Meta Analysis: Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?


Annual Death Rate per 1000, United States Navy, 1918
Topics

1. General Observations
2. Plasmatherapy
3. “Blood Products for Spanish Influenza-pneumonia…..”
   - Seasonal Influenza
   - H5N1
5. Conclusions
Pandemic Influenza Observations

- An effective vaccine will take months to develop and produce in quantity.

- Oseltamivir and other anti-virals will not be universally available and may not be effective.

- Supportive care – Access to ICU’s, ventilators, antibiotics and medical care will be limited.

- Many people will not have access to any vaccine, anti-viral or other standard treatment.
Plasmatherapy

1. Convalescent Plasma and Serum has been used in the prophylaxis and treatment of pathogens in humans and in animal models.
   - H5N1
   - Spanish flu
   - SARS
   - Measles
   - Hepatitis A
   - South American Hemorrhagic Fevers (Junin/Muchapo)
   - Anthrax
   - Orthopox (variola/vaccinia)
   - Many others

2. Will likely be used in the future during outbreaks and epidemics.

3. No standardized methodology to study, collect and administer convalescent plasma for the treatment of current or new and emerging infectious diseases.
Meta Analysis: Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?
Study Characteristics

• **Background:** Studies from the Spanish influenza era reported that transfusion of influenza-convalescent human blood products reduced mortality in patients with influenza complicated by pneumonia.

• **Purpose:** To determine whether transfusion with influenza-convalescent human blood products reduced the risk for death in patients with Spanish influenza pneumonia.

• **Data Sources:** Manual search of prominent English-language journals from 1918 to 1925.

• **Study Selection:** Published English-language studies that had at least 10 patients in the treatment group, used convalescent blood products to treat Spanish influenza pneumonia in a hospital setting, and reported on a control or comparison group.

• **Limitations:** Studies had many methodological limitations by modern standards.
Findings

• 27 reports were found. Eight studies involving 1703 patients met inclusion criteria. Treated patients were often selected because of more severe illness.

• The most common laboratory finding was leukopenia. The most common clinical finding was cyanosis and dyspnea.

• Convalescent whole blood, plasma or serum was obtained from donors one to 6 weeks after recovery from influenza.

• Patients typically received one or two treatments. The average amount of “plasma” in the treatment product was 100 to 150 milliliters (2 ml/kg).

• All eight studies reported a survival benefit. Overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls.
21% absolute risk difference in mortality among patients treated with convalescent blood products versus controls

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Mortality Rate, n/n (%)</th>
<th>Risk Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Stoll (17)</td>
<td>25/56 (45)</td>
<td>201/379 (53)</td>
</tr>
<tr>
<td>O’Malley and Hartman (18)*</td>
<td>3/46 (7)</td>
<td>28/111 (25)</td>
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<tr>
<td>Ross and Hund (19, 20)</td>
<td>6/28 (21)</td>
<td>9/21 (43)</td>
</tr>
<tr>
<td>Kahn (21)</td>
<td>12/25 (48)</td>
<td>12/18 (67)</td>
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<tr>
<td>Gould (22)</td>
<td>2/30 (7)</td>
<td>82/290 (28)</td>
</tr>
<tr>
<td>McGuire and Redden (23, 24)*</td>
<td>6/151 (4)</td>
<td>120/400 (30)</td>
</tr>
<tr>
<td>Overall</td>
<td>54/336 (16)</td>
<td>452/1219 (37)</td>
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</tbody>
</table>

41% ARD in mortality among patients who received early (< 4 days) versus late (> 4 Days) treatment

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<tr>
<td></td>
<td>Early Treatment</td>
<td>Late Treatment</td>
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<td></td>
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<tr>
<td>Stoll (17)</td>
<td>10/31 (32)</td>
<td>15/25 (60)</td>
</tr>
<tr>
<td>Ross and Hund (19, 20)*</td>
<td>3/22 (14)</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>Sanborn (25)</td>
<td>6/55 (11)</td>
<td>28/46 (61)</td>
</tr>
<tr>
<td>Maclachlan and Fetter (26)</td>
<td>9/40 (23)</td>
<td>4/7 (57)</td>
</tr>
<tr>
<td>Overall</td>
<td>28/148 (19)</td>
<td>49/83 (59)</td>
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</table>

Other Outcomes

• **Clinical**: All 8 studies reported a clinical judgment that a distinct and beneficial improvement often occurred in treated patients after transfusion. The improvement was characterized by reductions in cyanosis, respiratory rate, nausea, vomiting, fever, malaise, or delirium within 2 to 24 hours after 1 or 2 transfusions. Improvements generally seen in those who received early treatment but also occurred in some who received late treatment.

• **Adverse events**: The most commonly reported adverse event was a brief "chill" reaction with a transient elevation in body temperature of 1° to 2°F 30 to 120 minutes after the transfusion. Serious complications relating to transfusion were rare.
Study Conclusions

1. Spanish influenza pneumonia patients who received transfusion with influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death.

2. Convalescent human plasma could be an effective, timely, and widely available treatment for patients with H5N1 (or other new and emerging infectious disease) during outbreaks and pandemics, and this therapy should be studied in clinical trials.
3. A central body of experts should be convened to consider plasma therapy and to make recommendations regarding a research strategy and the development of guidelines in the event that therapy is required before the research is completed.
Supporting Studies in Humans and Animal Models

- Seasonal Influenza
- H5N1 Influenza
Mouse Models for H1/H3 Influenza

- Mice with influenza-pneumonia (including immunodeficient nude and SCID mice) treated with MABs and convalescent serum with up to 100% survival (1 to 7 days after virulent challenge).


3. (Many others)
Human Plasmatherapy for Seasonal Influenza

• Soviet and German studies in 1950’s and 60’s on the prophylaxis and treatment of seasonal influenza/influenza-pneumonia with convalescent serum.

• Recent Treatment of an H3 ARDS patient
Mouse H5N1 Antibody Therapy Studies

Figure 1. Passive Immunization and Survival after Challenge with A/Vietnam/1203/04 (H5N1). Dose of Sheep Sera (1 ml).

Figure 4. 50 mg/kg mAb Therapy and Survival in Mice with Established A/Vietnam/1203/04 (H5N1) Infection

Human Plasmatherapy for H5N1 Influenza

- Chinese treatment of H5N1 patients with convalescent plasma.
Figure 1. Influenza A (H5N1) Viral RNA Load in Tracheal Aspirates and the Patient’s Response to Treatment.

The green line represents the patient's body temperature, and the purple line represents the viral load. The orange line represents the beginning of oseltamivir therapy, and the blue line represents the beginning of convalescent plasma therapy.
Kinetics of H5N1 serum neutralization antibody response

Modern Plasma Therapy

- Plasma is routinely acquired and safely used for the treatment of coagulopathies, other serious diseases, and for IVIG production.

- Current FDA regulations allow donors to donate 1000-1200 milliliters of plasma per week.

- A single donor could supply a quantity of plasma sufficient to treat multiple patients.

- Convalescent plasma could be an effective treatment for *seasonal* or *pandemic* “influenza-pneumonia” or other disease for which no good treatment exists.
Questions?