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A Study in Scarlet - Convalescent Plasma for Severe Influenza

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In patients with severe influenza disease, treatment with currently available antivirals (e.g oseltamivir) decreases mortality (1, 2) but remains unacceptably high in patients with 2009 pH1N1 [10–17%] (3, 4) and H5N1 [40%]. (2) Additionally, the emergence of widespread oseltamivir or adamantane resistance to circulating influenza strains or resistance developing during treatment, the reports of dual oseltamivir-adamantane resistance, and person-to-person transmission of these viruses highlight the need for new approaches and better treatments. (5–8) Passive immunotherapy with influenza strain-specific convalescent plasma (containing polyclonal antibodies) has been proposed as a potential treatment option for serious influenza disease. (9, 10)

Case reports in H5N1 influenza have described dramatic defervescence and cessation of viral shedding after administration of convalescent plasma. (11) After the emergence of pH1N1, Hung et al, conducted a prospective cohort study in which seriously ill pH1N1 patients in Hong Kong were treated with 500 ml of convalescent plasma with an HAI titer of $\geq 1:160$ in addition to standard care versus standard care alone. (12) While the cohort design limits the interpretation of this study, the mortality rate between the treatment and control group was reported to decrease by 34% [20.0% vs 54.8%; $P = .01$]. Additionally, respiratory tract viral load and cytokine levels were lower in the treatment group on days 3, 5, and 7 [$P < .05$].

An article in this edition of *Critical Care Medicine* provides additional important insights into the potential efficacy of passive immunotherapy (manuscript citation) in treating highly pathogenic avian influenza. Rockman et al., using a lethal challenge model, infused 10 ml of convalescent serum with an HAI titer of 1:128 into young ferrets and then challenged them with 10^6 EID₅₀ of highly virulent A/Vietnam/1203/2004 H5N1. Euthanasia was scheduled at 10% bodyweight loss within 7 days of virus exposure or exhibition of signs consistent with involvement of other organ systems. Animals received H5N1 convalescent serum 24 hours prior to, or 24 hours or 72 hours after challenge [or control H3N2 serum or PBS 24 hours prior to challenge]. The infusion of H5N1 convalescent serum in the treatment

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animals resulted in an HAI of 1:4–1:8. While no control animals survived, 100% [4/4] of animals given H5N1 convalescent serum infused 24 hours prior to viral challenge, 75% [3/4] infused 24 hours after, and 25% [1/4] infused 72 hours after, survived. Additionally, nasal viral titers in the treatment groups tended to be much lower than in controls at the time points tested. Rockman et al.'s study design [the low 1:4–1:8 HAI titers achieved in the treated animals, the large infectious dose and the euthanasia of animals at a conservative 10% weight loss] may have masked the full effect and analysis of convalescent plasma. However, this study suggests that convalescent plasma can be a beneficial treatment for highly pathogenic avian influenza [HPAI] at “low doses” and adds significantly to the literature on this topic.

In a comparable high lethality model using oseltamivir as the intervention, Govorkova et al., infected young ferrets with 10^2 EID₅₀ A/Vietnam/1203/2004 H5N1 [compared to 10^6 EID₅₀ in the current paper]. (13) They administered 10 or 25 mg/kg/day of oseltamivir twice daily for 5 days, starting 24 hours after challenge. Euthanasia was scheduled for animals that had both severe disease and lost 25% of body weight. They reported that the oseltamivir twice-daily 10 mg/kg/day group [resulting in a comparable AUC drug level to a licensed dose in humans] experienced 0% [0/3] survival, a maximal weight loss of 22% and nasal viral shedding on Day 3 of 4 log₁₀ EID₅₀. The twice-daily 25 mg/kg/day group experienced 100% [0/3] survival, a maximal weight loss of 13% and nasal viral shedding on Day 3 of 3 log₁₀ EID₅₀. This is compared to 75% [3/4] survival, a weight loss of 13% and nasal viral shedding on Day 3 of 2 log₁₀ EID₅₀ in the current paper. Though these were not direct comparative arms in a single study, the data suggests that administering a single dose of convalescent plasma with a moderate HAI titer may be as or more effective than oseltamivir.

The true clinical question is not if convalescent plasma is as effective as oseltamivir in the treatment of HPAI or seasonal influenza. Convalescent plasma will not supplant small molecules in the treatment of uncomplicated influenza. The clinical need is to modify the outcomes in severe disease – new therapeutic approaches that are synergistically or additively beneficial with the standard-of-care are desirable. To test this hypothesis, the National Institute of Allergy and Infectious Diseases is currently conducting a randomized multi-center clinical trial to test the efficacy of immune plasma to treat serious type A influenza infections [ClinicalTrials.gov Identifier: NCT01052480].

Many questions remain about convalescent plasma – how much of severe disease is due to viral replication versus inflammation, what is the target HAI in recipients, can plasma help to address situations in which resistance arises, etc. More definitive animal and human studies are still needed to answer these questions. However, plasma therapy is an approach worth fully exploring.

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