ANSWERING REVIEWERS

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Dear Editor,

Thank you very much for your review of our manuscript entitled: Intravenous Vitamin C as Adjunctive Therapy for Enterovirus/Rhinovirus Induced Acute Respiratory Distress Syndrome. We very much appreciate the reviews you have provided us and feel the suggestions made by the Reviewers will make the manuscript more robust. Below are our responses to the reviewers.

Reviewer 1:
Comment 1: A cause and effect relationship is difficult to prove with a single case report; nonetheless, it could be a preliminary report and the basis for a larger randomized trial.
Response: As the reviewer suggests, a rigorous randomized controlled trial is critical to determine the effectiveness of intravenous vitamin C employed as we are reporting here. We are currently performing a Phase II NIH-sponsored trial that is a multi-center, randomized, double blind, placebo-controlled trial, examining the extent to which intravenous vitamin C attenuates sepsis-induced ARDS. We are two years into the trial. It will conclude in approximately 10 months. The patient reported here was not part of the trial. She was treated with the identical dosing regimen of intravenous vitamin C which is employed in the trial.

Reviewer 2:
Comment 1: In the abstract, under conclusions, the statement that the treatment 'resulted in rapid resolution of lung injury' is too definitive for a single case report, and could probably be better phrased 'was associated with' or some other wording.
Response: As the reviewer has suggested, the statement is too definitive. We have changed the conclusion wording in the revised manuscript (page 4) to read: Infusing high dose intravenous vitamin C into a patient with virus-induced ARDS was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae.

Comment 2: In the description of the case report, the daily I & O balances for the first few days on ECMO would be helpful, as the rapidity of clearing of the chest x-ray is striking between Day 1 and Day2 on ECMO, and one wonders if diuresis played a role.
Response: We thank the reviewer for noting our lack of attention to the fluid balance. The patient was initially hemodynamically unstable and was on vasopressors. Fluid balance during the first two ECMO days was even (equal fluid in/equal fluid out). The revised manuscript now reads: Given the patient's hemodynamic instability and vasopressor requirements, the critical care physician staff and nursing staff were very careful to keep the patient's intake and output fluid balance even, being careful not to volume load a patient who was suffering from permeability pulmonary edema.

Comment 3: In Conclusions, it should be discussed that this is a single case report, that the role of Vitamin C in this patient's recovery is not certain, and perhaps that additional investigation will be necessary before this can be recommended as a therapy for ARDS.

Response: In the final conclusion (page 8) we have added: Importantly, it should be noted that this is a single case report. The role of Vitamin C in this patient's recovery is not certain, and clearly additional investigation will be required before this can be recommended as a therapy for ARDS.

Reviewer 3:
Comment 1: The semiotic paradigm is one of the canonical forms of scientific thought that allows to authorize the progression of medical knowledge from particular deductions to general applications. It must be considered the above distinction for this work and it useful effectiveness proposed by their authors.
Response: We are most humbled by the reviewer's comment. The *vehicle* on which we based our decisions to move forward with infusing vitamin C in humans was based on extensive "preclinical research." In hindsight, our preclinical research gave us the rationale to explain our subsequent actions (i.e., human research infusing intravenous vitamin C). We are moving forward with our research, robustly examining the impact of intravenous vitamin C on sepsis-induced ARDS with our NIH-sponsored Phase II multi-center treatment trial.

Reviewer 4:
Comment 1: The authors should specify the viral respiratory panel used for enterovirus/rhinovirus detection.
Response: The molecular detection viral respiratory panel employed to detect Enterovirus/Rhinovirus was the FilmArray Respiratory panel manufactured by BioFire Diagnostics, LLC, SaltLake City, Utah. This identity of the panel employed is now in the revised manuscript (page 7).

Comment 2: The plasma levels of ascorbic acid during the hospitalization should have been determined.
Response: The reviewer's question concerning plasma ascorbic acid levels in this case is very important. Any clinician tasked with caring for a patient with ARDS reading this case report would want to know the resulting plasma ascorbic acid levels in a patient receiving intravenous vitamin C at 200 mg/kg/24 hours for 4 days. Although we did not measure the plasma ascorbic acid level in this patient, we have significant experience quantifying plasma ascorbate concentrations in a cohort of severely septic patients (J Translational Med 2014;12:32. [PMID: 24484547]). In our studies, we found plasma ascorbate concentrations increased rapidly from an average of 11 micromolar (which is critically low) to approximately 900 micromolar at 12 hours. Plasma ascorbate levels subsequently increased to an average of 3200 micromolar (3.2 millimolar) by day 4. We have added a brief statement at the end of the case report to note this fact (page 8).

Comment 3: Which was the rationale for reduction of vitamin C dosing?
Response: We appreciate the reviewer's question. Currently, we are conducting an NIH-sponsored multi-center trial employing vitamin C to treat sepsis-induced ARDS. We are studying the identical dosage reported in this case (200 mg/kg/24 hours). The VCU Institutional Review Board (IRB) approved 4 days of therapy for the trial. The clinicians directly caring for the patient described in this report wanted appealed to me to continue the full dosage intravenous vitamin C (200 mg/kg/24 hours) when day 4 was completed. Their rationale was that this patient had a viral illness which led to ARDS and they were concerned that discontinuing the infusion after 4 days would possibly lead to a recurrence of ARDS. Since we had no treatment data beyond 4 days and were not wanting the

ARDS to flare back up, we all agreed that a gradual dosage reduction was the best decision rather that discontinuing vitamin C abruptly. We fully realize that we are just at the very beginnings of understanding the proper dosing schemes for intravenous vitamin C in certain disease processes.

Comment 4: The effects of vitamin C infusion on markers of disease severity could have been assessed.

Response: We appreciate the reviewer's question. In the recently completed clinical trial mentioned above in our response to Reviewer Number 4's comment #2, we employed intravenous vitamin C (200 mg/kg/24 hours x 4 days) in patients with severe sepsis (J Translational Med 2014;12:32, [PMID: 24484547]). In that study, we measured three important biomarkers. We measured two biomarkers of inflammation (i.e., C-reactive protein, Procalcitonin) and one biomarker when elevated is indicative of vascular injury (i.e., thrombomodulin). We showed that vitamin C infused intravenously at the 200 mg/kg/24 hours for 4 days dosing scheme significantly lowered the two biomarkers of inflammation compared to placebo. Furthermore, we found that patients randomized to placebo showed significant elevations of thrombomodulin indicating severe vascular injury. Patients with severe sepsis who were randomized to receive the high dosage of intravenous Vitamin C exhibited no elevations in plasma thrombomodulin, indicating a dramatic lessening of vascular injury. In the NIH-sponsored multi-center trial we are quantifying a panel of 5 biomarkers.