

Background: Ebola Virus Disease (EVD) has ravaged three countries in West Africa. The mortality rate is extremely high, and it is perceived not only as threat to all of Africa but to the entire world. There is no known treatment to date other than administration of convalescent blood or experimental monoclonal antibodies, which both often fail. Ozone therapy (OT) has been in clinical use for decades and has been found to have physiological effects, which should directly inactivate the virus itself, as well as modulate its damaging effects. We present the scientific background and the possibility of ozone therapy as a cure or prevention for EVD in five consecutive patients. Materials and Methods: Ozone therapy administration by a combination of direct intravenous gas administration, rectal gas administration and ozonized water was administered to three patients with known acute EVD, one with apparent acute infection, and one case of extremely high risk. Treatment was carried out for up to ten days despite fast total remission of symptoms. Vitamin C and glutathione supporting supplements were administered. Results: Four symptomatic patients, three with test positive EVD confirmation and one (who suffered Ebola contaminated needle stick contamination three days earlier) without lab confirmation all remitted symptoms within 2-4 days and fully recovered. All four ill cases had an immediate recovery course upon initiation of therapy. The single case of non-symptomatic high-risk exposure treated preventively did not develop symptoms. Conclusion: Ebola virus may have a very narrow window of redox infectivity capacity, which can be easily exploited with OT. OT may be a useful modality in EVD and other viral diseases and should be immediately studied to save lives that might otherwise be lost.

Key words: Ebola, Hemorrhagic Fever, ozone therapy, oxidation, virus, antiviral therapy

Introduction

A Filovirus of several strains, commonly known as Ebola, causes hemorrhagic fever (EVD). Incubation ranges 2-21+ days. Ebola virus enters dendritic cells shutting down their immune system alerting alarms. While unchecked, it replicates wildly, infecting and damaging critical organs, inclusive of liver and kidneys. The cells explode releasing new viruses and debris. This can result in a cytokine storm (Tisoncik et. al., 2012), characterized by massive capillary leakage and tissue destruction. Then, the immune system may do more harm than good (Amarasinghe, 2014). Mortality is extremely high (60% in the current Zaire species outbreak). WHO reported that the current Ebola epidemic ravaging parts of West Africa is the most severe acute public health emergency seen in modern times (Watson, 2014). To date, there is no known proven effective treatment” (Choi and Croyle, 2013). A recent JAMA editorial proclaimed need for “utmost urgency” of fast tracking promising vaccines (Giesbert, 2015). Effective treatment is emergently needed. Ozone is an oxygen allotrope, O₃, created by solar UV radiation and lightning. It’s the strongest naturally occurring oxidant. Scripps Institute reported that ozone is actually generated by immune cells (Bablor, et. al., 2003) as part of its armamentarium of oxidants, which can be hurled against pathogens. Other immune system generated anti-infection oxidants include singlet oxygen, H₂O₂, NO, and NaOCl. Ozone kills bacteria in easily reachable concentrations nearly instantly (Leusink and Kraft, url) and some 100 times faster than chlorine containing disinfectants (decontaminants) (Oregon State Univ., 2011). Nikola Tesla patented the first commercial medical ozone generator in 1896. In World War I, German physicians disinfected wounds with medical OT. German physicians soon discovered that ozone application to various body fluids or cavities resulted in additional benefits, including enhanced circulation, oxygen delivery, and faster healing. OT has been continuously used for nearly 100 years, especially in Europe for a variety of infectious, immunological and circulatory conditions. Velio Bocci, MD of Italy investigated OT’s immune effects. He published results first in a series of studies (over 175) in peer reviewed medical journals, now found succinctly in his book “Ozone, A New Medical Drug” (2011), which details ozone’s many mechanisms to help many medical conditions including: 1) immune system modulation balancing its inflammatory/anti-inflammatory cytokines, 2) increase in production of RBC oxygen releasing 2,3 DGP (also reported by Viebahn-Hansler, 2003), and improved rheology properties of blood (increased RBC flexibility) 3) elevation of key anti-oxidant enzymes such as SOD, and increased glutathione. Cuban ozone researchers have independently verified these findings (Menendez, et. al., 2008).

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Medical OT induces vasoprotective prostacyclin production (Schulz, et. al., 2012). OT increases muscle (Clavo, et. al., 2003) and tumor oxygenation (Clavo, et. al., 2004) in humans studied by direct polarographic electrode measurement. Additionally, ozone protected against hepatic ischemia free radical reperfusion injury (Perralta, et. al., 1999). Cuban researchers found that OT preconditioning inhibits TNF-alpha production during endotoxic shock. In addition, OT exerts influence on the antioxidant-prooxidant balance for preservation of cell redox state by stimulating endogenous antioxidant systems (Zamora, et. al., 2005). Many viruses require reduced sulfhydryl groups on their lipid envelope glycoproteins for cell entry. Mirazimi's group speculated on the richness of disulfide bonds in viral glycoproteins as a factor for infectivity. Studying Cytomegalovirus, (CMV) they found the virus requires sulfhydryl groups to infect cells (Mirazimi, et. al., 1999). If the thiol groups were oxidized, CMV lost infectivity. When thiols were chemically rereduced (by dithiothreitol), the virus regained 65% infectivity. Reflecting on the reduction of "critical" disulfide bonds for vaccinia virus cellular entry, Markovic, et. al., (2004) found that protein disulfide isomerase inhibitors limited HIV-1 entry into T cells. Ozone inactivates many viruses including polio, Norwalk, coliphage MS2, hepatitis A and others (Kekez and Sattar, 1997; Shin and Sobsey, 2003; Herbold, et. al., 1989; Emerson, et. al., 1982). Ebola appears no different. Studies by Sanders et al. have been able to determine the disulfide-bond map of the Ebola glycoprotein and, as a result, have proposed that reduction of the disulfide bond between the two subunits of the Ebola glycoprotein complex, GP1 and GP2, "is a critical step in the entry of Ebola virus into cells" (Sanders Lab, url). Ozone, in vitro, instantly oxidizes reduced sulfhydryls to disulfides as shown in the chemical reaction below: $SH+SH+O_3 \rightarrow S-S+H_2O+O_2$. While ozone itself lasts only microseconds in blood, the reaction of ozone and blood lipids leads to the production of more stable but still highly reactive oxygen species (such as peroxides), which would react similarly, and perhaps mimic the pro-oxidant mechanism of immune system defense. Aerobic cells are designed for redox shuttling and oxidant stresses. Viruses lack repair capacity. Shut out of the cell (inactivated), they cause no damage, but remain antigenically intact for immune response. However, aerobic mammalian cells can and do quickly repair membrane oxidation effects. One repair pathway activates the hexose-monophosphate shunt, which, incidentally, produces 2,3 DGP. Finally, intravenous oxygen gas has been administered in significant volumes for decades in Europe. Numerous papers have reported beneficial effects on several physiological parameters. Regelsberger observed a general improvement in oxygen availability, eosinophilia, which can be valued as an increase in undetermined cellular immunological resistance. "Furthermore, rheological qualities of the blood as well as diuresis are improved, the release of oxygen into the tissue is increased, and the blood pH is normalized" (Schmidt, 2002). Intravenous oxygen gas in human volunteers induces eosinophil generated 15-LOX-1, a powerful anti-inflammatory enzyme, believed to be a key factor in inflammatory modulating effects of IV oxygen gas (Chaitidis, et. al., 2004). These considerations caused lead author Rowen to speculate that OT might be an ideal candidate to actually cure EVD (and other viruses). Rowen has been using OT to treat virus and bacterial infections (outpatient setting) since 1986. He recruited Dr. Howard Robins, who refined a very inexpensive and relatively medical waste free technique of ozone administration- direct intravenous gas administration (DIV). DIV administers an oxygen/ozone gas mixture intravenously using a 27g winged infusion set. The clinician sets an ozone concentration up to 55 mcg/cc. (Approximately 98% O₂ and 2% O₃). Great care is taken to prevent "air", which is 79% nitrogen gas and can cause an embolus, from entering the body. There are no reports in the worldwide literature, even after decades of use, that intravenous oxygen gas causes embolism. Desaturated venous blood is "thirsty" for it. A protocol (Rowen-Robins Method) for EVD was developed inclusive of oral vitamin C, and a supplement supporting recycling of glutathione (Thiodox®, Allergy Research Group).

Figure 1: Robins demonstrating DIV technique on Rowen before gathering of SL professionals. Sixty cc of gas is administered in this treatment.

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Rowen and Carew visited the Freetown Hastings Ebola Center and taught the method on 10/24/2014. The staff acknowledged a current 60% EVD mortality rate, considered, among the best results in Sierra Leone. For unknown reasons Ministry of Health authorities suddenly forbade the administration of OT on patients at the center while the educational session was in progress. Since all confirmed cases of Ebola

suffered mandatory quarantine, it became extremely difficult to locate and treat cases outside this mandate. However, four cases did arise from within the facility amongst front line providers. These managed to receive OT. We now report these four case results. The first case, who was not tested, had had an accidental needle prick from Ebola contaminated blood three days earlier. All patients executed informed consents.

Materials and Methods

“DIV” ozone indicates direct intravenous ozone gas at 55 mcg/cc at a volume between 20-40 cc. “Rectal ozone” indicates ozone gas administered rectally at a concentration of 36 mcg/cc and volume between 150-350 cc. “Ozone water” was made by bubbling ozone gas at approximately 70 mcg/cc into water for 15 minutes. Administration volume was 300-500 cc, and administered orally. All cases were provided nutritional supplements Thiodox® and Buffered Vitamin C® (donated by Allergy Research Group). Thiodox dose: one twice daily. Vitamin C: four to eight grams daily during the days of ozone treatment.

Case Reports

Case 1 – Physician SK, 28, male, at the Hastings Ebola Center in Freetown jabbed himself with a contaminated needle. He was fearful to get an Ebola test, knowing if positive he would have been forcibly picked up and placed in quarantine and denied OT, which he feared would cost him his life. He was a physician Rowen and Carew had trained in OT at Hastings. He received 20 cc of DIV on October 23, 2014 as part of the training. The following is his verbatim and signed report edited only to remove names. What appears in brackets is editing by the authors for accuracy.

14th November: Needle prick in the red zone while trying to cannulate an EVD positive patient. This patient was in the recovery ward with no complaint and symptoms. She had done the blood (test) but it came positive and was waiting for the second specimen to be taken. The needle went through the PPE and pricked me a finger length anteriorly above the wrist. I was wearing Tybek (the thinnest PPE). The prick happened just above the margin of the gloves, making me more exposed. Had it gone through the gloves, as in the case of another doctor, it wouldn't have penetrated the skin. 15th November: No symptoms but planning to start OT. 16th November: No symptoms- feeling fine. Called Dr. Carew and went to see him. DIV [30 cc, 55 mcg/cc] done [one session]. [He also received 500 cc ozone water]. Was given Vit. C, Thiodox, colloidal silver. I was also given the ozone machine, couldn't use it - gas leak. 17th November: Fever at night, loss of appetite, bowel movements (unusual) and urge to empty my bowel. The urge was very strong. I tried to suppress it. I took ciprofloxacin, paracetamol, doxycycline, drank ORS. Couldn't sleep because of fever and the urge. I went after midnight to pass stools and I felt some comfort. The stool was not watery but not too hard (it was very soft). I came and slept. 18th November: Loss of appetite in the morning and weakness. Slightly febrile, muscular pain and joint (suppressible). Went directly to Blue Shield and finally Dr. Carew came with Jeff [McNamara]. Before their arrival I was really weak and couldn't stand. For too long had to sit down. But after drinking the ozone water Jeff prepared I regained my strength and felt much better. I also tried the [ozone] fog. Started rectal ozone [36 mcg/cc]. 19th November: Slight weakness. Appetite is much better. DIV done, started working again. Did rectal ozone. 20th November: For the first time I did rectal ozone 3 times a day [36 mcg/cc]. One DIV. Slight weakness. Slept well at night. My temperature was 37.1 degrees Celsius. 21st November: My appetite is improving. DIV and rectal [as before]. 22nd November: DIV and rectal. No complaints. Prepared ozone water. 23rd November: No complaints. Ozone water but no DIV and rectal. 24th-29th November: Ozone water only.

SK fully recovered, resuming his duties within just days of commencement of therapy.

Case 2 - Physician MB, 35, male, had close personal contact (hug) with another physician after the latter initially tested negative for Ebola. However, within 2 days a repeat test (PCR) came positive on the other physician (who died shortly thereafter). MB subsequently developed typical Ebola symptoms (fever, abdominal pain, vomiting, appetite loss, and later diarrhea) within 3 days. He was placed in quarantine, but was offered and accepted OT administered by the recovered physician SK. At the appearance of symptoms, he received 30 ml DIV. When PCR testing returned positive, he was given an additional 2 DIV administrations consisting of: 40 cc each, 12-16 hours apart, at 55 mcg/cc. He also drank 300-500 cc of ozonated water after the intravenous treatments. Within 4 days, all symptoms had cleared. A follow-up test for presence of Ebola virus was negative 2 weeks later. The government publicly announced this

case as a complete Ebola recovery in a physician national, but did not mention he had received OT.

Case 3- SS, 25, male nursing student on the Ebola front line, who was present for the Rowen and Robins ozone training in October 2014. He documented exposure to Ebola via damaged protective gloves enabling an Ebola patient's blood to come in contact with his skin. He also, without protective gear, cared for a friend, who later was confirmed to have EVD. On December 2, 2014, SS developed fever, malaise and headache. He received 2 DIV ozone gas injections of 20 and 30 cc respectively at 55 mcg/cc, and drank ozone water (100 cc) on 3 consecutive days. Upon testing positive for EVD, (PCR) he was taken to the Kerry Town Ebola treatment center where he was not permitted further OT. However, he had a complete and non-complicated recovery.

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Case 4 - IB, 24, male aid. Working in "red zone". While bathing an Ebola patient, on or about November 24, 2014, he accidentally splashed body fluid contaminated water that went through his facemask and entered his eyes and mouth. Within 5-7 days, he developed progressive symptoms of extreme fatigue, body pains and vomiting. He started on anti-malarials. The next day, he informed the facility physician who immediately administered DIV ozone, 40 mcg/cc, 40 ccs. Within a few hours of the gas injection, almost all symptoms subsided. He also received two rounds of ozonated water (as in case 2). However, by then, he was about symptom free. His Ebola test proved positive (PCR) and he was placed in the treatment unit and prohibited from further DIV ozone. He did receive their usual treatment protocol consisting of D5W, Ceftriaxon (IV), Metronidazole (oral), Immunoboost (oral vitamin). He had an uneventful stay within the Ebola containment unit and was discharged in the first week of December.

Case 5 - GK was the female companion of a 67-year-old Sierra Leone senior physician who died of EVD. She had intimate contact with him at the time of his falling ill. Authorities placed her under home military quarantine (armed military guards), preventing any entry and exit, inclusive of anyone who might bring her OT. She was in great fear for her life and very much aware of OT, having urged her partner to accept it before he died. In the middle of the night she scaled a razor wire fence shredding her skin and evaded the guards. She arrived at Dr. Carew's "Blue Shield" facility where she received: one DIV ozone treatment, and daily rectal ozone and ozone water for ten days. She also received vitamin C and Thiodox® twice daily. No symptoms developed. An ozone-fogging device was deployed at Dr. Carew's Blue Shield facility for decontamination and protection of Dr. Carew and all exposed to patients who were treated there.

Discussion

EVD has a progressively explosive downhill course from the time of symptom appearance. Typically, death occurs within a week or less in the majority of cases. In all our ozone treated cases, symptoms did not progress from the start of OT, and symptomatic patients were totally free of all symptoms, inclusive of fever, generally by day 3 of treatment. Through December 2014, Sierra Leone lost 11 out of 13 national physicians diagnosed with confirmed or probable Ebola. Both survivors received OT and quickly recovered. Following Rowen-Robins' mission, one senior physician was offered and refused OT. He received convalescent serum and was transferred to the USA and died only 2 days later. Another senior physician likewise refused OT opting for ZMapp. He died while it was thawing. (Source: public news wires). A third EBV positive physician, Hastings trained, requested OT. Authorities refused and quarantined him. He died within 3 days. Both senior authors had expected rapid recovery with OT, but admittedly not this fast (within a few days and with limited treatments). Rapid recovery was expected because of the violent nature of EVD, and the known direct countering biological benefits/effects of OT. This merits further discussion. Ebola induced pathology includes rapid cellular entry, an explosion of viral particles into circulation, and rapid cellular re-entry perpetuating the cycle viciously. Then the repressed immune system "awakens" and pulls out all its weapons to do battle. But unfortunately, that battle results in a cytokine storm, wherein the immune system does more damage to the vascular system and tissues than does the virus. Death occurs due to capillary leaks, hemorrhage and organ failure. Circulatory compromise – The final common denominator in any vascular insult is oxygen deprivation and resultant cellular injury and death. OT is known to improve rheological properties of blood, increase 2,3 DGP, shifting the oxyhemoglobin curve to the right and releasing more oxygen in tissues. Bocci, Menendez,

and others have well demonstrated that OT enhances oxygen delivery and utilization. Ozone itself is oxygen. Clearly, in advanced EVD with vascular damage, tissues are starved of oxygen and energy production. Any oxygen delivery enhancement could potentially salvage cells that might otherwise die. Viral entry – The need for reduced sulfhydryl groups to enter cells, may be the Achilles heel for reversing the lethality of EVD (and other viruses). Sulfhydryl groups are key to activity of many cellular enzymes; aerobic cells may control enzyme activity by redox, providing means to activate/inactivate these enzymes. It appears from our cases EBV has a very narrow redox window, and that its envelope glycoproteins must be reduced as literature suggests. The symptomatic patients began a recovery essentially with the first oxidation (ozone) treatment. The senior authors did expect recovery, but within 5-7 days, considering the natural course of EVD. These symptomatic cases improved with the very first treatment. An oxidant stress to the blood stream carrying newly emerging viruses may be capable of oxidizing and inactivating sulfhydryl entry mechanisms. Such inactivated viruses will be incapable of entering the cell for further replication, while able to encourage healthy immune responses. Gonzales et. al., (2014) reported on a case of another vicious virus now likely endemic in the USA. A man (54) developed high fever and severe arthralgia among other symptoms. He was positive for Chikungunya virus. After receiving two intravenous infusions of vitamin C, 100 grams each, he immediately began recovery and was clear of symptoms in two days. A second paper reported combined ascorbate and intravenous hydrogen peroxide on symptomatic cases of Chikungunya virus observing fast symptomatic relief (Marcial-Vega, et. al., 2015). This parallels our observations with ozone. Importantly, ascorbate in these doses has been found to undergo a newly discovered metabolism. The lab of Mark Levine at the National Cancer Institute research reported a heretofore-unknown effect of high levels of plasma ascorbate. “Pharmacologic ascorbate can act as a pro-drug for H₂O₂ formation, which can lead to extracellular fluid [accumulation of H₂O₂]” (Chen, et. al., 2005). Bocci, et. al., (1998) theorized that the key mediator in ozone’s beneficial effects is H₂O₂. Oxidation therapy was reported as far back as 1920 to dramatically cut the mortality rate of influenza pneumonia in the great epidemic of that time. British physician Oliver (1920), in India, took only hopeless cases and nearly halved the death rate with intravenous H₂O₂ therapy. In the 1940’s, ozone’s sister therapy, ultraviolet blood irradiation therapy, was used to rapidly resolve viral influenza (Miley, 1942) and polio (Miley and Christensen, 1944). We have nothing, even in today’s modern world, which compares. Cytokine storm - Ebola induces a cytokine storm. OT has been shown to significantly modulate TNF-alpha and inflammatory cytokines. Bocci has investigated and reported ozone as a cytokine inducer (Bocci, et. al., 1993). Bocci (personal communication to Rowen) called ozone the “ideal cytokine inducer”, inclusive of anti-inflammatory cytokines. EVD instigates pathologically high levels of NO. Ozone modulates NO (Bocci, et. al., 2007). The actual extraordinary rapid recovery of the treated patients suggests that all three mechanisms may be at play, particularly viral inactivation. Ozone easily oxidizes SH groups to S-S groups, which, according to literature, is expected to inactivate viral entry. Ozonides, reactive

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oxygen species generated by OT such as peroxide species, would also easily oxidize reduced sulfhydryl groups based on simple chemistry. Our experience suggests that EVD has an extremely narrow redox window of infectivity. Even ozone exposures (rectal and water), far less powerful than DIV, appear to have assisted in dispatching symptoms and aiding recovery. We believe that the temporary oxidant stress to EVD patients oxidizes viral surface glycoproteins. The virus particles are unable to recover since they lack means to self-repair damage to their glycoprotein spikes. Also, the temporary oxidative stress created by ozonetreatment stimulates the immune system to respond in more favorable conditions to the Ebola virus. Additional damage to viral infectivity could be inflicted on the lipid envelope. The virus incorporates lipids from our own cell membranes. Infectivity is dependent upon a functional lipid membrane. Agents that attack the lipid envelope may be useful as antiviral drugs (Lorizate, 2011). Ozone directly attacks unsaturated fatty acids, which would be expected to be part of the Ebola lipid envelope. Aerobic cells repair such alterations. Viruses cannot. Lorizate lamented that compounds which could attack viral lipids lack specificity and are “thus unacceptably toxic.” OT, in use for decades, has no reported toxicity and may serve as an ideal lipid altering anti-viral agent. Statistical probability: With

Hastings center's survival rate of only 40%, the statistical probability of 100% recovery arising from mere chance is 0.4(4), or 0.026%. Furthermore, lack of disease progression upon therapy commencement greatly magnifies the significance. Ethics: International agencies, inclusive of the WHO (2014), called for the use of any reasonable treatment in the fight against Ebola. ("...the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.") Considering the high mortality of EVD, we then believe it unethical to withhold a known, decades old, safe therapy from EVD patients, which has a 60% probability of death, to do a double-blind study, or to deny OT for prophylaxis. Effectiveness will be self-evident. Cost: The ozone cost of treatment per patient was less than 10 USD excluding cost of ozone generator. Medical waste was limited to one 27 gauge "butterfly" needle per treatment (0.75 USD) and one syringe (reusable as ozone sterilizes the syringe as it fills each time) for each patient. Beyond modest cost of a reliable generator (1700 USD or less), the cost of DIV ozone will largely rest in labor costs. Safety: The world literature is devoid of medical ozone toxicity reports when administered within the guidelines of the Robins DIV method or the more common method of major autohemotherapy. In the latter, between 50-200 cc of blood is removed, treated with ozone, and returned to the patient. During training, we treated several Sierra Leoneans with DIV ozone without any toxicity except rare vein irritation. Both senior authors have performed thousands of ozone treatments with negligible untoward effects. Both have observed repeatedly rapid resolutions of both viral and bacterial infections in hours to days. Availability: OT is not patentable; therefore it will fail to generate a profit for any developer or promoter. Hence, OT, though widely practiced, is not industry or mainstream promoted, and remains relatively unknown. This was a major reason Rowen and Robins chose to travel at their own risk and cost. By achieving success for the most dread virus on the planet, OT might attain its rightful place in healing and saving lives, regardless of lack of profit potential and industry glamour. Weaknesses of this report: We acknowledge that these cases were treated early (soon after symptoms developed). None were critically ill. Ozone benefits on late stage EVD remain unknown.

Conclusion

Ozone therapy, a modality not well known or understood by conventional Western medicine, has performed as a safe and ideal therapy for EVD in all infected patients receiving it. EVD symptoms cleared within 2-4 days in all (four) symptomatic cases involving front-line health workers. No symptoms developed in a fifth extremely high-risk person. In contrast, two leading Sierra Leone physicians who contracted EVD and refused treatment both died, and one who requested, but was denied ozone treatment, also died, within weeks after our visit. DIV ozone is inexpensive, safe and leaves virtually no contamination. International organizations and governments would do well to immediately conduct a formal trial of this unique therapy for EVD, which could provide significant security, both for EVD prevention and treatment, and for dangerous front-line work.

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fogging" technology for front line protection.

Author contributions: Dr. Rowen sourced the scientific references, drafted the manuscript, and compiled the transmitted information from Sierra Leone. Dr. Robins provided training, education and expertise in his method of ozone delivery and traveled together with Dr. Rowen to Sierra Leone. Dr. Carew coordinated all training in Sierra Leone, both didactic and practical, bringing in scores of health care professionals. Dr. Kamara coordinated difficult retrieval of information and results back from Sierra Leone. Additionally, he visited each of the named patients and subsequently deceased physicians at his own peril to offer the therapy and obtain informed consent. Dr. Jalloh was the supervisory physician to the treatment of case 2 and assisted with training at the Sierra Leone Ebola center

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