Emerging Infections in Solid Organ Transplantation

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Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

<table>
<thead>
<tr>
<th>Name of the enterprise / Nature of the interest</th>
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<tr>
<td>Enterprise</td>
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<td>None</td>
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Organ Transplants: Balancing Resources

- Over 25,000 organ transplants in the US every year
- Over 100,000 patients on waitlist
- Limited availability of organs
- Few criteria for donor exclusion
Infections in Transplant Recipients

- **Non Donor-Derived**
  - Primary infection
  - Reactivation of a latent infection

- **Donor-Derived**
  - Expected (screening): CMV, EBV, HBV, HCV, Toxoplasmosis
  - Unexpected
Unusual Donor-derived Infections Associated with Organ Transplantation

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

Single donor → Multiple recipients
unexpected donor-derived infections

will any organ do?

by gretchen reynolds

ny times, 2005 (rabies)

ny times, 2005 (lcmv)

ny times, 2009 (amoeba)

ny times, 2002 (wnv)
Investigation and Identification Novel and Emerging Donor Derived Solid Organ Transplant Transmitted Infections, 2002–2018

- West Nile Virus (6)
- Rabies: (2)
- Lymphocytic choriomeningitis virus (5)
- Balamuthia: (2)
- Microsporidiosis: (2)
- Eastern Equine Encephalitis (1)
Infection 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

Blood components from 63 donors

Stimulated trace back investigations

Only one component WNV IgM positive
Only one component WNV PCR positive, WNV IgM negative

BUT, IHC and PCR showed WNV encephalitis

Iwamoto M et al. NEJM 2003;348(22):2196-2203
Single donor and Four Transplant Recipients, 2003

Organ DONOR
✓ Male who died of a head trauma.

All 4 organ RECEIPIENTS died (9-76 days post-transplant)

Massive hepatocellular necrosis

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

Initial IHCs for herpesviruses and adenoviruses were negative

LCMV culture results after 6 weeks.

Second LCMV Cluster, in Three Transplant Recipients, 2005

Organ DONOR
- Woman who died of a stroke.

IHC and PCR confirmed LCMV in tissues from all 4 recipients.

Stimulated trace back investigations

3 organ recipients die between 23-26 days post-transplant
1 renal recipient alive

Massive hepatocellular necrosis
Where Did the Virus Come From?

- The donor’s daughter had a pet hamster that was sick
- The patient cleaned the cage and the areas of the hamster’s activities
Pet Rodents and Fatal Lymphocytic Choriomeningitis in Transplant Patients


Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 5, May 2007
<table>
<thead>
<tr>
<th>Patient or Source of Specimen</th>
<th>Outcome or Status</th>
<th>Immunohistochemical Staining</th>
<th>Quantitative Real-Time RT-PCR†</th>
<th>Blood and Serum Testing</th>
<th>Culture</th>
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<tbody>
<tr>
<td>Donor†</td>
<td>No reported disease</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Liver recipient‡</td>
<td>Death 26 days after transplantation</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Lung recipient¶</td>
<td>Death 23 days after transplantation</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<tr>
<td>Kidney Recipient B</td>
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<td>Death 23 days after transplantation</td>
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<tr>
<td>Kidney Recipient A**</td>
<td>Survival</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Hamster in donor’s household††</td>
<td>No reported disease</td>
<td>+</td>
<td>+</td>
<td>NT</td>
<td>+</td>
</tr>
<tr>
<td>Hamster’s caregiver‡‡</td>
<td>No reported symptoms</td>
<td>NA</td>
<td>−</td>
<td>+</td>
<td>+</td>
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A New Arenavirus in a Cluster of Fatal Transplant-Associated Diseases

Gustavo Palacios, Ph.D., Julian Druce, Ph.D., Lei Du, Ph.D., Thomas Tran, Ph.D., Chris Birch, Ph.D., Thomas Briese, Ph.D., Sean Conlan, Ph.D., Phenix-Lan Quan, Ph.D., Jeffrey Hui, B.Sc., John Marshall, Ph.D., Jan Fredrik Simons, Ph.D., Michael Egholm, Ph.D., Christopher D. Paddock, M.D., M.P.H.T.M., Wun-Ju Shieh, M.D., Ph.D., M.P.H., Cynthia S. Goldsmith, M.G.S., Sherif R. Zaki, M.D., Ph.D., Mike Catton, M.D., and W. Ian Lipkin, M.D.

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 technique may provide an alternative approach to DNA sequencing.

- 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
  Fragmentation of DNA followed by attachment of adaptor sequences
Transmission of an infection from an organ donor to four transplant recipients (2004)

- CDC contacted by pathologist in TX concerned about WNV in a cluster of patients
- Two deaths unexplained, third with altered mental status
- Detection of a common donor among cases was determined by families in the ICU

Donor

20 year black male

Agitated, confused, delirious
Intubated in ER
Urine drug screen positive
Heart Attack
Sub-arachnoid Hemorrhage

Fallen 3 times
“hyperventilating”
“He is very, very anxious”

Nausea/Vomiting
“I can’t even swallow my own spit”

Hospital C

Declaration of Death

Thought to have died from cocaine induced brain hemorrhage. Organs transplanted

Hospital B

April – May, 2004
Organ recipient timeline, April - June, 2004

Background
Hospital A, Dallas, TX

Alabama: Recipient dies in OR

Liver: Home -> ICU

Kidney: Home -> Mild rejection -> ICU

Kidney: Home -> ICU

Hospital A, Dallas, TX
Histopathology & IHC Rabies
The Persistent Pathologist…

- Recalled 4th death due to encephalitis

- Reviewed autopsy
  - Consistent with viral encephalomyelitis due to WNV
  - Received liver transplant
  - Different donor

- Specimens sent to CDC
Rabies!
Source of Infection

Was there a link?

- Was infection in recipient unrelated to transplantation.
- Was the second donor infected?
- Healthcare-associated rabies?
OPTN changed their policies
Instituted better tracking of donor organs and stored vessels
Donor’s serum positive
Sequence from all
three recipients were
exactly the same
Raccoon Rabies Virus Variant Transmission Through Solid Organ Transplantation, 2013

- Kidney transplant recipient died 18 months after receiving transplant from an infected donor.
- Donor with a history of raccoon exposure died with fever, vomiting, seizures and dysphagia. Also tested Rabies positive by histopathology and PCR.
- 3 other organ recipients remained asymptomatic with serum rabies neutralizing antibodies after completion of PEP.

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 weeks later**
- 1 kidney recipient admitted with seizures and altered mental status.
- Liver and heart recipients asymptomatic.

**Donor Autopsy tissues received at CDC**
- Granulomatous amebic encephalitis caused by *Balamuthia mandrillaris*.

*Balamuthia mandrillaris was confirmed in 2 kidney recipients
3 recipients recovered with therapy*
Another Balamuthia mandrillaris in an Organ Donor and Four Transplant Recipients, 2010

August 2010: Two of four transplant recipients with encephalitis

Common donor died from presumed stroke

One recipient already dead; other was unconscious

Two other asymptomatic recipients in other states
Liver Recipient

- **Post-transplant day (PTD) 18**
  - Double vision and difficulty with walking
  - Febrile; loses consciousness
- **Neuroimaging:** ring-enhancing lesions
- **Brain biopsy inconclusive**
  - Died

Autopsy

Liver

Liver
Kidney-Pancreas (K-P) Recipient

MRI showing ring-enhancing lesions

Heart and Kidney recipients were placed on preemptive therapy and survived

Brain biopsy IHC and PCR Balamuthia positive
A Missed Connection in Donor

MRI showing wedge-shaped lesion

Large skin lesion for 6-month duration
37 y.o. Mexican woman living in El Paso
- Died of CVA in September 2011
- Left Kidney and double lung recipients have fever, tremors, neutropenia and encephalopathy
- Right renal recipient doing well
- Outside tests show brucella IgM positive serologies

Left kidney recipient clinical condition deteriorates necessitating nephrectomy
Microsporidia in renal tubules of nephrectomy specimen
All three recipients were infected by same genotype III

Interstial nephritis

IHC; *Encephalitozoan* species

Right kidney recipient recovered after 6-months albendazole therapy
Lung recipient received albendazole but succumbed to PTLD
Single donor and Four Transplant Recipients, 2017-2018

Donor:
44 year old female from rural GA
Limited autopsy was performed for bullet retrieval; body cremated.

Patient 1:
42 year old female from VA
Adriamycin-induced cardiomyopathy
Heart transplant on 9/29/2017
8 days post-transplantation, developed high grade fever and neurologic signs

Patient 2:
42 year old female from GA
History of autoimmune hepatitis and had 1st liver transplant in April 2015
Due to recurrent disease, she received a 2nd liver transplant on 9/29/2017
6 days post-transplantation, developed high grade fever and CNS signs

Patient 3:
59 year old female from GA
History of COPD
Bilateral lung transplant on 9/29/2017
7 days post-transplantation, developed high grade fever and CNS signs

All recipients presented with acute onset encephalitis and fever 7-10 days after transplant
Summary and Conclusions

- Unusual Transplant-associated Infections: Just How Unusual?
- Lessons learned about screening of donors for rabies, amebic infections, LCMV WNV and EEE. Clinical picture, Lab Questioners?
- Importance of donor autopsies (rabies, amebic infections, WNV)
- Prolonged storage of donor specimens to allow future investigations after identification of novel infectious agents for which improved screening tests become available.
- Frontline role of pathology
  - Recognition of emerging infectious diseases
  - Guiding epidemiologic investigations
Since Mr. Sims is a vegetarian, I'll be submitting a request for an artichoke heart.