“New” Infectious Diseases in the United States and Donation of Human Tissues and Cells

European Eye Bank Association
XXII Annual Meeting
Sitges, Spain
Saturday, 23 January, 2010

Scott A. Brubaker, CTBS
Chief Policy Officer
Overview

- RCDADs - what are they?
- Some statistics, demographic data
- Proposed (draft) Guidance from FDA
  - WNV NAT, *T. cruzi* Ab
- Disease relevance to tissues for transplant
  - Scientific studies
- Other diseases
  - HTLV, XMVR, Arboviruses
- V&S and working together
- Some history & considerations
Relevant Communicable Disease Agents and Diseases (RCDADs)

FDA’s collective term for:

- HIV 1/2
- HBV
- HCV
- Human TSEs
- Syphilis
- Xenotransplantation risk
- SARS
- WNV
- Vaccinia
- Sepsis
- HTLV I/II: for viable, leukocyte-rich tissue only
- C. trachomatis & N. gonorrhea: Repro tissue only

...and anything else that becomes a threat to public health!!!
West Nile Virus
Approximate Geographic Range in 1998
West Nile Virus Activity

Non-human WNV activity
Human Disease Cases

National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2008 calendar year reported as of November 03, 2008
Approximate Global Distribution of West Nile Virus, by State/Province, 2007

West Nile Virus - The most widespread of the flaviviruses
Acknowledgement

The last 11 slides are from a presentation by:

Roger S. Nasci, Ph.D.
Division of Vector-Borne Infectious Diseases, CDC

Presented at:
WNV National Conference - Ten Years Later
AMCA-CDC
February 19-20, 2009
Savannah, Georgia, USA
Chagas’ Disease

Geographic distribution of Trypanosoma cruzi (Chagas disease)

Courtesy of C. Ben Beard, PhD - CDC
AABB Chagas’ Biovigilance Network

http://www.aabb.org/Content/Programs_and_Services/Data_Center/Chagas

Voluntary *T. cruzi* Ab testing of most of the US blood donor population began in 2007
AABB Chagas’ Biovigilance Network
http://www.aabb.org/Content/Programs_and_Services/Data_Center/Chagas

3,958 repeat reactive donations were tested by the supplemental RIPA test for the antibody to T. cruzi, the agent for Chagas’ disease. 1,081 of the repeat reactive donations were RIPA positive; 2,781 were RIPA non-reactive. 58 had indeterminate results. The remaining results are pending. Nineteen testing laboratories reported data into the Chagas Network; twenty testing laboratories now access the Chagas Network for reporting purposes.
FDA Draft Guidance(s)

- Propose that all donors of HCT/Ps be:
  - tested using WNV NAT (issued April 2008)
    - Must individually test blood samples (no pooling of samples)
    - Require year-round testing (seasonal testing not an option)
    - If reactive = ineligible donor
  - tested for antibodies to *Trypanosoma cruzi* (issued March ‘09)
    - New RCDAD (Chagas’ Disease)
    - Screening for risk history alone is not sufficient
    - If reactive = ineligible donor
FDA exempts “Source Plasma” products from both guidance documents....

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of Trypanosoma cruzi Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

Additional copies of this draft guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-831-4709 or 301-827-1600, or from the Internet at http://www.fda.gov/ohier/guidelines.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2009

AATB sent 12 pages of comments and recommendations w/rationale

Guidance for Industry

Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

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For questions on the scientific content of this guidance regarding blood donors, contact Maria Rice, Ph.D., in the Division of Emerging and Transmitted Transmissible Disease, Office of Blood Research and Review at 301-827-3108. For questions regarding labeling or licensing issues, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3524. For questions regarding HCT-P donors, contact Melissa Greenwald, M.D., in the Division of Human Tissues, Cell, and Tissue Gene Therapies at 301-827-3202.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2009

AATB sent 20 pages of comments and recommendations w/rationale
AATB’s View

• Relevance of *T. cruzi*?
  ✦ Lack of science-based evidence
    ✦ We have designed a study that will provide sufficient data to support suspicions regarding relevance
  ✦ Consulting with experts (CDC & tissue bank science officers)
    ✦ ? Parasite’s survival in host after host dies?
    ✦ ? Survival after prolonged refrigeration, simple freezing? (normal handling steps – “processing” not being studied....)
    ✦ Mouse model; chronic disease state treated as if acute (worse-case)
    ✦ Study protocol includes bone, soft tissue, cardiac, skin, and ocular tissue (reproductive tissues = separate protocol)
  - Estimated cost USD $33,431; initial results may lead to more studies
• **Relevance of WNV?**
  ✦ Lack of science-based evidence
    ✦ Virus not characterized for tissues that can be donated; same issue for processed tissue
    ✦ Waning prevalence in the US; no transmissions IDed

• **Do allografts that do not contain red blood cells pose a risk?**
  ✦ Promote scientific workshop and studies
    ✦ WNV Workshop planned by AATB in late Spring 2010
Alexander the Great and West Nile Virus Encephalitis

John S. Marr* and Charles H. Calisher†

Infections

Alexander’s death occurred in late spring, upon his return to Babylon from the Indian subcontinent. Environmental conditions were unremarkable (8). Babylon, located on the Euphrates River (90 km south of present-day Baghdad), was bordered on the east by a...
Persistent Infection with West Nile Virus Years after Initial Infection

Kristy Murray, Christopher Walker, Emily Herrington,
Jessica A. Lewis, Joseph McCormick, David W. C. Beasley,
Robert B. Tesh, and Susan Fisher-Hoch

School of Public Health, University of Texas Health Science Center at Houston,
Houston and Brownsville, and University of Texas Medical Branch, Galveston

(See the editorial commentary by Gould, on page 1.)

West Nile virus (WNV) RNA was demonstrated in 5 (20%) of 25 urine samples collected from convalescent patients 573–2452 days (1.6–6.7 years) after WNV infection. Four of the 5 amplicons sequenced showed >99% homology to the WNV NY99 strain. These findings show that individuals with chronic symptoms after WNV infection may have persistent renal infection over several years.
Disease Relevance - US FDA

• HTLV I & II

✦ A cell-associated disease; only relevant for cells/tissues that are considered to be leukocyte-rich and contain viable leukocytes.

⭐ Examples are semen and hematopoietic progenitor/stem cells (HPCs); HTLV I/II Ab testing only required for these donors

⭐ This is an example of FDA’s “tiered, risk-based approach” to regulating human tissues and cells

Compare with European Commission Directive 2006/17/EC
Testing determination based on donor risk assessment, not assessment of risk associated with type of tissue. A handful of Member States require HTLV Ab testing without consideration of donor risk.
H1N1 Influenza

- Status quo for screening tissue donors per AATB’s Physicians’ Council
  - No test developed for donor screening; rapid test yields a false negative result 30% of the time
  - Continue to screen donors for active viremia
    - Most prominent symptoms: Fever, cough, sore throat, fatigue, malaise
    - Younger ages dying
    - Be vigilant!

DONE VIDA
> 75 CDC Updates Posted; 2 AATB Bulletins and a News Release issued
“New” Diseases

• Retrovirus
  ✦ XMRV (xenotropic murine leukemia virus-related virus)?
    ✤ linked to prostate cancer and chronic fatigue syndrome?
    ✤ sexually transmitted?
    ✤ More studies needed.....

• Arboviruses (arthropod borne viruses)
  ✦ WNV, Dengue, JE, TBE, St. Louis Encephalitis (SLE), EEE, WEE, LCE, Powassan Virus
A great resource....

Eurosurveillance – Europe’s journal on infectious disease epidemiology, prevention and control

Eurosorevance, Volume 15, Issue 1, 07 January 2010

Editorials
EUROSUREVANCE – KEEPING AN EYE ON INFECTIOUS DISEASES
I Steffens (ines.steffens@ecdc.europa.eu)1, K Ekdahl 1

1. European Centre for Disease Prevention and Control, Stockholm, Sweden

2010 will be the 15th year for Eurosurveillance, and as always, the editorial team will do their best to provide their readers with timely, relevant and up-to-date information about infectious disease outbreaks, surveillance, prevention and control. The journal is constantly evolving and as in previous years, there were considerable, positive, changes for both editors and readers in 2009. First and foremost, the joint efforts of contributors, editorial board and team have paid off and Eurosurveillance has been accepted and is now listed for an impact factor with Thomson Reuters [1]. This development poses obvious challenges for the future and we are convinced that we will be able to present an attractive factor in two years time.

2009 was a special year for all public health experts, physicians and policy makers working with infectious diseases. Since the end of April, the 2009 influenza pandemic has been an overwhelming priority for all and required considerable resources and efforts. From the start when it was uncertain how this pandemic would evolve, we followed it closely and kept our readers informed.

In this issue:
- Eurosurveillance – keeping an eye on infectious diseases
- A new decade, a new seasonal influenza: the Council of the European Union Recommendation on seasonal influenza vaccination
- A nosocomial outbreak of 2009 pandemic influenza A(H1N1) in a paediatric oncology ward in Italy, October – November 2009
- When should we intervene to control the 2009 influenza A(H1N1) pandemic?
- Genesis of a KPC-producing Klebsiella pneumoniae after in vivo transfer from an imported Greek strain
- Outbreak of 2009 pandemic Influenza A(H1N1), Los Lagos, Chile, April-June 2009
- Eurosurveillance reviewers in 2009
- Addendum for Euro Surveill. 2009;14(47)
Main ProMED-mail

about ISID | membership | programs | publications | resources | 14th ICID | site map
The global electronic reporting system for outbreaks of emerging infectious diseases & toxins, open to all sources. ProMED-mail, the Program for Monitoring Emerging Diseases, is a program of the International Society for Infectious Diseases.

** Notice **
Because of Electrical Maintenance outside of our control, the ProMED SUBSCRIPTION web site and ISID HOME PAGE and 14th ICID web site will be unavailable from Fri., 22 Jan 2010, 5 PM (EST) until Sat., Jan 23, 2010 12:00 (EOT) We apologize for any inconvenience.

Today on ProMED-mail

** January 23, 2010 **
PRO/AH> Foot & mouth disease, bovine - China (02): (BJ) OIE
PRO/AH/EDR> Alkhurma virus - Saudi Arabia (02): (MK) correction

** January 22, 2010 **
PRO/AH/EDR> Anthrax - UK (08): (Scotland)
PRO/AH/EDR> Nipah virus, fatal - Bangladesh: (FR)
PRO/PL> Orange rust, sugarcane - Brazil: (SP) 1st rep
PRO/AH> Rabies, raccoon - USA (NY)
PRO/PL> Multiple diseases, cassava - SE Asia: alert

Posting from last 30 days...

Latest Information on Influenza A (H1N1)

21-JAN-2010 / Influenza pandemic (H1N1) (10): PAHO update
19-JAN-2010 / Influenza pandemic (H1N1) (09): WHO update
17-JAN-2010 / Influenza pandemic (H1N1) (08): USA (vaccine safety): Mongolia
15-JAN-2010 / Influenza pandemic (H1N1) (07): China, travel alert
14-JAN-2010 / Influenza pandemic (H1N1) (06): USA (SD) Native Americans

More...
Dengue

With more than one-third of the world’s population living in areas at risk for transmission, dengue infection is a leading cause of illness and death in the tropics and subtropics. As many as 100 million people are infected yearly. Dengue is caused by any one of four related viruses transmitted by mosquitoes. There are not yet any vaccines to prevent infection with dengue virus (DENV) and the most effective protective measures are those that avoid mosquito bites. When infected, early recognition and prompt supportive treatment can substantially lower the risk of developing severe disease.

Dengue has emerged as a worldwide problem only since the 1950s. Although dengue rarely occurs in the continental United States, it is endemic in Puerto Rico, Samoa and Guam, and occurs in many popular tourist destinations in Latin America and Southeast Asia.

Dengue Topics

- Frequently Asked Questions & Fact Sheet
  Key dengue information...

- Epidemiology and Statistics
  Transmission, information on epidemics and stats...

- Travel/Outbreak Notices
  Critical information for travelers...

- Entomology/Ecology
  Mosquito that spreads dengue and its ecology...

- Prevention
  Avoid getting infected whether at home or on travel...

- Clinical/Laboratory Guidance
  Tools for clinicians and laboratorians...

- Education/Training
  Dengue educational tools...

- If You Think You Have Dengue...
  Symptoms and actions to take...
Dengue Surveillance Weekly Report

Data through December 4, 2009

Week 46
148 suspected cases reported
This number is ABOVE the historical average.¹

Week 45
170 suspected cases reported
17 (10%) confirmed in the laboratory²
11 (14%) municipios ** had confirmed cases

Serotypes
In the last 8 weeks:
- 68% DENV-1
- 28% DENV-2
- 12% DENV-4
- 0% DENV-3

Accumulated in 2009
5,525 suspected cases reported
1,822 (33%) confirmed in the laboratory³
52 confirmed cases of dengue hemorrhagic fever (DHF)
2 confirmed fatal cases of dengue

Geographic classification³
The level of dengue activity is EXTENDED.

¹ The historical average represents the years 1986 - 2008. The threshold level is the 75th percentile of the distribution of cases in the same years.
² In this report laboratory confirmation refers to a positive IgM or PCR test.
³ Activity is classified as SPORADIC (no health region with positive dengue cases confirmed by IgM or PCR in more than 2 municipios), REGIONAL (one to four regions with positive cases in more than 2 municipios), or EXTENDED (more than four regions with positive cases in more than 2 municipios). Guayama and Patillas are not included in the report because they are involved in an enhanced surveillance project.
** Municipios are administrative units roughly equivalent to counties.
Public Workshop: Emerging Arboviruses: Evaluating the Threat to Transfusion and Transplantation Safety

December 14, 2009
8:30 a.m. - 5:30 p.m.

December 15, 2009
8:30 a.m. - 5:30 p.m.

Workshop Goals and Objectives

The Food and Drug Administration (FDA) is announcing a public workshop entitled “Emerging Arboviruses: Risk Assessment for Blood, Cell, Tissue and Organ Safety.” The purpose of the public workshop is to assess the risk and discuss approaches to minimize the incidence of transmission of arboviruses (arthropod-borne viruses) via transfusion, infusion, implantation or transplantation in the United States (U.S.). The public workshop will feature presentations and roundtable discussions led by experts from academic institutions, government, and industry.

Arboviruses are a large group of viruses that are spread by certain invertebrate animals, most commonly blood-sucking insects. Arboviruses are found throughout the world, including the U.S. Arboviruses such as Dengue virus, Japanese Encephalitis virus (JE), tick-borne encephalitis virus (TBE) and West Nile virus (WNV) are becoming increasingly widespread. Transmission of WNV and Dengue virus through blood transfusion has been well documented. Transfusion transmission of the Colorado tick fever (CTF) virus, a tick-borne agent present in the U.S., also has been reported. Other arboviruses, including JE, TBE, and St. Louis Encephalitis are of concern to blood, cell, tissue and organ safety because of the possibility of viremia in asymptomatic human infections. Dengue outbreaks have recently occurred in Texas, Hawaii, Puerto Rico and the U.S. Virgin Islands. Dengue virus, as well as TBE and JE, have the potential to become endemic in certain regions of the U.S. Therefore, proactive discussions among the HHS Public Health Agencies, including the FDA, National Institutes of Health and the Centers for Disease Control and Prevention, academia, industry, blood establishments, cell and tissue establishments, and other stakeholders are necessary to address blood, cell, tissue and organ safety in response to the emerging arboviruses.
2:00 pm Discussion:
Moderators: Melissa Greenwald, MD & Paul Mied, PhD

Session 6b. State-of-the-Art of Pathogen Inactivation - Industry Presentations
Chairs: Harvey Klein, MD & Harvey Alter, MD

2:25 pm PPTA Nathan Roth, PhD
2:35 pm Clearant Steve Burns
2:45 pm LifeNetHealth Alyce Linhurst Jones, PhD, RAC

2:55 pm Discussion:
Moderators: Harvey Klein, MD & Harvey Alter, MD

3:30 pm Coffee Break

4:00 pm NIH Funding Opportunities – NIAID
**Scope:** Disseminate information on the opportunities provided by NIAID/NIH for funding the development of screening and diagnostic assays, vaccines and therapeutics for arboviruses.
Patricia B. Repik, PhD

4:15 pm Round Table Panel Discussion: Arboviruses and Transfusion and Transplantation Safety
**Scope:** Safety issues based on biology of virus and scientific report of transmissions by transfusion and transplantation, autochthonous transmission, importation by trade and travel
Moderator: Hira Nakhasi, PhD

Discussants:
Paul Mied, Ph.D. & Indira Hewlett, PhD
Celia Witten, MD, PhD & Melissa Greenwald MD
Lyle Petersen, MD, MPH & Matthew Kuehnert, MD
Sally Hojvat, PhD
Steven Kleinman, MD & Louis Katz, MD
Michael Ison, MD, MS
Dennis Confer, MD
David Gocke, MD
My favorite picture of a mosquito!!
“Emerging” Infectious Diseases
Speed of Global Travel in Relation to World Population Growth

From: Murphy and Nathanson, Semin, Virology, 5,87, 1994
The challenge

Epidemics and newly-emerging infections are on the move as never before, threatening the health of people around the world and affecting travel and trade in the global village. Globalization, climate change, the growth of megacities and the explosive increase in international travel are increasing the potential for rapid spread of infections. Deforestation and urban sprawl bring humans and animals in closer contact and allow animal pathogens to “jump species” more easily and new epidemics to emerge.

Communicable Disease Surveillance
& Response (CSR)
“Emerging” Infectious Diseases
(many are emerging zoonoses)

• Respiratory/airborne
  ▸ Tuberculosis, SARS ?, pandemic influenza

• Parasitic diseases
  ▸ Malaria, Chagas, leishmaniasis, babesiosis

• Other mosquito-borne
  ▸ West Nile Virus, Yellow fever

• Tick-borne
  ▸ Tick-borne encephalitis virus (TBEV), Lyme disease

• Viral haemorrhagic fevers
  ▸ Ebola, Dengue, Marburg, CCHF, hantavirus w/renal syndrome
“Emerging” Infectious Diseases
(many are emerging zoonoses)

• Arenaviruses (from rodents)
  ‣ LCMV (Lymphocytic choriomeningitis virus), Lassa fever, plague, Hantavirus Pulmonary Syndrome (HPS)

• Human TSEs
  ‣ CJD, vCJD . . . . . . . . . . (CWD ? ? ?)

• Antibiotic resistant infections
  ‣ MRSA, VRE, and others
  ‣ MDR-TB, XDR-TB

• Xenotransplantation risk
  ‣ Porcine or baboon endogenous retroviruses (ERVs)

• Bioterrorism potential?
  ‣ smallpox, anthrax, plague, glanders
Regulators, working with tissue banking and tissue transplantation professionals, must be successful in properly assessing risk and determining relevance of diseases.

How do we do this on a global scale?
Vigilance & Surveillance of Recipients

- Processes must improve (outcomes & serious adverse reactions)
- AATB is developing identification, reporting & investigation guidelines
- Need buy-in from all stakeholders, especially Clinicians

EBAA’s OARRS  TSN  Canada’s CTOSS
FDA’s MedWatch  EUSTITE  + ?
Australia’s CGR
Infectious Disease Testing

The ‘window period’... time from beginning of infectious phase to test positive:

- HBsAg & HBcAb $\approx$ 5-7 weeks (ID NAT $\approx$ 8 days)
- HCV Ab $\approx$ 70 days (ID NAT $\approx$ 7.4 days)
- Syphilis testing $\approx$ 3 months
- HIV Ab from 3 weeks to months; depends on the type of testing performed as well as viral load at exposure (ID NAT $\approx$ 9 days)

This assumes: 1) qualification of the blood sample was evaluated without error, 2) sample handling requirements are met, 3) the best test kit was selected for use, 4) the test was performed following the test kit manufacturer’s instructions, and 5) the technician performing the testing made no errors....
James Reason’s Human Error Model

The Swiss cheese model of how defenses, barriers, and safeguards may be penetrated by an accident trajectory
US FDA’s 5 Layers of Blood Safety

FDA’s approach is to optimize each safety layer and then have them work together:

1. Donor screening based on geographic, behavioral and medical risk factors;
2. Laboratory testing;
3. Deferral registries to prevent use of blood from deferred donors;
4. Quarantine controls to prevent unit release pending verification of donor suitability; and
5. Investigation and correction of deviations.

Among other critical areas, the Quality Assurance System is assessed in each of these layers, and all 5 work collectively to provide recipient safety.

(Note applicability to cell & tissue safety)
“That men do not learn very much from the lessons of history is the most important of all the lessons of history.”

Aldous Huxley (1894-1963)
## Disease Transmission by “Tissue” Allografts
(Fresh, Frozen, and Cryopreserved...since 1954)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>Fresh bone, Frozen tendon</td>
</tr>
<tr>
<td>HBV</td>
<td>Fresh cornea, Cryopreserved heart valve</td>
</tr>
<tr>
<td>HCV</td>
<td>Frozen bone, Frozen tendon, Cryopreserved vein</td>
</tr>
<tr>
<td>CMV</td>
<td>Fresh skin</td>
</tr>
<tr>
<td>EBV</td>
<td>Fresh nerve</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Frozen bone</td>
</tr>
<tr>
<td>Rabies</td>
<td>Fresh cornea, Fresh artery (“organ” use)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Fresh cornea</td>
</tr>
<tr>
<td>CJD</td>
<td>Fresh cornea, Freeze-dried dura mater</td>
</tr>
<tr>
<td>TB</td>
<td>Frozen bone, Cryopreserved heart valve</td>
</tr>
<tr>
<td>Yeast, Fungus</td>
<td>Fresh cornea, Cryopreserved heart valve</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Fresh cornea, Fresh skin, Fresh cartilage, Frozen tendon, Frozen bone, Frozen pericardium, Cryopreserved heart valve</td>
</tr>
</tbody>
</table>

Information supplied by Ted Eastlund, M.D.
Annals of Internal Medicine

Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor

Balza D. Tugwell, MD; Priti R. Patel, MD, MPH; Ian T. Williams, PhD, MS; Katrina Hedberg, MD, MPH; Feng Chai, PhD; Omana V. Nair, PhD; Ann R. Thomas, MD, MPH; Judith E. Woll, MD; Beth P. Bell, MD, MPH; and Paul R. Cieslak, MD

Background: Although hepatitis C virus (HCV) transmission through tissue transplantation has rarely been reported, a donor with undetected viremia may infect several recipients. A patient developed acute hepatitis C shortly after tissue transplantation. Ninety-one tissues or organs had been recovered from the donor.

Objective: To determine whether the donor was the source of infection and the extent of transmission to other organ and tissue recipients.

Design: Descriptive epidemiologic study; serum testing for HCV infection.

Setting: Recipients were located in 16 states and 2 other countries.

Participants: Donor and graft recipients.

Measurements: Hepatitis C virus infection was defined as the presence of anti-HCV or HCV RNA. The authors determined the genetic relatedness of viral isolates from the donor and recipients by genotype comparison and quasi-species analysis.

Results: The donor was anti-HCV-negative but was HCV RNA-positive (genotype 1a). Forty persons received transplants during 22 months. Five persons were HCV-infected before transplantation or had a genotype other than 1a, and 5 persons had no post-transplantation serum specimens available. Of the remaining 30 recipients, HCV infection occurred in 8 recipients: 3 of 3 organ recipients, 1 of 2 saphenous vein recipients, 1 of 3 tendon recipients, and 3 of 3 tendon with bone recipients. These 8 recipients had viral isolates genetically related to those of the donor. No cases occurred in recipients of skin (n = 2), cornea (n = 1), or irradiated bone (n = 16).

Limitations: Post-transplantation serum specimens were unavailable for 5 recipients.

Conclusions: An anti-HCV-negative donor was the source of HCV infection for 8 recipients of organs or tissues. Although HCV transmission from anti-HCV-negative donors is probably uncommon, changes in donor screening to include routine testing for HCV RNA merit further consideration to improve the safety of transplantation.

For author affiliations, see end of text.
HCV Transmission - 2000

- Male in his 40’s; intracranial hemorrhage
- Parents gave medical/social history
- Infectious disease testing all acceptable (includes non-reactive HCV 2.0 Ab)
- Liver aminotransferase levels normal
- Liver biopsy showed mild steatohepatitis with no significant fibrosis
- Organ, tissue, and ocular donor (October)
- Family physician responded to tissue bank’s routine inquiry regarding donor’s medical history (reported HTN, alcohol abuse)
HCV Transmission - 2000

2002 - 2 yrs later tissue bank received report that recipient of patellar ligament allograft had developed acute HCV, 6 weeks post implant; no other risk hx

• Discovery that 3 other recipients had been diagnosed with HCV by late 2001 but clinicians had not linked these infections with patient receipt of allografts
  ✦ 1 organ, 2 tissues

• Archived donor serum stored by the tissue bank was re-tested and negative using HCV 2.0 and 3.0 Ab tests, but reactive when using an HCV NAT assay (HCV RNA positive).
### HCV Transmission - 2000

#### Table. Classification of Graft Recipients from a Hepatitis C Virus–Infected Donor, United States, 2000–2002*

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Manner of Processing</th>
<th>Recipients, n</th>
<th>Classification</th>
<th>Proportion Infected, n/n$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unassociated HCV Infection, n†</td>
<td>Unable To Test Post-Transplantation, n</td>
</tr>
<tr>
<td>Organ</td>
<td>Fresh</td>
<td>6</td>
<td>3‖</td>
<td>0</td>
</tr>
<tr>
<td>Cornea</td>
<td>Fresh</td>
<td>2</td>
<td>0</td>
<td>1‖</td>
</tr>
<tr>
<td>Skin</td>
<td>Cryopreserved</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Saphenous vein</td>
<td>Cryopreserved</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tibialis tendon</td>
<td>Cryopreserved</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tendon–bone</td>
<td>Fresh frozen, Allowash**</td>
<td>4</td>
<td>0</td>
<td>1‡‡</td>
</tr>
<tr>
<td>Bone</td>
<td>Lyophilized, Allowash**, irradiated</td>
<td>20</td>
<td>3</td>
<td>1‡‡</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40</td>
<td>5</td>
<td>22</td>
</tr>
</tbody>
</table>

*HCV = hepatitis C virus.*
† These recipients were HCV-infected but did not meet the case definition. Four were reported to have been infected before transplantation (documentation unavailable for 2 recipients), and another was infected with HCV genotype 3a.

‖ The recipient had negative anti-HCV (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois) and negative qualitative HCV RNA test results 2 years after transplantation, but information on the specific HCV RNA assay used is unavailable.

†† Recipient located in another country with limited information available.
‡‡ Recipient’s name was not retained by the transplanting hospital.
Significant Communication Delay

Figure 1. Transplantation of grafts from a donor with hepatitis C virus (HCV) infection 
(n = 38), United States, 2000–2002.

Dates of transplantation for 2 recipients were unknown. Hepatitis C virus infection was diagnosed in 3 recipients in September, October, and November 2001. These recipients had undergone transplantation in February 2001, October 2000, and April 2001, respectively.

Better communication could have halted tissue release.
“Vigilance is an attitude!”

Dr Luc Noel, WHO
July 2007, EUSTITE Meeting,
Vigilance & Surveillance Medical
Advisory Committee
Rome, Italy
**Desires**

The provision of safe tissue for recipients in need is everyone’s goal and science should support practice, which includes establishing donor eligibility criteria and donor testing that makes sense. The ‘science’ must come from you.

Eye and tissue banking professionals must communicate and work closely with regulators to establish sound requirements and there should be information sharing and international harmonization when possible.

Implementing vigilance and surveillance programs regarding tissue recipient adverse reactions and outcomes can play an important role in supporting decision-making so this must also evolve.
¡Muchas gracias!

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