

Fatal Amebic Encephalitis Caused by Transplant-Transmitted *Balamuthia* *mandrillaris*—Arizona, 2010

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National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



Organ Transplants: Balancing Resources

- ❑ Over 25,000 organ transplants
- ❑ Over 100,000 patients on waitlist
- ❑ Limited availability of organs
- ❑ Few criteria for donor exclusion



Transplant-Transmitted Infections

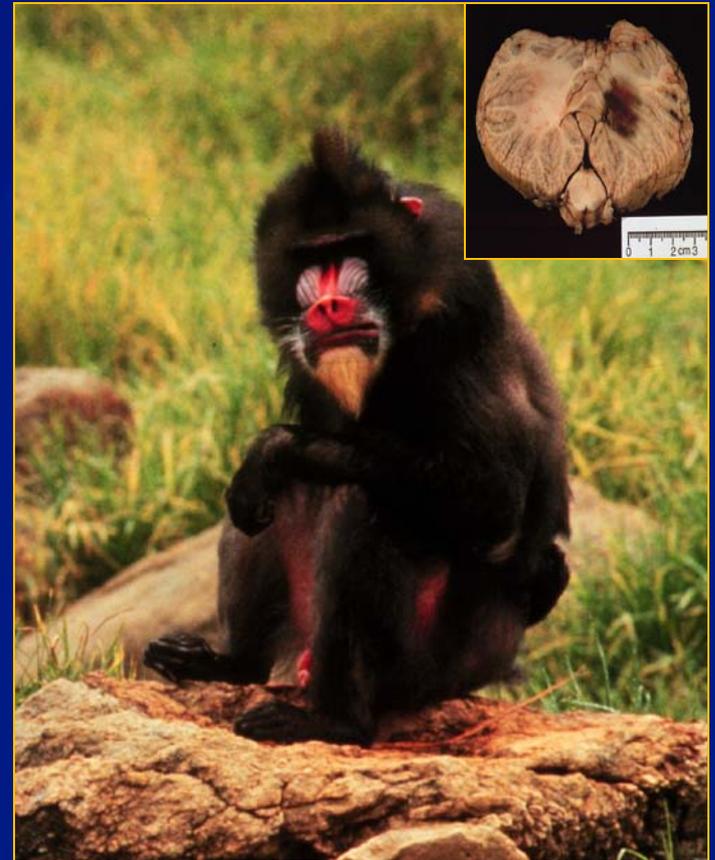
- ❑ Inadvertent consequence of transplants
- ❑ Transplant-transmitted encephalitis
- ❑ Potentially fatal
- ❑ Several implicated pathogens
 - *Rabies*
 - *West Nile Virus*
 - *Lymphocytic Choriomeningitis Virus*

An Unusual Event in Arizona

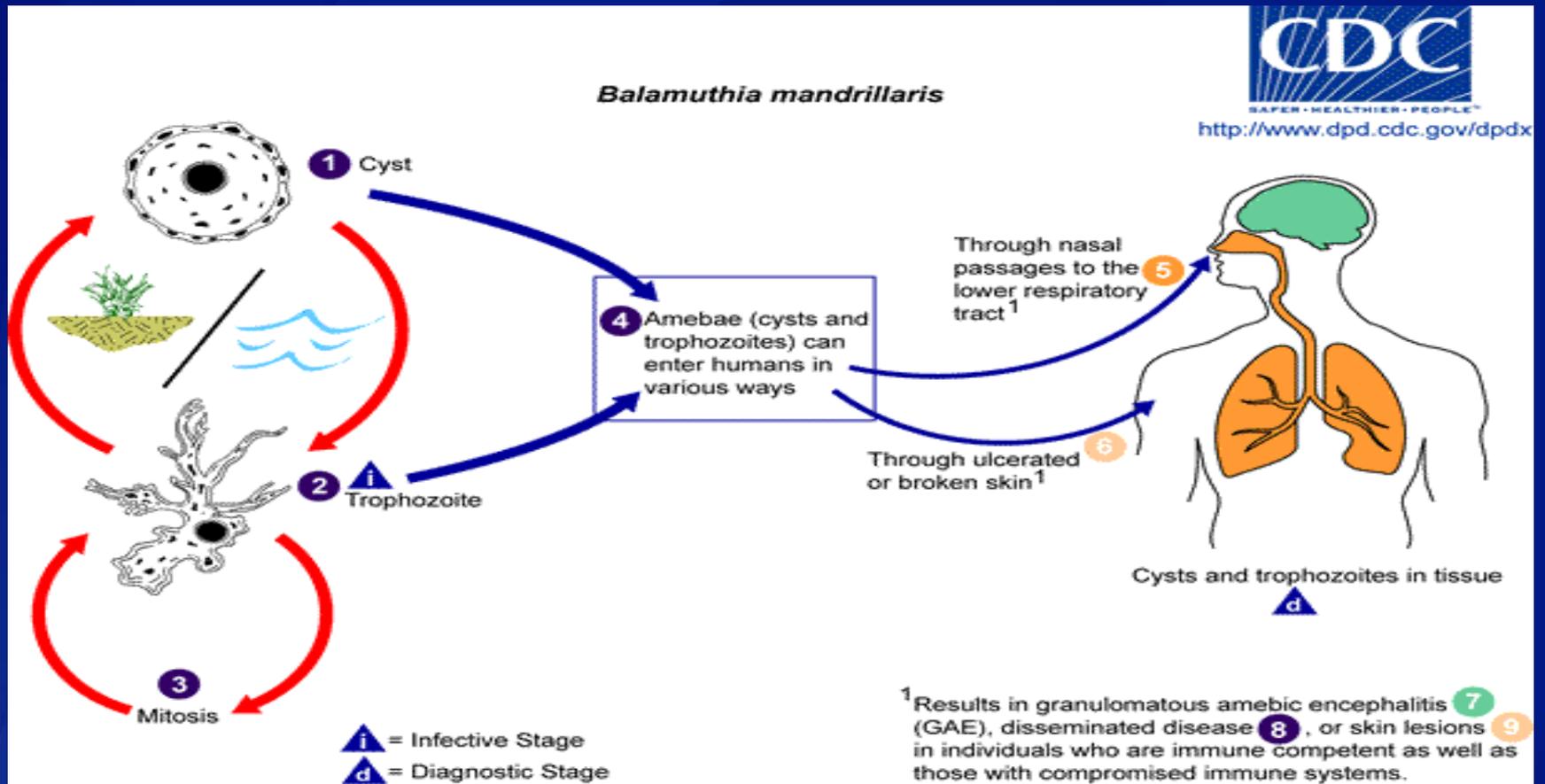
- ❑ **August 2010: Two transplant recipients with encephalitis**
- ❑ **Common donor died from presumed stroke**
- ❑ **One recipient already dead; other was unconscious**
- ❑ **Two other asymptomatic recipients in other states**
- ❑ **Preliminary testing suggested *Balamuthia* infection**

Balamuthia mandrillaris

- ❑ Free-living amoeba
- ❑ Postmortem specimen of mandrill baboon
- ❑ Rare but highly fatal
 - <200 human cases
 - >95% case fatality
- ❑ Special diagnostic techniques
 - CDC and California



Possible Routes of Transmission



Public Health Response: Objectives

- ❑ Provide assistance with laboratory testing of specimens from donor and all recipients**
- ❑ Describe clinical course of the donor and ill recipients**
- ❑ Identify diagnostic and treatment challenges**
- ❑ Identify opportunities for preventing transplant-transmitted encephalitis**

Laboratory Methods

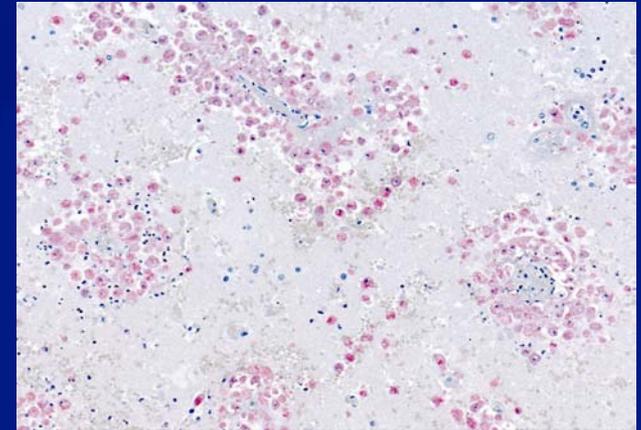
- ❑ **Immunohistochemistry (IHC)**
 - Free-living ameba antigens

- ❑ **Indirect immunofluorescence**
 - *Balamuthia* antigens

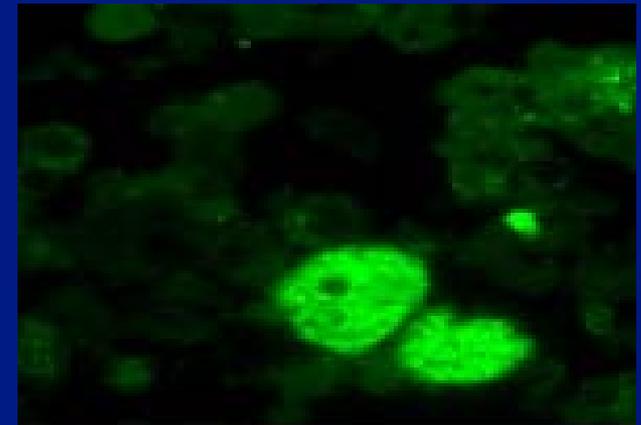
- ❑ **Immunofluorescence assay (Serology)**
 - *Balamuthia* antibodies

- ❑ **Real-time PCR**
 - *Balamuthia* DNA

Immunohistochemistry



Indirect Immunofluorescence



Field Investigation in Arizona

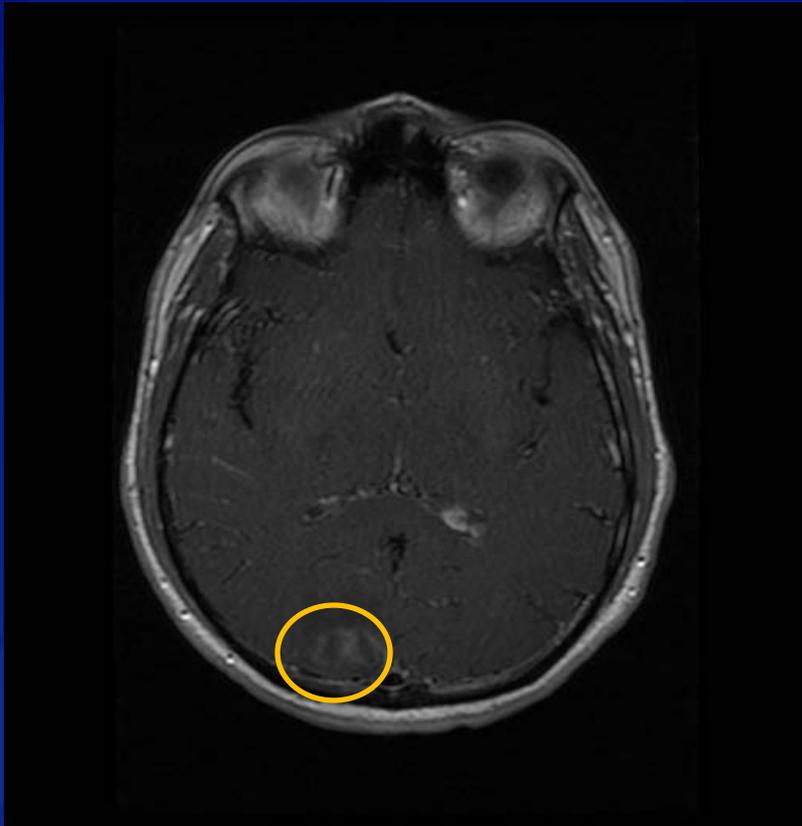
- ❑ Interviews with healthcare providers**
- ❑ Interviews with donor's coworkers**
- ❑ Medical record review and abstraction**
- ❑ Serological survey of landscapers**

Organ Donor

- ❑ **27-year-old Hispanic male landscaper**
- ❑ **Presented with headache, nausea, vomiting**
 - Confused, febrile, and hypertensive
 - Hyperglycemic, hyponatremic (later hypernatremic)
 - History of cocaine use (10 years)
- ❑ **Presumptive diagnosis of cocaine-induced stroke**

A Missed Connection

MRI showing wedge-shaped lesion



Clinical photograph showing skin lesion



Organ Donor: Rapid Clinical Progression

Admission Day 2: Lost vital reflexes, became comatose

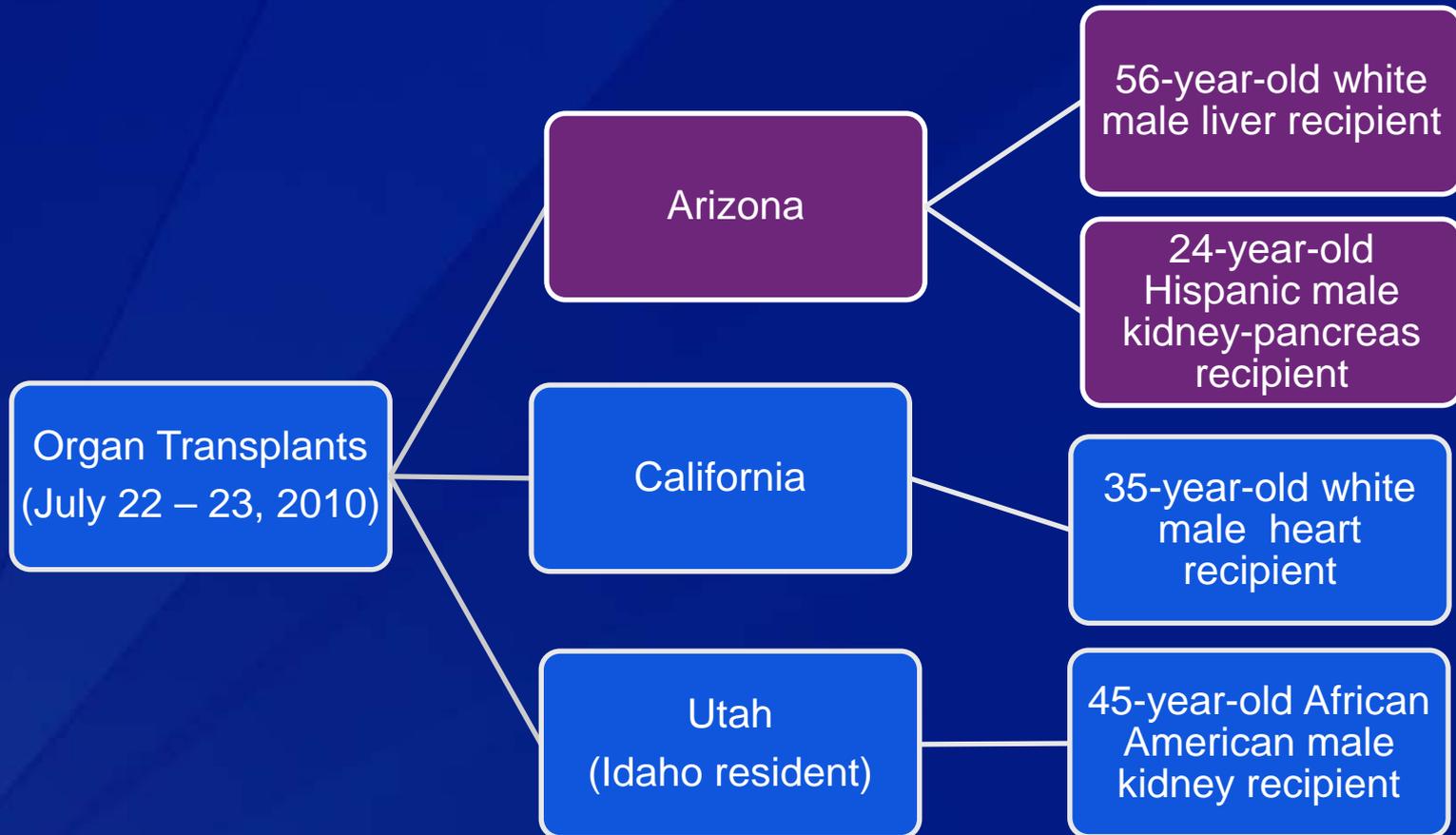


Admission Day 5: Pupils fixed and dilated, evaluated for brain death



Admission Day 6: Died, evaluated for organ donation

Organ Transplants



Liver Recipient

□ Post-transplant day (PTD) 18

- Double vision and difficulty with walking
- Loss of appetite and incontinence
- On admission: febrile; lost consciousness

□ Medical history

- Hypertensive and diabetic (type 2)
- Hepatocellular carcinoma

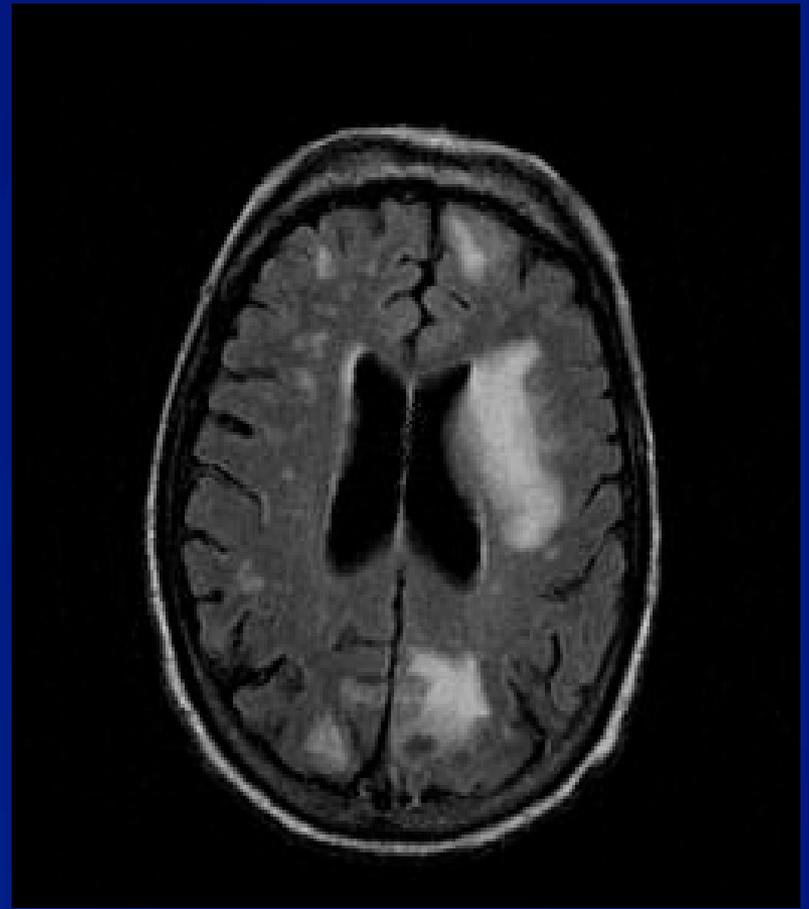
□ Differential diagnoses

- Metabolic encephalopathy
- Progressive multifocal leukoencephalopathy (PML)

Liver Recipient

- ❑ **Ring-enhancing lesions**
 - Broad antimicrobial coverage
- ❑ **Abnormal CSF**
 - ↑ Glucose (92mg/dL) and protein (140mg/dL)
 - ↑ White blood cells (70/ μ L)
- ❑ **Brain biopsy inconclusive**
 - Suggestive of atypical infection
- ❑ **Died on PTD 26**

MRI showing ring-enhancing lesions



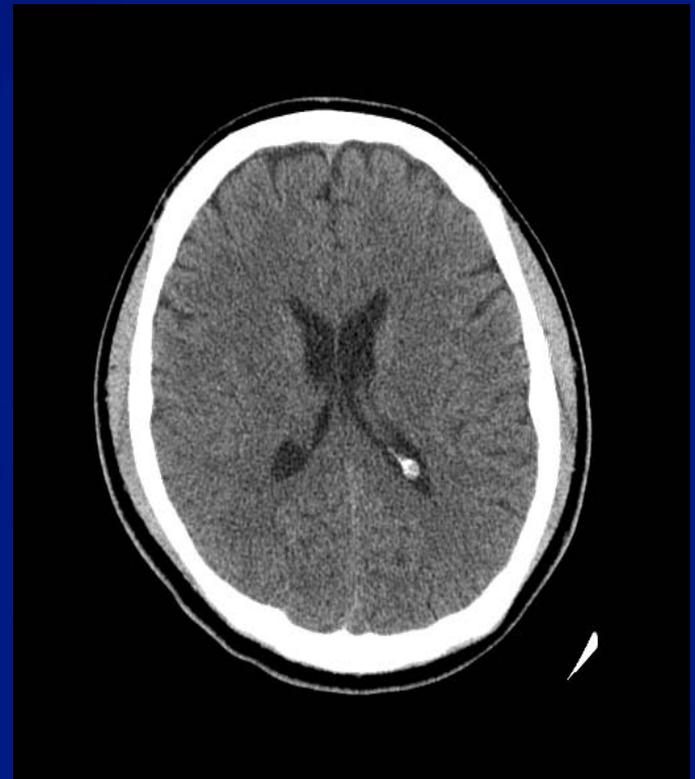
Kidney-Pancreas Recipient

- ❑ **PTD 24: headache, nausea, and vomiting**

- ❑ **Medical history**
 - Hypertensive and diabetic (type 1)
 - Thymoglobulin induction

- ❑ **Differential diagnoses**
 - Transplant pancreatitis
 - Intra-abdominal abscess

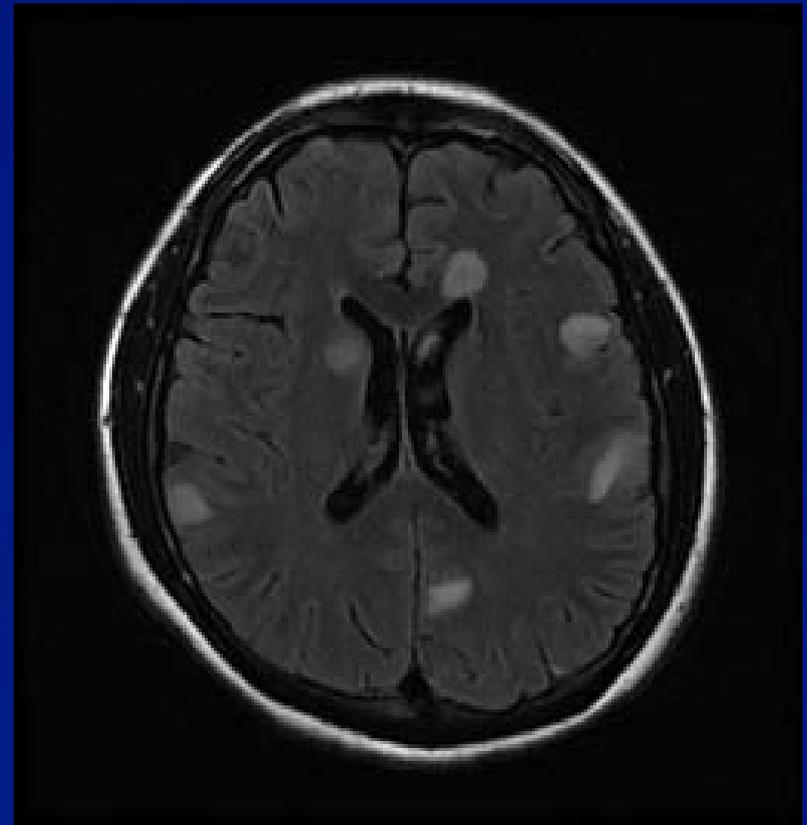
CT scan of head on admission



Kidney-Pancreas Recipient: Three Days Later

- ❑ Fever on PTD 26
- ❑ Multiple ring-enhancing lesions
- ❑ CSF: elevated protein and white blood cells
- ❑ Broad antimicrobial coverage

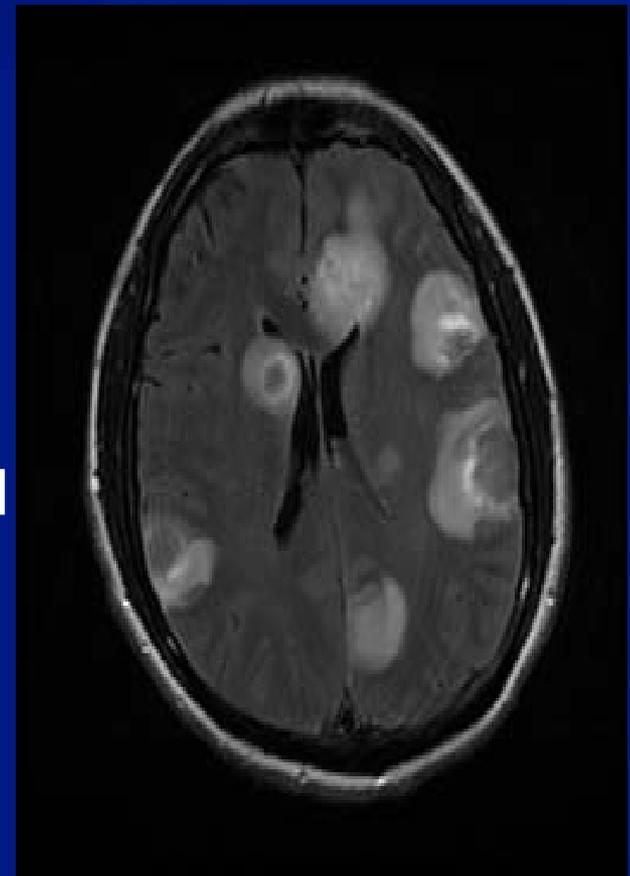
MRI Showing Ring-Enhancing Lesions



Neurologic Decline

- ❑ Headache, nausea and vomiting progressively worsened
- ❑ Marked neurologic changes on PTD 31
- ❑ PML and prion disease considered among possible differentials
- ❑ Neuroimaging on PTD 32 showed worsening ring-enhancing lesions

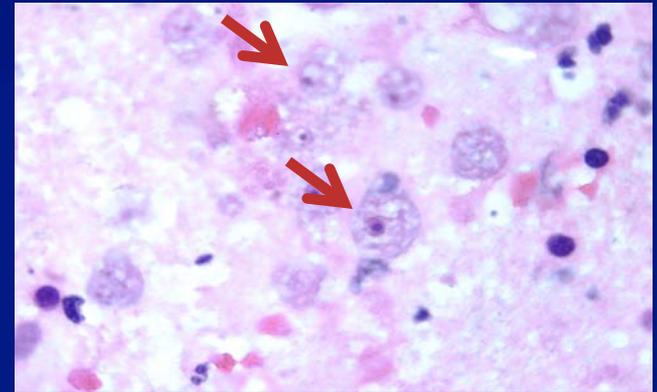
MRI showing ring-enhancing lesions



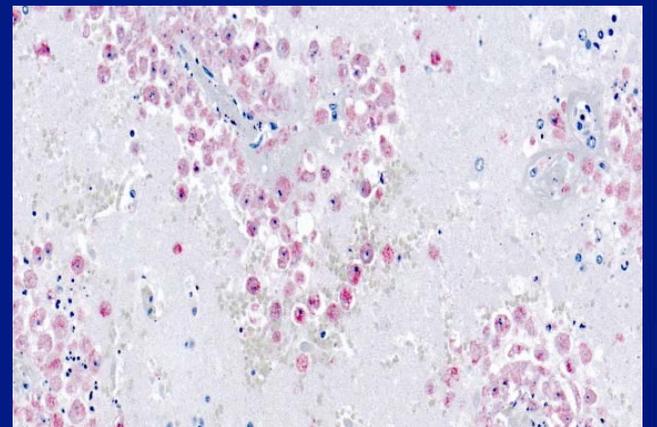
Brain Biopsy Provides Direction

- ❑ Ameba seen on brain biopsy
- ❑ Morphology indicates *Balamuthia*
 - Multiple nucleoli
 - Confirmed by immunohistochemistry and PCR
- ❑ Targeted treatment
 - Combination antimicrobial therapy
 - Miltefosine

Routine histopathology shows ameba



Immunohistochemistry confirms *Balamuthia*

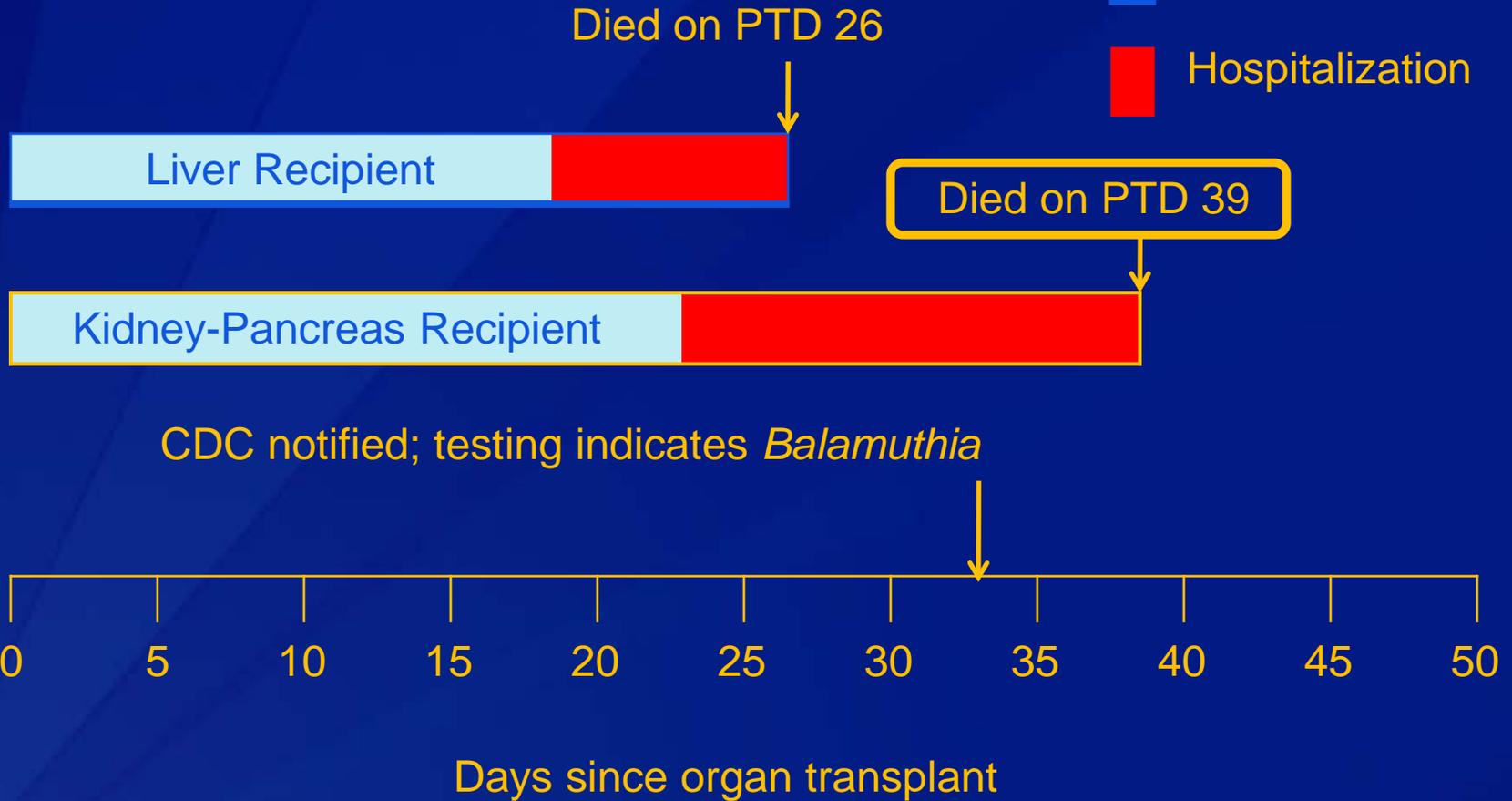


Miltefosine

- ❑ **Pharmacologic name: hexadecylphosphorylcholine**
 - Originally developed as antineoplastic drug
- ❑ **Effective in the treatment of visceral and cutaneous leishmaniasis**
 - 100 –150 mg daily for adults in 2–3 (oral) doses
 - Antifungal activity also reported: *Candida spp.*, *Cryptococcus spp.*
- ❑ **Successful treatment of few *Balamuthia* survivors**
 - Not approved for routine use in the US
 - Emergency investigational new drug protocol

Timeline

- Pre-hospitalization
- Hospitalization



Heart and Kidney Recipients

- ❑ **Preemptive treatment**
 - Miltefosine
 - Pentamidine
 - Flucytosine
 - Fluconazole
 - Sulfadiazine
 - Azithromycin

- ❑ **No symptoms of encephalitis**

- ❑ **Specimens sent to CDC**

CDC Laboratory Tests for *Balamuthia*

Patient	Outcome	Serology	Real-time PCR	IHC
Donor	Died	+	ND	ND
K-P Recipient	Died	+	+	+
Liver Recipient	Died	ND	+	+
Heart Recipient	Alive	+*	–	–
Kidney Recipient	Alive	+*	ND	–

ND – Not Done because required specimens were not available

* – Serology for this patient was initially positive but became negative following preemptive treatment

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Kidney Recipient	Alive	+*	ND	-

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Summary of Evidence

□ Epidemiologic

- Common organ donor, same state
- Temporality and duration of illness
- Similar clinical and radiologic findings

□ Laboratory

- CSF findings suggested atypical infection
- Brain biopsy indicated amebic encephalitis
- Novel tests at CDC confirmed *Balamuthia*

Not the First Time

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 59 / No. 36

September 17, 2010

Balamuthia mandrillaris Transmitted Through Organ Transplantation — Mississippi, 2009

On December 14, 2009, a physician in Mississippi contacted CDC to report possible transplant-transmitted encephalitis in two kidney transplant recipients who shared the same organ donor. Histopathologic testing of donor autopsy brain tissue at CDC showed amebae, and subsequent testing of specimens from the donor and the two kidney recipients confirmed transmission by transplantation of *Balamuthia* granulomatous amebic encephalitis (GAE), a rare disease caused by *Balamuthia mandrillaris*, a free-living ameba found in soil (1). One kidney recipient, a woman aged 31 years, died; the other recipient, a man aged 27 years, survived with neurologic sequelae. Recipients of the heart and liver from the same donor received preemptive therapy and have shown no signs of infection. The

prescribed antivirals; his symptoms resolved without hospitalization. On November 3, the boy had sudden onset of headache and seizures and was hospitalized (Table 1). Cerebrospinal fluid (CSF) demonstrated lymphocytic pleocytosis (170 white blood cells/mm³) and normal protein (29 mg/dL); magnetic resonance imaging (MRI) of the brain showed numerous small enhancing lesions and edema (Table 2). An extensive search for viral, bacterial, and fungal etiologies of encephalitis was unrevealing. His clinical presentation, CSF findings, and MRI were thought to be most consistent with a diagnosis of ADEM, an immune-mediated encephalitis that can follow influenza or other infections. He was treated symptomatically and discharged on November 6.

First Recognized Cluster of Transplant-Transmitted *Balamuthia*

- ❑ **4 organ recipients in Mississippi, December 2009**
- ❑ **2 kidney recipients developed encephalitis**
- ❑ **Four-year-old male organ donor**
 - Presented with headaches and seizures
 - Presumed post-influenza ADEM
 - Died from subarachnoid hemorrhage
- ❑ **One kidney recipient died, other survived**
 - Combination antimicrobial therapy (plus miltefosine)
 - Survivor has neurologic sequelae

Conclusions

- ❑ ***Balamuthia* amebic encephalitis often unrecognized, misdiagnosed**
- ❑ **Transmissible through solid organ transplantation**
- ❑ **Diagnosis of *Balamuthia* highly dependent on laboratory techniques that are not widely available**
 - Routine histopathology useful for identifying ameba

Recommendations

- ❑ **Need for prompt notification of organ procurement organizations, public health departments and CDC**
- ❑ **Increased awareness of *Balamuthia* infection in patients with neurologic signs and skin lesions**
- ❑ **Better assessment of potential organ donors with possible encephalitis**

Acknowledgments

Arizona Department of Health Services

Pima County Health Department

California Department of Health Services

Utah Department of Health

Idaho Department of Health & Welfare

Participating Transplant Centers

CDC

Office of Blood, Organ and Other Tissue Safety, **DHQP**

Division of High-Consequence Pathogens & Pathology

Infectious Disease Pathology Branch, **DHCPP**

Waterborne Disease Prevention Branch, **DFWED**

Parasitic Diseases Branch, **DPMD**

Division of Media Relations

FDA

Division of Special Pathogen and Transplant Products

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Extra Slides

Balancing Resources

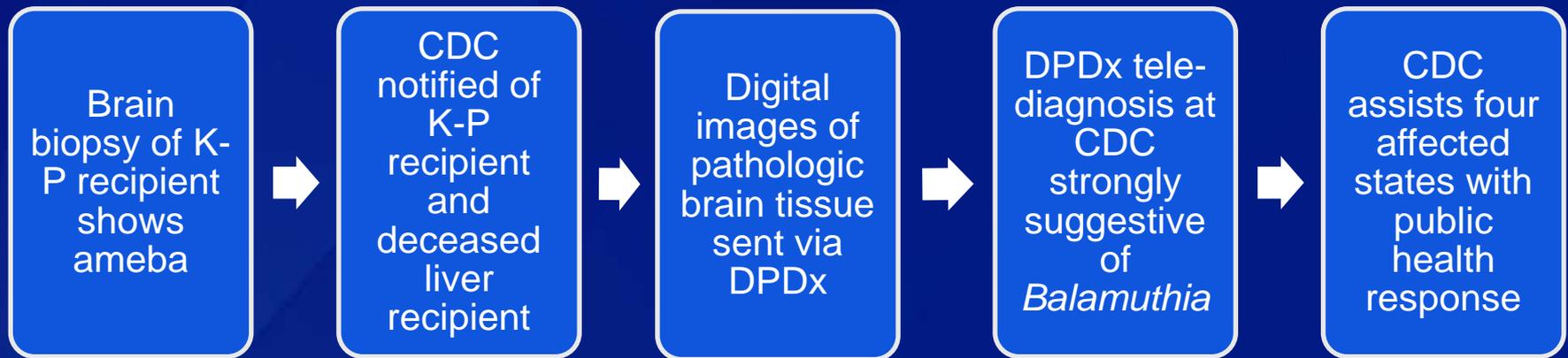
SAFETY



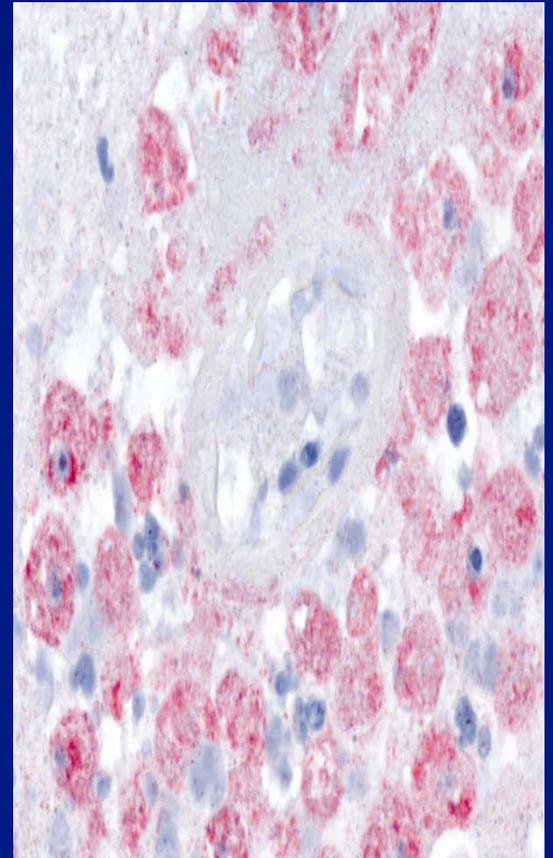
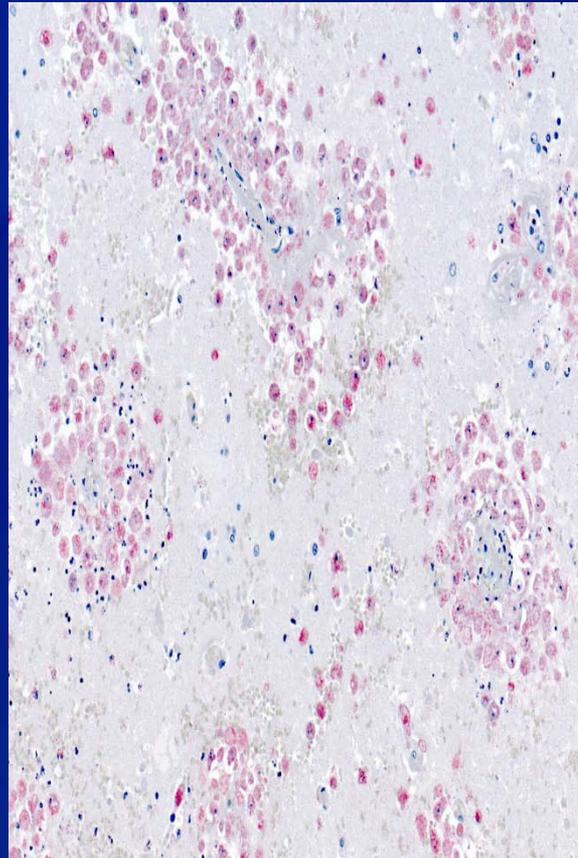
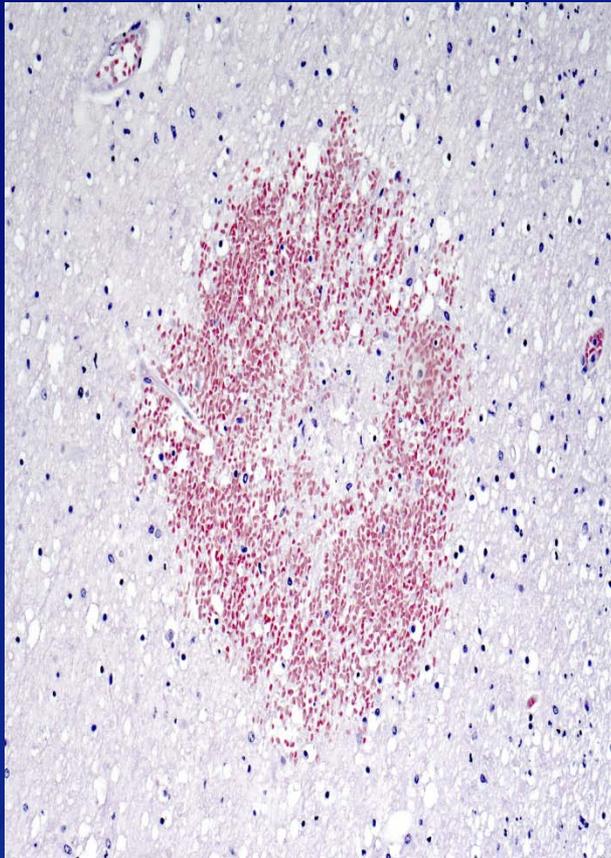
AVAILABILITY

For organ transplantation, the emphasis is on availability, and safety is a lesser concern, unlike for blood transfusion.

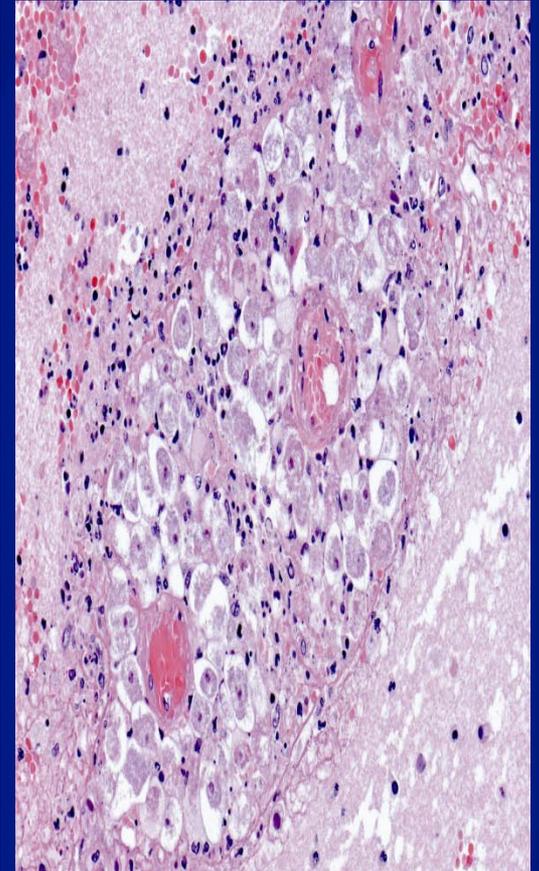
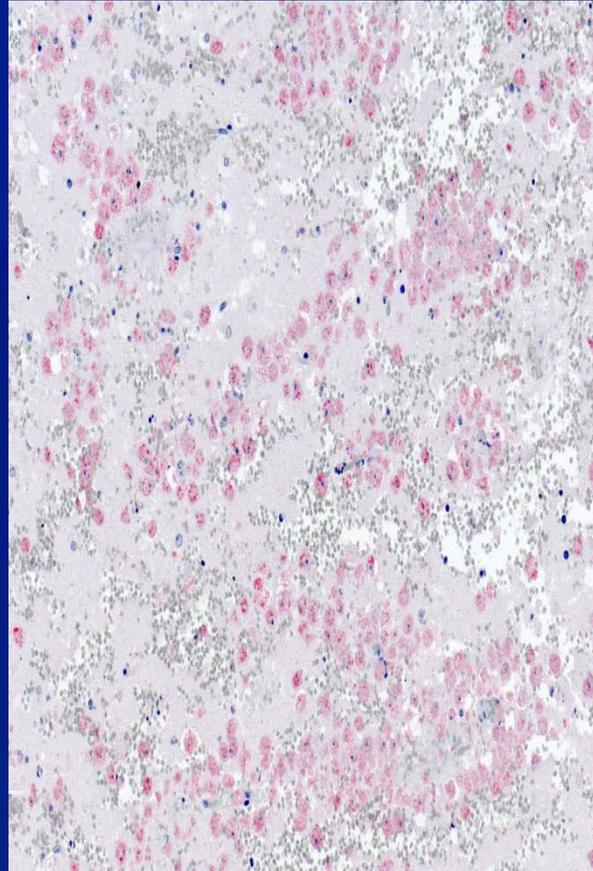
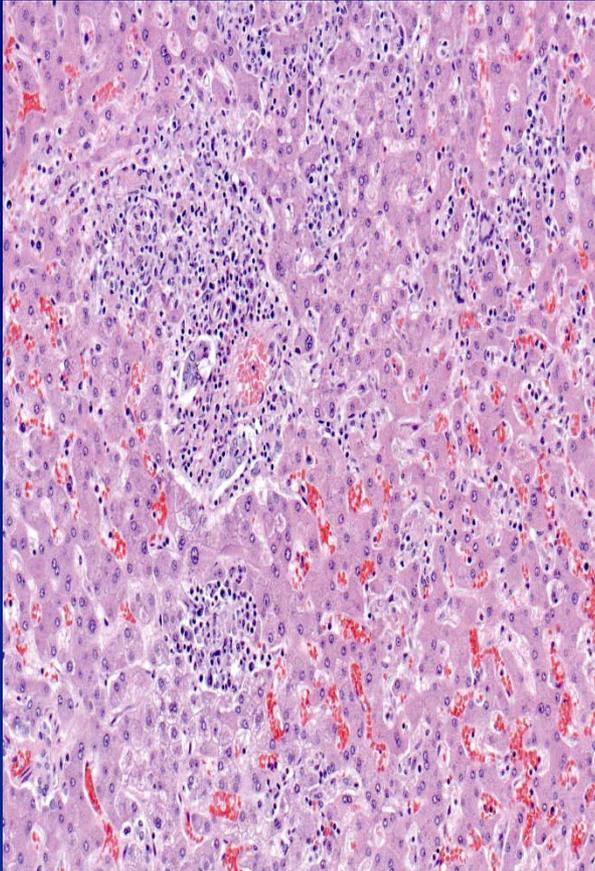
24 Hours Means A Lot...



Liver Recipient: Immunohistochemistry and Histopathology Images



K-P Recipient: Immunohistochemistry and Histopathology Images



Cerebrospinal Fluid (CSF) Findings

Patient	Protein (mg/dL)	Glucose (mg/dL)	RBC (/mm ³)	WBC (/mm ³)	Polymorphs (%)	Lymphocytes (%)	Monocytes (%)
Liver Recipient	140	92	1,230	70	80	1	19
Kidney- Pancreas Recipient	57	51	N/A	24	24	47	22

Liver Recipient: Antimicrobial Treatment

Patient	Antimicrobial Drug	Route of Administration	Start Date	End Date
Liver Recipient	Acyclovir	Intravenous	August 11	August 17
	Amphotericin B	Intravenous	August 11	August 16
	Ampicillin	Intravenous	August 11	August 17
	Ceftriaxone	Intravenous	August 11	August 11
	Co-Trimoxazole	Oral	August 11	August 12
	Fluconazole	Oral (NG Tube)	August 11	August 12
	Meropenem	Intravenous	August 12	August 17
	Primaxin	Intravenous	August 11	August 11
	Pyrimethamine	Oral	August 11	August 12
	Sulphadiazine	Oral	August 11	August 12
	Valganciclovir	Oral	August 11	August 11
	Vancomycin	Intravenous	August 11	August 16

Kidney-Pancreas Recipient: Antimicrobial Treatment

Patient	Antimicrobial Drug	Route of Administration	Start Date	End Date
Kidney-Pancreas Recipient	Albendazole	Oral (NG Tube)	August 24	August 30
	Amphotericin B	Intravenous/Intrathecal	August 24	August 27
	Azithromycin	Intravenous	August 24	August 30
	Ceftriaxone	Intravenous	August 23	August 24
	Ciprofloxacin	Oral	August 15	August 18
	Fluconazole	Intravenous	August 19	August 24
	Ganciclovir	Intravenous/Oral	August 22	August 24
	Meropenem	Intravenous	August 23	August 24
	Miltefosine	Oral	August 26	August 30
	Piperacillin/Tazobactam	Intravenous	August 18	August 20
	Vancomycin	Intravenous	August 17	August 20
	Voriconazole	Intravenous	August 23	August 24

