Ebola virus disease: clinical care and patient-centred research

It is often stated that there are no proven therapies for Ebola virus disease but that potential treatments, including blood products, immune therapies, and antiviral drugs, are being evaluated.[1] This view is inaccurate. Ebola virus disease is a febrile illness with severe gastrointestinal symptoms. Nausea, vomiting, and diarrhoea cause profound water and electrolyte depletion leading to circulatory collapse and death.[2–4] Raised blood concentrations of urea and creatinine, indicators of severe dehydration and impaired renal function, are strongly correlated with mortality.[2] Low serum concentrations of potassium, sodium, and calcium are common in affected patients.[2] Dehydration and electrolyte abnormalities are important causes of death for which there are proven treatments.

Administration of parenteral fluids is a proven treatment for dehydration that cannot be managed by oral replacement, and electrolyte supplementation is a proven treatment for low concentrations of potassium and sodium. Whereas many patients with Ebola virus disease receive oral rehydration and some electrolyte substitution, the use of intravenous fluids and electrolytes varies and it is likely that many patients die from deficiencies in fluid volume and electrolytes. Barriers to the more widespread use of parenteral fluids include time constraints on personnel, in particular shortages of nursing staff at night, and heat stress from wearing personal protective equipment in a hot climate.[4] Overcoming these barriers and implementing practical protocols for managing fluids and electrolytes have not been given sufficient priority. There are also proven therapies for pain, agitation, secondary bacterial infection, and malaria. We must avoid therapeutic nihilism in the context of Ebola virus disease.

On the basis of the available data on the clinical and biochemical course of patients with Ebola virus disease and the best evidence from critical care research, practical protocols for fluid and electrolyte management can and should be developed. WHO could use its convening powers to bring together relevant clinical experts to examine the data and write protocols. As shown in the accompanying film (video), there are several ways to achieve parenteral access for fluid and electrolyte administration. We are not advocating any particular approach, rather we summarise some of the options that might be used clinically or evaluated in trials.[5] Simple algorithms, based on clinical signs and symptoms, to stratify patients according to the level of dehydration would help to ensure that fluid administration is sufficient to replace deficits and ongoing losses. Gastrointestinal losses can be as much as 5–10 L per day.[6] A fluid and electrolyte protocol for the average adult with Ebola virus disease might include around 5 L of a balanced crystalloid solution with potassium supplementation to cover ongoing losses. Hyponatraemia, defined as a serum concentration of sodium below 135 mmol/L, is common in Ebola virus disease and can cause brain swelling with raised intracranial pressure.[2,7] Clinical manifestations include headache, confusion, somnolence, seizures, and coma. Hyponatraemia can be treated with sodium chloride injection.[7] Electrolyte substitution would ideally be guided by point-of-care biochemistry results but, in the absence of such information, should be based on results from case series and clinical judgment.

The widespread implementation of pragmatic protocols for the management of fluids and electrolytes might substantially reduce case

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fatality. However, there are important therapeutic uncertainties that need to be resolved. An iterative process of pragmatic clinical trials of alternative management protocols, with the aim of achieving the lowest possible case fatality rate whilst also ensuring the safety of health-care workers, is urgently needed. Although there has been debate about whether randomised controlled trials can and should be done in patients with Ebola virus disease, there should be no objection to their use to resolve therapeutic uncertainties about fluid and electrolyte management.[8] Pragmatic clinical trials in critically ill patients are routinely done in high-income, middle-income, and low-income settings and have led to major therapeutic advances. With a resolute focus on improving patient outcomes, patient involvement, and full transparency, there is no reason why trials should undermine trust in health-care workers or public authorities. On the contrary, patient-oriented research should deepen trust. Before assuming that west Africans will reject the benefits of high quality clinical research we should first seek their opinions.

The roles of blood products, immune therapies, and antiviral drugs are currently being evaluated, but there has been a neglect of other uncertainties outlined here that could have an immediate impact on the care of patients with Ebola virus disease. Indeed, the potential for benefit from antiviral drugs is likely to be limited without better critical care, given that usually patients have been infected for about 2 weeks before they present to hospital and that the average time from hospital admission to death is only about 4 days.[2] We need better information on the volume and type of fluid needed to prevent shock, multiorgan failure, and death. Although gastrointestinal losses vary, standardised protocols have a role. Patients with septic shock in high-income settings would commonly receive about 4 L of crystalloid over 8 h.[9] Fluid requirements in patients with Ebola virus disease could be higher than this due to gastrointestinal losses. Pragmatic trials of the effects of higher versus lower parenteral fluid volumes on case fatality rate would resolve this uncertainty.[10] The choice of crystalloid solution is also uncertain and can affect acid-base status and electrolyte concentrations. The role and extent of electrolyte supplementation must also be examined.

A stronger policy focus on providing effective care for patients with Ebola virus disease is not only a humanitarian imperative, but could also help to bring the epidemic under control. Patients cared for in Ebola treatment centres are less likely to infect other people than those cared for in the community. However, Ebola treatment centres must be more than a setting for quarantine.[2,8] Patients will be reluctant to attend treatment centres unless the care they receive from them is superior to the care provided by family members. Treatment centres must be a setting where the best information is applied in the interest of improving patient outcomes, and where valid information is generated in the interests of future patients.

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