Evaluating the impact of intravenous fluid resuscitation on survival for the management of patients with Ebola Virus Disease

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In their manuscript, AR Aluisio and colleagues retrospectively evaluate the relationship between intravenous fluid (IVF) administration and survival amongst 424 patients with Ebola Virus Disease (EVD) admitted to Ebola Treatment Units (ETUs) run by the relief agency, International Medical Corps, in Liberia and Sierra Leone during the 2013-2016 EVD outbreak in West Africa (1). With access to an invaluably sizeable database of clinical information collected on EVD patients, the authors make a commendable attempt to provide meaningful input into a critical, but yet unanswered, question about the importance and extent of IVF resuscitation as a component of optimized supportive care for EVD patients managed in endemic resource-constrained settings. Although a stark difference in case fatality ratio (CFR) during the 2013-16 EVD outbreak existed between patients who were treated in West Africa compared to those treated in high-income countries (40% vs 18.5%) (2), it remains unclear to what extent supportive care alone contributed to this difference in CFR and, if it did, which components of supportive care contributed most to this improved survival.

Indeed, prospective clinical trials from sub-Saharan Africa that have evaluated aspects of supportive care, such as IVF resuscitation, in other conditions involving severe infections have yielded results showing excess mortality in intervention arms, running counter to prevailing international guidance (3,4). These unexpected results have pushed clinicians and investigators from high-income countries to question the quality of the evidence on which their guidelines are based and have highlighted the importance of generating data from clinical trials that are contextually relevant to the populations where the intervention might eventually be introduced.

In order to qualitatively evaluate the association between administration of IVF and 28-day survival, Aluisio and colleagues' primary analyses incorporated propensity score matching and marginal structural proportional hazard modeling (MSPHM). Specifically, propensity scores were derived for each patient from a model incorporating potential confounders and covariates deemed to be clinically relevant from previous studies. Patients were then matched by their propensity scores based on whether or not they received IVF in the first 24 hours or first 48 hours. In the MSPHM, inverse probability weighting was used to handle covariates that varied throughout the course of a patient's hospitalization as potential confounders in a proportional hazards model. The authors concluded from both analyses that no difference existed in 28-day survival when comparing patients who did and did not receive IVF. Notably, in a *post hoc* sub-group analysis using MSPHM which categorized patients by IVF volume administered [<20 ml/kg/d vs ≥ 20 ml/kg/d], patients in the low fluid volume stratum had a greater 28-day survival (35% vs 7.6%).

Though the authors conclude that these results "provide the highest quality evidence to date that IVF, by itself, does not improve survival in patients with EVD…", limitations of this retrospective analysis of observational data (categorized as low quality using the widely-accepted GRADE criteria) preclude the study from identifying any causal relationship between fluid administration and survival, given difficulties in controlling for unknown factors.

Nonetheless, this study highlights important questions which strengthen the justification for more robust future studies to evaluate unanswered questions about IVF resuscitation and other supportive care components in the management of EVD. Such questions include:

1) *What volume cut-off is most clinically meaningful when evaluating the efficacy of IVF administration for survival of EVD patients?* In this study, the mean daily volume administered to patients receiving IVF was 658 ml/day, a volume that is likely insufficient for replacing daily

insensible volume losses from diaphoresis in a febrile EVD patient. As a consequence, comparing outcomes in this study of patients receiving IVF to patients receiving no IVF might not represent a sufficient enough volume difference to be clinically meaningful and might explain why no difference in primary outcome was observed in these analyses.

2) *What physiologic resuscitation targets should be used when administering IVF?* Bedside evaluation of physiologic targets can be useful in guiding the clinical management of EVD patients. Although mean arterial pressure is difficult to measure in an ETU because of logistical challenges, measurement of systolic blood pressure (by palpating for return of radial pulse after decompressing an inflated sphygmomanometer cuff) and heart rate can be performed to help assess the extent to which a patient is in hypovolemic or septic shock. In addition, a recent randomized clinical trial (RCT) evaluating efficacy of two IVF resuscitation strategies (capillary refill testing-guided vs lactate-guided) in adult patients with sepsis demonstrated a trend towards improved 28-day survival among patients whose IVF resuscitation was guided by capillary refill testing [HR 0.75 (95% CI, 0.55-1.02), p=0.06] (5). Such pragmatic solutions for bedside monitoring of EVD patients warrant further evaluation.
3) *Is it appropriate to extrapolate data from IVF management trials of sepsis to guide management of EVD?* Both clinical trials of IVF resuscitation in African pediatric and adult patients with sepsis excluded patients with gastroenteritis (3,4). Yet, while EVD can result in sepsis-like physiology, clinical observations from the West Africa outbreak suggested that the clinical presentation of EVD was likened more to a severe viral gastroenteritis with profound dehydration instead of septic shock. Accordingly, it may not be appropriate to apply the findings suggesting harmful effects of IVF resuscitation from these sepsis trials to guide the clinical management of EVD patients.

These queries regarding IVF management contribute to a broader set of questions about supportive care for EVD patients. We do not know, for example, whether to give antibiotics routinely to cover for gut translocation of Gram negative bacteria, how this approach may contribute to local antimicrobial resistance, or how antibiotic-related diarrhea or colitis may worsen fluid balance losses. We also neither know whether to give mass drug administration for malaria, the frequency of symptomatic coinfection, or whether any anti-malarial agent may have an anti-EVD therapeutic effect (as suggested through another observational study (6)), nor do we know which are the best agents for control of emesis, diarrhea, pain, or distress. For example, it is unclear whether anti-diarrheal agents will be beneficial in preventing electrolyte loss and renal dysfunction, or whether they promote paralytic ileus.

Given these unknowns, the authors of this retrospective evaluation of the association between IVF administration and 28-day mortality in EVD patients should be applauded. The challenges limiting such retrospective analyses, including working with historic databases; employing sophisticated statistical methods to account for changes in presentation, treatment protocol, and familiarity with disease management over time; and controlling for unknown factors, highlight the need for prospective trials which include arms that evaluate parameters of standard care. At the least, clinical intervention data can be collected in such a manner as to make future analyses easier to address these vital questions. Despite efforts currently underway to evaluate, through a RCT, the efficacy of novel therapeutics on survival during the ongoing EVD outbreak in Democratic Republic of Congo (7), a definitive answer to the question regarding the potential impact of IVF on survival of EVD patients may as yet go unanswered. With an evolution in clinical care during this outbreak (8), however, optimism should persist for deriving

meaningful data on the impact of IVF and optimized supportive care on survival through this ongoing RCT.

Both authors have no potential conflicts of interest to disclose.

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