ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Understanding Bleeding in Ebola Virus Disease

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H&O Could you please give a brief description of Ebola?

AM Ebola viruses are found in Africa and can cause severe disease in humans. Outbreaks of this virus typically are rare and self-limiting, and can be controlled easily with appropriate infection-control measures. In contrast, the current ongoing outbreak in West Africa has proven to be very difficult to control. There have been more than 15,000 cases so far in this outbreak.

The Ebola viruses are thought to be maintained in fruit bats. Humans get infected through either direct contact with bats, or contact with nonhuman primates that became infected via contact with the bats. Once a human is infected, the disease passes person to person through direct contact with infected bodily fluids.

H&O What are the signs and symptoms of Ebola virus disease?

AM Unfortunately, they are nonspecific: fever; malaise; myalgia; gastrointestinal symptoms such as nausea, vomiting, and diarrhea; and headache. Of course, these overlap with a number of far more common diagnoses found in Africa, such as malaria and typhoid fever. Some other signs and symptoms that have been reported include hiccups, abdominal pain, sore throat, and an erythematous maculopapular rash that is more likely to be apparent in lighter-skinned individuals. There also seems to be an increase in gastrointestinal manifestations with the current outbreak compared with previous ones.

H&O How common is bleeding in patients with Ebola?

AM Ebola virus disease used to be referred to as Ebola hemorrhagic fever, but this was a misnomer because bleeding has never been a universal feature of the illness. In the first descriptions of Ebola in 1976 in the Democratic Republic of the Congo and Sudan—which was published in the *Bulletin of the World Health Organization* in 1978—up to 75% of patients had hemorrhagic manifestations. Since then, hemorrhagic manifestations have been reported less often. In the 1995 outbreak of Ebola virus (EBOV; species: *Zaire ebolavirus*) in Kikwit, Democratic Republic of Congo (previously known as Zaire), which was reported on by Bwaka and colleagues in the *Journal of Infectious Diseases*, 41% of the patients had hemorrhagic manifestations. In the 2001 outbreak of Sudan virus (SUDV; species: *Sudan ebolavirus*) in Uganda, which was discussed in *Tropical Medicine and International Health* in 2002, 30% of the patients had hemorrhagic manifestations. A total of 46.5% of people affected by Bundibugyo virus (BDBV; species: *Bundibugyo ebolavirus*) in Uganda in 2007 had hemorrhagic manifestations, as discussed in *Emerging Infectious Diseases* in 2010.

Some reports suggest that hemorrhagic manifestations appear to be even less common in the current outbreak, which is caused by EBOV. Schieffelin and colleagues, who reported on the outbreak in Sierra Leone in the *New England Journal of Medicine* in 2014, noted that bleeding occurred in just 1 of 87 Ebola patients. This is a striking finding, and quite in contrast to the one by Bah

and colleagues in 2014 that looked at the outbreak in 37 patients with laboratory-confirmed disease in Guinea. In this group, 51% of the patients experienced hemorrhage.

H&O How do bleeding and hemorrhage manifest in patients with Ebola virus disease?

AM Most of the clinical manifestations that have been described are consistent with platelet dysfunction. Oozing from the venipuncture site, conjunctival bleeding, petechiae, and bleeding into the gastrointestinal tract all have been reported, and sometimes epistaxis or gingival bleeding.

H&O What is the underlying cause of this bleeding?

AM The bottom line is that we do not really know. One theory has been that the cause is disseminated intravascular coagulopathy (DIC), which may be the case in very ill patients who are in the terminal phase of their disease process. Unfortunately, we are not able to establish whether DIC is a common cause because we need clinical measurements of fibrinogen, prothrombin time, fibrin split products (usually measured as D-dimer levels), and platelets in order to make the diagnosis. These measurements are not routinely taken in rural Africa, which is where most of these outbreaks have occurred. There is a published report by Richards and colleagues of a patient who met the criteria for DIC; this is a patient who was cared for in a tertiary care center in South Africa.

Several case reports have demonstrated that platelets are low in patients who have Ebola virus disease, but prothrombin time, fibrinogen, and fibrin split product measurements are not routinely performed. I think that we are going to learn a lot more about the disease from the patients who have been repatriated for treatment to either the United States or Europe, where we can take the measurements required to determine whether the DIC criteria have been met.

We recently performed a study using blood samples from the Gulu outbreak in Uganda in 2000 and 2001, which was caused by SUDV. (This study was published in the *Journal of Infectious Diseases* in 2014.) We did not see any association between D-dimer levels or fibrinogen level and bleeding, which was quite striking.

These data suggest that DIC probably is not the real etiology of the bleeding in Ebola virus disease. We have some other theories as to the cause, but at this point we cannot say conclusively what causes these patients to bleed.

H&O If the bleeding is caused by DIC, how does this affect treatment?

AM There are guidelines from the British Committee for Standards in Haematology for the management of DIC in intensive care settings using fresh frozen plasma, platelet transfusions, and cryoprecipitate, but unfortunately we do not have proof of the efficacy of these treatments from rigorously controlled studies. We also have no evidence that treating coagulopathy increases survival; data from nonhuman primates shows that the use of activated protein C or the recombinant nematode anticoagulant protein c2 produce only minimal improvement in survival. I think the bottom line is that we might make bleeding worse by giving an unproven therapy, especially if we do not know the true cause of the bleeding. We need to understand the cause before we can talk about interventions.

H&O What laboratory tests are in use in Western countries that might predict the onset of bleeding complications?

AM This is a tricky undertaking because most of the tests to predict the cause of bleeding in the modern critical care setting are not done preemptively, but rather after bleeding has occurred. In the case of Ebola virus disease, the testing is done retrospectively rather than in real time. In these retrospective studies, we often do not know the timing of the bleeding manifestation, only whether a patient had bleeding. So I think that at this point, there is no laboratory test that can predict whether patients are going to develop bleeding with the possible exception of platelet count, which is not being done in the field.

H&O Is bloody diarrhea in Ebola caused by dysentery or by hemorrhage?

AM That is an interesting question, and one that we cannot answer right now. Based on the data from Sierra Leone, Guinea, 2 US patients, and 1 German patient—all published in the *New England Journal of Medicine* in 2014—the diarrhea that has been reported in the current outbreak tends to be profuse, watery, and nonbloody. In the cases in which bloody diarrhea has been reported (only in the study from Guinea), it is not clear if this is an inflammatory process with mucosal breakdown and direct oozing into the gastrointestinal tract, or frank hemorrhage. Learning the answer to this question would require additional studies that are not routinely available in the care of patients with Ebola virus disease.

H&O Is bleeding associated with a worse prognosis?

AM This question has been addressed in 3 studies, and the answer is no. In our study of the Sudan virus that was published in the *Journal of Infectious Diseases* in 2014, there was no statistically significant association between bleeding

and outcome. There also was no association between fatal outcome and hemorrhage in the studies of the 1995 Kikwit Ebola virus and the 2007 Bundibugyo virus.

H&O What is the purported mechanism by which blood transfusion from Ebola survivors might aid patients?

AM There is one study that was done in association with the Kikwit outbreak (published by Mupapa and coinvestigators in the *Journal of Infectious Diseases* in 1999) in which convalescent whole blood was saved from several survivors and administered to 8 patients. The assumption was that the antibodies produced by these surviving patients would protect the acutely infected patients. There are 2 problems with this study: the numbers were small and there was no control group. Furthermore, even though 7 of the 8 patients survived, all 7 of these patients received their convalescent plasma transfusion during the second week of their illness. If you look at the survival statistics from this outbreak, there is a dramatic increase in the chance of survival as a patient goes into the second week of illness.

The 1 person in the study who died received the convalescent whole blood on day 4. A statistical analysis of these results that was published in the *Journal of Infectious Diseases* by Sadek and colleagues in 1999 strengthened the case that this therapy probably had nothing to do with the survival of these patients.

There are nonhuman primate studies that have come out in the last couple of years, including one by Dye and colleagues in 2012 and another by Qiu and associates in 2014, showing antibodies being efficacious in preventing the disease both before and after exposure. So I think that antibodies may have a role, but whether convalescent plasma is going to reduce fatalities in humans has not been established at this point.

Suggested Readings

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