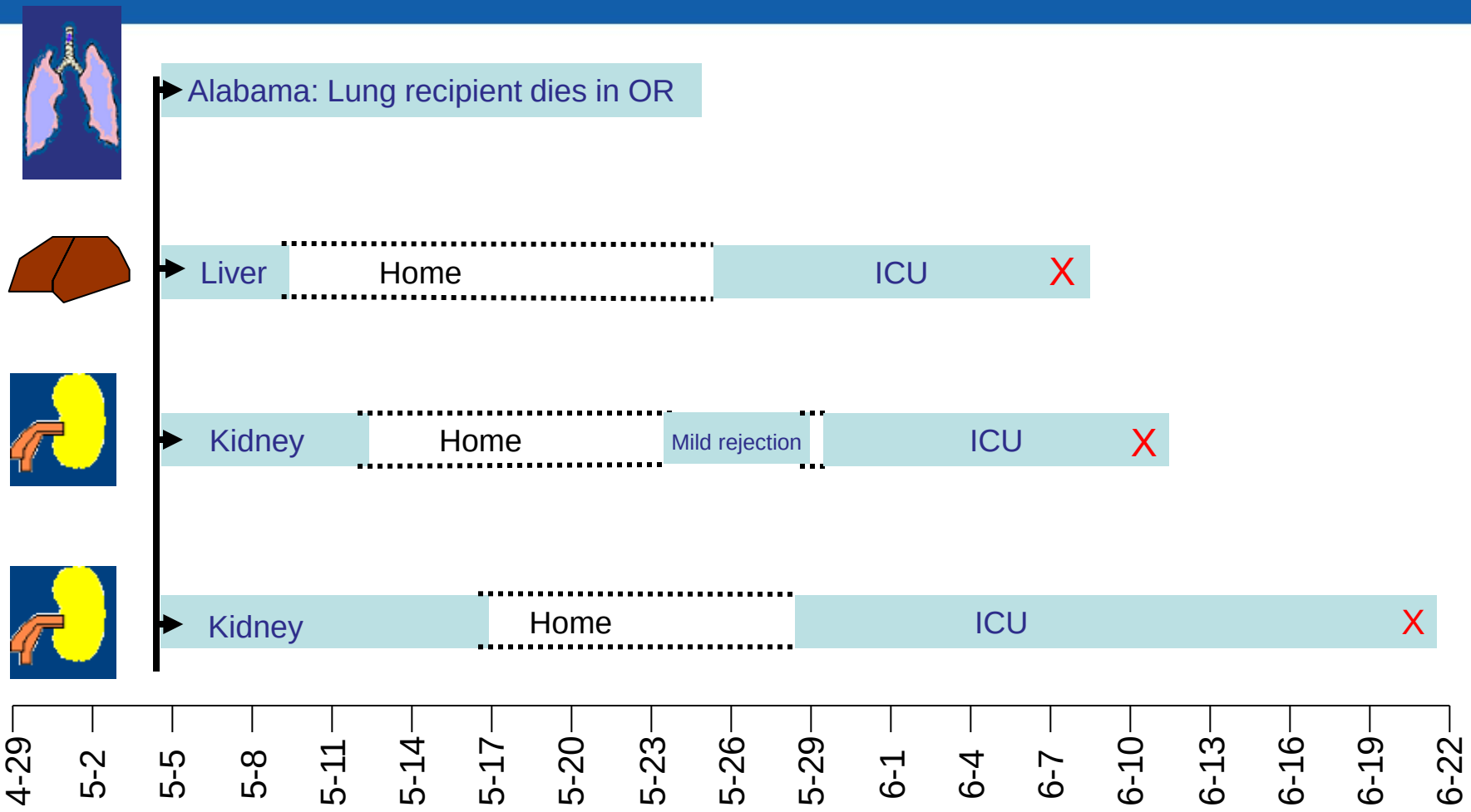
Srinivasan A, et al. *NEJM* 2005.

Twenty year-old Male Donor



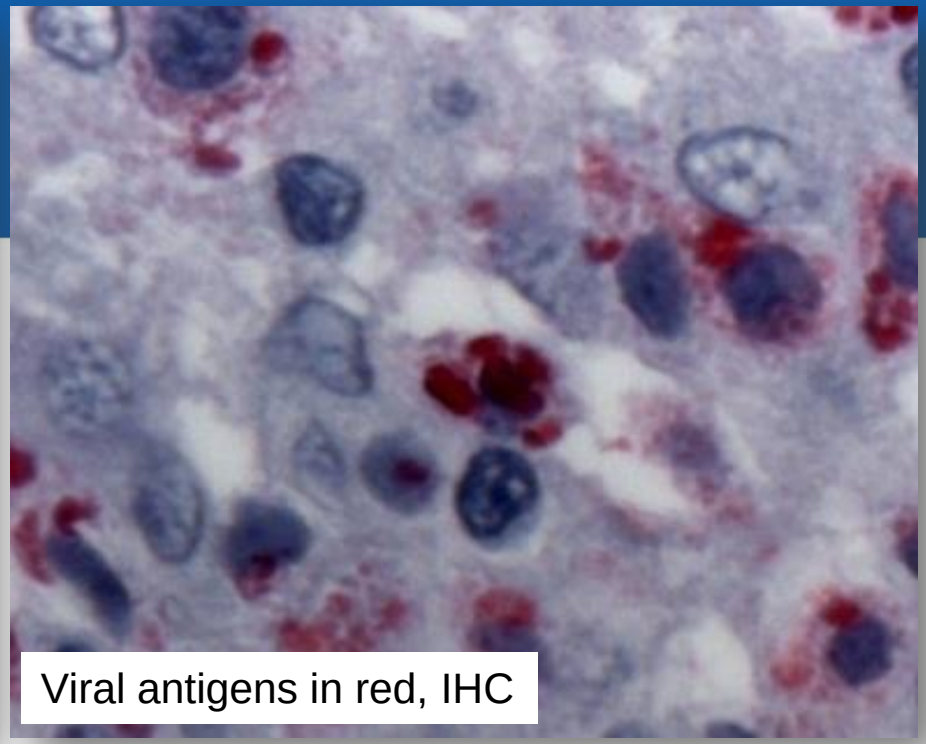
Organ donor timeline, April–May 2004

Background on the Four Recipients at Hospital A, Texas

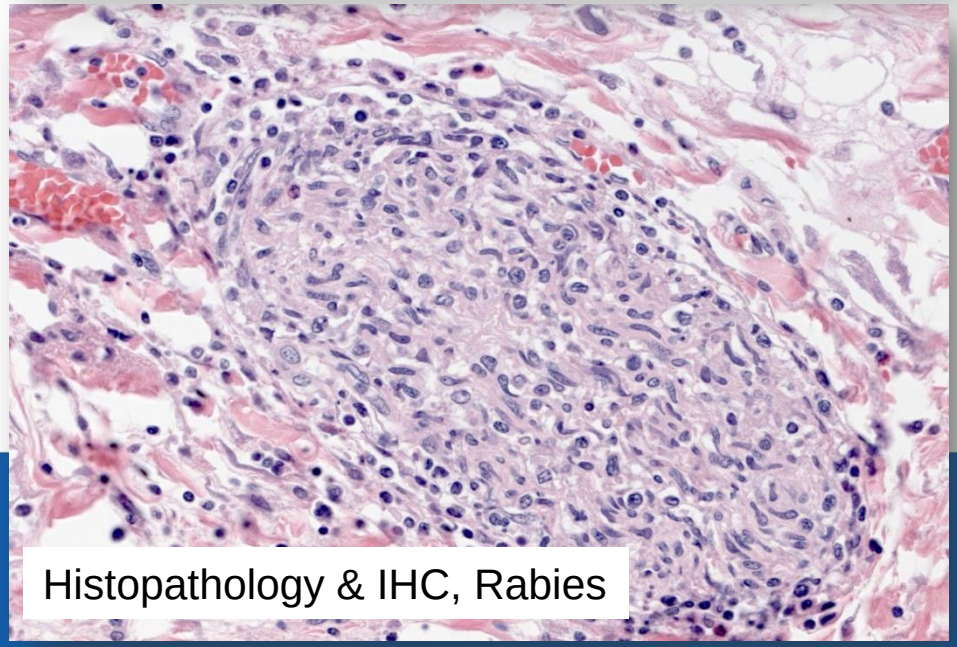


Organ recipient timeline, April–June 2004

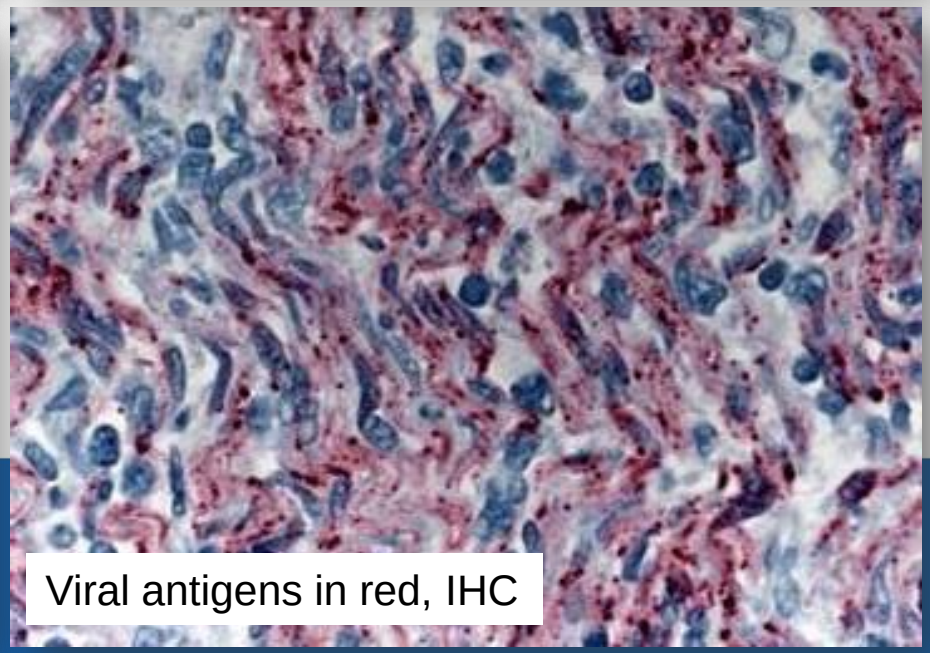
Negri bodies, indicating rabies!



Viral antigens in red, IHC



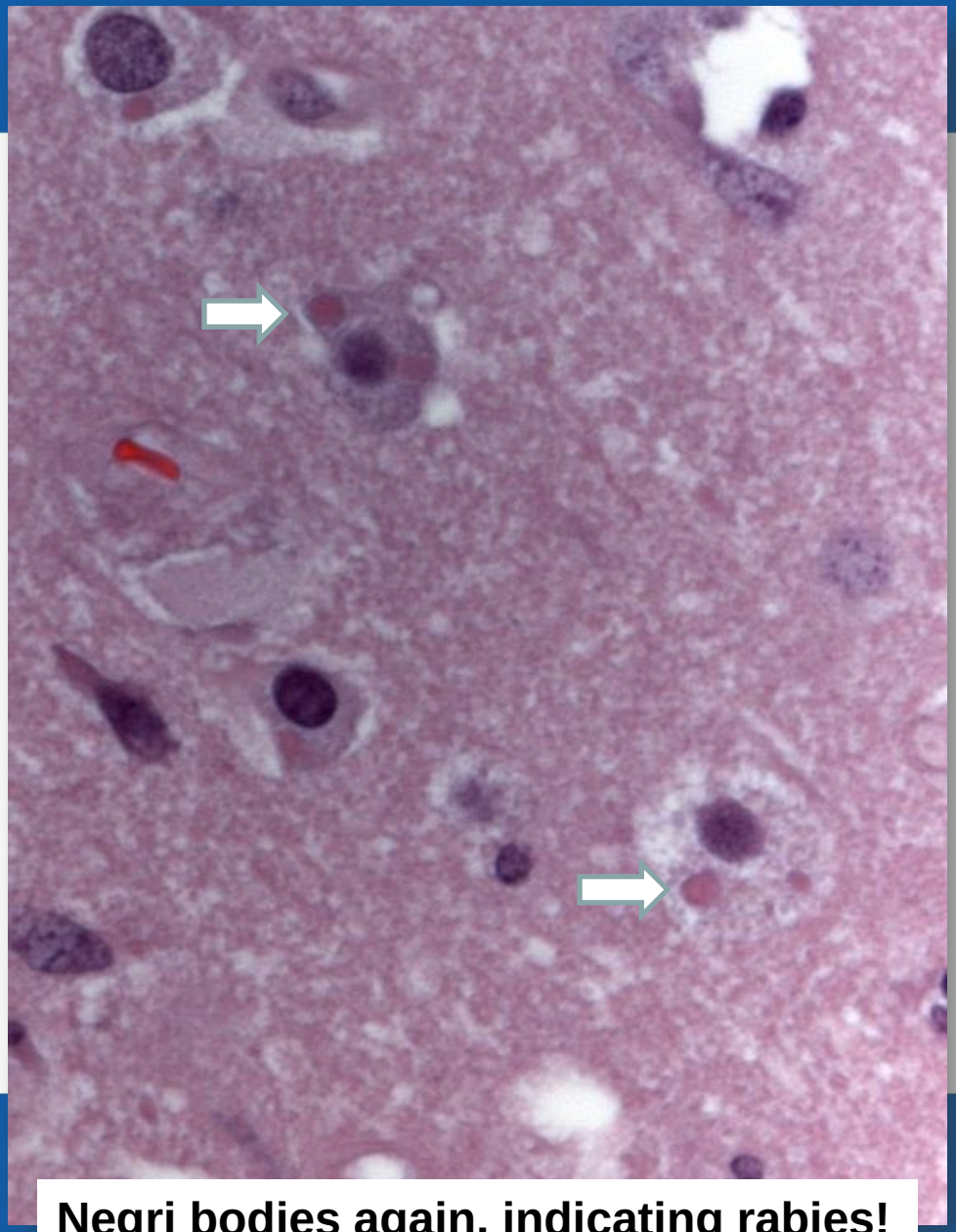
Histopathology & IHC, Rabies



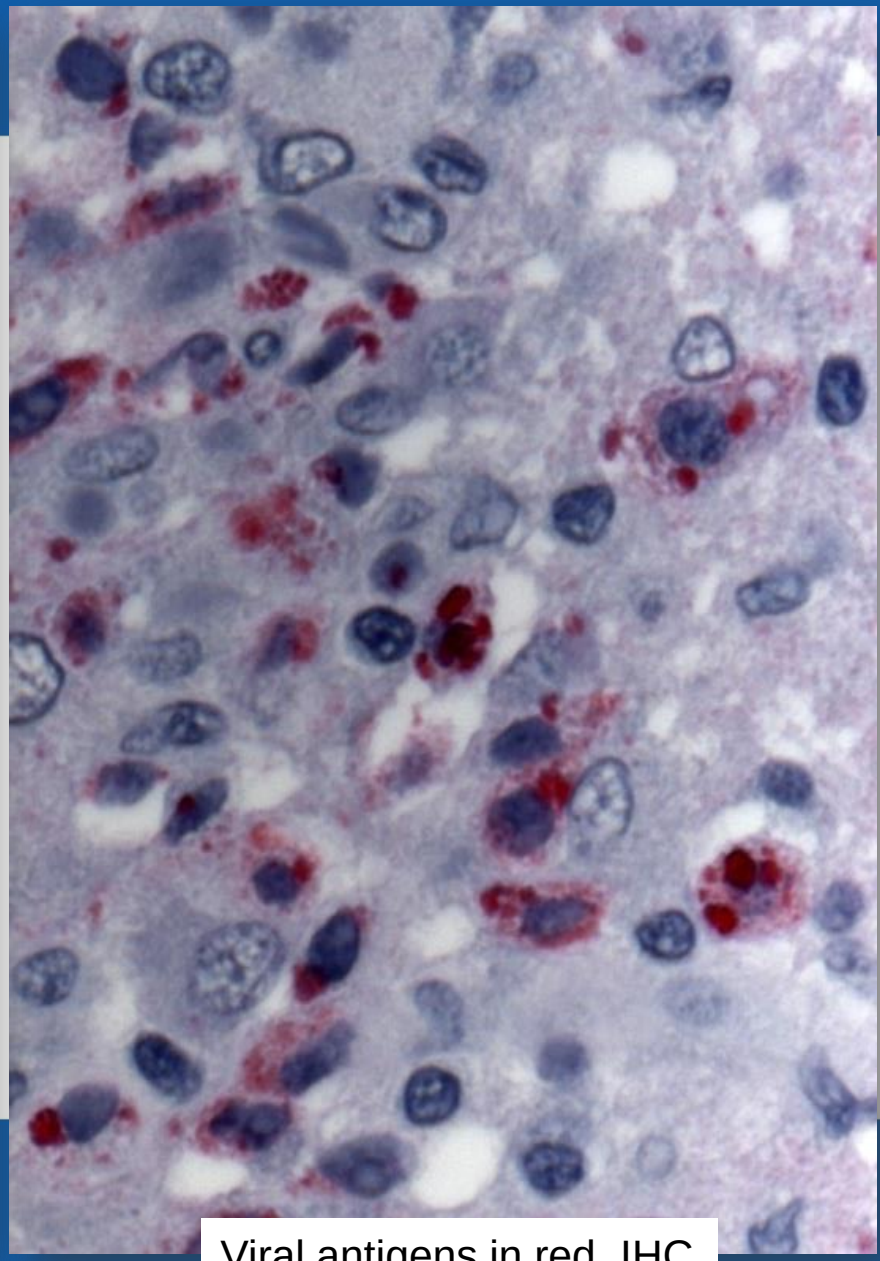
Viral antigens in red, IHC

The Persistent Pathologist…

- **Recalled 4th death due to encephalitis in organ transplant recipient**
- **Reviewed autopsy**
  - Consistent with viral encephalomyelitis due to West Nile virus
  - Received liver transplant
  - Different donor than other cases
- **Specimens sent to CDC for further investigation**



Negri bodies again, indicating rabies!

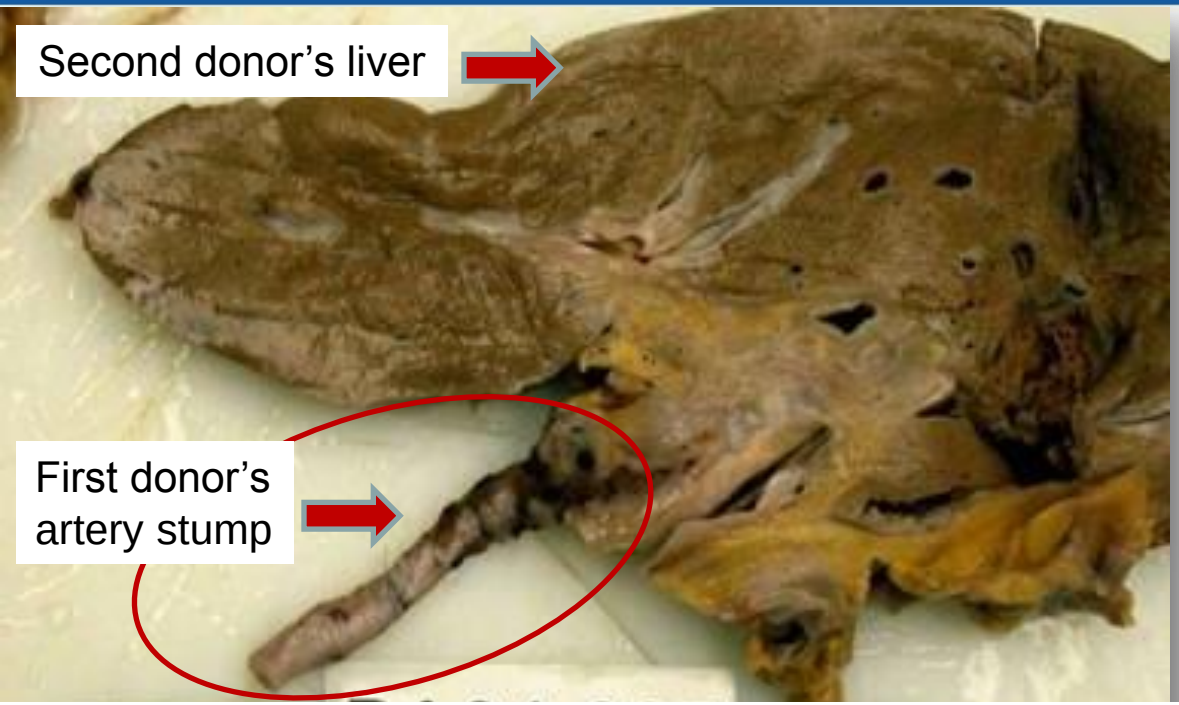


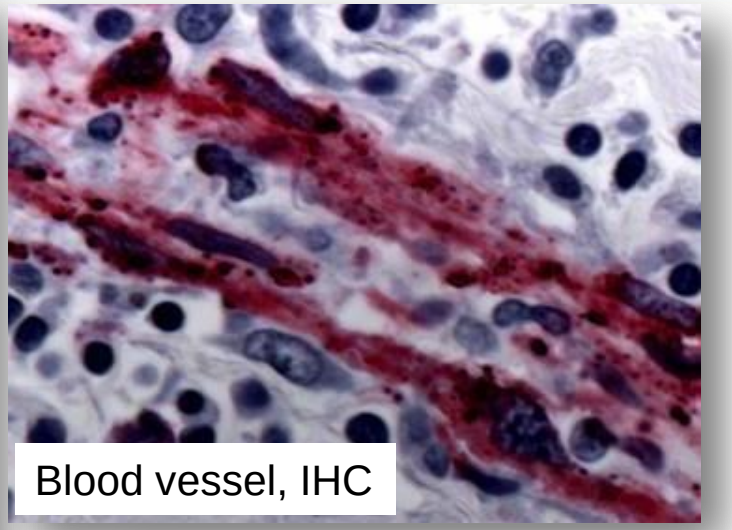
Viral antigens in red, IHC

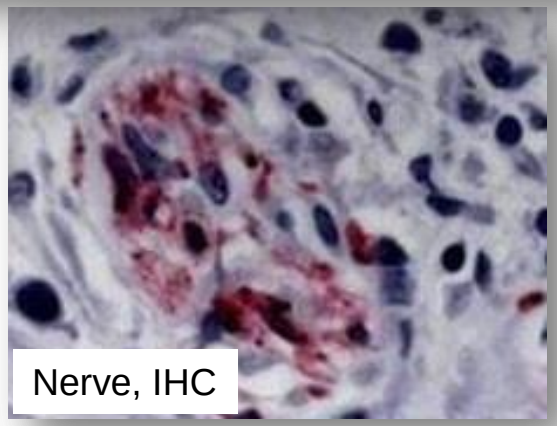
What Was the Source of Infection?

- Was there a link between first three cases and this case?
- Was the recipient's infection unrelated to transplant?
- Was the second donor infected?
- Was this healthcare-worker transmitted rabies?

Two Donors for One Transplanted Organ

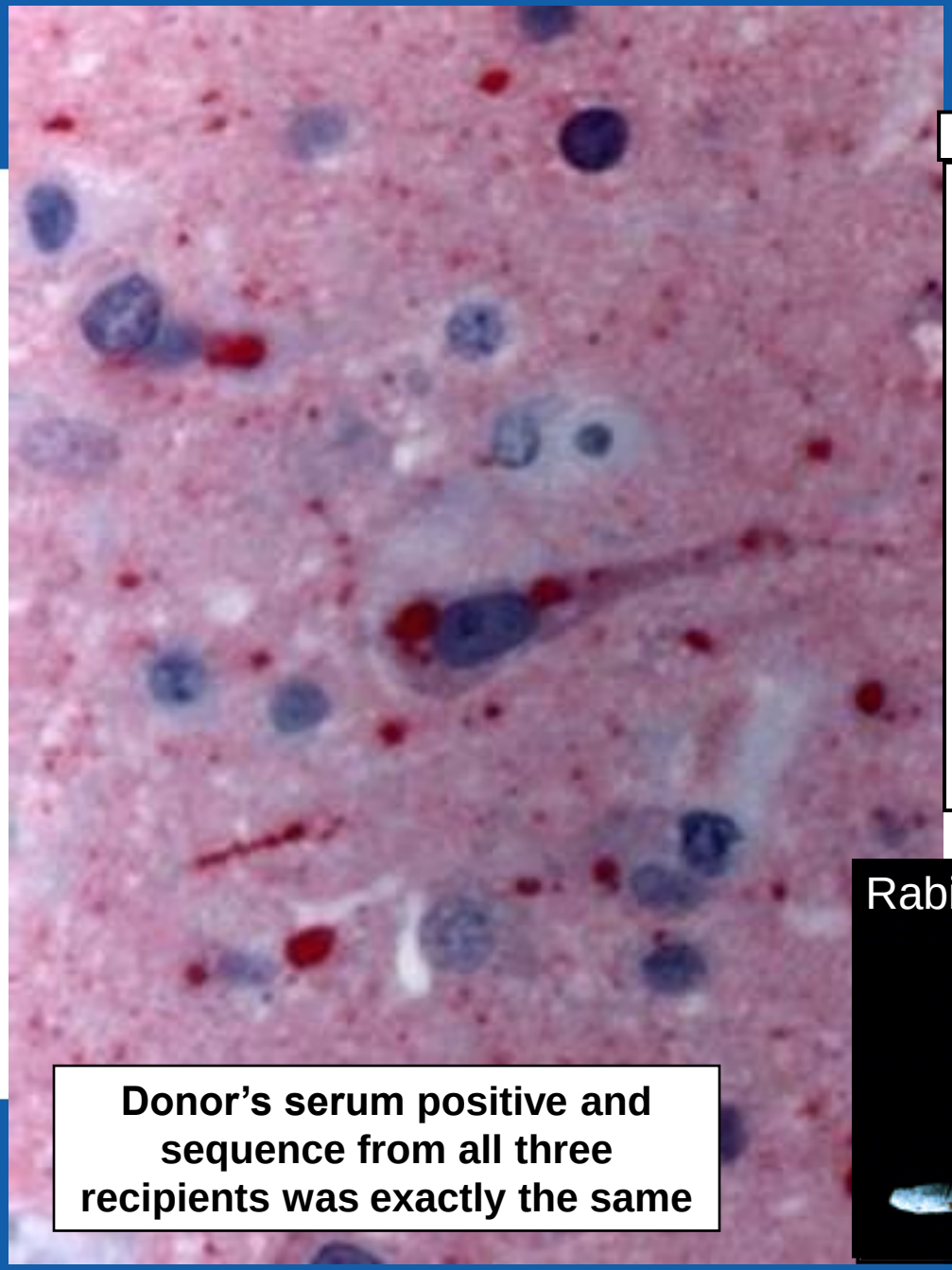






- **As a result, OPTN changed their requirements and instituted better tracking of donor organs and tissues**

IHC: Immunohistochemistry
OPTN: Organ Procurement and Transplantation Network



Donor's serum positive and sequence from all three recipients was exactly the same

N ENGL J MED 352;11 WWW.NEJM.ORG MARCH 17, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

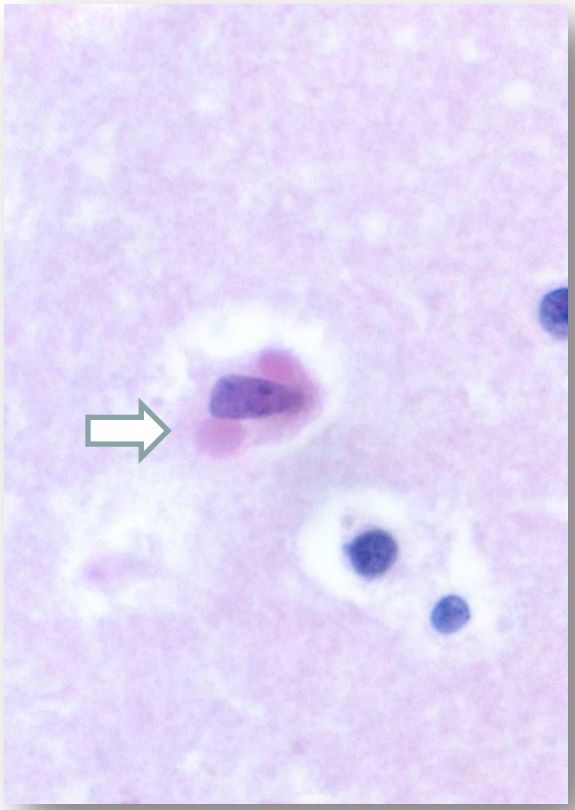
Transmission of Rabies Virus from an Organ Donor to Four Transplant Recipients

Arjun Srinivasan, M.D., Elizabeth C. Burton, M.D., Matthew J. Kuehnert, M.D., Charles Rupprecht, V.M.D., Ph.D., William L. Sutker, M.D., Thomas G. Ksiazek, D.V.M., Ph.D., Christopher D. Paddock, M.D., Jeannette Guarner, M.D., Wun-Ju Shieh, M.D., Ph.D., Cynthia Goldsmith, M.S., Cathleen A. Hanlon, V.M.D., Ph.D., James Zoretic, M.D., Bernard Fischbach, M.D., Michael Niezgoda, M.S., Waleed H. El-Feky, M.D., Lillian Orciari, M.S., Edmund Q. Sanchez, M.D., Anna Likos, M.D., M.P.H., Goran B. Klintmalm, M.D., Denise Cardo, M.D., James LeDuc, Ph.D., Mary E. Chamberland, M.D., M.P.H., Daniel B. Jernigan, M.D., M.P.H., and Sherif R. Zaki, M.D., Ph.D., for the Rabies in Transplant Recipients Investigation Team*

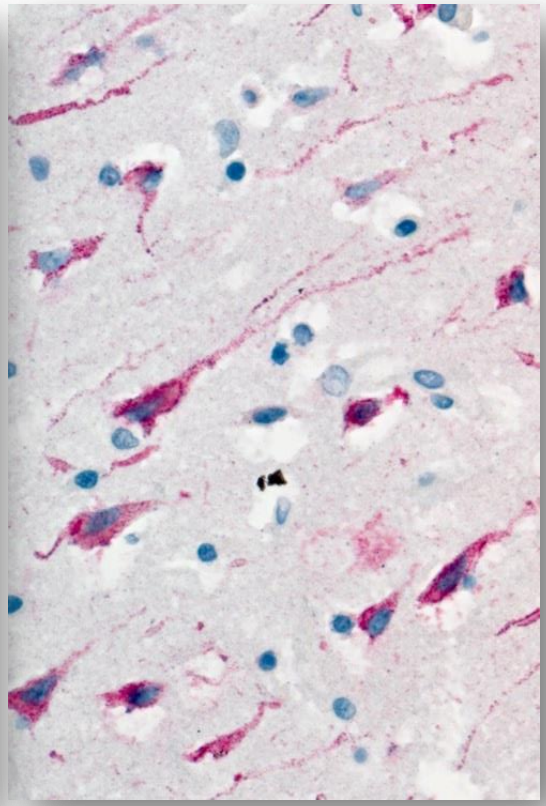
Rabies variant from Mexican Free-Tailed Bat

Raccoon Rabies Virus Variant Transmission Through Solid Organ Transplantation, 2013

- Kidney transplant recipient died 18 months post-transplant
- Donor with a history of raccoon exposure died with fever, vomiting, seizures and dysphagia
- Rabies positive by histopathology and PCR
- Three other organ recipients completed post-exposure prophylaxis and remained asymptomatic with serum rabies neutralizing antibodies



Negri bodies



Viral antigens in red, IHC

IHC: Immunohistochemistry
PCR: Polymerase chain reaction
Vora NM, et al. *JAMA* 2013.

Impact from Clusters of Transmitted Rabies

- **From the bat cluster, we learned**
  - Rabies could be transmitted through solid organ transplant
  - Tracking the organs and tissues of each donor is critical
- **Instituted better mechanism to track donor and the multiple recipients**

- **From the raccoon cluster, we learned**
  - Rabies transmitted from raccoons may have a longer incubation
  - Three recipients were pre-emptively treated
- **Post-exposure prophylaxis was effective in recipients who received donor-infected organs, even for rabies**

An Unusual Infection in an Organ Donor and Four Transplant Recipients, 2009

Organ DONOR
- ✓ 4 year-old male
- ✓ Presumed to have died from ADEM following Influenza A infection
- ✓ Ring-enhancing brain lesions

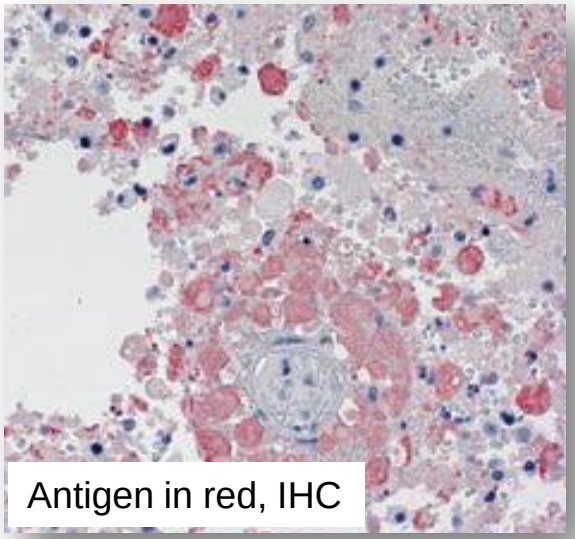
3 organ RECEPIENTS
- ✓ 3 weeks after transplant, kidney recipient admitted with seizures and altered mental status
- ✓ Liver and heart recipients asymptomatic

From donor autopsy tissues, CDC found

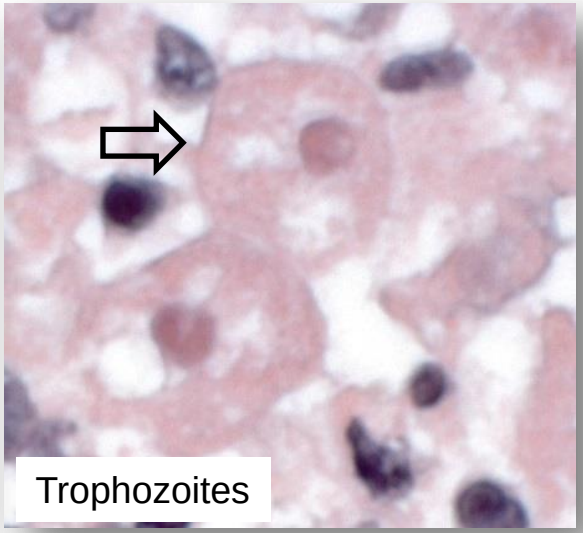
- ✓ Granulomatous amebic encephalitis caused by *Balamuthia mandrillaris*

From further investigation

- ✓ Confirmed in both kidney recipients
- ✓ One kidney recipient died
- ✓ Other three recipients recovered with therapy



Antigen in red, IHC



Trophozoites

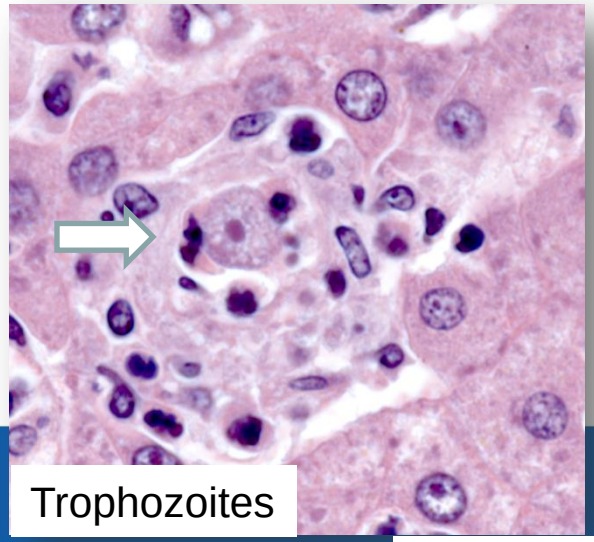
ADEM: Acute demyelinating encephalomyelitis
IHC: Immunohistochemistry

Another *Balamuthia* Infection Transmitted by Organ Donor to Four Transplant Recipients, 2010

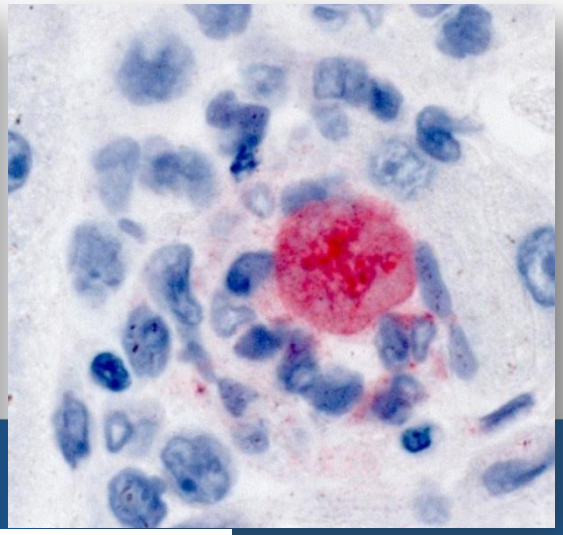
- **Two of four transplant recipients present with encephalitis**
  - Common donor died from presumed stroke
- **Of the four transplant recipients**
  - Liver recipient already died
  - Kidney-pancreas recipient unconscious
  - Heart and other kidney recipients asymptomatic

Liver Recipient

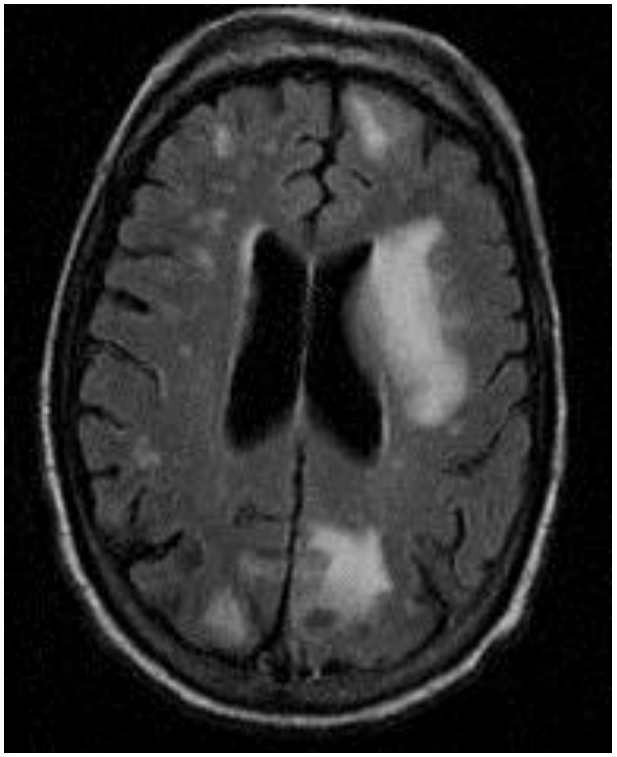
- **Post-transplant day (PTD) 18 presents with**
  - Double vision and difficulty with walking
  - Febrile; loses consciousness
- **Brain biopsy inconclusive**
- **Died on PTD 26**



Trophozoites

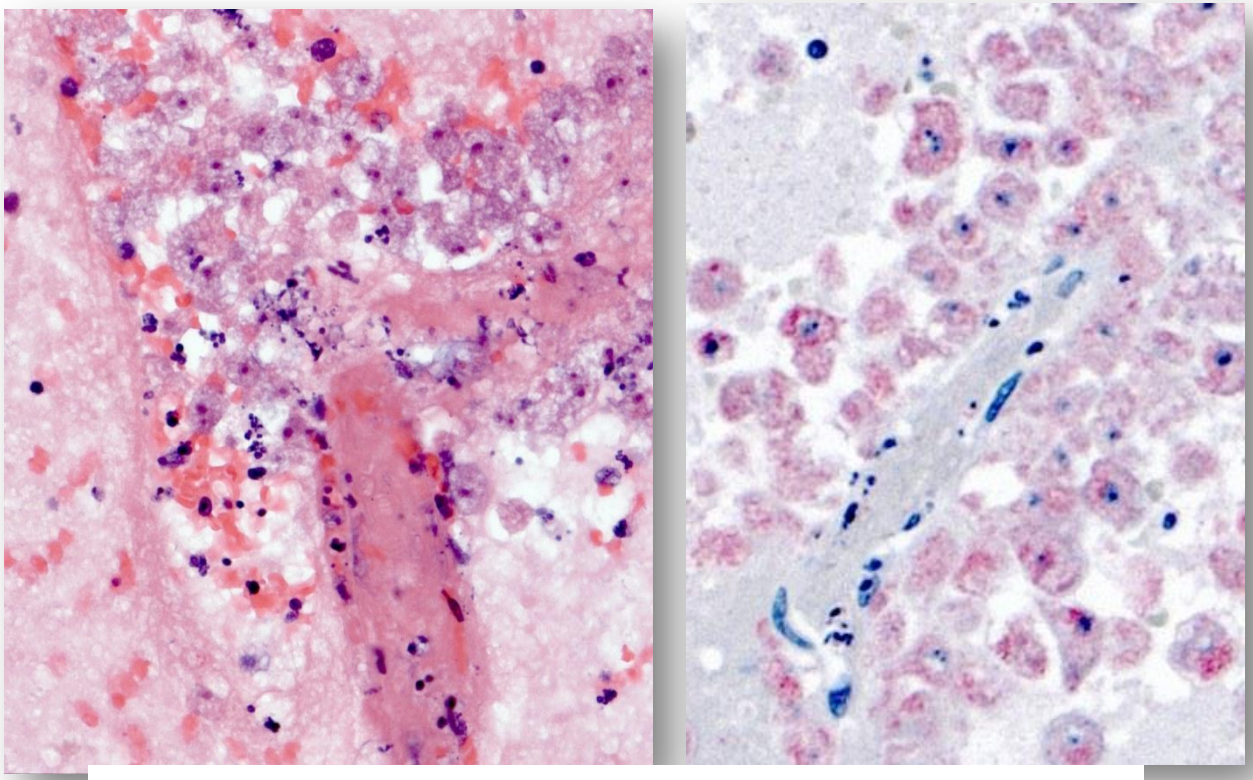


Liver at autopsy

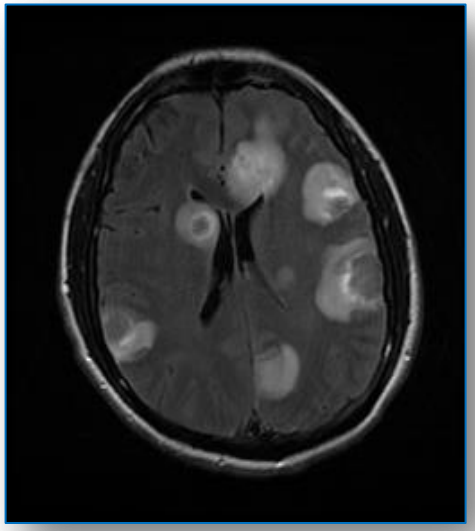


Neuroimaging:
Ring-enhancing lesions

Kidney-Pancreas Recipient



Brain biopsy: IHC and PCR Balamuthia positive



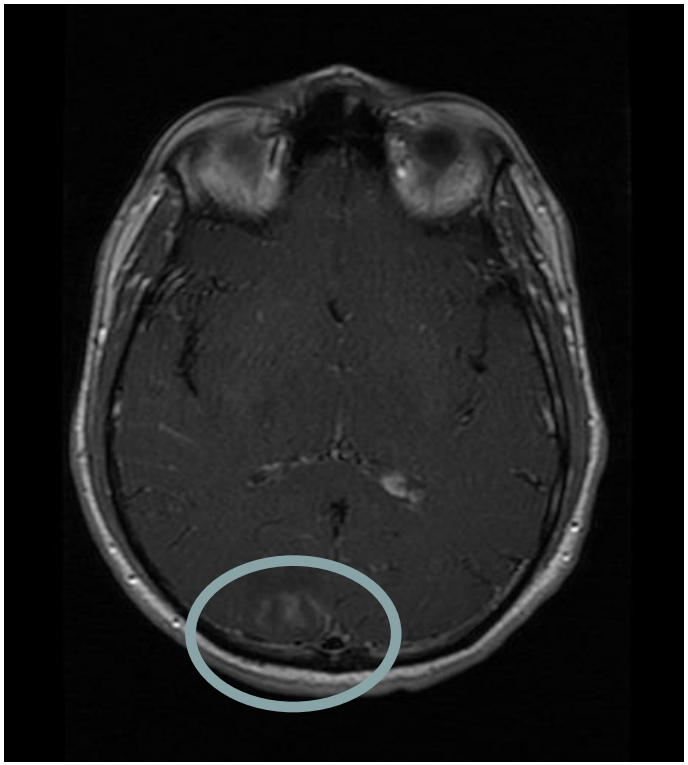
Neuroimaging:
Ring-enhancing lesions

IHC: Immunohistochemistry
PCR: Polymerase chain reaction

Heart and Other Kidney Recipients

- **Heart and other kidney recipients placed on pre-emptive antifungal therapy and survived**

A Missed Connection in Donor



Neuroimaging:
Ring-enhancing lesion

Large skin lesion for
6-month duration

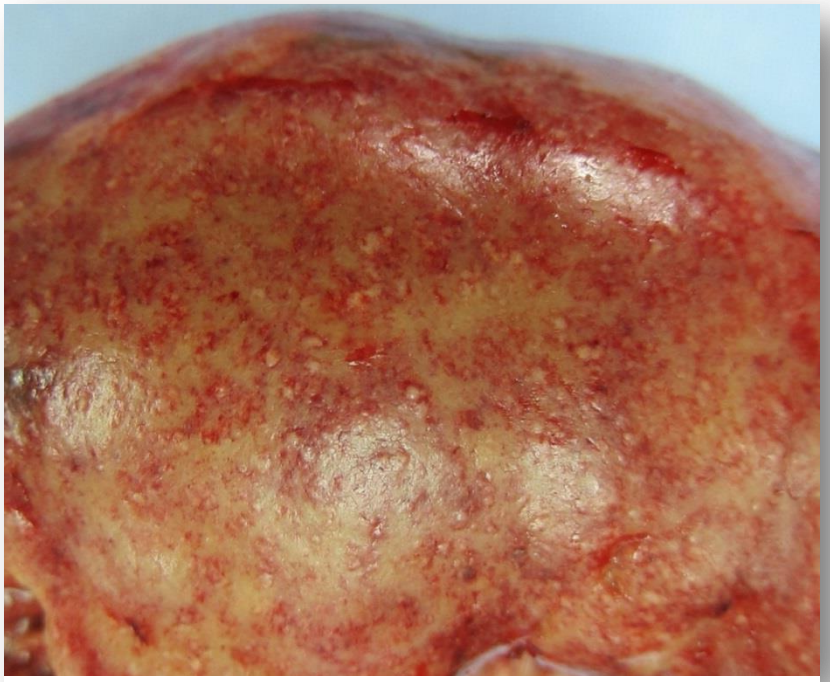
Another Unusual Infection Acquired Through Solid Organ Transplantation, 2012

- **37 year-old Mexican woman living in El Paso**
  - Died of cerebrovascular accident (CVA) in September 2011
- **Left kidney and double lung recipients present with fever, tremors, neutropenia and encephalopathy**
- **Right kidney recipient doing well**
- **Outside tests show brucella IgM positive serologies**

Hocevar S, et al. *Ann Intern Med* 2014.

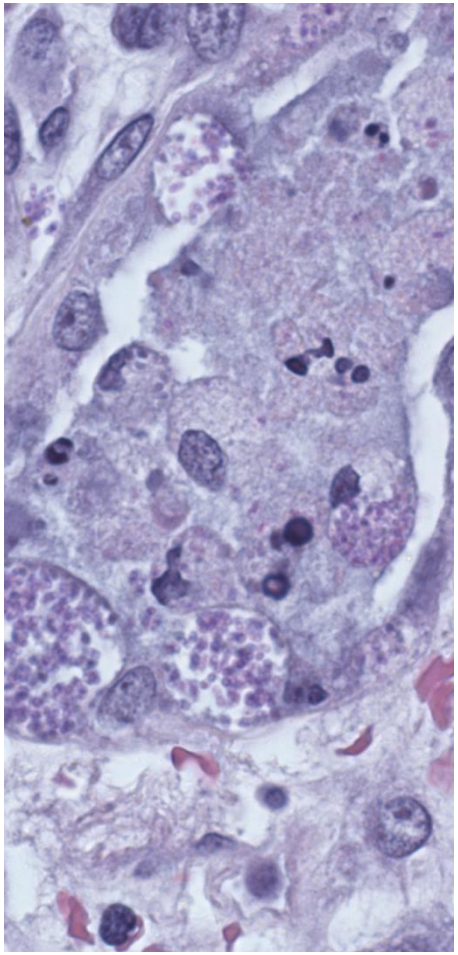
Left Kidney Recipient

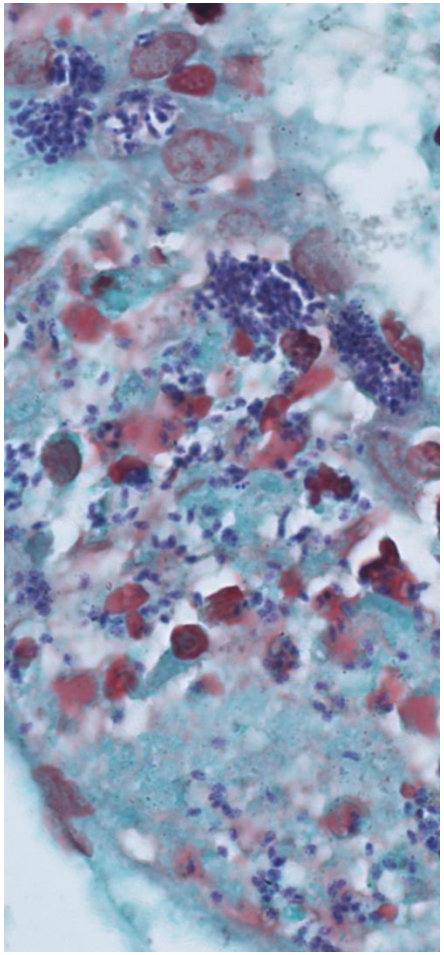
- **Left kidney recipient clinical condition deteriorates, necessitating nephrectomy**

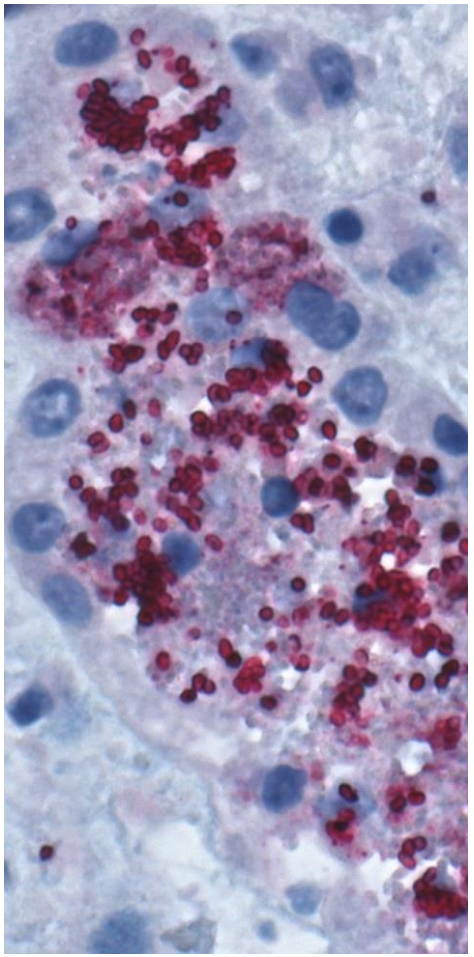


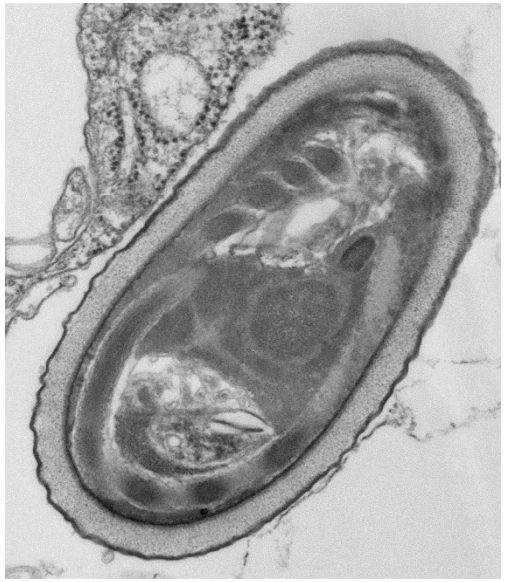
Micro-abscesses on surface of kidney

Microsporidia in Renal Tubules of Donor Left Kidney





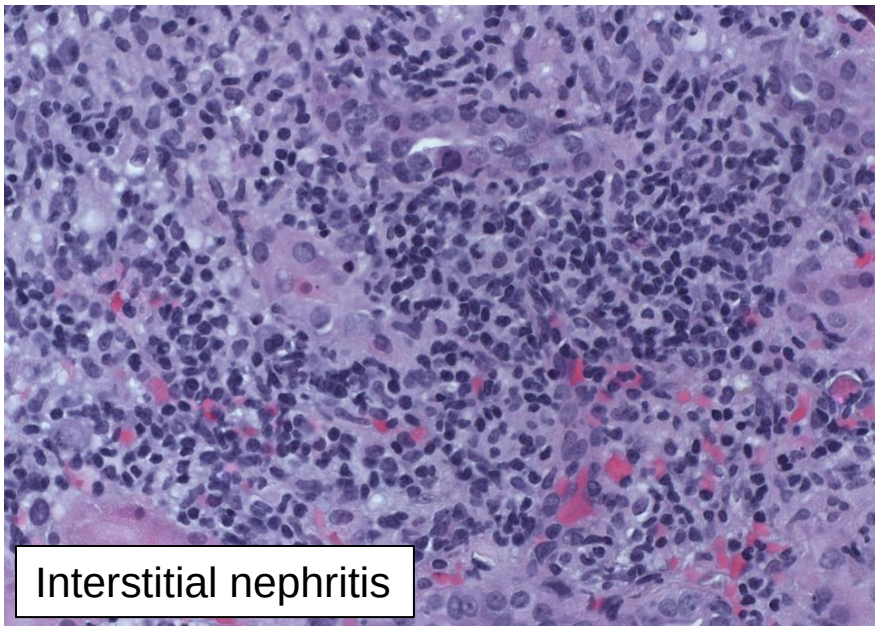




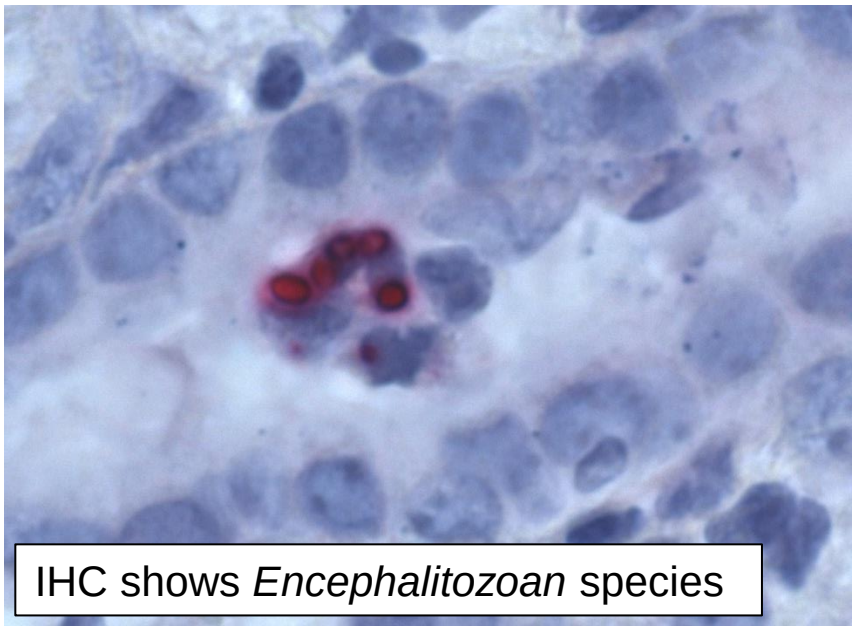
Hematoxylin and eosin	Gram stain	Immunohistochemistry	Electron micrograph

Biopsy from Right Kidney Recipient

- All three recipients were infected by same genotype
- Right kidney recipient recovered after six months of albendazole therapy



Interstitial nephritis



IHC shows *Encephalitozoan* species

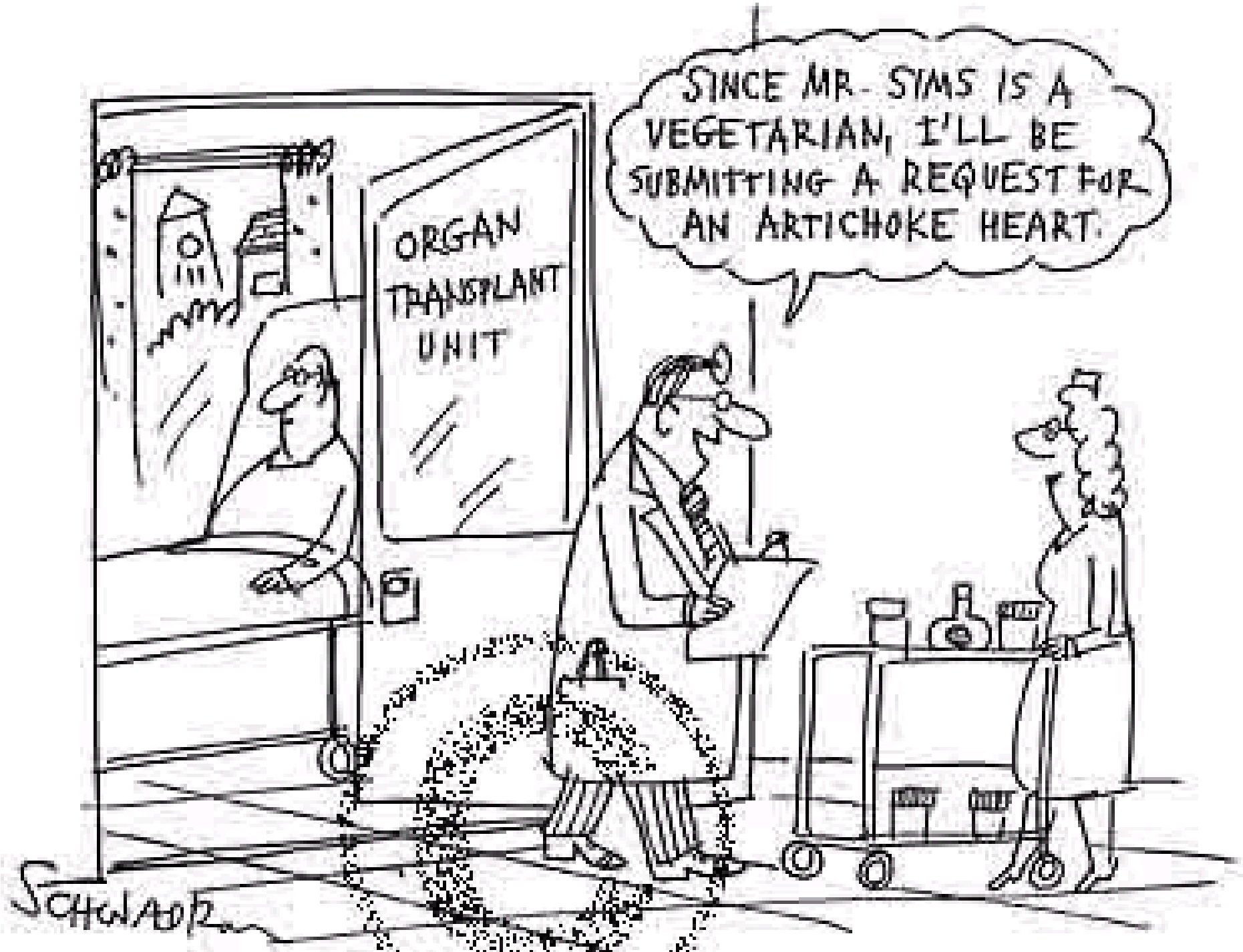
IHC: Immunohistochemistry

Unusual Transplant-associated Infections

- **While unusual, they are more common than previously suspected**
  - Once identified, the next one is easier to recognize
- **Pathology plays a frontline role**
  - Recognizing emerging infectious diseases
  - Guiding epidemiologic investigations
- **Donor screening and autopsies are important**
- **Donor specimens should be stored**
  - Allow future investigations after identification of novel infectious agents

Acknowledgements

- **Division of High-Consequence Pathogens and Pathology**
  - Infectious Diseases Pathology Branch
  - Viral Special Pathogens Branch
  - Poxvirus and Rabies Branch
- **Division of Vector-Borne Diseases**
- **Division of Parasitic Diseases**
- **Division of Foodborne, Waterborne, and Environmental Diseases**
- **Division of Healthcare Quality Promotion**
- **Office of Blood, Organ, and Other Tissue Safety**
- **State Health Departments**
- **Academic Institutions**


SINCE MR. SIMS IS A VEGETARIAN, I'LL BE SUBMITTING A REQUEST FOR AN ARTICHOKE HEART.
ORGAN TRANSPLANT UNIT
SCHWADRON

Preventing Unusual Transplant-associated Infections

Sridhar V. Basavaraju, MD
Medical Officer, Office of Blood, Organ, and Other Tissue Safety
Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Unusual Transplant-transmitted Infectious Encephalitis Clusters

Clusters in the United States, Reported to CDC, 2002-2014			
Infectious Agent	Total donors and clusters	Total Recipients	Total Deaths
West Nile virus	6	16	4
LCMV	4	13	10
Rabies	2	8	5*
Balamuthia mandrillaris	2	7	3**
Total	14	44	22

* Three recipients received rabies post-exposure prophylaxis and survived.
** Four recipients received prophylatic treatment.

LCMV: Lymphocytic choriomeningitis virus.
Basavaraju SV, et al. *Emerg Infect Dis* 2014.

Common Th[redacted]Unusual Transplant-transm[redacted]ction Clusters

- **Donor infection is unrec[redacted]**
  - Diseases are rare and infrec[redacted]ntered
  - Some donors have no evide[redacted]us cause of death
  - Other donors diagnosed wit[redacted]ephalitis of unknown cause, but have evidence o[redacted]logy including abnormal lumbar puncture
- **Disease risk factors are [redacted](e.g., microsporidia)**
- **Donor risks and exposures are not clearly identified**
  - Next of kin complete the donor history questionnaire, but they may be unaware of exposures or certain behaviors

Common Themes in Unusual Transplant-transmitted Infection Clusters

- **Except for West Nile virus, donor screening tests are not available**
- **Difficulty in linking donor and recipient infections**
  - Difficult to recognize and diagnose in recipient
  - Geographic distance
  - Timeliness of information
- **Lack of active surveillance system**

Opportunities for Prevention
Passive versus Active Surveillance

- **Current reporting mechanism is passive**
  - Current passive reporting by transplant centers and OPO to OPTN/UNOS
  - Only report if concern for donor-derived infection arises

- **Establishment of active national surveillance system**
  - Routine reporting of total transplants performed
  - Implementation of case definition criteria
  - Electronic notification of all transplant centers if a case is suspected

OPO: Organ procurement organizations
OPTN: Organ Procurement and Transplantation Network
UNOS: United Network for Organ Sharing

Opportunities for Prevention
Better Screening of Donors

- **Improve screening of donors**
  - Standardized donor history questionnaire across all organ procurement organizations

- **Balance need to identify donors with an increased risk of infectious encephalitis with the need to make the best use of every organ donated**

Improving Recognition of Infectious Encephalitis in Donors

- **Identifying donors with increased risk of infectious encephalitis through surveillance**
  - Recognize signs and symptoms of infectious encephalitis
    - Use all information available (e.g., clinical data and donor history)
  - If increased risk is identified
    - Additional laboratory screening is triggered
    - Follow-up and monitor all recipients

- **If infectious encephalitis is identified earlier, therapeutic or prophylactic intervention in recipients may save lives**

Risk Stratification Model
Identifying Donors with Infectious Encephalitis

1. **Clinical tool to identify donors with infectious encephalitis**
   - Must distinguish infectious from non-infectious encephalitis
   - Use available clinical data including
     - Fever and other symptoms
     - Cerebrospinal fluid analysis
     - Imaging results (e.g., CT, MRI and x-rays)
   - Incorporate donor history questionnaire

Risk Stratification Model
Optimizing Organ Allocation

2. **Properly allocate organs from donors with infectious encephalitis**
   - Maximize survival benefit for recipients

3. **Re-optimize organ allocation algorithm**
   - Reduce the overall “opportunity cost” on the organ match system
   - Ensure the best fit for an organ identified as at increased risk

Risk Stratification Model
Steps to Implementation

- **CDC clinicians and epidemiologists identify clinically relevant variables from infectious and non-infectious case reports**
- **OPTN/UNOS provides data on patient characteristics for those waiting for organs**
- **Data analyzed by a team in ISyE at Georgia Tech using process optimization techniques aimed at solving efficiency problems**

OPTN: Organ Procurement and Transplantation Network
UNOS: United Network for Organ Sharing
ISyE: Industrial and Systems Engineering Department

Improving the Safety of Organ Transplantation

- Risk for these unusual donor-derived infections is low
- Benefits of organ transplant far outweigh the risks
- Risk assessment should use relevant data to inform decision-making
- CDC and organ transplant community continue to collaborate to reduce the risk of transplant-transmitted infections

Organ donors save more than 75 lives every day.

Register as an organ, eye, and tissue donor.

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