

Convalescent Plasma Therapy

The Need for Guidelines

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Convalescent Plasma Therapy

- Background
 - History of Plasma Therapy
- Implications with H5N1 and other pathogens
 - Recent Publications
 - Luke, et al.
 - Zhou, et al.
- The need for guidelines
- The way ahead
 - DHB's role

Background

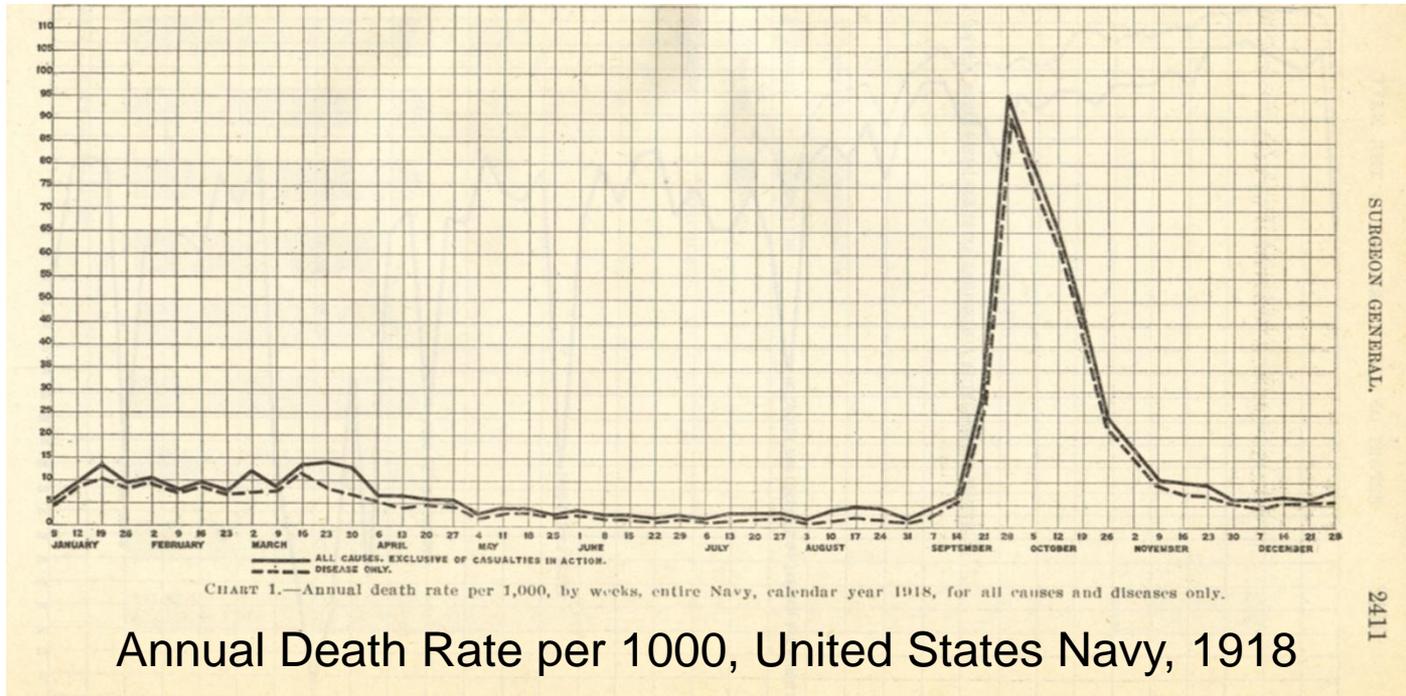
1. Convalescent Plasma and Serum has been used in the prophylaxis and treatment of pathogens in humans and in animal models.
 - H5N1 - Spanish flu - SARS - Measles - Hepatitis A
 - South American Hemorrhagic Fevers (Junin/Muchapo)
 - Diphtheria - Orthopox (variola/vaccinia) - Many others
2. Will likely be used in the future during outbreaks and epidemics.
3. DoD personnel are at high risk for epidemics of infectious disease (natural or bioterror).

4. DoD can collect, produce and transfuse large volumes of convalescent plasma from military volunteers who have recovered or have been vaccinated.
5. The convalescent plasma (or an IVIG product) can be used within DoD and/or in the civilian population.
6. An expert opinion guideline and data collection format can reduce morbidity and mortality in DoD by standardizing the therapeutic approach and collection of clinical data and outcomes.

Plasma

- Plasma is routinely acquired and transfused for the treatment of coagulopathies and other serious diseases – typically after patient consent.
- Plasmapheresis donors can safely donate 1000-1200 milliliters of plasma per week.
- A single donor could supply a quantity of plasma sufficient to treat multiple patients.
- Convalescent plasma collected at the local level could have an immediate impact during the next pandemic of influenza or other disease for which no good treatment exists.
- Donor motivation high during emergencies.

Plasma Therapy for Spanish flu and H5N1



Annual Death Rate per 1000, United States Navy, 1918

Data (Examples)

- Spanish flu and H5N1

- Thomas C. Luke, MD, MTMH; Edward M. Kilbane, MD, MPH; Jeffrey L. Jackson, MD, MPH; and Stephen L. Hoffman, MD, DTMH. Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment? *Ann Int Med*, 17 October 2006;145(8):599-609.
- Zhou, B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med*. 2007 Oct 4;357(14):1450-1.
- Animal studies (see backup slides)

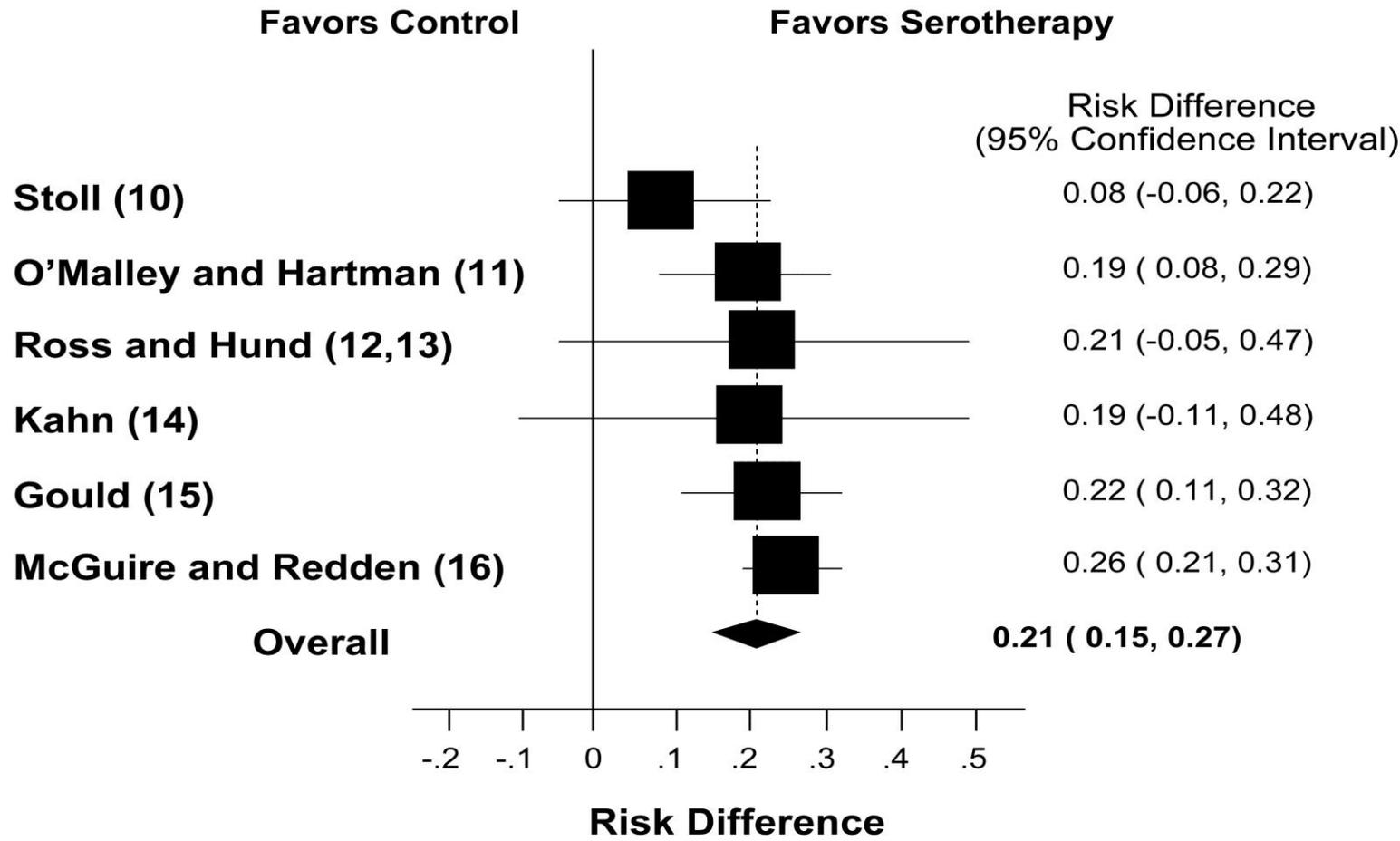
- Argentine Hemorrhagic Fever

- Ruggiero, et al. [Treatment of Argentine hemorrhagic fever with convalescent's plasma. 4433 cases]. *Presse Med*. 1986 Dec 20;15(45):2239-42.
- Maizetgui, et al. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. *Lancet*. 1979 Dec 8;2(8154):1216-7.

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

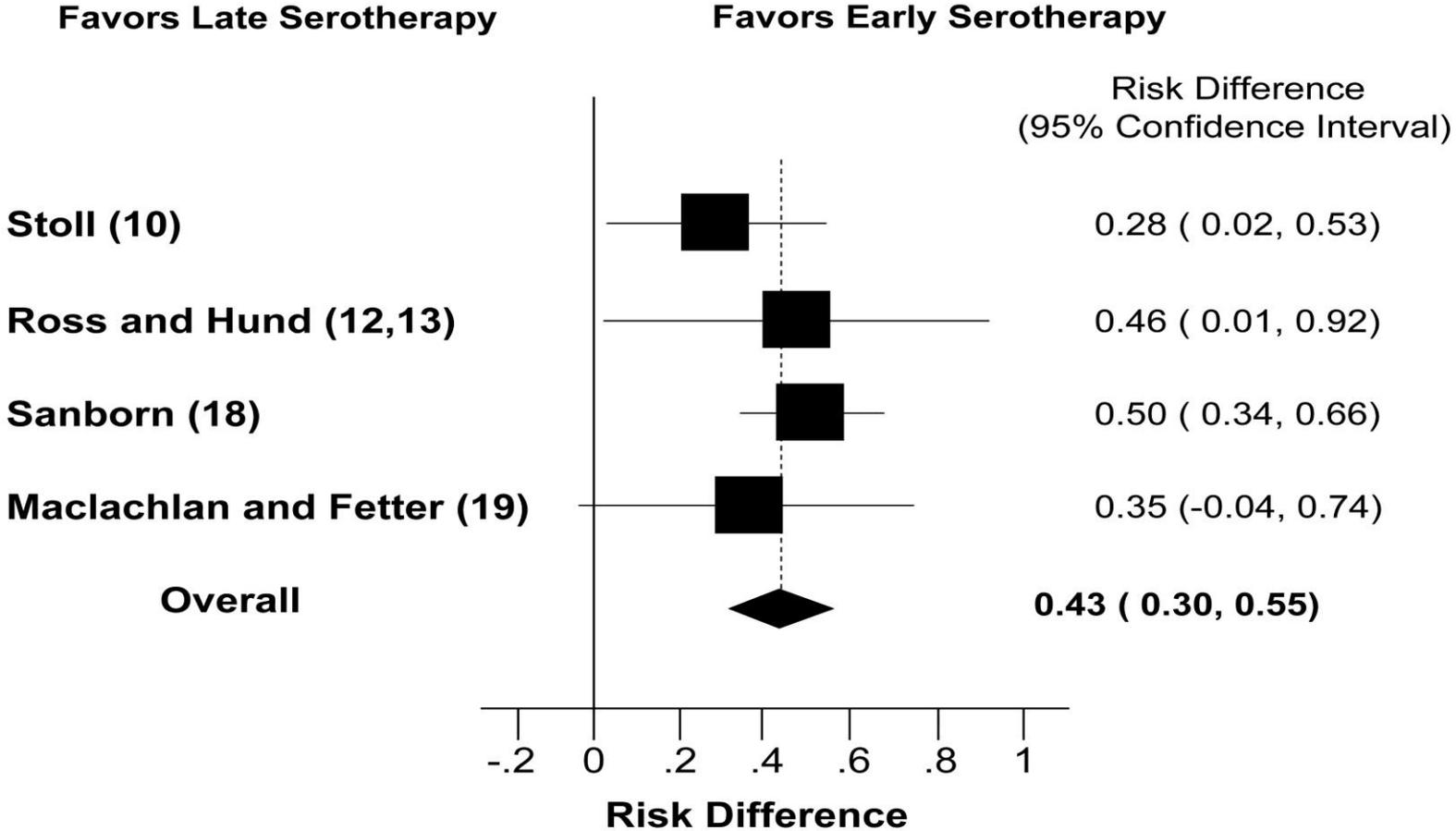
- 27 reports were found. Eight relevant studies involving 1703 patients met inclusion criteria. Treated patients were often selected because of more severe illness.
- The most common laboratory finding was leukopenia. The most common clinical finding was cyanosis and dyspnea.
- Convalescent whole blood, 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.

Absolute risk differences in mortality among patients treated with convalescent blood products and controls



The overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls. The range of absolute risk differences in death was 8% to 26% (pooled risk difference, 21% [95% CI, 15% to 27%] between the treatment and control groups

Absolute risk difference in mortality among patients who received early (< 4 days) versus late treatment (>/= 4 days)



The overall crude case-fatality rate was 19% (28 of 148) for patients treated within 4 days of pneumonia complications and 59% (49 of 83) for patients treated at 4 days or later. The range of absolute risk difference in death was 26% to 50% (pooled risk difference, 41% [CI, 29% to 54%].

Treatment with Convalescent Plasma for Influenza A (H5N1) Infection

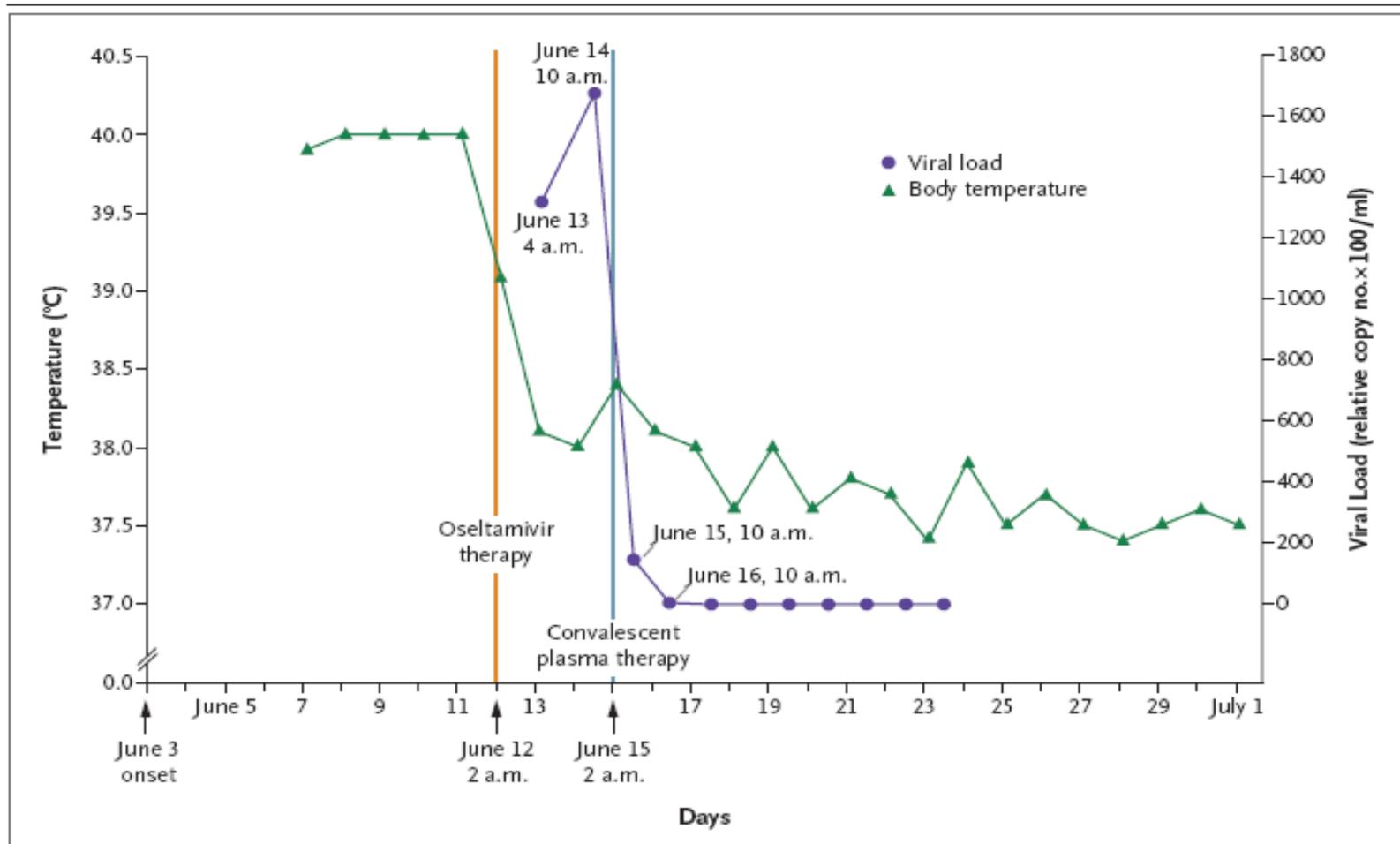


Figure 1. Influenza A (H5N1) Viral RNA Load in Tracheal Aspirates and the Patient's Response to Treatment.

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.

Plasma Therapy for Argentine Hemorrhagic Fever

(CDC Bioterrorism Category A Pathogen)

- A group of 4,433 patients with AHF were treated with convalescent's plasma; the overall mortality rate was 3.29%. Before convalescent's plasma was used, the mortality rate in 448 patients who received the conventional treatment was 42.85%.
- In a double-blind trial, patients with Argentine haemorrhagic fever treated with immune plasma within 8 days of the onset of the disease had a much lower mortality than those given normal plasma.
- Convalescent plasma is the standard of care.

Key Issues and Questions

1. Consideration of the implications of convalescent plasma therapy to DoD.
 - National security implications
 - Multiple agency involvement
2. Concept: Bring together experts and other entities to create consensus convalescent plasma therapy guidelines to treat H5N1 or other novel pathogen for which effective and plentiful therapeutics do not, or may not, exist.
 - Technical, logistical and clinical issues
3. DHB's role?
 - Endorsed the need for guidelines and recommendation was accepted by ASD(HA).
 - The next step?

Backup slides

H5N1 Antibody Animal Studies

- Lu J, et al., Passive immunotherapy for influenza A H5N1 virus infection with equine hyperimmune globulin F(ab')₂ in mice *Respir Res.* 2006; 7(1): 43. 24 hours after infection, 50 μ g of anti-H5N1 F(ab')₂ were required to give 70% protection. 100 and 200 μ g of anti-H5N1 F(ab')₂ were required to give 100% protection.
- Hanson BJ, et al., Passive immunoprophylaxis and therapy with humanized monoclonal antibody specific for influenza A H5 hemagglutinin in mice *Respiratory Research* 2006, 7:126 three days after infection (figure [3C](#) and [3D](#)), 10 mg/kg bodyweight of VN04-2-huG1 was required to confer complete protection, with lower doses (1 and 5 mg/kg bodyweight) showing 80% protection. The lower dosages of antibody also showed increased signs of disease; however all of the mice that did not succumb to infection recovered the initial weight loss by day 15.
- Simmons CP, et al., Prophylactic and **therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. (in Press)** In vivo, prophylaxis and post-infection therapy with 3F3 and 5F12 conferred 100% protection from lethality in mice challenged with A/VietNam/1203/04 (H5N1).