Large-scale Convalescent Blood and Plasma Transfusion Therapy for Ebola Virus Disease

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An effective therapy for Ebola virus disease (EVD) not only will lower the case-fatality rate but also will provide an incentive for patients to seek treatment, thereby enhancing primary and secondary prevention efforts. While several experimental drugs are being considered, the World Health Organization (WHO) has prioritized Ebola convalescent whole blood (CWB) and convalescent plasma (CP) transfusion for evaluation because this can be done relatively quickly and, if proven to be safe and effective, could be implemented without delay [1]. The use of blood from recuperated individuals has a long history of use for treatment of other serious infectious diseases and, with appropriate precautions, is generally considered safe [2]. However, the WHO has indicated that this intervention must be considered as experimental for EVD and, therefore, that initial studies should be conducted within a clinical trial framework [1].

In this issue of The Journal of Infectious Diseases, Gutfraind and Meyers [3] extend an Ebola virus transmission model published by the Centers for Disease Control and Prevention (CDC) [4] to include large-scale hospital-based convalescent donations and transfusions. Using epidemiological estimates for Ebola in Liberia and assuming that convalescent transfusions reduce the case-fatality rate to 12.5% [5], they calculated that, under a 30% hospitalization rate, CWB and CP transfusions are estimated to reduce the number of deaths in Liberia by 65 (0.37%; 95% confidence interval [CI], .07%–2.6%) and 151 (0.9%; 95% CI, .21%–11%), respectively. They conclude that transfusion therapy for Ebola is a low-cost measure that can potentially save many lives in Liberia but will not measurably influence incidence.

There are, however, at least 8 major issues to consider in determining the advisability of implementing a large-scale CWB or CP transfusion program in West Africa. First, the evidence for the efficacy of CWB and CP transfusions remains limited. There is mainly the positive experience during the 1995 Kikwit EVD outbreak in the Democratic Republic of the Congo (7 of 8 patients survived; case-fatality rate, 12.5%) [5]. However, this rate is most likely an optimistic estimate since only 1 of 5 other patients with EVD in Kikwit who received blood transfusions (for bleeding manifestations) from convalescent patients survived. Inclusion of these patients would yield a case-fatality rate of 38% (5 of 13) [5]. And although many healthcare workers airlifted for EVD treatment to Europe or the United States also received CP and survived, they also received other experimental therapies, combined with optimal supportive treatment, that are not practical in West Africa.

Second, proving the safety and efficacy of CP will be difficult in the absence of randomized clinical trials, and for the moment only nonrandomized trials to evaluate CP transfusions are planned. CWB transfusions are currently not being considered because of the additional risk for laboratory personnel when performing blood compatibility testing [6].

Three CP trials are pending. Clinical Research Management recently started a CP trial funded by a grant from the Bill and Melinda Gates Foundation in Monrovia, Liberia, at the ELWA-2 hospital [7]. A second trial will take place at the Donka Ebola center in Conakry, Guinea, led by the Antwerp Institute of Tropical Medicine in cooperation with Médecins Sans Frontières, is being funded by the European Union, the Wellcome Trust, and the Flemish government [8]. And Sierra Leone Action, an organization comprising a team of Sierra Leonean physicians and other professionals, working with the Government of Sierra Leone, is also planning a trial of CP.

Given the current high case-fatality rate in most EVD treatment centers (ETCs), the organizers of these trials determined that a randomized trial comparing CP
transfusions with locally available supportive treatment was unacceptable [8]. However, nonrandomized trials have a substantial risk of not generating definitive data. Historical case fatality rates are irrelevant if current study patients receive better supportive care. And parameters that may differ between EVD treatment cohorts influence outcome; these include not only viral load, signs and symptoms, and age [9, 10], but also the health-seeking behavior of individuals and the ETC-specific referral practices.

EVD case-fatality rates in West Africa for patients receiving only supportive care vary from 36% to 74% [9–12]. Case-fatality rates in CP trials will be influenced not only by patient risk factors for death, but also by the level of supportive care that is provided, and these factors vary over time and by center. Therefore, it is advisable that the 3 CP trial sites collaborate to allow meta-analysis of the data. Indeed, this will help to evaluate not only the safety and efficacy of CP, but also to identify the patients most likely to benefit from the treatment, the frequency and volumes of CP infusions required, and, potentially, the criteria for determining ideal donors.

Random assignment to either a new treatment regimen, such as CP transfusions, plus existing supportive care or to an optimal-supportive-care control arm would be an acceptable trial design. However, given the large and fluctuating number of patients, the weak local medical infrastructure, the difficult working conditions, the lack of skilled healthcare workers and their high turnover, it is challenging to provide consistent optimal supportive care in the affected countries. Nevertheless, US investigators are planning a randomized trial aimed at comparing different antiviral regimens plus supportive care with a supportive care arm only [8, 13].

Third, in their calculation, Gutfraind and Meyers use hospitalization rates of 10% and 30%. The actual current hospitalization rate may be higher. Indeed, on 12 January 2015, for every confirmed and probable EVD case, there were 3.1 available beds in Guinea, 6.4 beds in Sierra Leone, and 13.9 beds in Liberia [14]. However, although capacity may be sufficient at a national level, some areas with relatively high incidence rates remain remote from an ETC, which impedes early and consistent hospitalization.

Fourth, predicting the evolution of the epidemic by mathematical models has been shown to be difficult because of the strong influence of unpredictable human behavior and response of communities [15]. Most models, including the CDC model, have overestimated the number of cases [16].

Fifth, Gutfraind and Meyers state that CWB donations are expected to remain in short supply until very late in the epidemic. We are not convinced that lack of donors will be the main bottleneck. With an estimated number of Ebola virus–infected individuals of >21 000 in West Africa [14], on assumption of a case-fatality rate of 70%, there are at least 6000 EVD survivors. Taking into account that, currently, the severity of the EVD epidemic has lessened considerably in all 3 affected countries [14], we are cautiously optimistic that a sufficient number of blood donors will be found despite ongoing stigmatization of EVD survivors and local misconceptions concerning blood transfusions [17]. Many ETCs try to remain in contact with EVD survivors and involve them in patient care activities, active contact tracing, or community mobilization activities [16]. Associations of EVD survivors are being established and could play a major role in motivating their members to donate plasma. It is important to support these associations and to follow-up survivors because they may develop late-onset complications and may need psychosocial support [18, 19]. A total of 843 healthcare workers are known to have developed EVD up to 11 January 2015, 500 (59%) of whom have died [7]. It is encouraging that several surviving healthcare workers have been willing to donate plasma to save the life of a colleague.

Sixth, once the safety and efficacy of CWB or CP transfusions has been established, the absence of adequate sustained supportive care nationwide would severely limit the overall reduction in fatalities. Providing adequate supportive care should include, at a minimum, adequate amounts of oral rehydration solution and intravenous fluids to replace massive fluid loss from diarrhea and vomiting; maintaining levels of electrolytes such as magnesium, calcium, and potassium, which requires diagnostic laboratory capacity for monitoring levels; and testing and/or empirical treatment for secondary infections from gut bacteria and malaria [20–22].

Seventh, programs should offer treatment to donors identified with a transfusion-transmissible infection, such as human immunodeficiency virus infection, hepatitis B, hepatitis C, and syphilis. Currently, in the affected countries, adequate treatment options for these infections may not be available.

Eighth, a large-scale implementation will require a considerable amount of financial and human resources. Given the very weak healthcare infrastructures, large-scale implementation of a relatively complicated and potentially risky procedure for the healthcare workers will simply not be feasible in the 3 affected countries without massive external support. And if such a program will have a limited effect on EVD incidence, as stated by Gutfraind and Meyers, and human and financial resources remain limited, choices about allocation to competing public health and therapeutic (eg, brincidofovir, favipiravir, ZMapp, and TKM-Ebola [Tekmira, Vancouver]) measures will be paramount [8, 23].

In conclusion, the current Ebola epidemic has rapidly and unpredictably evolved, and it continues to challenge our ability to respond adequately. The safety and efficacy of CWB and/or CP therapy must be evaluated. However, whether it is advisable on a large-scale remains to be determined.

Note

Potential conflict of interest. Both authors: No reported conflicts.
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References


