Potential Use of Convalescent Plasma During a Flu Pandemic

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Why Discuss Convalescent Plasma?

• H5N1 infection in Asia has killed 30-80% of patients despite current therapy
• In a pandemic, vaccines, effective antiviral drugs, respirators and antibiotics may not be available timely, with resultant high mortality
• Convalescent plasma can be made locally, and evidence exists suggesting that transfusion of convalescent plasma could save lives
• Convalescent plasma is likely to be used!
What is the General Evidence for Efficacy of Antibody Therapies?

- Since 1892 and until the antibiotic era, serum therapy was used effectively to prevent and treat many bacterial (e.g. diphtheria, pneumococcus, meningococcus) and some viral (e.g. measles, mumps, etc.) infections.
- Specific immune globulins are effective therapies in many viral diseases (HBV, CMV, rabies, RSV, etc.)
- Convalescent plasma is standard of care for Argentine Hemorrhagic Fever (Junin virus) preventing ca. 90% of deaths [Maiztegui et al, 1979]
Is There Pre-clinical Evidence for Efficacy of Convalescent Plasma in Flu?

• Mouse models of influenza pneumonia have shown benefit of convalescent serum (H1 and H3 challenge), equine hyperimmune F(ab’)2 globulin (H5N1 challenge), and monoclonal antibodies (H1, H3 and H5N1 challenge):
  – Many other articles
Is There Clinical Evidence for Efficacy of Convalescent Plasma in Flu?

• Human experience with convalescent plasma therapy for influenza is limited, coming from small, non-randomized, unblinded trials

• Efficacy has been suggested by
  – A recent meta-analysis on reports of use of blood products for Spanish Influenza in 1918 (eight evaluable studies of 1703 patients)
  – Soviet and German studies on prevention and treatment of seasonal flu in the 1950’s and 1960’s
  – Two recent case reports: a patient with H3 ARDS; and a patient with H5N1 pneumonia
# Absolute 21% Less Mortality in Patients Treated with Convalescent Blood in the 1918 Flu Pandemic*

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Mortality Rate, n/n (%)</th>
<th>Risk Difference (95% CI), percentage points</th>
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<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Control Group</td>
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<tr>
<td>Stoll (17)</td>
<td>25/56 (45)</td>
<td>201/379 (53)</td>
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<tr>
<td>O’Malley and Hartman (18)*</td>
<td>3/46 (7)</td>
<td>28/111 (25)</td>
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<td>Ross and Hund (19, 20)</td>
<td>6/29 (21)</td>
<td>9/21 (43)</td>
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<td>Kahn (21)</td>
<td>12/25 (48)</td>
<td>12/18 (67)</td>
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<td>Gould (22)</td>
<td>2/30 (7)</td>
<td>82/289 (28)</td>
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<tr>
<td>McGuire and Redden (23, 24)*</td>
<td>6/151 (4)</td>
<td>120/400 (30)</td>
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<td>Overall</td>
<td>54/336 (16)</td>
<td>452/1219 (37)</td>
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Rapid Response to Convalescent Plasma in a 31y Male with H5N1 Pneumonia*

*Zhou et al. NEJM 357:14, 2007
Scientific Uncertainties in Empirical Use of Convalescent Plasma for Flu

- When is it safe to obtain plasma from a donor who has recovered from influenza (e.g. three weeks post onset of illness and at least one week after fever resolved)?
- Can donor selection be based solely on history of influenza or should an antibody titer (e.g. HI) be obtained at donation?
- What is the appropriate dose of convalescent plasma (e.g. 3-5 mL/Kg per day)? Should patients receive plasma from at least two donors to address expected variations in titer and antibody profile?
- What are the indications for use (e.g. prophylaxis, pneumonia, ARDS, multiple organ system failure)?
Precautionary Notes on Use of Convalescent Plasma

• Plasma collection should be done under SOPs in a regulated routine collection facility. Impact on normal collections should be considered

• Donors should meet standards for prevention of transfusion transmitted diseases. Additionally,
  – Number of donations should be limited (e.g. ≤6 per donor)
  – When feasible, male donors are preferred to reduce TRALI
  – Donors and recipients should be ABO compatible

• Scientific and ethical controls should apply to convalescent plasma as an experimental therapy (IRB approval, informed consent, special product labeling, outcome monitoring and reporting, etc.)
Summary and Conclusions

- Animal models and limited human experience suggest that convalescent plasma (and other antibody therapies) may have value in treatment of influenza pneumonia and ARDS.
- Convalescent plasma is likely to be used in a flu pandemic when alternative prevention and therapy modalities are lacking or fail to be effective.
- Experimental preparation and use of convalescent plasma should be carried out in a controlled environment.
- Gathering and reporting of patient outcome data in relation to donor and product characteristics (e.g. antibody titers) and dosing regimens are needed to establish the true value of convalescent plasma in influenza.