Ebola Virus Infection: What Should Be Known?

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Abstract

Ebola virus infection is the present global consideration. This deadly virus can result in a deadly acute febrile hemorrhagic illness. The patient can have several clinical manifestations. As a new emerging infection, the knowledge on this infection is extremely limited. The interesting issues to be discussed include a) the atypical clinical presentation, b) new diagnostic tool, c) new treatment, and d) disease prevention. Those topics will be discussed in this special review.

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Introduction

In 2014, there is a big outbreak of a new emerging infection in Africa. This outbreak is believed to be one of the biggest clusters in medical history. The new emerging Ebola virus infection causes many thousand infected cases with high mortality.[1,2] Until present, (October 2014), the disease is still uncontrollable and the widespread of disease in Africa can be seen, and this can be the threat to the global public health due to possible worldwide pandemic.[3] Basically, the Ebola virus is a filovirus that can cause acute febrile illness.[4] Another important in the same group is Marburg virus.[4] The important clinical feature is the hemorrhagic complications that can lead to death. The recent report in early phase of outbreak in Africa shows that the new virus with genetic aberration is the cause of emerging infection.[2] As a new emerging infection, the knowledge on this infection is extremely limited. The interesting issues to be discussed include a) the atypical clinical presentation, b) new diagnostic tool, c) new treatment, and d) disease prevention. Those topics will be discussed in this special review.

Atypical Clinical Presentation of Ebola

Ebola virus infection is the present global consideration. This deadly virus can result in a deadly acute febrile hemorrhagic illness. The patient can have several clinical manifestations.[1] Generally, the patient presents with high fever and develop hemorrhagic complication. As a viral hemorrhagic fever, the blood abnormalities can be seen. The main finding is the decreased platelet. The mucocutaneous petichiae can be observed. However, there are also other important clinical presentations. Pathophysiologically, Ansai noted that "the virus appears to sequentially infect dendritic cells disabling the interferon then macrophages and finally endothelial cells that contribute to blood leakage.[5]" Apart from the blood system, there are also other organ involvements. The atypical infection can be seen and this is little mentioned.

These include cardiac, renal, lung, neurological, gastrointestinal, and hepatic manifestations. Focusing on the cardiac problem, several severe cases of Ebola infection have heart problem and heart failure as well as cardiac arrest is common in severe infection.[2] Nevertheless, the remained myth is on the pathogenesis of heart failure in Ebola infection. This might be due to the hemodynamic change due to severe hemorrhage or the direct viral involvement of the heart. There are some reports considering the effect of Ebola virus on heart. Ray *et al.* noted that Ebola virus glycoprotein could directly affect the primary human cardiac microvascular endothelial cells and this could further result in cardiac symptoms.[6] The cardiac damage is believed to be due

to the cytokine change.[7] Nevertheless, there is still no autopsy reports on the Ebola infected case with cardiac failure to clarify the exact pathology of heart. Nevertheless, Kortepeter *et al.* recently performed an animal model study and found that ventricular failure could be observed in the course of severe infection.[8] The cardiopathology in Ebola virus infection is an actual interesting topic for further study.

Focusing on the renal problem in Ebola virus infection, the renal problem can be seen in the infected case. However, it is still questionable that the renal problem is due to the direct viral invasion or hypovolemic change in acute hemorrhagic phase. Nevertheless, in animal model of Ebola infection, the renal involvement is the main problem in histopathology study.[9] The similar observation is on the lung complication. In animal model, the severe acute respiratory disease due to Ebola can be seen.[10] The confirmed lung involvement in histopathology in non-human primate is also reported.[11] However, the lung involvement is not mentioned for the human infected case. For the neurological problem, the neurological problem is not an important finding. The spinal and brain involvement has never been reported in the infected patients. But the brain involvement is not mentioned for the non-human primate infected case.[11] Of interest, Van der Waals studied the relationship between past infection and post-encephalitic epilepsy and reported for no inter-relationship.[12] Focusing on gastrointestinal and hepatic manifestation, Ansai noted that the virus involved liver and gastro-intestinal tract.[5] Diarrhea is an important finding in the present outbreak.[2] The hepatitis becomes another important clinical feature in infected cases.

Rollin *et al.* noted that "liver function tests showed higher levels of aspartate aminotransferase (AST) in blood samples from patients with fatal cases than in samples from patients with non-fatal cases.[13]" Finally, it should be noted that the most considerable atypical manifestation is the asymptomatic cases.[14,15] This can be seen and might be the silent carrier to transmit disease to the others.

New Diagnostic Tool for Ebola Infection

The diagnosis of Ebola virus infection is an actual challenge since the early detection means the success in disease management and control. Normally, the identification of Ebola virus required molecular diagnostic tools.[16,17] There are some reports on new molecular diagnostic tools, most are from China,[18-20] but there is still no new publication corresponding to the present outbreak. The rearrangement of the available diagnostic tool to correspond to the possible outbreak is needed.[21] The aim to educate the practitioner is required and the development of "point-of-care" system is promoted.[22]

Several problems are on the diagnosis of Ebola virus. First, to directly manipulate with the virus particle, the highest biosafety level is needed but it is not available in many countries, especially for those poor countries with the present outbreak. Specific protocol for management of safety is needed and any accidental exposure in the laboratory becomes the serious consideration.[23] Second, using molecular diagnostic tool requires cost and this can still be the problem for many poor underdeveloped countries. In addition, the standardization of the tool is needed. The problem of false diagnosis can be expected.[24] The quality control becomes the issue for further discussed.

New Treatment for Ebola Infection

Until present, the specific treatment for Ebola infection is not available. Routinely, supportive and symptomatic treatment can be used, similar to other viral hemorrhagic fever. Finding new effective antiviral drug is the hope.[16] There are many attempts to discover the new drug to combat Ebola virus infection. In the rush period, many international agencies launched many rapid new trials for the new drugs.[25] The good drug candidate is "cyanobacteriallectinscytovirin," which can bind to mannose-rich oligosaccharides on the envelope glycoprotein of the virus.[26] This biochemical is test *in vitro* and *in vivo* in animal model and a favorable outcome can be seen. Hence, cyanobacteriallectinscytovirin is a hope for development of new drug. In addition to finding new drug, the trial of available drug should also be mentioned. A recent report by Smither *et al.*, it was found that favipiravir was proved to be effective in animal model.[27] Some centers also proposed alternative method, additional to antiviral drug, to combat the virus. The good example is the use of antibody in serum from non-fatal infected cases for management of the others.[28] Qiu *et al.* recently proposed that "mAbs and Ad-vectored interferon (IFN)-α therapy rescue Ebola-infected non-human primates when administered after the detection of viremia and symptom.[29]" For the available antibody, the ZMapp should be mentioned.[30-32] Qiu *et al.* showed that ZMapp was effective in infected non-human primates.[32] Another interesting alternative is the use of melatonin. Tan *et al.* firstly mentioned for the use of the new alternative.[33] This is not the method that acts directly towards virus but towards the hemorrhagic pathogenesis.[33]

The possibility of using melatonin as the new therapeutic alternative choice for Ebola is interesting. And as described in the principle described by Tan *et al.*,[33] it seems possible. But it is clearly no doubt that the

alteration of cytokine process might be useful for control of disease. However, there is still no evidence of successful use in Ebola and other hemorrhagic fever. Also, another important concern is the modification of cytokine process takes time and this might not effectively correspond to the abrupt serious pathology in Ebola infection.

Disease Prevention for Ebola Infection

For prevention for Ebola infection, it is very difficult due to high contagiousness. The hope is development of new vaccine. Similar to new drug finding, there are many attempts to develop new vaccine at present.[34] The rapid development of the vaccine can be useful; however, it is a presently widely discussed ethical issue[35]. Kanapathipillai *et al.* noted that there were two interesting vaccine candidates, "cAd3-EBOV (cAd3), from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and rVSVΔG-EBOV-GP (rVSV), from NewLink Genetics and the Public Health Agency of Canada" that can be the hope for prevention and management of Ebola virus infection.[36]

Conclusion

As a new emerging disease, 2014 African Ebola virus outbreak is a global concern. For general practitioner, several issues in clinical medicine on this infection needs closely follow.

References

1. Ansari AA. Clinical features and pathobiology of Ebolavirus infection. J Autoimmun 2014.
2. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, *et al*. Emergence of Zaire Ebola virus disease in Guinea. N Engl J Med 2014;371:1418-25.
3. Osterholm MT, Moore KA, Gostin LO. Public health in the age of Ebola in west Africa. JAMA Intern Med 2014.
4. Takada A. Filoviruses. Uirusu 2012;62:197-208.
5. Ansari AA. Clinical features and pathobiology of Ebolavirus infection. J Autoimmun 2014.
6. Ray RB, Basu A, Steele R, Beyene A, McHowat J, Meyer K, *et al*. Ebola virus glycoprotein-mediated anoikis of primary human cardiac microvascular endothelial cells. Virology 2004;321:181-8.
7. Bowick GC, McAuley AJ. Meta-analysis of high-throughput datasets reveals cellular responses following hemorrhagic fever virus infection. Viruses 2011;3:613-9.
8. Kortepeter MG, Lawler JV, Honko A, Bray M, Johnson JC, Purcell BK, *et al*. Real-time monitoring of cardiovascular function in rhesus macaques infected with Zaire ebolavirus. J Infect Dis 2011;204 Suppl 3:S1000-10.
9. Baskerville A, Fisher-Hoch SP, Neild GH, Dowsett AB. Ultrastructural pathology of experimental Ebola haemorrhagic fever virus infection. J Pathol 1985;147:199-209.
10. Nfon CK, Leung A, Smith G, Embury-Hyatt C, Kobinger G, Weingartl HM. Immunopathogenesis of severe acute respiratory disease in Zaire ebolavirus-infected pigs. PLoS One 2013;8:e61904.
11. Larsen T, Stevens EL, Davis KJ, Geisbert JB, Daddario-DiCaprio KM, Jahrling PB, *et al*. Pathologic findings associated with delayed death in nonhuman primates experimentally infected with Zaire Ebola virus. J Infect Dis 2007;196:S323-8.
12. Van der Waals FW, Pomeroy KL, Goudsmit J, Asher DM, Gajdusek DC. Hemorrhagic fever virus infections in an isolated rainforest area of central Liberia. Limitations of the indirect immunofluorescence slide test for antibody screening in Africa. Trop Geogr Med 1986;38:209-14.
13. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-Dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. J Infect Dis 2007;196:S364-71.
14. Leroy EM, Baize S, Debre P, Lansoud-Soukate J, Mavoungou E. Early immune responses accompanying human asymptomatic Ebola infections. Clin Exp Immunol 2001;124:453-60.
15. Leroy EM, Baize S, Volchkov VE, Fisher-Hoch SP, Georges-Courbot MC, Lansoud-Soukate J, *et al*. Human asymptomatic Ebola infection and strong inflammatory response. Lancet 2000;355:2210-5.
16. Wiwanitkit V. New emerging West Africa Ebola 2014: The present global threaten. Asian Pac J Trop Biomed 2014;4:S539-40.
17. Kelly JD. Make diagnostic centres a priority for Ebola crisis. Nature 2014;513:145.
18. Liu Y, Shi ZX, Ma YK, Wang HT, Wang ZY, Shao DH, *et al*. Development of SYBR Green I real-time RT-PCR for the detection of Ebola virus. Bing Du Xue Bao 2012;28:567-71.
19. Yang Y, Bai L, Hu KX, Yang ZH, Hu JP, Wang J. Multiplex real-time PCR method for rapid detection of Marburg virus and Ebola virus. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2012;26:313-5.
20. Huang Y, Wei H, Wang Y, Shi Z, Raoul H, Yuan Z. Rapid detection of filoviruses by real-time TaqMan polymerase chain reaction assays. Virol Sin 2012;27:273-7.
21. Hill CE, Burd EM, Kraft CS, Ryan EL, Duncan A, Winkler AM, *et al*. Laboratory test support for Ebola patients within a high-containment facility. Lab Med 2014;45:e109-11.
22. Mandl KD. Ebola in the United States: EHRs as a public health tool at the point of care. JAMA 2014.
23. Günther S, Feldmann H, Geisbert TW, Hensley LE, Rollin PE, Nichol ST, *et al*. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. J Infect Dis 2011;204 Suppl 3:S785-90.
24. Vladyko AS, Zaïtseva VN, Trofimov NM, Shkolina TV, Scheslenok EP, BoshchenkoIu A, *et al.* False-positive reactions in laboratory diagnosis of Lassa, Marburg, and Ebola viral hemorrhagic fevers and AIDS. Vopr Virusol 1997;42:66-70.
25. McCarthy M. FDA allows second experimental drug to be tested in Ebola patients. BMJ 2014;349:g5103.
26. Garrison AR, Giomarelli BG, Lear-Rooney CM, Saucedo CJ, Yellayi S, Krumpe LR, *et al*. The cyanobacterial lectin scytovirin displays potent *in vitro* and *in vivo* activity against Zaire Ebola virus. Antiviral Res 2014;112C:1-7.
27. Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral Res 2014;104:153-5.

28. Goodman JL. Studying "secret serums" — toward safe, effective Ebola treatments. N Engl J Med 2014;371:1086-9.

29. Qiu X, Wong G, Fernando L, Audet J, Bello A, Strong J, *et al*. mAbs and Ad-vectored IFN-α therapy rescue Ebola-infected nonhuman primates when administered after the detection of viremia and symptoms. Sci Transl Med 2013;5:207ra143.

30. McCarthy M. US signs contract with ZMapp maker to accelerate development of the Ebola drug. BMJ 2014;349:g5488.

31. Zhang Y, Li D, Jin X, Huang Z. Fighting Ebola with ZMapp: Spotlight on plant-made antibody. Sci China Life Sci 2014;57:987-8.

32. Qiu X, Wong G, Audet J, Bello A, Fernando L, Alimonti JB, *et al*. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 2014;514:47-53.

33. Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: Potential use of melatonin as a treatment. J Pineal Res 2014;57:381-4.

34. Hantel A, Olopade CO. Drug and vaccine access in the ebola epidemic: Advising caution in compassionate use. Ann Intern Med 2014.

35. Cohen J, Kupferschmidt K. Infectious diseases. ebola vaccine trials raise ethical issues. Science 2014;346:289-90.

36. Kanapathipillai R, Restrepo AM, Fast P, Wood D, Dye C, Kieny MP, *et al*. Ebola vaccine — an urgent international priority. N Engl J Med 2014.