Update on Transfusion-Transmitted Infectious Diseases

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I have no conflicts of interest to disclose.
Global changes and the spread of disease

- Changing environmental dynamics provide opportunities for new niches for vectors
  - Diseases previously identified as being geographically-restricted are emerging in new areas
- Travel has increased both in frequency, distance and numbers of individuals
- Global trade has increased
  - Including items such as used tires

Transfusion-Transmitted Infection

• Bacteria, viruses, parasites or prions present in blood products that can cause disease in a recipient when transfused

• Traditionally, blood supply protected by several mechanisms:
  • Donor history and physical exam
  • Screening tests (nucleic acid, serologic, culture, POC)
  • Pathogen reduction
  • Leukoreduction
  • Failure to survive storage conditions
Transfusion-Transmitted Infection: Donor questions

• Utility of donor screening questions versus donor education material

• Though new questions and material can be rapidly developed, implementation at blood centers can be cumbersome

• Travel questions can be nebulous
  • Travel to an endemic area – does airport connections count?

• Areas of disease activity can change or be unfamiliar to the donor

• Some questions are simply unknown
  • Have you had sexual contact with someone who has travelled to an area with...
Transfusion-Transmitted Infection: Donor Questions

• Utility of donor screening questions versus donor education material
  • Recent guidance from the FDA (1-2017) regarding Ebola
    • Recommends adding to the education materials that donors with a history of Ebola virus infection do not donate blood
    • Recommends updating donor history questionnaire to assess travel and contact history should areas with widespread transmission of the virus develop
Transfusion-Transmitted Infection: Screening tests

• Development and licensing of approved screening tests for infectious diseases takes significant time and capital
  • FDA licenses diagnostic and screening tests differently

• Serologic and nucleic acid testing are used for virus detection

• Culture and POC testing are used for bacterial detection

• Cost
Should We Test or Not?

Asymptomatic Infection

Significant Clinical Disease

Proven Transfusion-Transmission

(Adapted from Harvey Alter, M.D.)
Pathogen reduction

• FDA approved technology that reduces (but not eliminates) the viability and infectivity of infectious agents in platelets and plasma

• Not approved for RBCs in the United States

• Cost

• Availability

• If fully implemented, capacity issues may arise
Arboviruses

• Any virus transmitted by an arthropod (insects and ticks)

• Wide variety of diseases and risks

• Most immediate challenge facing the United States’ blood supply today
Emerging Diseases: Zika

• *Flaviviridae* family, genus *Flavivirus*
  • Same as WNV

• May cause asymptomatic virema or present with fever, rash and arthralgias

• Transmitted through mosquito bites, perinatal exposure, sexual contact, transfusion

• Potentially transmissible up to 6 months after infection
Emerging Diseases: Zika

Triangle of Transfusion Testing

Should We Test or Not?

Asymptomatic Infection

Significant Clinical Disease

Proven Transfusion-Transmission

(Adapted from Harvey Alter, M.D.)
Emerging Diseases: Zika

- Challenge for blood collections centers

Emerging Diseases: Zika

• Challenge for blood collections centers
Emerging Diseases: Zika

• 1947 Discovered, with cases reported in equatorial Africa and Asia
• 2007 Spread to island of Yap in Pacific
• 2013-14 Outbreak in French Polynesia
• 2015 First report in Brazil in March
• 2016 FDA issues guidance on Transfusion Transmission in February with questionnaire guided restrictions
• 2016 FDA revises guidance in August that includes recommendations to test all donations collected in the US with individual donor nucleic acid testing (IND) or pathogen reduce all platelets/plasma
Emerging Diseases: Zika

- Roche cobas Zika ID-NAT has screening 358,789 donations

- 23 initially reactive, 14 confirmed positive (all from Florida)

- 10/14 travelled to Zika endemic areas (Caribbean or Miami)

- When a minipool testing was simulated, 7/14 were not detected

Emerging Diseases: Zika

• Procleix ID-NAT has screening 466,834 donations

• 5 confirmed positive (all from non-endemic areas)

• Estimated 1:93,000 units in non-endemic areas
Emerging Diseases: Zika

• Currently, PR is not available for red blood cells, so ID-NAT is used by most major blood suppliers to screen donations for Zika

• Neither available ID-NAT test is licensed and both are currently used under IND exemption

• Unknowns
  • Is testing units permanent?
  • Does PCR positivity correlate with infectivity?
  • What are the performance characteristics of these tests?
  • Will the FDA use this model to approach other diseases?
Arboviruses to watch

• Dengue fever
  • Up to 87% of infected individuals can be asymptomatic
  • During a large epidemic in Brazil, up to 0.8% of donations tested positive for viremia, with 1/3 of these transmitting disease by transfusion
  • Reported in Brazil, Figi, Saint Lucia, Belize, Grenada, Argentina

Teo et al. Transfu Med 2009
Arboviruses to watch

• Yellow fever

• Vaccinated individuals can donate blood that contains vaccine virus
Arboviruses to watch

- Chikungunya
Arboviruses

• Likely a continual issue
  • Climate
  • Travel
  • Population density

• Zika is unusual in its association with microcephaly

• Yellow Fever, Dengue, Chikungunya have the potential for transfusion transmission
Hepatitis E

• Positive-sense single-stranded non-enveloped RNA virus

• Four Genotypes (Type 3 is common in North America)

https://www.cdc.gov/hepatitis/hev/hevfaq.htm
Hepatitis E

• Transmission is mostly food-borne or fecal-oral

• Usually asymptomatic, with some patients have usual hepatitis symptoms (fever, nausea, vomiting, jaundice)

• Self-limited unless immunocompromised or pregnant

• Worldwide, 56,600 deaths per year

• Potentially treatable with ribavirin

https://www.cdc.gov/hepatitis/hev/hevfaq.htm
Hepatitis E

• Transmission from transfusion has been documented in Europe, Japan and the middle east

• Transplant recipients can develop fatal complications from transfusion-transmitted HEV
  • Liver abnormalities (elevated AST/ALT) can lead to a misdiagnosis of GVHD in allogeneic hematopoietic stem cell transplant recipients

• Patients with compensated liver failure
HEV RNA and confirmatory results

<table>
<thead>
<tr>
<th>#</th>
<th>US Region</th>
<th>Procleix HEV Assay Results (S/CO)</th>
<th>Sanquin PCR Results</th>
<th>Antibody Results (S/CO)</th>
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<tbody>
<tr>
<td></td>
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<td>Initial</td>
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18,829 donations TMA screened (Procleix HEV Assay) from six different regions of the US with 9 TMA initial reactives and two confirmed positive (i.e., 1 TMA repeat reactive and PCR positive, and 1 initially TMA reactive and PCR positive in 1 of 2 replicates).

Prevalence is based on the two confirmed positives and equals 1:9500 (95%CI:1:2850-1:56,180). One additional TMA initial reactive was IgG reactive. Stramer et al. Transfusion 2016
Hepatitis E

• Present in blood donations, with an estimated 544 to 952 donations with Hepatitis E viremia in the USA

• No licensed screening test

• No licensed diagnostic test
  • Under-recognized clinically

• Not effectively inactivated with pathogen reduction techniques
Chagas disease

• Possible autochthonous Chagas disease in Texas?
• Testing the first donation for Chagas antibodies relies on no autochthonous transmission of disease

Am J Trop Hyg 2015
Chagas disease

• In 11-2016, FDA issued an Amendment to Guidance for Industry on Chagas
  • Recommends that one time testing alone is sufficient to protect blood supply
  • No questions of donor are needed
    • Most donors did not know their status and the question proved to be of very low yield

• Should autochthonous transmission become a reality, more frequent testing may be required
Babesia
Babesia

- 165 reported cases of transfusion-transmitted babesiosis
  - Hematologic (19%), neonate (10%), Cardiovascular (8%), GI (6%)
  - 32/165 died, 25 of which was due to Babesiosis
  - Usually due to RBC transfusions
Babesia

• FDA Blood Product Advisory Committee recommended nationwide year-round antibody screening in addition to NAT screening in high-risk states

• No licensed tests available

• Regional disadvantages for some blood suppliers
Tranfusion-related fatalities

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Fatalities</th>
</tr>
</thead>
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<tr>
<td>TRALI</td>
<td>FY08: 16, FY09: 13, FY10: 18, FY11: 10, FY12: 17</td>
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<tr>
<td>HTR (non-ABO)</td>
<td>FY08: 7, FY09: 8, FY10: 5, FY11: 6, FY12: 5</td>
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<tr>
<td>HTR (ABO)</td>
<td>FY08: 10, FY09: 4, FY10: 2, FY11: 3, FY12: 3</td>
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<td>Microbial Infection</td>
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<td>Anaphylaxis</td>
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</tr>
<tr>
<td>Other</td>
<td>FY08: 0, FY09: 1, FY10: 1, FY11: 1, FY12: 0</td>
</tr>
</tbody>
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FDA
TTD bacterial deaths
Bacteria

Loza-Correa et al. Transfusion 2017
Bacteria

• FDA guidance for apheresis platelets for blood collection services
  • Pathogen reduction
  • Culture-based testing
    • Cx no sooner than 24 hours after collection

• FDA guidance for apheresis platelets for transfusion services
  • Purchase PR platelets
  • For cultured platelets
    • On day 4 or 5, perform rapid testing of unit or
    • Culture platelet on day 4, for at least 12 hours
Summary

• Global factors are changing transfusion-transmitted disease risk

• The FDA has reacted to emerging threats with zero-tolerance approaches with major economic implications

• New technologies and tests are being developed and implemented to keep our blood supply safe
Blood Suppliers

• Donor education material and donor health questions require updates and can initially be the first response to a new infectious threat
  • Questionably efficacy

• Adding new screening tests is costly, time consuming, and requires significant workflow changes/validation

• The FDA has required unlicensed testing with Zika
Blood Suppliers

• Educating clients

• Blood supply is not always local with significant movement of products at the regional/national level

• To PR or not to PR? Limiting collection to double units?

• Should we have a universal travel deferral?
Transfusion Services

• Added testing or pathogen reduction strategies affect budget

• Pathogen reduction may be useful to combat emerging diseases, but is there a trade off in efficacy or reactions?
  • No licensed RBC technology yet

• Complex FDA guidance like issued for bacteria can present significant challenges in terms of workload and budget
Transfusion Services

• Little or no information for clinicians who consent recipients
  • Education is important

• Suspected transfusion-transmitted diseases cannot always be routinely tested
  • Zika and Hep E
Questions?