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Ebola virus disease: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine

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ABSTRACT

Ebola virus is a filovirus that can cause fatal hemorrhagic fever (HF) and five distinct species exist that vary in terms of geographical distribution and virulence. Once the more virulent forms enter the human population, transmission occurs primarily through direct contact with infected body fluids and may result in significant outbreaks. The devastating has been the recent West African outbreak.

Clinically, signs and symptoms are similar to those of the other VHFs [4]. The incubation period is 2–21 days, followed by fever, headache, myalgia, diarrhoea, vomiting and dehydration; thereafter, there may be recovery or deterioration with collapse, neurological manifestations and bleeding, that can lead to a fatal outcome.

Elevated hepatic transaminases is common and severe hepatitis is more common in fatal cases and frequently there is associated fluid depletion. Real time reverse transcription-PCR (RT-PCR) techniques on blood specimens are the gold standard for diagnosis [6].

Management is discussed and is essentially supportive with strict attention to infection control and prevention. None of the pharmacological interventions have shown conclusive benefit and future management of epidemics should centre around prevention and containment, specifically isolation, hygiene, and vaccination.

Contents

1. Introduction

Ebola virus disease (EVD) and Marburg Virus Disease are categorised as filoviruses and can cause fatal hemorrhagic fever (HF) [1]. Five distinct species have been ascribed to the Ebolavirus genus, namely Zaire,

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Sudan, Taï Forest, Reston and Bundibudyo Ebola viruses [2]. These viruses vary enormously in terms of geographical distribution and in their virulence in humans, with Ebola Zaire one of the most lethal infections known to mankind. The recent West African outbreak was caused by a Zaire Ebola virus very similar to those that have caused previous outbreaks in the Democratic Republic of the Congo and Gabon [3].

The natural ecology of Ebola viruses remains largely obscure. Evidence hints that a specific arboreal species of bat may be the reservoir for the Zaire species [4], but the specific mechanism of transfer from bat to human or bat to other forest-dwelling animals is not known. However, various human outbreaks have been traced to contact with "bushmeat", including the slaughtering of chimpanzees and bats [5].

Once the virus enters the human population, transmission is primarily through direct contact with infected body fluids such as blood, faeces and vomitus. Owing to this mode of transmission, the virus has a propensity to spread in the hospital setting and between close contacts. The possibility of a viral HF should always be considered as delay in diagnosis increases the potential for mortality and transmission [6].

More than 20 outbreaks of EVD have been reported since 1976 [7]. Before 2014, these occurred in isolated settings with the largest involving 425 laboratory-confirmed cases reported from Gulu, Uganda, in 2000 and 2001 [8]. By April 13, 2016 however, after the World Health Organization (WHO) had declared the West African epidemic to be over, the disease had accounted for a total of 28,652 cases with 11,325 deaths. During this period >800 healthcare workers (HCW) inclusive of nurses and nurse aides (accounting for >50% of infections), doctors and medical students (12%), laboratory workers and trade and ancillary workers (janitors, maintenance staff, etc.) (7% each), contracted this disease with nearly 500 losing their lives [9]. Importantly although the majority of infections were confined to West Africa, EBV had been transmitted to 7 countries including Nigeria, Senegal, the USA, the United Kingdom, Italy and Spain [10]. On the 13 May 2017 another outbreak with 3 deaths was reported in a remote area of the Democratic Republic of Congo emphasising the an ongoing risk of future epidemics and potential for international spread [11].

As such, it is wise always to maintain a high index of suspicion, especially for patients presenting with a compatible clinical syndrome and who have histories that indicate a risk of having contracted an HF-causing virus such as travel to endemic regions or contact with animals, raw bushmeat or sick patients.

2. Clinical features

Clinically the signs and symptoms of EVD are not dissimilar to those of the other VHFs [12]. Following an incubation period of 2–21 days (mean 4–9 days), three phases occur; initially fever, headache, and myalgia, followed by diarrhoea, vomiting and dehydration; thereafter, in the second week, there may be recovery or deterioration with collapse, neurological manifestations and bleeding that can lead to a fatal outcome. The differential diagnosis of VHF is broad and may include many treatable infectious diseases, most notably malaria, bacteraemia (including meningococcemia), African tick bite fever, and even non-infectious conditions such as haematological malignancies, liver failure and heatstroke. In a report subsequent to the epidemic describing the clinical features in patients admitted to one hospital in Sierra Leone, the presenting features were compared with other infections presenting to the same hospital. No clinical feature was diagnostic, the odds ratio (OR) for the disease being EBV was calculated as follows; fever [OR: 1.2 (0.8–1.8)], vomiting [OR: 1.6 (1.1–2.1)], diarrhoea [OR: 1.5 (1.1–2.0)], intense fatigue [OR: 1.7 (1.2–2.4)], anorexia [1.1 (0.8–1.5)], abdominal pain [OR: 0.9 (0.6–1.2)], muscle pain [0.8 (0.6–1.1)], and joint pain [OR: 0.6 (0.4–0.9)] [13]. The bottom line is that diagnosis cannot be made by clinical features alone and prompt laboratory diagnosis is critical.

3. Laboratory diagnosis

Rapid diagnosis facilitates management and triage of suspected cases, the optimisation of infection prevention and control (IPC) and allocation of clinical resources, assists with surveillance and contact tracing and also determines when the patient can be discharged into the community [14].

The laboratory features are not diagnostic, however can narrow the differential and give an indication of prognosis. In a recent study [15] documenting the laboratory features of the disease abnormal liver function was common, with 70% of patients having elevated alanine transaminase (ALT) or aspartate transaminase (AST) >five times the upper limit of normal (ULN) [15]. Severe hepatitis (AST >15 times ULN) was more common in fatal cases (93% vs 44%) as was a higher mean haemoglobin concentration, haematocrit, and median platelet count, possibly indicating fluid depletion. Thrombocytopenia was more common in non-fatal cases with values of 146×10^9/L versus 197×10^9/L. Similarly, low median white cell count, lymphocyte count and granulocyte count predicted survival, with granulocytosis and lymphocytosis more common in fatal cases. Overall the strongest risk factors for mortality were RIFLE-3 acute kidney injury, severely raised AST, high haematocrit, low Ebola virus Real time reverse transcription-PCR (RT-PCR) cycle threshold, hyperkalaemia, C-reactive protein >100 mg/dL, and granulocytosis [15].

RT-PCR techniques on blood specimens have become the standard for diagnosis and RT-PCR performed on oral fluid is the standard for post-mortem testing [16,17].

Novel tests have reached the field, and these include automated nucleic acid amplification (NAATs) and rapid antigen detection tests. WHO guidance documents state that nucleic acid amplification tests are preferred when feasible and that rapid antigen detection tests should serve as "presumptive" or "screening" tests in remote settings without access to immediate molecular testing or to assist in triaging high-risk patients when caseloads are high [14,18,19].

4. Management

The sophistication with which these patients are treated will depend on the environment and on the facilities available [20]. One patient in 1996 was treated in an ICU in South Africa and in the recent epidemic 27 patients were managed in nine countries outside of West Africa, with a survival of 81.5%. The accounts of these patients have shown that intensive care management in a modern ICU is feasible [21,22].

Given the extremely high mortality rates and the highly infectious nature of VHFs, (infectious doses are as low as one viral particle for some), the haemorrhagic fever (HF)-causing viruses have to be handled and stored in the highest biosafety- and security-level laboratory conditions, and patient management must adhere to stringent isolation and barrier nursing protocols.

During an epidemic or even between epidemics a case definition must be established. This heightens awareness and increases potential for early recognition [23]. Thereafter consideration must be given as to the design of the ICU to ensure that the possibility of infection is reduced. This has been well described previously [22,24]. Essentially, a large area with isolation rooms, a large antechamber for donning and doffing of protective clothing, and an observation area should be available. Dedicated diagnostic apparatus including X-ray, ultrasound and point-of-care laboratory equipment, infusion pumps, ventilators, and dialysis machines should be accessible within the area. Waste, including soiled linen (we use condemned linen which is incinerated post use) must be disposed of appropriately.

All Staff involved in the care of patients should be adequately trained and educated with well-defined roles. Multidisciplinary teams are necessary which include non-clinical staff such as administration, laboratory staff, cleaners, morticians and security [25].

The appropriate use of adequate personal protective equipment (PPE) is critical in all instances. There is some controversy regarding the use of surgical masks or N95 respirators. Whereas the principal mode of transmission is through direct contact with blood and body fluids, or contaminated medical instruments (including needlestick injuries) several animal studies have shown transmission without direct contact and numerous health workers using PPE in the current epidemic have contracted Ebola despite no direct contact [26,27]. This, coupled with the fact that aerosolization is frequent during disinfection procedures and if patients have vomiting and/or diarrhoea, it is recommended that respirators, impermeable one-piece suits and visors should be used at all times during patient contact and that healthcare workers be observed by infection control staff to reduce transmission that could occur from contact of the virus with the face or neck, most frequently during removal of PPE or on inadvertently touching the face. The CDC has issued detailed guidelines regarding personal protection [28].

With regard to management, no clear guidelines for Ebola exist and as such general principles applicable to any patient with severe sepsis are considered to be relevant. If in a high-resource intensive care unit (ICU) where isolation units and appropriate IPC equipment are available, patients should be managed supportively in a fashion similar to any other critically ill septic patient [22,29]. Of course this should be the situation in all units however many areas of the world are critically under-resourced and appropriate IPC facilities are just not available. Actual management would involve standard monitoring procedures and where hemodynamically unstable, fluid status, stroke volume, cardiac index and calculated systemic vascular resistance would be helpful. Where such facilities are not available fluid resuscitation should be the bare minimum requirement. This is however the first step in supportive care in all environments and can be successfully achieved even in poorly resourced settings with minimal risk to staff. Peripheral intravenous (IV) access with large bore catheters is suitable if hemodynamically stable. Central venous catheters may make venous access easier and should be utilised when more invasive hemodynamic monitoring or vasoactive drugs are required. Fluid replacement should be guided by losses, by clinical parameters such as urine output, blood pressure, the straight leg raising test, the presence or absence of edema, and by more invasive parameters such as the urea, lactate and stroke volume variation. Crystalloid is adequate initially, the composition of which should be dictated by the electrolyte status. On admission, multiple boluses of 250mls or more may be required, guided by the parameters above. Caution should however be employed that the patient does not become fluid overloaded, and if peripheral or pulmonary edema ensues in the presence of hypotension, an inotrope/pressor may be required as determined by more invasive monitoring.

Blood and blood products should be administered as with any other patient that is haemorrhaging or has potential to haemorrhage. A target haemoglobin of >7 g/dL is recommended however if blood losses are expected to be large and ongoing a higher target such as 9/dL may be used [30]. Platelets should be administered if the platelet count is $<20 \times 10^9$/L. If bleeding actively or a surgical procedure is planned, administer platelets if $<50 \times 10^9$/L; similarly if bleeding and the INR is >2, fresh frozen plasma or prothrombin complex concentrate should be administered. If the fibrinogen level is low and significant haemorrhage is occurring despite having corrected the INR and administered platelets, cryoprecipitate should be transfused.

Airway management may be required for airway protection as for example in the setting of a decreased level of consciousness or massive upper GI bleeding. Pulmonary involvement by Ebola is not a common feature but secondary causes of respiratory failure may include shock, fatigue, metabolic acidosis, secondary bacterial infection, and iatrogenic complications such as transfusion-associated lung injury.

Renal failure is common in severe cases, and dialysis should be considered if indicated; the mode of dialysis should be individualised based on the patient's status. The use of continuous renal replacement therapy offers the advantage of minimising the need for additional staff to enter the patient's room if this therapy is routinely managed by the critical care nurses. The US CDC has developed a document on recommendations for safely performing acute haemodialysis in patients with Ebola virus disease [31]. Liver dysfunction progressing to liver failure is a major consideration in severe EVD however therapy should be supportive only.

The use of extracorporeal membrane oxygenation (ECMO) for cardiorespiratory failure has not been reported in severe EVD, and is not currently recommended.

Routine strategies for avoiding nosocomial infections should be instituted, along with stress ulcer prophylaxis for mechanically ventilated patients and prophylaxis for deep vein thrombosis should be considered, particularly intermittent pneumatic compression devices where platelets are low.

Secondary bacterial infection is always possible and use of biomarkers such as procalcitonin may be helpful to determine when to initiate antibiotics. The benefit or otherwise of prophylactic antibiotics has not been investigated [22].

Nutritional support is important and should be parenteral where there is excessive vomiting or enteral access is not possible or intake inadequate.

Psychosocial support services for both the patient and their family, and for staff must be provided and all must be made aware of the potential for the virus to exist in secluded sites long after the patient has recovered [32].

5. Pharmacotherapy

Numerous candidate therapeutic agents have been utilised and these include; EVD—ZMapp (a cocktail of 3 human-mouse chimeric anti-EBOV monoclonal antibodies), GS-5734 (the prodrug of a nucleoside viral RNA polymerase inhibitor), brincidofovir (an oral nucleotide analog that has shown in vitro antiviral activity against DNA viruses) and recombinant interferon-B1a (rIFN-β1a) [33].

However none of these have not shown conclusive benefit. All of the patients treated outside of Africa during the major East African epidemic received experimental therapies. However most were not part of randomised controlled trials, many of the patients received multiple agents and the drugs were administered while the patients were receiving advanced supportive therapy. As such it is not certain that they made a difference to outcome [33].

6. Vaccines

Future management of EVD epidemics should centre around prevention and containment, specifically isolation, hygiene, and vaccination. The most advanced of the vaccine candidates is a recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of the Zaire ebolavirus rVSVΔG-EBOV-GP (rVSV) [34].

7. Conclusion

The recent large Ebola epidemic took the world by surprise. As it progressed countries around the globe prepared ports, healthcare systems and laboratories to detect and manage such cases. It is hoped that such preparations do not lapse and that this level of awareness is maintained, hopefully to reduce the potential for another epidemic whatever the cause may be.

Task force planning

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