Abstract: Ebola virus disease is caused by a highly contagious and pathogenic threadlike RNA virus of the Filoviridae family. The index human case is usually a zoonosis that launches human-to-human transmission interface with varying levels of sustainability of the epidemic depending on the level of public health preparedness of the affected country and the Ebola virus strain. The disease affects all age groups in the population. Clinical diagnosis is challenging in index cases especially in the early stages of the disease when the presenting features are usually nonspecific and only similar to a flu-like illness. However, in the agonal stages, hemorrhage frequently occurs in a high proportion of cases. The diagnostic gold standard is by detecting the antigen using reverse transcription-polymerase chain reaction. Mortality rates in the past 28 outbreaks since 1976 have ranged from 30% to 100% in different settings among adults, but lower mortality rates have been documented in children. This review aims to describe Ebola virus infection, clinical presentation, diagnosis and outcomes in children.

Key Words: Ebola virus disease, children, epidemic, West Africa

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The ongoing Ebola virus disease (EVD) in West Africa is the worst in the 5-decade history of the disease in Africa and marks the climax following a recent increase in the frequency of outbreaks in the continent.

There are few data on EVD in children. However, it has been observed to be sparing of children, a fact that may suggest that in children, there is disease variation in epidemiology, clinical features and outcomes.

Trends based on the CDC data (Fig. 1) indicate that the epidemic curves (epi curves) in all 3 most affected West African countries indicate that the epidemic has undergone two stages. First, the phase represented by the period March to June 2014 where the affected population has been continuously exposed to EVD with a gradual rise in the number of cases. Second, the exponential phase represented by the period June to November 2014 indicative of massive infections without matching impact from epidemic prevention and control activities. The epidemic has not reached the plateau phase yet. On the other hand, there are 2 separate patterns in the current trends (Fig. 1). The pattern in Liberia and Sierra Leone is similar suggesting common source of infection. The pattern in these 2 countries, however, differs from that in Guinea where the infection rate seems less rapid but with higher mortality rates. This may suggest differences in EVD species virulence in 3 West African Countries. This interpretation, however, needs to be cautiously made especially because there are no data to suggest that other factors including population level immunity and the country’s public health level of preparedness for epidemic response were controlled for.

Virology, Transmission and Pathophysiology

EVD is caused by a lipid-enveloped RNA virus of the Filoviridae family, whose genome is capable of encrypting 7 proteins. Structurally, it is a threadlike, occasionally branched virus with a diameter and length of 80 nm and 14,000 nm respectively (Fig. 2). Of the 5 Ebola species known to date, 4 of them including Sudan Ebola virus, Zaire Ebola virus, Bundibugyo Ebola virus and Tai Forest Ebola virus are the known causes of epidemics in humans. Conversely, Reston Ebola virus, the fifth species was first isolated in pigs in Philippines in 1989, but has since not been documented to cause clinical disease in humans.

Recent understanding has abridged debate on the exact natural habitat of Ebola virus. Increasing evidence suggests that the virus naturally lives in small animals, especially bats. It is therefore plausible that there are large numbers of bats in Ebola epidemic dawns. Once in humans, the virus is extremely contagious, especially in the acute phase when the viral load is very high. Transmission follows direct contact with infected blood, secretions, organs, contaminated sharps and/or semen. Clinical disease manifests within 2–21 days, with a majority of cases showing clinical disease within 1 week following infectious contact. The EVD disease characteristics including, but not limited to the variable incubation period with disease manifestations occurring as early as 2 days or as late as 21 days after contact, high virulence, contagiousness and ability to live for several hours in blood at room temperature. In addition, the rapid disease progression with multigang involvement results in high-case fatality rates. This background together with longer transmission periods lasting up to 42 days after clinical recovery of survivors makes it difficult to control Ebola outbreaks in the community. The epidemic outbreak in any one setting is considered resolved after 2 completed cycles of incubation period without a new case from the time of the last clinically recovered patient or death from EVD.

The factors for viral virulence are not fully understood but have partly been attributed to the viral surface glycoprotein, which is favorably adapted to binding with high affinity for receptors in the cell membrane and subsequent efficient effusion mechanism into the cells. The situation is compounded by the lack of safe and effective treatment, therapeutic vaccine or preventive vaccine.

Epidemiology

Ebola epidemic first broke out in 1976 from both Sudan and Zaire (present day Democratic Republic of Congo),7 though the Filoviruses were first discovered in 1969. Initially, the virus was thought to be native to East Africa.7 Recently outbreaks have shown epicenters outside this region and may be attributed to the migratory effect of the bats.4 The distributions of the outbreaks seem to follow a pattern yet to be described specifically. Other than the fact that the bats potentially migrate in epidemic epicenters; there are frequent epidemic outbreaks in countries undergoing civil strife or emerging from conflict states in East and Western Africa. These are also countries with poor socioeconomic status, suggesting ill-prepared public health responses to the epidemics. Internationally, however, travelling including.
The mode of spread to Europe and the USA. The risk to EVD in children is attributed to contact with their sick parent(s), caretakers and relatives. Spread through breast-feeding has also been described. Peacock et al reported pediatric EVD data from various recent outbreaks. These data suggest that the proportion of children infected has varied in different settings and over time. For instance, the proportions of children involved was 27/315 (9%) in the Zaire EVD in 1995, 90/218 (41%) in Gulu, Uganda (Sudan EVD) in 2000–2001 and 147/823 (18%) in the current outbreak in the 4 most affected West African countries as of August 2014. In addition, data from Gulu in Uganda particularly indicated that female children had a higher risk of developing EVD compared with their male counterparts. The authors thought this was because of the fact that female children in African settings often take on household chores and patient care roles, though this trend has not been reported elsewhere in affected African countries. Despite these risks, the reported case rates in children are lower compared with adults. The reasons for this observation remain debatable. Lower susceptibility to disease in children is a possibility, however, in Gulu, Uganda it was observed that children were in isolation rooms and in contact with their EVD-infected parents. Conversely, pediatric EVD’s sparing nature is attributed to low-risk exposures. This is consistent with another observation in Gulu, Uganda where some parents were known to have prevented risk of exposure by isolating uninfected children from sick siblings or family members. Dowell, therefore, proposes that the high case rates of EVD in adults is because of lack of immunity to the disease, high exposure to infectious sources and increased likelihood to manifest severe disease.

CLINICAL FEATURES OF EBOLA IN CHILDREN

EVD has nonspecific symptoms. In children, the symptoms for common conditions overlap with those of EVD and this causes a dilemma even in areas of established EVD outbreak. There is a similarity between the adult and pediatric EVD clinical symptoms. This finding should be interpreted carefully, especially because there is not adequate prospective data on childhood EVD. None-theless, a typical clinical case of pediatric EVD is a child aged less than 12 years of age but often younger than 5 years, who at the time of clinical assessment presents with a 2- to 21-day history of contact with a case or victim of EVD and clinically may have symptoms including fever, weakness, loss of appetite, profuse diarrhea, vomiting and bleeding. Additional clinical features may be found in older children who may complain of headache, backache, chest pain, abdominal pains and/or sore throat.

These clinical features are not specific for Ebola, and if children have to be diagnosed accurately highly specific criteria are needed. Based on the available data, only 2 criteria would be clinically useful diagnostic benchmarks. First, the epidemiological criterion
valuable for assessment of risk is the history of contact with patient or victim of EVD. All children with Ebola reverse transcription-polymerase chain reaction confirmed cases had history of contact. 2,3 Second, 100% of confirmed cases had fever, with temperature of greater than 38°C. 2,3 The rest of the clinical features reported in confirmed childhood Ebola cases including hemorrhage occurs in varying proportions and may be reflective of disease complications or progression, thus useful for description of the clinical spectrum and surveillance, but not for primary clinical diagnosis.

DIAGNOSIS

Clinical definitions categorizing children at risk as suspected, probable or contacts cases have been suggested. 2 These definitions lack the needed descriptive specificity especially to be clinically useful in full scale and widespread epidemic. Even in the early stages of the epidemic, the relevance of these definitions may be limited to assessing the extent of potential spread of the epidemic but not the likelihood of developing the disease, planning therapeutic benefit or predicting prognosis. Furthermore, because of the short incubation period and highly aggressive nature of the disease, there are neither well-defined limits nor clear relation of these classifications to the prodromal stages of the illness. Finally, these definitions do not provide for the stages of disease progression partly because of the belligerent nature of the disease. Even then, these categories do not apply to other exposures recently known to result in infections, for instance, health workers in full protective gear. 11

The gold standard of laboratory diagnosis is based on detection of the reverse transcription-polymerase chain reaction Ebola antigen. 12 Other laboratory diagnostic criteria including, ELISA for IgM and IgG antibody against Ebola virus remains useful, cheap and quick laboratory methods of diagnosis and surveillance. 13

TREATMENT

There are no approved specific antiviral treatments for EVD. 14 The recent use of ZMapp for the treatment of EVD was based on a rare situation where the EVD outbreak in West Africa outweighed the available control measures. The WHO therefore allowed its use without human clinical trials and FDA approval. ZMapp, a drug made up of monoclonal antibodies, binds to the Ebola virus rendering it harmless. 15 The initial antibodies were extracted from mice but recent developments indicate that plant monoclonal antibody extracts may be cheaper and easier to extract in larger quantities. 7 The differences in the physiological and immunological responses in children with EVD 16 may suggest that children may respond to future trial medications differently and these must be considered in the design of treatment interventions in this age group. Other than trial drugs, supportive treatment including management of severe anemia, respiratory distress, correction of metabolic derangements, fluid replacement and nutritional support remain the mainstay of case management. 17

PREVENTION

The mainstay of prevention is avoidance of contact with patients or victims of EVD. A number of vaccines have been developed, but remain far from clinical use because most of them are in Phase I clinical trials. To date none of these are being tried in children; however, in adults, early data on safety and effectiveness of some of these vaccines in trial now are expected after mid-2015.

CONCLUSIONS

In children, despite similar risks, the case rates are lower than in adults. The risk is mainly through contacts and for the African female child, domestic chores including caring for the sick increases the possibility of contracting the disease than their male counterparts. The 2 most useful clinical diagnostic criteria are history of contact with patient or victim of EVD and subsequent evidence of fever 2-21 days after contact. Currently, there are no FDA-approved specific antiviral, therapeutic vaccines or preventive vaccines. A number of proposed trial antivirals and vaccines are available; however, their efficacy and safety have not been proven and may be a long way before these are achieved. Prevention and control are mainly by public health measures including avoidance of contact. Supportive treatment remains the mainstay of case management.

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