New Transfusion Infections

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Hira Nakhasi, Ph.D.
Director
Division of Emerging and Transfusion Transmitted Diseases
FDA/CBER/OBRR
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• Email CBER:
  – Manufacturers: matt@cber.fda.gov
  – Consumers, health care professionals: octma@cber.fda.gov
Challenge for Blood Products

Enhance Product Safety, Purity and Potency

Avoid Product Shortages & Major Increased Costs

Critical Path opportunities exist that could improve blood product safety, efficacy and availability while minimizing disruptions to the blood system.
New Challenges

• West Nile virus (WNV)
  – Approval of tests
• Malaria, Leishmanina and Chagas
  – Donor guidance and testing
• Counterterrorism
  – Guidance and Detection technologies for BT agents
• Inactivation technologies
• Evaluation of candidate diagnostic and donor screening test for transmissible spongiform encephalopathies (TSEs)
New Challenges......

• Development and validation of nucleic acid based test to detect bacteria and parasites in blood.
• Nanotechnology: Novel technology for blood and patient safety
• Development of a valid animal model to predict immunogenecity of factor VIII products
• Development of standards for plasma-derived products (e.g., Alpha 1 PI)
Update on West Nile virus and Blood Safety
Background Information

- WNV is an enveloped single stranded RNA virus
- WNV is a mosquito-borne Flavivirus
  - Primarily infects birds
  - Occasionally infects humans and other animals
- About 80% of human infection is asymptomatic, and 20% develop mild febrile illness (flu-like illness)
- Approximately 1 in 150 infections results in meningitis or encephalitis
  - Advanced age is by far the most significant risk factor for severe neurologic disease
- Viremic period can occur up to 2 weeks prior to symptoms and last up to a month from the initiation of the infection
The 2002 US outbreak of WNV resulted in the identification of other modes of transmission including:

- blood transmission (RBCs, plasma and platelets), transplantation, breast-feeding, transplacental and occupational by percutaneous injury

The magnitude of the risk of WNV from transfusion is unknown.

Virus titer in blood is low compared to other transmissible viruses.

- Viremia in encephalitis patients can be as high

IgM can persist for a long time in some cases up to 2 years

No chronic stage of WNV infection has been reported
WNV Blood Safety Measures

- FDA’s Office of Blood Research and Review has provided guidance to blood establishments on donor screening and unit management to prevent transmission of WNV by blood transfusion as follows:
  
  - August 17, 2002, FDA issued an alert to blood establishments to exercise vigilance to exclude potential donors with flu-like symptoms even though there had been no reports that it could be transmitted by blood.
  
  - October 25, 2002, FDA issued a guidance document, “Final Guidance for Industry on Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection” to prevent donors with symptoms from donating and to manage implicated products.
  
  - May 1, 2003 FDA issued a revised guidance to include deferral of donors who are healthy but had symptoms of fever with headache within the week before donation.
WNV Blood Safety Measures

- **FDA has encouraged and worked with manufacturers to develop suitable WNV blood-screening tests**
  - In cooperation with the Department of Health and Human Services, FDA issued a call to industry to rapidly develop blood donor screening tests in September 2002.
  - FDA sponsored a public workshop in November 2002, and discussed issues in development of WNV donor screening at various public forums including meetings of FDA’s Blood Products Advisory Committee
  - FDA is developing reference materials and standards that companies can use to validate their tests similar in format.
  - FDA is participating in meetings with AABB task force to coordinate the epidemiological data on WNV infection and to monitor the outcome of nation wide testing.
  - The experimental kits in use are nucleic acid amplification tests, which detects WNV RNA in the human blood sample, are similar to those already licensed for screening blood donors for HIV and hepatitis C virus infection.
WNV Blood Safety Measures

- **WNV testing:**
  - WNV NAT testing of whole blood, blood components source plasma, bone marrow, cord blood, hematopoietic progenitor cells, tissue and organ donors is being done under IND.
  - Nationwide testing started as of July 1, 2003 using Roche and Gen Probe tests.
  - Clinical trials are being performed in both pooled (16 for GenProbe and 6 for Roche) and individual samples.
  - The regulatory pathway for WNV testing includes testing all donors under IND, link product release to WNV test results, require confirmatory testing (alternate NAT and IgM), unit donor management (follow up, counseling and look back).
WNV Blood Safety Measures

FDA’s current recommendations for donor deferral

- FDA most recent recommendations targeting prevention of transmission by donors with current or recent symptoms (about 20% of infected individuals) was issued on May 1, 2003.
- FDA regulations already require that blood establishments determine donors to be in good health at the time of donation and defer donors with current clinical symptoms.
- During the epidemic season of June 1 to November 30:
  - Donors who report a medical diagnosis of WNV infection were deferred for at least 28 days from onset of symptoms or until 14 days after the condition is resolved whichever is longer.
  - Donors who report fever and headache in the week before donation were deferred for 28 days from the date of the interview.
WNV Blood Safety Measures

Pathogen inactivation

– Available information indicates it is unlikely that WNV is transmitted through plasma derivatives.
  • Approved procedures for pathogen inactivation such as solvent/detergent will inactivate lipid-enveloped viruses. Model flaviviruses such as BVDV served as models for HCV and have been shown to behave similarly to WNV.

– Experimental use of psoralins, riboflavin, and Inactine for viral inactivation in plasma, platelets, and red cells also showed high level inactivation of WNV ( > 4 log reduction ).
Status of WNV epidemiology and testing in the US in year 2004

• During 2003 total number of human cases reported to CDC ArboNET were 9862 and 264 deaths
• 46 states reported WNV activity
• As of January 11, 2005 total number of WNV human cases in 2004 reported to CDC’s ArboNET were 2470 and 88 deaths, of the total infections 36% cases of WNM&E (neuroinvasive) and 41% cases of WNV fever (milder disease) and 22% were clinically unspecified
• WNV activity was reported in 47 states
West Nile Virus and Blood Safety:

• Nationwide testing of WNV under FDA approved INDs resulted in:
  – Donations interdicted from asymptomatic donors with confirmed or suspected WNV infections

  – In 2003, 818 WNV presumptive viremic blood donors officially reported to CDC’s ArboNet
    • 6 confirmed T-T cases (4/6 had low viremia ~0.11 pfu/ml)

  – As of January 11, 2005; 199 presumptive viremic donors officially reported to CDC’s ArboNet from 28 states using MP-NAT as well as ID-NAT in select areas starting May ’04
    • one reported case of T-T (detectable only by ID-NAT)
Proposed model for stages of WNV infection based on results found on MP-/ID-NAT and IgM/IgG EIA

| Stage  | IDNAT+/MPNAT- | MPNAT+ | IDNAT+/MPNAT- | IDNAT+/
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<tbody>
<tr>
<td>Stage-I</td>
<td>IgM-</td>
<td>Stage-II</td>
<td>IgM-</td>
<td>Stage-III</td>
</tr>
<tr>
<td>Stage-V</td>
<td>IgM+</td>
<td>Stage-V</td>
<td>IgM+</td>
<td>Stage-V</td>
</tr>
</tbody>
</table>

Days post infectious mosquito bite

Days: 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

WNV RNA (gEq per mL)

Log scale: $10^1$ to $10^5$
West Nile Virus and Blood Safety: Trigger for ID-NAT

• Based on the experience of ID-NAT testing in high incidence areas during 2003 epidemic.

• Retrospective study of MP-NAT negative donations

• Based on the availability of adequate resources, especially equipment, reagents, and trained technologists.

• Following criteria were recommended for the trigger of ID-NAT testing in 2004
  – Monitor reactive rates by zones, daily and rolling 7 days
  – 2-4 cases in any geographic area (blood collection) and a frequency of 1 per 1000.
  – Revert back to MP-NAT based on one week of absence of reactivity by ID-NAT or 0 cases in consecutive 3-4 day period or rate less than 1:1000.
West Nile Virus and Blood Safety: Duration of WNV Viremia

• ARC and BSL studied WNV RNA dynamics in limited number of reactive blood donors from 2003 epidemic, F/U to determine the rate of disappearance of RNA, and SC of IgM and IgG (Unpublished observations)

  – WNV viremia may last up to 49 days
  – WNV RNA may coexist with IgM
WNV and Blood Safety: Gaps in current knowledge

• **Donor and product management recommendations:**
  – donor follow up identified a period of viremia of 49 days
  – Donor deferral period extended from 28 days to 56 days, what next?
  – Entry of donors after testing ID-NAT (-): time limit

• **Symptoms with WNV infectivity**
  – Correlations of headache with fever in the week before donation

• **Trigger for ID-NAT testing**
  – ID-NAT vs MP-NAT to further reduce risk of WNV T-T
West Nile Virus and Blood Safety: Gaps in knowledge

- **Genetic variations in WNV strains – limited data in human disease cases**
  - Detection by currently available WNV assays

- **Determination of residual risk of WNV infection in the presence of antibody**
  - MP-NAT low titer, MP-NAT (-), ID-NAT (+) units

- **Usefulness of WNV surveillance data to predict epidemic**
  - Detection in birds, mosquitoes, equines, symptoms in human, etc.
  - Severity of epidemic from year to year
Acknowledgements

- Task force which consists of public health agencies (FDA, CDC, NIH, DOD) and blood establishments for weekly updates and monitoring the progress of WNV epidemic and testing
- Test kit manufacturers for development of investigational tests in a timely manner
- FDA staff for interactive review and formulating policies
- Blood establishments for timely implementation of WNV testing
Update on TSE and Transfusion
TSEs of Humans
(5 to 8, depending on classification)

• Creutzfeldt-Jakob disease (CJD)
  – Sporadic (sCJD): most common, ? source
  – Familial (fCJD): ~10% of total CJD; also
    Gerstmann-Sträussler-Scheinker syndrome (GSS) ≈
    fCJD with prominent amyloid plaques, different associated PRNP
    mutations
  – Iatrogenic: pituitary hormones, dura, instruments
  – Variant (vCJD): food-borne, transfusion-transmitted

• Kuru: instructive example

• Fatal insomnias: familial (FFI), sporadic—both rare
History of TSEs and FDA Blood Safety Policies

- 1978: Manuelidis & al detected CJD agent in guinea pig blood buffy coat.
- 1983: Kuroda, Gibbs detected GSS ("fCJD") agent in mouse blood—highest concentration in buffy coat.
- 1983 to present: TSE agents in blood confirmed
  Hamster scrapie, mice BSE, sheep BSE & nat'l scrapie, chimp GSS
- 1987: FDA recommended deferring donors Rx with pit-hGH, later other donors at increased TSE risk
  Dura mater allograft, family history of CJD
- 1995: FDA recommended precautionary withdrawal of blood components and plasma derivatives
  (rescinded for plasma derivatives except for vCJD in Sept 1998) from donors at increased risk.
Most Recent History of TSEs and FDA Blood Safety Policies to Reduce Risk of vCJD

- 2002: FDA recommended enhanced precautionary geographic vCJD deferrals—current guidance.
- 2003: UK reported a case of presumptive transfusion-transmitted (TT) vCJD non-leukoreduced RBC in one of a small cohort of recipients—“TMER” Study.
- July 2004: UK reported a 2nd TT vCJD case (1st PRNP-129-met/val heterozygote, ≅ 50% UK population).
- July 2004: UK appendix (and tonsil) PrPsc survey ? >200 persons/million in UK incubating vCJD
- Sept 2004: UK notified certain recipients of plasma derivatives that they were at increased risk of vCJD.
Final Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) & Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products
Jan 9, 2002
www.fda.gov/cber/guidelines.htm

- **Phase I** (for implementation by May 31, 2002)
  Indefinitely defer all donors who
  - have any form of CJD or are at increased risk of CJD
  - (no change from previous FDA guidance)
  - spent ≥3 mo in UK from Jan 1, 1980 to Dec 31, 1996
    - or who ever had blood transfusion in UK from 1980 to present
    - or who ever injected UK bovine insulin prepared in or after 1980
  - spent ≥5 yr in France from Jan 1, 1980 to the present
  - spent ≥6 mo on US military bases from Jan 1, 1980 to end of 1990 north of Alps or end of 1996 south of Alps
Final Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) & Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products
Jan 9, 2002
www.fda.gov/cber/guidelines.htm

- **Phase II** (for implementation by October 31, 2002)
  - Indefinitely defer all donors of Whole Blood but not donors of Source Plasma who spent $\geq 5$ yr in Europe from Jan 1, 1980 to the present (including time in spent in UK 1980-1996 and France 1980-present)

**Exempt from deferral are**
- Donors of Source Plasma who spent any period of time in Europe except UK and France
- Donors of plasma/serum to manufacture CBER-approved non-injectable products (specially labeled)
Variant CJD: Reasons for Greater FDA Concern about Potential Infectivity of Blood

- Lymphoid tissues of patients with vCJD contain much more protease-resistant prion protein than do those of patients with conventional forms of CJD. Infectivity of those tissues is not yet clear. (Note: Lymphoid tissues of some patients with conventional sporadic CJD [sCJD] have been infectious for non-human primates [Brown P et al. Ann Neurol 1994;35:513].)

Implication: Blood, containing lymphoid cells, might be more infectious in vCJD than in classical forms of CJD.

- vCJD differs markedly from sCJD; distribution of infectivity in patients with sCJD might not be predictive for vCJD.

- vCJD is a new emerging disease not found in the USA except in one long-time UK resident.

- Actions of UK authorities implied lack of confidence in safety of blood of UK donors.

Two presumptive transfusion-transmitted cases of vCJD
### 170 Cases of vCJD Worldwide
(as of 06 Feb 2005)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
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<tbody>
<tr>
<td>UK</td>
<td>154</td>
</tr>
<tr>
<td>France</td>
<td>9</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
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Cases of vCJD in **France** and **Italy** had no history of travel to UK. Five others were current or former UK residents, one (in Japan) for a period of only 1 mo during a high-risk period (1990).
Variant CJD in UK each Year since 1994
(from Will RG, unpublished Oct 2003)

New Cases

Deaths
Possible Incubation Periods of v CJD
(R Will’s prior estimates from time resident left UK or history of receiving a vCJD-implicated transfusion)

● **Food-borne cases**
  - US 9-21 yr
  - Canadian 11-19 yr
  - [Irish 5-10 yr]
  - [Japan 12yr]*

● **Blood-borne cases**
  - First case 6 yr
  - Second case > 5 yr
### PrP<sub>sc</sub> in Appendix, Tonsils: Association with vCJD


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<tr>
<td><strong>Postmortem vCJD</strong></td>
<td>19/20</td>
</tr>
<tr>
<td><strong>Preclinical vCJD</strong></td>
<td>2/3</td>
</tr>
<tr>
<td><strong>1&lt;sup&gt;st&lt;/sup&gt; Surgical Survey</strong></td>
<td>1/8318</td>
</tr>
<tr>
<td><strong>2&lt;sup&gt;nd&lt;/sup&gt; Surgical Survey</strong></td>
<td>3/12,674</td>
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**Estimated UK prevalence of abnormal PrP in lymphoid tissues**

- **1<sup>st</sup> survey:** ~120/million (95% CI 0.5 – 900/million)
- **2<sup>nd</sup> survey:** ~237/million (95% CI 49-692/million)

*1 yr, 2 yr, 10 yr (neg) before onset of symptoms; 3 yr, 4 yr, 11 yr (neg) before death*
March 1996
- Clinically healthy young blood donor donated Whole Blood to the UK National Blood Service.
- RBC—not leukoreduced—transfused into 63 yr-old surgical patient.

About March 1999
- Donor developed signs of variant CJD, later died; vCJD confirmed by autopsy.
- UK Transfusion Medicine Epidemiology Review (TMER) enrolled recipient (with 49 other recipients of vCJD-implicated labile blood components from 16 donors later Dx with vCJD—13 now living >5yr).

December 2003
- The recipient died age 69; post-mortem diagnosis was typical vCJD (PRNP-129-met/met homozygous).
- The recipient's age-adjusted food-borne risk of vCJD estimated by UK authorities to have been ~ 1:15,000 to 1:30,000.
2\textsuperscript{nd} Transfusion-Transmitted Case of vCJD

1999
- Clinically healthy young blood donor donated Whole Blood to the UK National Blood Service.
- RBC—not leukoreduced—transfused into a surgical patient.

2000
- Donor developed signs of variant CJD 18 mo later, died in 2001; vCJD confirmed by autopsy.
- UK Transfusion Medicine Epidemiology Review (TMER) enrolled recipient (with 49 other recipients of vCJD-implicated labile blood components from 16 donors later Dx with vCJD—13 now living >5yr).

2003
- The recipient died of ruptured abdominal aortic aneurysm.
- No history of dementia and CNS, tonsils and appendix were normal.
- PrP\textsupersc was present in several areas of spleen, cervical lymph node.
- The recipient's age-adjusted food-borne risk of vCJD was estimated by UK authorities to have been \( \sim 1:15,000 \) to \( 1:30,000 \).
- Recipient’s genotype was \( PRNP 129\text{-}\text{met/val heterozygous} \).
Some Implications for Public Health of Recent Findings Regarding vCJD

- vCJD was transmitted by transfusions of non-LR RBC.
- \(PRNP-129\)-met/val genotype (\(\approx 50\%\) UK population) did **not** convey absolute resistance to infection with the BSE agent, at least after adaptation to humans and IV exposure.
- A second wave of vCJD cases in \(PRNP-129\)-met/val (? and val/val) persons in UK is possible, perhaps smaller than the first wave but of unknown magnitude.
- A recent survey of \(PrP^{sc}\) in appendices (and tonsils) of normal surgical patients in UK estimated a rate of 237 infected people per million people in UK; that estimate might be low (because uncertain when appendix becomes positive).
- Number of persons in the UK—? other BSE countries—potentially having vCJD agent in blood might be significant.
- BSE geographic-based blood donor deferral policies have been prudent and justifiable.
General Approaches of FDA Policies to Reduce Risk of Transmitting vCJD by Blood Products

- Reduce risk that donor was exposed to BSE agent
  - Dietary exposure: Residence in BSE country (or military base importing beef from UK)
  - Other exposure: Use of UK bovine insulin

- Reduce risk that donor was exposed to vCJD agent of human origin
  - Transfusion in UK after 1980
  - [Surgery in other BSE country after 1980: suggested by TSEAC member]
# Estimated vCJD Blood Risk Reduction and Donor Loss from Possible Enhanced Deferral Policies

(from A Williams, FDA, TSEAC 14 Oct 2004)

<table>
<thead>
<tr>
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<th>Reduced Risk (in add’n to current 91%)</th>
<th>Donor Loss (in add’n to current 6.4%)</th>
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<tbody>
<tr>
<td>UK 3 mo (’80-96)</td>
<td>4%</td>
<td>3%</td>
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<tr>
<td>↓ to 1 mo</td>
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<tr>
<td>Transfusion in France (’80-now)</td>
<td>Uncertain but very small</td>
<td>1.4/10,000</td>
</tr>
<tr>
<td>Transfusion in Non-UK W Eu (’80-now)</td>
<td>Uncertain but very small</td>
<td>3/10,000</td>
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</tbody>
</table>
1. Should FDA recommend deferral of Whole Blood donors transfused after the beginning of 1980?
   - In France: Yes 12, No 3, Abstain 1
   - Other W Europe: Yes 0, No 15, Abstain 1

2. Should FDA recommend deferral of Source Plasma donors transfused in/after 1980?
   - In France: Yes 5, No 7, Abstain 4
   - Other W Europe: Yes 0, No 16, Abstain 0
Acknowledgements

- David Asher-FDA
- Dot Scot-FDA
- TSEAC Advisory committee members
• Thank you