Pandemic Influenza: Identifying the Gaps of Knowledge in Transfusion and Transplantation Medicine

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Pandemic Influenza - Background

- Influenza viruses are noted for their antigenic variability and adaptability resulting in periodic epidemics
- Therefore, despite annual vaccinations, the US faces approximately 36,000 deaths and more than 200,000 hospitalizations each year

Pandemic flu – con't

- Pandemics caused by Influenza A strains occurred intermittently in 1918, 1957 and 1968 causing millions of deaths worldwide
- Current pandemic threat is from unprecedented outbreak of avian flu in Asia with recent spread to Europe
- Heightened concern due to possibility of mutation/re-assortment during spread and generation of new strains with potentially higher efficiency for human to human transmission

History of recent avian flu epidemic

- Primary causative agent is the H5N1 strain
- H5N1 strains of highly pathogenic avian influenza established infection in poultry in several parts of Asia during the past decade
- Highly pathogenic form erupted in 1997
- Avian flu strains are not generally infectious for humans but several cases of human infection noted since 1997
- WHO reports 142 cases of infection, 74 deaths due to H5N1 strain

Concerns for Transfusion and Transplantation

Major outbreaks of avian flu infection in the US could raise several concerns for transfusion and transplantation including but not limited to:

- **Donor availability due to illness**
- **Deferral due to potential viremia**
- **Deferral due to treatment with medications**
- **Potential for falsely reactive screening tests either from influenza or vaccination**
- **Potential increased demand for blood and organ/tissue**
- **Illness in blood/organ/tissue center personnel affecting collection capabilities**

Knowledge gaps

It is difficult to accurately estimate the magnitude and impact of avian influenza infection on these effects, in the absence of critical scientific knowledge, and data regarding avian influenza infection and transmission in humans

Knowledge gaps in avian flu infection and blood/organ/tissue safety

- What is the extent and duration of viremia in H5N1 infection ?
- What is the length of the asymptomatic incubation period ?
- Is there viremia during the asymptomatic phase ?
- What is the infectivity of blood during the aymptomatic phase ?

Knowledge gaps –con't

- Is there viremia during the convalescence period and is the virus infectious ?
- What are the most effective means of virus spread to contacts ?
- What is the range of organs and tissues that may be affected ?
- What is the infectivity of virus in organs and tissues ?

Knowledge gaps – con't

- How will virus mutation/re-assortment and drug-resistant H5N1 affect the evolution of a potential pandemic and transmissibility through transfusion and transplantation ?
- Would vaccination and antibody responses in recent infections cause interference with tests used to screen the blood supply ?
- Should vaccination and/or medications for treatment of avian flu infection affect donor deferral ?

Human Influenza A

- The asymptomatic period is generally 1-4 days
- Viremia in most Influenza A virus infections lasts from 1-3 days post inoculation
- Virus has been detected in mouse models and in infected individuals
- Virus was most frequently isolated from nasopharyngeal swabs, during the first 3 days of illness up to 9 days after onset and 1-2 days before onset of fever

Human Influenza A – con't

- Khakpour et al (1969) identified live virus in blood of influenza virus infected individuals and one contact during the asymptomatic period
- The contact became ill 12 hours after virus was isolated during the asymptomatic period
- There is little additional data on viremia
- Therefore, presence of virus in blood has not been well established and infectivity during the asymptomatic period is not known

Avian Influenza - H5N1

- Pathogenesis of H5N1 may be different from that of usual human subtypes H1-H3
- To et al, J. Med. Virol. 2001: 18 cases of H5N1 infection
- Infection is characterized by significant cytokine perturbations (IFN-gamma, TNF-alpha, IL-6 and sIL-2) in early phase
- Initial replication of avian influenza virus may trigger hyper-cytokinemia complicated by reactive hemophagocytic syndrome, the most prominent feature in 2/6 fatal cases

H5N1- con't

- WHO consultation on Human Influenza: NEJM, Sept. 2005
- Incubation period may be longer, 2-4 days, upper limit 8-17 days
- Viral RNA levels higher in pharyngeal than nasal respiratory tracts and higher than levels observed with usual human flu
- Two patients presented with encephalopathic illness and diarrhea without apparent respiratory symptoms

Proposed studies of H5N1 infectivity

Informal PHS group developed a study plan to address scientific knowledge gaps in highly pathogenic avian influenza infection particularly viremia and transmission through blood transfusion

Proposed studies -con't

- Animal model studies would be a feasible approach to address major gaps in scientific knowledge of H5N1
- Cynomolgus macaques are known to be susceptible to infection by H5N1 and would be an ideal model for infectivity and viremia studies

Specific aims

- To demonstrate transmission (or lack of) by transfusion and determine viremia in infected macaques using autologous blood spiked with H5N1 as inoculum
- To determine the infectivity of blood during the asymptomatic phase by secondary infection of macaques
- To identify infection in organs other than the lung, and in certain cell types, in order to identify tropism and source of viremia
- To determine the utility of current inactivation methods for H5N1 in plasma

Specific aims - con't

- To determine the effect of antivirals (oseltamivir) on viremia, infectivity, drug resistance and transmissibility by blood
- To develop sensitive methods to detect and quantitate H5N1 nucleic acid using PCR/nano-particle assays and virus by culture methods, for accurate measurements of virus

Anticipated outcomes

- Identify possible transmission by blood transfusion during asymptomatic phase
- Identify minimum infectious dose for transmission by blood
- Identify cell, tissue and organ tropism
- Establish utility of current viral inactivation methods for inactivation of H5N1 in plasma

Anticipated outcomes – con't

- Development of an animal model will aid in the study of T cell responses during acute infection and help establish a model to study pathogenesis and test new drugs and vaccines

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Infectivity study group

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