Keeping the Blood Supply Safe – Current and Future Strategies

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Overview

- **Pre-collection**
  - Donor Screening

- **Collection**
  - Visual Inspection
  - Aseptic Processing
  - Leukoreduction of Apheresis Collections

- **Post-Collection**
  - Infectious Disease Testing
    - Bacteria
    - Virus
    - Parasite
  - Blood Culture

- **Emerging Infectious Agents**

- **Pathogen Reduction Technologies**
Donor Screening Questions

- The first 3 questions on the UDHQ
  - Feeling healthy and well today?
  - Currently taking an antibiotic?
  - Currently taking any other medication for an infection?

- High risk behavior assessment questions
  - Sexual contacts with prostitutes, persons with HIV or Hepatitis, history of syphilis or gonorrhea, incarceration >72 hrs, etc.

- vCJD (prion) risk assessment questions
  - Time spent in United Kingdom, Europe or receiving blood transfusions in United Kingdom or France

- Untested infectious disease questions
  - Malaria, Babesia
Value of Donor Questions

- Protect the health of the donor

- Lower the risk of collecting an infectious unit
  - Deferral based on risk factors for transmissible infections prevents the collection of contaminated units
  - Risk factor screening compliments laboratory testing by avoiding collections in the “window period”
  - Safe guard against transmissible agents that are not currently tested (e.g. vCJD)
  - Donor selection may have surrogate value, i.e. deferral of malaria exposure in an endemic area might prevent transfusion risk from an emerging disease
Pitfalls of Donor Questions

- Low sensitivity and specificity
  - May result in significant loss of healthy donors
  - Undermine public confidence in the blood system
  - Trusting that donors are truthful
Risk Reduction During Collection

- **Visual inspection**
  - Looking for track-marks, or open wounds

- **Aseptic processing**
  - Iodine or chlorhexidine gluconate prep
    - 30 seconds of vigorous scrubbing of the venipuncture site
  - Diversion pouch

- **Leukoreduction of apheresis collections**
Infectious Disease Tests (IDT)

- **Bacteria**
  - Syphilis

- **Virus**
  - Hepatitis B & C virus
  - HIV 1/2/O
  - HTLV 1/2
  - WNV
  - CMV

- **Parasite**
  - T. cruzi
Syphilis

- Screening test
  - Anti-T. pallidum: microhemagglutination test (MHA-TP)

- Confirmation test
  - Anti-T. pallidum: EIA

- Supplemental test
  - RPR
Hepatitis B Virus

- **Serologic test**
  - Window period: 14-30 days
  - Risk of TTI: 1:280,000 to 1:357,000 units
  - HBs antigen (1970s)
    - Screening test: ChLIA
    - Confirmatory test: neutralization ChLIA
  - Anti-HBc (1986): ChLIA

- **Nucleic acid test (NAT)**
  - Introduced in 2006
  - Reduced window period to 14-20 days
  - Risk of TTI: 1:830,000 to 1:2 million units
Hepatitis C Virus

- Serologic test: anti-HCV (1990)
  - Window period: 50 days
  - Screening test
    - Anti-HCV: EIA
      - Third generation EIA screening assay with increased specificity in donor population
  - Confirmation test
    - Anti-HCV: Recombinant Immunoblot Assay (RIBA 3.0)
      - Helps to resolve false positive EIA result

- NAT
  - introduced in 2000
  - reduced the risk of transfusion transmitted Hep C to approximately 1:2 million units
  - Shortens window period to ~ 15-20 days
HIV

- **Serologic test**
  - Window period: 14 days
  - Screening test
    - Anti-HIV 1/2/O (1985): EIA
  - Confirmation test
    - Anti-HIV 1: IFA
  - Supplemental test
    - Anti-HIV 2: EIA
  - Referral test
    - Anti-HIV 2: Western blot

- **NAT**
  - Introduced in 2003 for HIV-1
  - Reduced the risk of transfusion transmitted HIV to approximately 1:2 million units
  - Shortens window period to 7 days
HTLV-I/II

- **Serologic test**
  - Risk of TTI: 1:3 million units
  - Screening test
    - Anti-HTLV-I/II (1988): ChLIA
  - Supplemental test
    - Anti-HTLV I/II: Inno-LIA

- **Leukocyte reduction may reduce risk of transmission**
  - No confirmed reports of transmission through acellular components (FFP, cryo) or plasma derivatives
WNV

- **NAT (2003)**
  - Screening test
  - Mini pool of 16 samples year round
  - Individual testing triggered by positive mini pool
    - 1st positive: individual testing for 7 days
    - 2nd positive: individual testing for 14 days
  - Individual testing during outbreak season: 6/1/11 to 10/31/11

- **WNV Panel Antibody (IgM/IgG) ELISA**
  - Confirmatory test
CMV

- **Serologic test**
  - Risk of TTI: unknown, presumed rare
  - Anti-CMV

- **Leukocyte reduction decreases the risk of transmission (essentially equivalent to seronegative units)**
  - No confirmed reports of transmission through acellular components (FFP, cryo) or plasma derivatives
Trypanosoma cruzi

Serologic test
- Risk of TTI: Unknown
- Screening test
- Referral test
  - Anti-T. cruzi: RIPA

One time testing
Value of IDT

- Improve safety of blood supply
- Individual donor benefit
  - Detecting unsuspected infection
  - Prevent secondary spread
- Recipient benefit
  - Provide safest blood possible
- Public health benefit
  - Provide epidemiological data to identify the sources of risk and the safest donors
  - Monitor epidemics, e.g. WNV outbreak
Pitfalls of IDT

- False positive results
- False negative results
- Window period
Bacterial Detection

Platelets

- Every single unit is cultured (starting in 2004)
- Bacterial contamination rate: 1:5,000 units
- Septic reaction rate: between 1:41,000 and 1:193,000 units
- Fatality rate: 1:500,000 units
- Most common bacteria
  - Staph epidermidis, Bacillus spp., Staph aureus or Strep spp.
- Kept at room temperature, optimal for bacterial growth
Bacterial Contaminations

- **RBCs**
  - Bacterial contamination rate: 1:31,000 units
  - Septic reaction rate: 1:250,000 to 1:500,000 units
  - Fatality rate: between 1:1 million to 1:10 million units
  - Most common bacteria
    - Yersinia enterocolitica, Serratia or Pseudomonas spp.

- **FFP/Cryo**
Emerging Infectious Agents

- Dengue Fever
  - Two clusters of TTI has been reported in Hong Kong and Singapore

- Chikungunya virus (CHIKV)

- Simian foamy virus (SFV)
Pathogen Reduction Technologies (PRT)

- Exposure of whole blood or blood components to a chemicals, often in combination with UV light which leads to irreversible DNA strand breakage and/or strand linkage

- This technology has the added benefit of inactivating leukocytes, thus reducing FNHTR, alloimmunization and TAGVHD

- Plasma pathogen reduction has been in use in many countries other than the US

- Platelet pathogen reduction has been implemented in some countries

- Whole blood or RBC pathogen reduction are not available
Clinically Approved PRT

- Solvent-Detergent Treatment
- Psoralen Phototreatment
- Methylene Blue Phototreatment
- Riboflavin (Vitamin B2) Phototreatment
Solvent-Detergent Treatment

- Solvent detergent (SD) system disrupts the lipid bilayers of the plasma membrane of cells/organisms and the lipid coat of enveloped viruses

- Only approved for non-cellular blood products, e.g. plasma

- Available in Europe – Octoplas

- Complex process using pooled plasma (100-1500 units)
  - Contains variety of antibodies against viruses
  - Reduce the incidence of TRALI through dilution of HLA antibodies
Solvent-Detergent Treatment

- SD plasma has demonstrated significant reduction of lipid-enveloped viruses ($>6 \log_{10}$), bacteria and protozoa.

- Less effective against non-enveloped viruses
  - Hepatitis A virus, Parvovirus B19

- Residual solvent (TNBP) and detergent (Triton-X100) are mostly undetectable

- SD plasma has been shown to reduce pro- and anti-coagulation factors
  - Factor V, VIII, antiplasmin and protein S
  - Routine coagulation times are not significantly prolonged
Psoralen Phototreatment

- **Amotosalen**
  - Psoralen compound found in nature that is able to intercalate between nucleotide base pairs of RNA and DNA
  - Requires photoactivation by UVA at 320-400nm

- **INTERCEPT**
  - Currently available system
  - Combines amotosalen with a compound absorption device containing activated charcoal to scavenge unincorporated amotosalen and residual photoproducts
Psoralen Phototreatment

- Effective in reducing lipid-enveloped virus ($3-6 \log_{10}$), bacteria and protozoa
- Less effective against non-enveloped viruses
- Long term toxicity due to residual psoralen is unknown
- Reduction in coagulation factors
- Reduction in platelet count recovery
- No evidence of antibody formation against psoralen or neoantigens development
Methylene Blue Phototreatment

- **Methylene blue**
  - Heterocyclic thiazine dye with long history of medical use
  - Primary mechanism of action through photoactivated (620-670 nm) cleavage of nucleic acid
  - It’s not incorporated into the nucleic acid product
  - After phototreatment, methylene blue is passed through a specialized filter that adsorbs it

- **Available in Europe, marketed by Macopharma**
  - Suitable for treatment of single donor plasma units
Methylene Blue Phototreatment

- Effective in reducing enveloped viruses ($>5 \log_{10}$), some non-enveloped viruses

- Some effects against parasites (T. cruzi)

- Unreliable reduction on bacteria or leukocytes
  - Methylene blue do not penetrate bacterial or eukaryotic plasma membrane well

- Reduction of coagulation factors

- Long term toxicology is unknown
Riboflavin (Vitamin B2) Phototreatment

- **Riboflavin**
  - Shares a similar structure and mechanism with methylene blue as a photoreactive compound
  
  - Photoreactivity can be induced by visible or UV light

- **Mirasol PRT**
  - The only commercial system approved for the production of riboflavin-treated plasma and platelets
Riboflavin (Vitamin B2) Phototreatment

- Effective against enveloped viruses ($4 - 6 \log_{10} \text{ reduction}$), non-enveloped viruses ($3 - 5 \log_{10} \text{ reduction}$) and bacteria ($3 - 5 \log_{10} \text{ reduction}$)

- Advantages
  - Physiological normal metabolic constituent
  - Photoproducts are products of its natural metabolism, no need for post-treatment removal
  - Long history and experience in clinical use

- Disadvantages
  - Riboflavin-treated platelets stored for 5 days showed greater changes in levels of coagulation, thrombolytic factors and inhibitors without functional deficits
Advantage of Pathogen Reduction

- Proactive approach to improving blood safety
  - Pathogen reduction can kill various kinds of microbes, e.g. virus, bacteria, parasites
  - Prevent spread of unknown blood born pathogens
  - Potential for increasing platelet storage
Limitations of Pathogen Reduction

- Pathogen reduction technology does not lead to complete eradication of infectious agents
- Bacterial spores are resistant to pathogen reduction methods
- No technology is available to inactivate prions
- Not available for pRBC or whole blood
Limitations of Pathogen Reduction

- Direct toxicity of the chemical presently used is negligible

- Indirect effect on blood products have been observed
  - Neoantigen development on RBCs that may induce antibody formation
  - Reduced platelet recovery and survival
Conclusion

- Maintaining a safe and plentiful blood supply is crucial and a tough balancing act
  - Pre collection
  - Collection
  - Post collection
    - Most promising step for reducing infectious disease transmission, especially with the improvements in pathogen reduction technologies