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The Role of the Laboratory and Transfusion Service in the Management of Ebola Virus Disease ☆☆☆



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ABSTRACT

The Ebola outbreak that began in 2013 infected and killed record numbers of individuals and created unprecedented challenges, including containment and treatment of the virus in resource-strained West Africa as well as the repatriation and treatment for patients in the United States and Europe. Valuable lessons were learned, especially the important role that the laboratory and transfusion service plays in the treatment for patients with Ebola virus disease (EVD) by providing data for supportive care and fluid resuscitation as well as the generation of investigational therapies such as convalescent plasma (CP). To provide treatment support, laboratories had to evaluate and update procedures to ensure the safety of laboratory personnel. Because there is no licensed EVD-specific treatment, CP was used in more than 99 patients with only 1 possible severe adverse event reported. However, given the biologic variability inherent in CP as well as the small number of patient treated in a nonrandomized fashion, the efficacy of CP in the treatment of EVD remains unknown.

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Ebola is an enveloped negative-strand RNA virus of the family Filoviridae, so named because of the filamentous morphology of the virions when examined by electron microscopy [1]. Five species of Ebola virus have been described and are named for the regions where infections were first identified [2]. The 2013–2015 outbreak stemmed from transmission of the Ebola species *Zaire ebolavirus*, which has been described as having the highest case fatality rate and virulence among Ebola species [3,4]. Ebola virus is presumed to be a zoonotic infection with reservoirs in bat and other wildlife populations that

episodically infects humans, thus allowing person-to-person contact to further spread the virus and cause outbreaks [5]. Close contact with infected individuals, especially via contaminated body fluids, is the main route of person-to-person transmission of Ebola [6].

The genome of Ebola virus contains 7 genes, encoding for 9 proteins [7]. The only protein on the surface of the Ebola virion and hence the only protein accessible to circulating antibodies is surface glycoprotein (GP), which mediates virus entry into multiple different cell types via endocytosis [8]. The pathogenesis of Ebola virus disease (EVD) is not well understood, but likely results from overwhelming cytopathic damage due to the ability of Ebola virus to replicate throughout many different tissues of the body, dysregulation of the immune response, and profound hypovolemia [9]. The most commonly reported symptoms of EVD are fatigue, fever, weakness, myalgia, headache, decreased appetite, and lethargy [10]. Although hemorrhagic complications did not predominate in patients infected during the 2013–2015 outbreak, reports of patients infected during previous outbreaks described severe

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hemorrhage possibly due to disseminated intravascular coagulation, hepatocellular necrosis, and endothelial disruption with vascular permeability [11,12].

The most recent Ebola outbreak was the largest and longest on record, infecting nearly 30 000 individuals, with fatality rates approaching 70% in some areas [13,14]. Many factors led to the magnitude and velocity of the outbreak in West Africa including poor health infrastructure, lack of awareness of symptoms and transmission, cultural barriers, population density, and travel [13]. These factors also led to additional significant events that had not previously occurred, including repatriation of patients with EVD from Africa to treatment centers in the United States and Europe, international travel of asymptomatic patients with EVD out of Africa, and infection of health care workers caring for patients with EVD in the United States and Europe. The reality and uncertainty of the 2013–2015 outbreak forced the heavily regulated health care systems in Europe and the United States to develop policies and procedures designed to protect patients and hospital staff in unprecedented circumstances. An important lesson learned was the invaluable role that the laboratory played in caring for patients with EVD by providing experimental therapy support in the form of convalescent blood products, as well as generation of laboratory results needed to replace fluid and electrolytes, the mainstay of supportive care treatment [9,10].

Laboratory Testing

The Centers for Disease Control and Prevention have guidance available for laboratories involved in Ebola virus testing that recommends each institution perform a risk assessment of all processes, procedures and activities and adjustment of practices as needed [15]. The highest-risk specimens include those from patients with known EVD, or from patients under investigation for EVD due to compatible symptoms and appropriate epidemiological risk factors. Because the small potential exists for laboratory personnel to handle specimens that, unbeknownst to them, contain Ebola virus, compliance with Bloodborne Pathogens Standard (29 CFR 1910.1030) is essential and part of good laboratory practice.

The main concern for laboratory personnel is exposure to an infectious dose of Ebola. The assumptions made when designing laboratory protocols to handle specimens with Ebola virus were that virus may persist for days in a specimen, body fluids may have a viral genome titer of 10^8 or higher, and as few as 1 to 10 virions may be infectious, meaning that a nanoliter of blood exposed to a mucous membrane could potentially cause disease [16–18]. As such, processes that involved open tubes, centrifugation steps, and/or aerosolization potential should be evaluated and risk mitigation steps taken when appropriate. A certified industrial hygienist can be helpful in determining risks in the laboratory, as well as potential safety engineering improvements [17]. For patients with known EVD, point-of-care testing located in a biosafety hood that minimizes specimen handling has been used with success [19]. Point-of-care testing must comply with all Clinical Laboratory Improvement Amendments (CLIA) regulations (42 CFR Part 493). In addition, testing in core hospital laboratories has been reported on specimens from patients with known EVD, as long as the instruments had closed tube sampling capability [17]. Although not available initially during the 2013–2015 outbreak, most major manufacturers now have decontamination protocols should any samples with Ebola virus be tested on an analyzer.

Other unique aspects of testing samples with Ebola virus that must be included in any risk assessment include specimen transport, infectious waste management, safe sharps handling, disinfecting testing surfaces, handling spills, and willingness of personnel to handle the specimens. Although any fluid with Ebola virus has bioterrorism potential, most specimens are not considered Federal Select Agents unless viable Ebola virus is intentionally isolated from that fluid (42 CFR 73.3 (d) (1)). Also, Ebola virus containing samples can be safely transported

by following the requirements of the Department of Transportation for Category A infectious substances.

Transfusion Testing and Conventional Blood Product Support for Patients with EVD

As part of their risk assessment, 2 Ebola treatment centers in the US determined that blood bank personnel faced an unacceptable risk when samples from patients with EVD were centrifuged and uncapped for routine testing on an automated analyzer, or when such samples were tested by manual methods that required a cell washer step [17,19]. ABO and Rh typing could instead be performed using commercially available reagents that are Food and Drug Administration (FDA) approved for slide agglutination, a process that poses a low risk of aerosolization when performed in a biosafety hood (Fig 1A) [17]. Knowledge of a patient's ABO type can be helpful for selection of both convalescent and nonconvalescent blood products. Because no red blood cell (RBC) allo- or auto-antibody testing was performed, and RBC units were not serologically crossmatched, both centers provided universally compatible blood products on an emergency release basis for patients with known EVD (group O RBCs, group AB, or ABO-compatible plasma containing products if type was known) [17,19]. The decision to forego screening for irregular RBC antibodies was not without criticism [20].

A total of 11 patients treated in Europe and the United States received nonconvalescent blood products, with 4 patients receiving whole blood, 6 patients receiving plasma, and 5 patients receiving platelets [10]. No adverse events from receiving nonconvalescent blood products in the absence of antibody screening and serologic cross-matching were reported. However, given the small number of nonconvalescent blood transfusions, an adverse reaction may not have

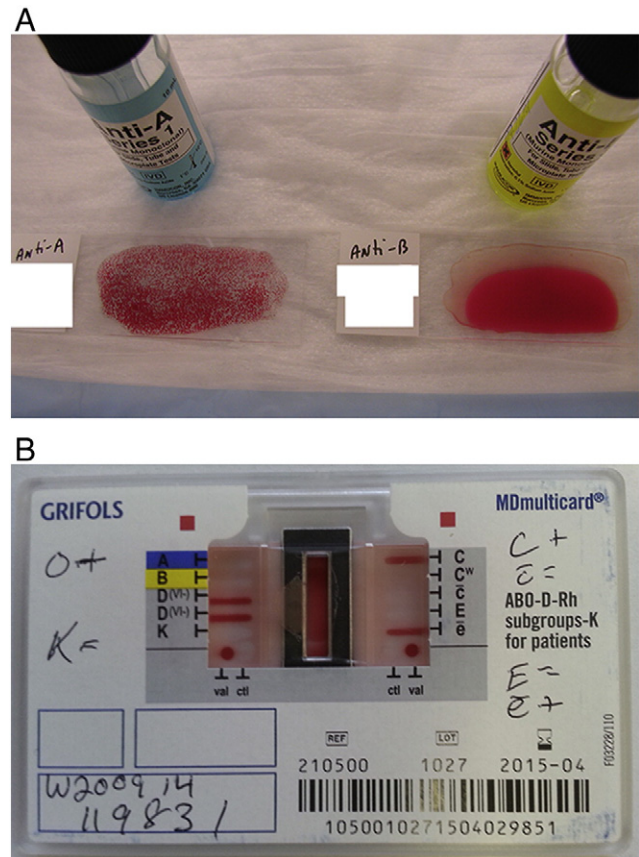


Fig. 1. A, ABO and Rh determination can be performed without centrifugation by slide agglutination with FDA-approved reagents. B, Emerging technologies allow for antigen typing without centrifugation, allowing for the selection of antigen-matched emergency release blood products.

been statistically likely. To further improve blood transfusion safety, especially RBC transfusions, alternative technologies have been examined. For example, the CE-marked MDmulticard (Grifols, Barcelona, Spain) can rapidly serotype Rh and K subgroups by placing a drop of the patient's blood onto a card impregnated with antisera without any centrifugation, so that in the event of an emergency release RBC transfusion, antigen-compatible units could be selected to minimize the risk of immune-mediated hemolysis (Fig 1B).

Passive Immunity as an Experimental Treatment of EVD During the 2013-2015 Outbreak

The transfusion of blood products from convalescent survivors into patients with active infections has a rich history as an immune therapy for influenza, measles, polio, and severe acute respiratory syndrome [21]. Convalescent blood products are often the only therapy readily available early on in outbreaks when no alternative licensed therapies are available. Recognition of convalescent plasma (CP) as a potential therapy for treating EVD emerged shortly after the first descriptions of Ebola in 1976–1977 when 201 units of CP from survivors were collected and stored [22]. This first EVD CP bank highlighted important challenges, namely, variable quality of the plasma product in terms of antibody titers, as well as transfusion-transmitted disease risk because most units contained filarial larvae [22].

The first use of CP as a passive-immune therapy for the treatment of EVD occurred in 1976, when a laboratory worker infected with Ebola received 2 doses of CP and survived (Table 1) [23]. However, over the course of several subsequent outbreaks, there was no record of CP transfusions. This changed during the 1995 Ebola outbreak centered on the city of Kikwit, when health care workers transfused convalescent whole blood from an EVD survivor into a patient with active disease [24]. The patient survived, and convalescent whole blood transfusion was administered to an additional 7 patients (Table 1) [24]. Of the 8 recipients, 7 survived, which appeared to be a higher survival rate than observed in nontransfused patients during that outbreak [24].

In following years, laboratory studies using animals have produced conflicting results on the efficacy of passive immune therapy in the treatment of EVD. For example, the use of convalescent blood transfusion did not protect nonhuman primates from succumbing to Ebola infection [25]. In contrast, recombinant antibodies derived from RNA recovered from survivors of the 1995 outbreak had neutralizing activity when the antibody bound to surface GP [26]. Also encouraging were studies showing that passive transfusion of immunoglobulins seemed to protect both nonhuman primates and mice from Ebola infection [27,28].

Because there are no licensed Ebola virus-specific therapies, medically evacuated patients of the 2013–2015 Ebola outbreak were initially treated with supportive critical care as well as experimental therapies consisting of monoclonal anti-Ebola antibodies and antivirals [10]. Passive immune therapy with ZMapp (Mapp Biopharmaceutical, Inc, San Diego, CA) or ZMab (Mapp Biopharmaceutical, Inc) appeared to be well tolerated and correlated with decreasing viral titers and resolution of symptoms [29]. However, as patients continued to be evacuated, the supply of these monoclonal antibody therapies was quickly depleted. As a result, EVD treatment teams turned to Ebola CP as a passive immune treatment, especially given the past nonhuman primate and human reports that used convalescent blood products or monoclonal antibodies [30].

Risks, US Regulatory Aspects, and Ethics of Transfusion of Convalescent Blood Products

Ideally, CP would be obtained from healthy, fully recovered donors with ample time to perform appropriate testing for safety and potency. Appropriate safety testing would include serology and nucleic acid testing for transfusion-transmitted infections (TTIs), including the disease of interest as well as any other additional testing needed based on donor risk factors, such as tests for *Plasmodium*. The risk of unusual TTI associated with CP is highlighted by studies of the first EVD CP bank, where most units contained filarial larvae [22]. Furthermore, an added layer of protection can be provided by pathogen reduction techniques, which have been reported to inactivate Ebola virus in vitro [31]. Optimal pathogen reduction techniques are those that minimally affect the therapeutic potential and yet inactivate parasites and infections not routinely tested for. In addition, transfusion-associated acute lung injury (TRALI) mitigation strategies should be considered, such as anti-HLA and antineutrophil serology. Convalescent plasma potency would optimally be assessed measuring the plasma's neutralizing antibody levels using a standardized assay that has been validated to reflect clinical benefit. The ideal CP therapy would be stored in a large bank that could support ABO-matched products with the highest potency for any patient in need.

Unfortunately, the ideal Ebola CP bank did not exist at the onset of the exponential growth phase of the 2013–2015 outbreak due to lack of foresight, resources, and evidence for efficacy. Therefore, because CP was evaluated by EVD treatment teams, issues that had to be considered in real-time included risks to both the donor and recipient of CP vs the potential benefits. The only guidance available to national health authorities and transfusion services to outline the necessary steps required to collect convalescent whole blood or ECP from EVD-recovered patients for transfusion to patients with early EVD, as an empirical

Table 1
Reported use of convalescent blood products for the treatment of EVD

Product	Dose	Survive (Y/N)	Serious adverse events	Reference
Plasma	450 mL × 1, 350 mL × 1	Y	N	[21]
Whole blood	400 mL	Y	N	[22]
Whole blood	150 mL	Y	N	[22]
Whole blood	150 mL	Y	N	[22]
Whole blood	250 mL	Y	N	[22]
Whole blood	250 mL	Y	N	[22]
Whole blood	250 mL	Y	N	[22]
Whole blood	450 mL	Y	N	[22]
Whole blood	400 mL	N	N	[22]
Plasma	500 mL × 2	Y	N	[28]
Plasma	500 mL × 6	Y	Possible TRALI	[28]
Plasma	880 mL	Y	N	[30]
Plasma	200 mL × 5	Y	N	[35]
Plasma	500 mL × 2	Y	N	[31]
Plasma	600 mL x1, 500 mL x1	Y	N	[31]
Plasma	200–250 mL × 2	58/84 patients	N	[36]
Overall		72/99 patients		

treatment modality, was from the World Health Organization. Of particular concern in the United States was the fact that the first 2 potential CP donors were 15 and 11 days after discharge from hospitalization for EVD when collection occurred [30]. Significant unknowns regarding CP at this time included safe plasma collection volumes from the donor, determination of the quality and quantity of antibody levels, and assessment of efficacy in the recipient. In addition, whether additional infectious disease testing was needed to be performed on the CP was unknown, and at the time of the collection and transfusion of Ebola CP in the United States, no pathogen-reduction techniques were available to potentially reduce transfusion-transmitted disease risk.

To allow CP collections from recovered donors for transfusion into patients with active EVD in the United States, protocols were approved under an emergent Investigational New Drug exemption from FDA that included appropriate institutional review board protocol clearances and consents for both donor and recipient. The Investigational New Drug requested documentation of Ebola antibody titers in the product, as well as recipient vital signs and pretransfusion and posttransfusion titers and viral quantification. The first Ebola CP donor in the United States donated 1000 mL, which was collected by plasmapheresis and replaced with 5% human albumin [30]. The initial volume was empirically determined based on donor safety considerations. Subsequently, this process was used to collect CP for transfusion to most of the remaining patients treated in the United States [10,30,32,33].

Ethically, many concerns have been expressed about the use of investigational therapies, including CP, for the treatment of EVD. Concerns include recruitment of donors who have just survived a serious debilitating infection, potential TTI because these donors would otherwise be ineligible, unknown efficacy of CP, inclusion or exclusion of children or pregnant woman, access to CP, and unknown risks [34]. In addition, if CP were shown to be an effective therapy, concerns about the access to CP would have to be addressed given the limited supply available. Evaluation of CP efficacy, collected on a large scale in Africa, raised additional ethical considerations including whether a randomized controlled trial was appropriate given the high case-fatality rate [35,36].

Efficacy and Safety of CP for EVD

Of the 15 case reports published on the use of CP in EVD, only 1 fatality has been reported (Table 1). In the case reports, CP was well tolerated, with 1 patient developing respiratory complications and evaluation of possible TRALI that were possibly attributed to the plasma infusion [37]. In West Africa, the largest study of CP in EVD to date was performed in a nonrandomized, comparative study that examined the use of CP with unknown antibody titers in 99 patients [38]. Overall, no serious adverse reactions were reported with CP use, and of the 84 patients analyzed, 58 survived [38]. However, the authors concluded that the administration of CP did significantly increase survival compared with the historical control group. Looking at the studies in combination suggests that CP in EVD is a safe therapy, with only 1 reported serious adverse event of 99 patients (Table 1).

Although conclusions regarding safety of CP can be made with available data, efficacy is difficult to determine. The criterion standard to gauge the effectiveness of CP would be a randomized controlled trial that compared CP of similar dose, timing of administration, and antibody titers to non-CP plasma infusion. Although standardizing the dose and timing of administration of CP is straightforward, determining antibody titers is not because there is no standardized assay available. Even when considering the assays used in Ebola virus research studies, variability exists in methodology, substrates, and nomenclature, making comparisons difficult. Owing to CP as a biologic product, many additional variables may affect any potential efficacy including the donor's immune response, whether the donor was infected by a similar strain of Ebola, and the epitopes recognized by the anti-Ebola antibodies. Because only GP is accessible on the virus surface, anti-GP antibodies mechanistically are more likely to be neutralizing [39]. As such, CP

collected from survivors of EVD may be different from donors who were vaccinated against Ebola. Possibly, a subset of donors with high-titer neutralizing antibodies as measured by a clinically validated assay would yield CP with measurable efficacy. Given these challenges, truly meaningful conclusions regarding the value of CP remain elusive. However, as new outbreaks of infections emerge, especially with a high case-fatality rate, CP will continue to be a useful frontline tool given its favorable safety profile and ability to be rapidly deployed, which is likely to only improve with more widespread pathogen-reduction availability.

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