Intensive Care Med (2014) 40:1738–1741
DOI 10.1007/s00134-014-3473-7

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Does this patient have Ebola virus disease?

Received: 25 August 2014
Accepted: 26 August 2014
Published online: 3 September 2014

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Introduction

Ebola virus is one of the most virulent human pathogens. Since 1976, Ebola virus disease (EVD) has caused more than 20 outbreaks in Africa, with case fatality rates of 30–90 % in the absence of any approved treatment or vaccination [1]. It is transmitted by direct contact through broken skin or mucous membranes with blood, urine, saliva, faeces, vomit, and other body fluids of symptomatic infected patients or convalescent persons, or through contaminated needle sticks [1, 2]. The current outbreak in West Africa probably began in December 2013 in Guinea [3], and is causing unprecedented concerns for the following reasons: (1) it is due to a strain with 97 % homology with *Zaire ebolavirus*, the most virulent species, with prior fatality rates as high as 90 %; (2) as of August 22, 2014, four countries have been involved, with 2,615 suspected cases, 1,528 laboratory-confirmed cases, and 1,427 related deaths, which is already many more than the largest epidemic reported to date (425 cases in Uganda, 2000–2001), and the situation is unlikely to be resolved soon [4, 5]; (3) the 2014 West Africa outbreak affects rural as well as urban areas, and recently reached the most populous African country (Nigeria); and (4) experienced governmental and non-governmental organizations, including Médecins Sans Frontières, have been active on the field since March 2014 [3], but have failed to control the epidemic.

Many factors contributed to this failure, including population poverty and authorities' distrust, disease denial in the context of strong religious beliefs, porous borders, weaknesses in public health systems, and inadequate salaries and lack of adequate protection for health care workers. On August 8, 2014, 9 months after the first documented cases, the World Health Organization (WHO) declared this outbreak a public health emergency of international concern and has called for a strong and coordinated international response, stating that "all nations should be prepared to detect, investigate, and manage Ebola cases" [6].

Ebola virus disease outside Africa

The risk that this outbreak will establish a foothold in high-income countries outside Africa is very low, as human-to-human transmission of EVD does not occur

when adequate infection control procedures are implemented. However, patients with EVD acquired in West Africa have already been transferred to America and Europe, and this is likely to become more common as the disease spreads. Hence, physicians working in emergency departments or intensive care units (ICU) outside Africa must be able to identify patients with possible EVD, and manage them appropriately, with two main objectives: (1) to prevent any human-to-human transmission of Ebola virus in contacts, including health care workers, relatives, and other patients; and (2) to ensure all EVD suspected patients receive appropriate care, whether or not affected. We aimed to describe epidemiological, clinical, and biological clues that may be used to classify patients with suspected EVD.

Epidemiological clues

As of August 2014, EVD has been essentially transmitted in three countries during the current outbreak: Guinea, Liberia, and Sierra Leone (Fig. 1). A fourth country, Nigeria, was more recently added to the list of countries where transmission of Ebola virus occurs, which indicates that spread may occur in countries not bordering the original epidemic area. For case definition, the Centers for Disease Control and Prevention (CDC) consider that residence in, or travel to, an area where EVD transmission is active is a risk factor for EVD (http://www.cdc.gov/vhf/ebola/hcp/case-definition.html). Although this makes sense for operational reasons, two issues deserve consideration. Firstly, outbreaks are dynamic processes, and this is particularly true for this EVD epidemic. Hence, we have no guarantee that countries bordering areas of active transmission (e.g., Mali, Ivory Coast), or even more remote African countries, will remain EVD-free. This remark is not an invitation to prematurely increase the list of countries to be considered at risk for EVD exposure, but a word of caution to governments and clinicians; in the context of the current outbreak, a patient returning from countries neighbouring those mentioned above and presenting with fever, a severe illness, haemorrhagic symptoms, and no alternative diagnosis should raise attention. Secondly, in subjects coming back from one of the four EVD countries, the level of exposure may differ from almost zero (e.g. airlines staff or passengers in transit who spent a few hours in a local airport), to very high (e.g. health care staff working in an Ebola treatment unit).

The second epidemiological clue is the incubation time or window period, conservatively defined as 3–21 days. These limits allow the ruling out of EVD in any patient with fever onset later than 21 days after returning from an endemic area. More reliable data, obtained in settings where a single well-defined exposure had occurred, indicated a range of 3–13 days for the incubation period (mean, 6–8 days). However, the mean incubation period may vary according to the inoculum and the route of infection, averaging 9.5 days for contact exposures and 6.3 days after injection during the 1976 *Zaire ebolavirus* outbreak [7, 8].

Clinical findings suggestive of Ebola virus disease

High-grade fever is a necessary criteria for EVD in most case definitions. Indeed, in all published series, fever was present in >97 % of cases [1, 2, 9–19], and a literature review found that 791 of 796 cases of EVD presented with a body temperature ≥101 °F (38.3 °C) [9]. Typically, fever is of abrupt onset, associated with flu-like symptoms (chills, malaise, arthromyalgias), and soon followed by digestive manifestations [1, 2]. In the current West Africa outbreak, severe diarrhea and vomiting have been invariably observed during the early disease course [3]. Subsequent signs and symptoms are variable, mostly respiratory (chest pain, shortness of breath, cough), cutaneous (in 25–50 % of cases, a mostly non-itchy, diffuse maculopapular rash with secondary desquamation occurs), and neurological (confusion). Brain involvement translates into a significant occupational risk for health care workers, as patients may become aggressive. Haemorrhagic manifestations, once considered the hallmark of EVD, arise during the peak of the illness in 50–70 % of patients, and may vary from petechiae to multiple foci of mucosal haemorrhage, up to uncontrolled bleeding after injections or vessel punctures. In fatal cases, death usually occurs between day 6 and day 16, due to a combination of hypovolaemic and septic shock, massive bleeding (typically gastro-intestinal), and multiorgan failure.

Laboratory abnormalities

Due to limited access to laboratory tests in involved countries, and the risk associated with improper handling of blood samples, less is known on laboratory features of EVD [1, 13]. Most patients show early moderate leukopenia, with deep lymphopenia attributed to massive apoptosis. Later, neutrophilia and/or atypical lymphocytes appear. Other common findings include moderate thrombocytopenia (50,000–100,000 cells per μL), highly raised liver enzymes (especially aspartate aminotransferase), hyperproteinemia (possibly related to capillary leak), and prolongation of

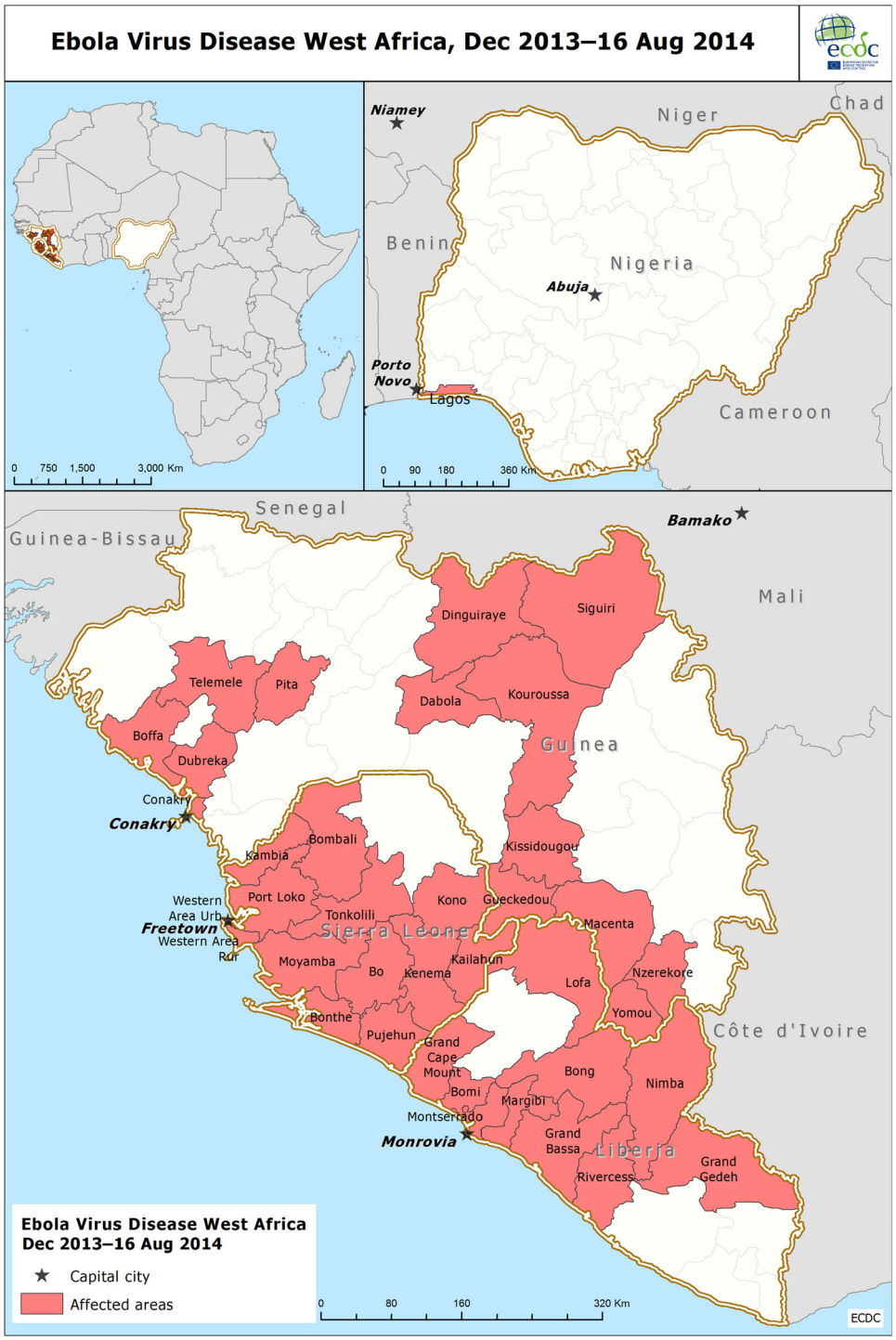

Fig. 1 Distribution of EVD cases (confirmed, probable, and suspected) by district in the affected countries from December 2013 to 16 August 2014. Source: European Centres for Disease Control and Prevention, adapted from National Reports and WHO (http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?List=8db7286c-fe2d-476c-9133-18ff4cb1b568&ID=1047)

prothrombin and thromboplastin times, often in the context of disseminated intravascular coagulation. No specific abnormalities have been reported at later stages, when multiorgan failure ensues.

Differential diagnosis

The definite EVD diagnosis hinges on detection of viral antigen by enzyme-linked immunosorbent assay or viral

RNA by polymerase chain reaction. IgM and IgG antibodies may become positive later in the course of illness. Alternative diagnoses must be carefully considered and ruled out, especially when early treatment may favourably impact prognosis (e.g. malaria, any bacterial severe sepsis or septic shock, enteric fever, leptospirosis, rickettsiosis, African trypanosomiasis). This is one of the main challenges in the management of suspected EVD, as the recommended infection control measures for collecting and handling biological specimens may delay necessary laboratory testing (e.g. traditional chemistry, haematology, blood cultures, malaria tests, serology), and jeopardise patient care, if not promptly performed. Likewise, basic imaging studies (ultrasound, chest X-ray) should not be deferred, provided adequate protection is used, so that the necessary process to rule out EVD in suspected cases will not translate into a loss of opportunity for those with alternative diagnosis. Of note, common detergents and hypochlorite are effective in neutralising the Ebola virus.

Conclusions

The 2014 EVD outbreak in West Africa is a public health emergency of international concern [6]. Given the extent of this outbreak, and the flow of transcontinental exchanges, every physician active in emergency departments or ICU worlwide may turn out to be involved in the care of patients suspected of EVD. Take-home messages from this paper, as of August 2014, are (1) suspect EVD in any patient who presents with fever within 3 weeks after a stay in Guinea, Sierra Leone, Liberia, or Nigeria; and (2), while implementing infection control procedures to prevent any secondary cases (in case EVD is confirmed), ensure that all plausible differential diagnoses are appropriately considered and managed.

Conflicts of interest The authors declare that they have no conflict of interest.

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