Submitted April 2015, accepted June 2015

REVIEW

Ebola virus disease: Basics the medical specialist should know

M.P. Grobusch[1]*, B.J. Visser[1], J. Boersma[1], M.A. Huson[1], S. Janssen[1], P. Greve[1], J.L. Browne[2], C. van der Ende-Bouwman[3], J. Van der Ende[3], N. Zwinkels[3], E. Huizenga[3], G.J. de Bree[1,4], C. Stijnis[1], M. van Vugt[1], A. Goorhuis[1]

[1]Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, [2]Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands, [3]Lion Heart Medical Center, Yele, Sierra Leone, [4]Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands

Correspondence

M.P. Grobusch – m.p.grobusch@amc.uva.nl

Keywords - **Ebola, Ebola virus disease, Ebola haemorrhagic fever, Ebolavirus, Sudan virus, Taï Forest virus, Ebola virus, Zaire Ebola virus, Bundibugyo virus, Reston virus, outbreak, epidemic, Liberia, Guinea, Sierra Leone, critical care**

Abstract

The largest outbreak of Ebola virus disease in history is currently ongoing in several West African countries. At the end of May 2015, a total of 27,181 cases with 11,162 deaths (average mortality rate of 41.0%) have been reported, almost exclusively from Guinea, Liberia and Sierra Leone, with a few cases recorded in neighbouring countries and, as a consequence of evacuating/repatriating selected individual healthcare workers, also overseas. This article summarises current insight into the epidemiology, pathogen biology, clinical features, prevention, and treatment measures. For the medical specialist being confronted with an Ebola suspect or a confirmed case, understanding of the routes of transmission and profound knowledge of infection prevention measures are vital. Whilst containment and avoidance of nosocomial spread are paramount, it has been clearly shown that even the most severely ill patients do have a fair chance of survival if they have access to good supportive, and where needed, intensive care. The current outbreak boosted progress in the development of specific therapeutics and vaccines; however, to date, none of those is readily at hand for routine use. Common basic intensive care treatment strategies of circulatory and vital organ function support with a focus on counterbalancing fluid and electrolyte loss and treating concomitant bacterial infections are essential for patient survival.

Epidemiology of Ebola virus disease in brief

The largest outbreak of Ebola virus disease in history is currently ongoing in several West African countries.[1] On 8 August 2014, the World Health Organization (WHO) declared the Ebola outbreak in West Africa a Public Health Emergency of International Concern,[2] emphasising the importance of continuous support and collaboration by the WHO and international partners to control the current outbreak. At the end of May 2015, a total of 27,181 cases with 11,162 deaths (mortality rate of 41.0%) had been reported, almost exclusively from Guinea, Liberia and Sierra Leone.[3] These absolute figures have to be treated with caution as in the beginning of an outbreak, as in this one, mortality rates can by far exceed 70-80%; there are missed cases and a high rate of loss to follow-up, whereas towards the end of an outbreak, recording and individual patient care improve on a scale that results in a significantly reduced overall mortality rate.

Following a significant decline of cases over the past couple of weeks, and whilst Liberia has been declared Ebola virus disease-free in the meantime, the overall decline stalled at the time of applying final edits to this manuscript. In mid-June 2015, transmission is ongoing at a comparably low level in Guinea and Sierra Leone, mainly around the respective capital cities, Conakry and Freetown, thus highlighting the tremendous challenges of reducing transmission to nil,[3] with the inability of being able to trace new infections back to contacts in all cases, or to link them to defined risks of exposure being a matter of concern. Although most diagnosed infections occur among monitored contacts of already infected patients, a significant number of infections are new, meaning that unmonitored transmission is still a problem that needs to be controlled. The case fatality rate remains high; however, as seen in other outbreaks, there is a decline in mortality now overall undercutting 50%, compared with well over 70% at the beginning of the outbreak. This may in part reflect the pathogen biology. There have been discussions

in the past that after the initial zoonotic transmission step, there seems to be a decline in virulence when the virus is passed from primarily infected humans to later generations in the infection chain. However, whilst this is not implausible, to the best of our knowledge there is to date no published evidence to support this notion. In fact, the increased survival is mostly owed to improved early case detection, the rapid increase in treatment facilities and consequently better availability, accessibility and higher quality of symptomatic treatment towards the end of this outbreak, as in previous outbreaks.

The scale of the current outbreak is unprecedented; past outbreaks were relatively small, occurred in remote tropical rain forest regions of Central Africa and were characteristically brought under control within weeks.[4] The disease was first described in Yambuku (in what used to be known as Zaire, now the Democratic Republic of Congo) in 1976 where the disease was spread nosocomially by close personal contact and by use of contaminated needles in hospitals.[5] The current outbreak started in December 2013, in the small village of Meliandou (in the southeast of Guinea), near the border of Liberia and Sierra Leone.[6] The disease had spread for several months before it was recognised as Ebola disease caused by the Zaire Ebola virus, the most virulent in the group of the five currently known distinct Ebola viruses. Local factors that contributed to the outbreak reaching epidemic proportions include local burial rituals (washing, touching and kissing the body of the deceased during ritual burials), lack of running water and hygiene, extreme poverty, and the rapid occurrence of the disease in densely populated regions. Important additional barriers resulted in failure of an early effective outbreak control, such as dysfunctional healthcare systems, scepticism regarding government officials and foreign helpers, as well as a delay in the national and international response. A number of Ebola cases were imported into Europe and the USA, resulting in secondary infections among healthcare professionals, which finally boosted international awareness and highlighted the necessity of implementing strict hygiene measures, including adequate use of personal protective equipment and training of personnel.[7]

Transmission and natural reservoir of Ebola virus

Four decades after the first recorded outbreak of Ebola virus disease, the exact mode of transmission and the natural reservoir of the virus are still debated. Higher mammals such as great apes also fall ill and succumb to Ebola virus disease. This indicated earlier that they are, like humans, classical end hosts rather than a primary reservoir species, with definite reservoir species not exhibiting disease symptoms by definition. Early attempts to identify the natural animal reservoir of Ebola have been challenged by Africa's vast biodiversity.[8] From the extensive list of possible definitive reservoir hosts, fruit bat species have now been identified as the most likely culprit.[9,10] Evidence exists for various modes of transmission, such as direct contact with infected animals, infection from person-to-person through contact with bodily fluids, transmission through contact with contaminated surfaces, and through iatrogenic transmission.[10] Aerogenic transmission is hotly debated; it has been demonstrated in animals and appears to be possible from man to man as well, yet remains unlikely even in high-risk situations such as accidents with handling of laboratory material.[11-13] On this basis, nosocomial human-to-human transmission following inhalation by an ill-protected caregiver using aerosols, e.g. during an intubation procedure complicated by coughing, appears to be theoretically well possible but has not been reported yet.

Pathogenesis of Ebola virus disease

Ebola enters the body through mucosal surfaces, skin breaches, and abrasions of the skin, by parenteral inoculation, and via vertical (mother-to-child) transmission. The first cell types to be infected are monocytes, macrophages, and dendritic cells. These cells transport the virus to the lymph nodes and spleen, from where the virus disseminates to other tissues.[10] The liver and adrenal glands are important targets, and infection of these organs is associated with several complications. Hepatocellular necrosis may result in decreased synthesis of coagulation factors, thereby contributing to haemorrhagic manifestations, while adrenocortical infection and necrosis may compromise blood pressure homeostasis, associated with the development of shock.[10] Although lymphocytes are not infected, Ebola virus can cause massive lymphocytic apoptosis, reflective of a direct virus effect on lymphocytes, which is associated with mortality.[14] The resulting lymphopenia may render patients with Ebola virus disease more vulnerable to secondary bacterial infections and sepsis. The coagulation system is triggered by increased expression of tissue factor on monocytes and macrophages, leading to coagulation abnormalities consistent with disseminated intravascular coagulation (DIC).[15] Recently, a new pathogenic mechanism was described, involving truncated surface glycoproteins, which are shed into the bloodstream of Ebola virus infected patients. These glycoproteins affect endothelial cell function and enhance vascular permeability, eventually resulting in haemorrhage.[14] In addition, these glycoproteins induce activation of uninfected dendritic cells and macrophages, which fuels secretion of pro- and anti-inflammatory cytokines, thereby contributing to an excessive and deregulated host response similar to sepsis.[16] Consequently, some experimental treatment approaches have capitalised on similarities between Ebola virus disease and bacterial sepsis, such as the successful post-exposure administration of recombinant human activated protein C in the macaque model.[17]

In order to evade the host immune response, Ebola virus employs several strategies.[18] First, by the expression of phosphatidylserine, a lipid exposed after apoptotic cell death,

Ebola virus apparently mimics an apoptotic body. Subsequently, it induces macropinocytotic uptake in an anti-inflammatory manner.[18] Second, viral proteins inhibit type I and II interferon signalling and block enhancement of antigen presentation to T cells.[18] Also, the generation of an effective neutralising antibody response is hampered by heavy glycosylation of the viral envelope, which limits access to critical epitopes required for efficient neutralisation. In addition, the shed glycoproteins act as an antibody decoy and present non-neutralising antibody epitopes to misdirect the humoral immune response.[19]

Clinical features of Ebola virus disease

The incubation period of Ebola virus disease is usually within a range of 2-21 days;[10,20,21] however, slightly longer incubation periods of up to 25 days appear possible.[22] Patients usually become symptomatic 6-12 days after exposure. Inoculum size and route of infection influence the duration of the incubation period. A rapidly growing number of publications have summed up large case series from all the countries that are hard-hit by the current outbreak.[1,21,23-25] Onset of symptoms such as fever, chills, malaise and myalgia is usually abrupt and the disease generally starts with a non-specific flu-like syndrome. However, it needs to be noted that fever was only recorded in 4581/5309 (86.3%) patients across all age groups in confirmed and probable cases from the ongoing outbreak in all three most-afflicted countries, highlighting that it cannot be taken for granted as lead symptom, and consistent with dramatic experience from members of this article's authors group (Huizenga and colleagues, unpublished).[26] Of note, within the first few days of illness, gastrointestinal symptoms often develop with nausea, vomiting and diarrhoea. Vomiting and diarrhoea may be severe and lead to significant fluid loss, electrolyte imbalance (e.g. hyponatraemia, hypokalaemia, hypomagnesaemia, and hypocalcaemia) not specific to Ebola virus disease, acid-base disturbances, and ultimately shock with multi-organ failure. The presence of massive diarrhoea and vomiting is associated with fatal outcome. High-volume watery (not bloody) diarrhoea is the most frequently and most consistently encountered symptom in this epidemic.

A diffuse, erythematous, non-pruritic, maculopapular rash may develop at day 5-7 after symptom onset, which is often difficult to recognise in dark-skinned patients. Also, conjunctivitis is a specific symptom at onset of disease. Patients may have a relative bradycardia, similar to typhoid fever. Coagulation abnormalities can lead to major bleeding or DIC, which can result in multi-organ failure. Multifocal hepatic necrosis can lead to liver failure. Despite its classification as haemorrhagic fever, major bleeding is not a common finding in Ebola virus disease. In the current outbreak, severe haemorrhagic events were seen in a minority of patients (<5%).[21,23] Bleeding complications most often occur in later stages of disease, commonly from the skin or mucosal surfaces, including conjunctival injection, epistaxis, or oozing from vena-puncture sites, which is reported frequently from terminally ill patients. Haemorrhagic events are associated with fatal outcome. Another symptom associated with fatal outcome is the presence of persistent hiccups, which is as yet unexplained.

Pregnant women are at higher risk of severe disease or death,[27,28] and have an increased risk of spontaneous abortion, stillbirth or antepartum or postpartum haemorrhage. Survival chances for the foetus appear to be extremely poor.[28] Systematic data on children have by-and-large been lacking so far. However, data from the large ongoing outbreak which are now emerging[26] suggest that absolute and per capita incidence amongst children is consistently lower than in adults and that mean incubation period, time from onset of symptoms to death and risk of death are higher in children under the age of five (comparable with individuals of high age who seem to have poorer odds of survival) than in older children and adults.[21] Of note, children younger than 16 were more likely to present with fever but less likely with abdominal, chest or joint and muscle pain, difficulty breathing or swallowing or hiccups than adults, which may in part be due to reporting errors.[21]

The increasing number of case reports from individuals with Ebola virus disease who were evacuated and admitted to specialised centres in the USA and Europe offer insight into the vast range of laboratory parameters assessed during intensive care treatment.[29-31] In summary, leukopenia (provided there is no complicating bacterial sepsis) and thrombocytopenia are common laboratory findings. Elevated liver enzymes may be a sign of multifocal hepatic necrosis. Elevated serum amylase levels have been reported as well. Coagulation abnormalities are frequently found, with prolonged bleeding times and elevated D-dimers.[32] Renal function is often normal at initial presentation, but after the initial week, urinary output may decrease as kidney function deteriorates due to a combination of dehydration and DIC in the renal vasculature. Accumulating data from larger outbreaks stimulated the search for biomarkers correlating with clinical outcome.[33]

Across outbreaks, reported fatality rates vary between 25% and 90%.[34] The clinical status of surviving patients often begins to improve during the second week after symptom onset. By contrast, among patients with a fatal outcome, complications frequently develop during the first week of illness, with death ensuing during the second week of illness. In summary, the main causes of death are cardiac arrhythmias, DIC and multi-organ failure, particularly renal and liver failure. An encephalopathic picture of possibly mixed pathogenesis may develop as a complication in severely ill patients.[29]

Convalescence may be protracted, and long-term sequelae such as myelitis, recurrent hepatitis and psychiatric problems have been described;[10] however, it is to be expected that reports from the outgoing outbreak will provide a significant increase in insight into long-term persistent health problems of Ebola virus

disease in survivors. For example, Varkey and colleagues[35] very recently reported on a severe acute unilateral panuveitis 14 weeks after onset of disease in a male physician who had been infected in Sierra Leone and airlifted for treatment to Atlanta, USA. Becoming unwell again following initial convalescence, viable Zaire Ebola virus was isolated nine weeks after viraemia clearance.

Differential diagnosis

As Ebola virus disease presents with unspecific signs and symptoms at disease onset, the differential diagnosis is broad and several other potentially fatal infectious diseases should be considered, based on the clinical presentation and epidemiological history of each individual. This list can hardly be entirely comprehensive as it encompasses basically all febrile 'tropical' conditions, at least in its initial stage. Because exposure most often occurs in West and Central Africa, particularly the following differential diagnoses should always be considered:

- Viral: influenza, mononucleosis, viral hepatitis, arboviral infections (Dengue, Chikungunya) and other haemorrhagic fevers (Marburg, Lassa, yellow fever);
- Parasitological: malaria, amoebiasis, African trypanosomiasis (where epidemiologically applicable);
- Bacterial: sepsis e.g. due to staphylococci, streptococci; meningococcal disease, typhoid fever, leptospirosis, rickettsioses.

As noted above, particularly malaria can occur concomitantly with Ebola virus disease as well as bacterial bloodstream infections, which may complicate the course of Ebola virus disease.[29]

Laboratory diagnosis

Handling of Ebola-suspected laboratory material requires the highest safety precautions, which should ideally be BSL4 laboratory facilities. The diagnosis of Ebola virus disease is confirmed by detection of viral antigens or RNA in bodily fluids. This can be done using immunoassays (ELISA) for IgM and IgG detection, or molecular tests (PCR).[10] The diagnostic gold standard and most commonly used test in the current epidemic is Real Time PCR detecting and quantitating viral RNA. Viral RNA can be reliably detected three days after onset of symptoms. A negative test >72 hours after symptom onset excludes Ebola virus as causative agent.[36]

According to the World Health Organization, individuals who no longer have signs and symptoms of Ebola virus disease can be discharged if they have two negative PCR tests on whole blood, separated by at least 48 hours.[37] After two consecutive negative PCR tests, the patient is no longer contagious with the exception of sweat, semen amniotic fluid, and breast milk.

Established therapy

Infection prevention, including wearing full personal protective equipment to avoid nosocomial transmission, must take precedence over invasive diagnostic and therapeutic procedures. To date, specific therapies are in early clinical testing phases, not routinely available, and empirical. In the absence of consensus guidelines on the treatment of patients with Ebola virus disease,[38] the mainstay of good clinical care for Ebola virus disease patients is rehydration and electrolyte deficiency correction, early treatment of potential secondary bacterial bloodstream infections, empiric malaria treatment, and in case of disease progression in settings which allow maximal care, vital organ function support (blood transfusion, mechanical ventilation, haemodialysis). It has been demonstrated that basic intensive care measures dramatically improved patient survival among the few patients who were repatriated and treated in highly specialised isolation units in Europe and the USA.[25,29,30]

Symptomatic management of nausea, vomiting and hyperpyrexia should be implemented following standard protocols. Enteral nutrition may be impossible in severely ill patients in whom paralytic ileus and severe hiccups may complicate the situation, thus requiring parenteral feeding.[29]

Early treatment with anti-emetic and anti-diarrhoeal agents and oral rehydration solution may improve outcomes.[23] Rehydration can be oral if there are no significant fluid losses and if the patient is able to drink; otherwise, intravenous fluid replacement is indicated. Intensive supportive treatment may in extreme situations require up to around 10 litres of fluids (e.g. 0.9% sodium chloride solution supplemented with potassium, or lactated Ringer's solution) and appropriate electrolyte rebalancing, administered intravenously through a central venous catheter per day if losses are massive, usually mainly through watery diarrhoea.[29] Lactic acidosis may require sodium bicarbonate replenishment.[29] Hypotension and tachycardia or bradycardia in patients with concomitant or ensuing bacterial sepsis may be refractory to treatment,[29] only to resolve gradually in the recovery period.

During recovery from encephalopathy, a delirious stage may ensue and require therapy.[29]

A range of adjuvant therapies has been put to clinical practice in individual cases, including steroids and medication interfering with the coagulation system or aiming at counterbalancing the vascular leak syndrome,[31] yet so far none have been validated in clinical trials, so experience remains by-and-large anecdotal.

Antimalarial therapy

As mentioned briefly above, the signs and symptoms of malaria and Ebola virus disease are both non-specific at least at onset, and may overlap considerably. Malaria and Ebola virus disease can also occur concomitantly, i.e. the establishment of the one diagnosis does not exclude the other. In the West African countries afflicted by the current Ebola outbreak, malaria is rife, and constitutes the most frequently established differential diagnosis, as recently demonstrated by a retrospective analysis of diagnoses in febrile patients from Sierra Leone, Liberia and Guinea, conducted by the GeoSentinel surveillance network.[39] When malaria cannot be excluded, e.g. on the grounds that

performing malaria diagnosis in a patient suspected of having Ebola virus disease is considered unsafe, empiric malaria treatment should be started with oral artemisinin combination therapy (ACT) or intravenous artesunate for severely ill patients.

Antimicrobial therapy

As discussed earlier, bacterial sepsis can be a complication[23,29] and thus antibiotic treatment should be administered to patients with clinical evidence of bacterial sepsis. In general, the antimicrobial treatment should provide adequate coverage for Gram-negative bacteria.[29] In patients with hospital-acquired pneumonia or central venous catheters that develop sepsis, Gram-positive therapy should be added.

Respiratory support

Shifts of intravascular fluids in Ebola patients can cause lung oedema leading to progressive respiratory failure. Intubation is probably the best mechanical ventilation option for Ebola patients who develop respiratory failure. Wearing full protective suits, this will not be an easy task. Validation of a correct tracheal intubation can also be difficult, since auscultation is impossible with peripheral 0_2 saturation and ventilation synchronic movements of the thorax being the only indirect signs.[31] Continuous measurements of end tidal $C0_2$ concentrations are therefore desirable. It should be mentioned that some types of mechanical ventilation support pose a risk of generating aerosols. Therefore, the use of non-invasive ventilation or high-flow 0_2 therapy is in general not recommended, assuming the potential risk for continuous aerosol production.

Figure 1. This impression from the field (Lion Heart Medical Center, Yele, Sierra Leone) highlights the level of personal protective gear applied in order to minimise risk of transmission.

Renal replacement therapy

Acute kidney injury has been observed in Ebola patients, and haemodialysis may be appropriate in patients who develop severe kidney injury in the setting of shock. A clinical practice guideline for successful renal replacement therapy has been proposed.[40] Continuous renal replacement therapy (CRRT) should be performed by experienced personnel only, and in the patient's isolation room. In short, CRRT is favoured over acute peritoneal dialysis. To extend filter life (and thus diminish the risk of potential operator exposures with filter exchanges) regional citrate anticoagulation is preferred in veno-venous haemodialysis. Following the Kidney Disease Improving Global Outcomes statements,[41] strive for the target CRRT dose to deliver a total effluent dose of 20-25 ml/kg per hour (unless higher dosing is needed for specific clinical problems such as acidaemia).[40] The Ebola virus should not be able to cross an intact dialyser membrane.[42] Dialysis effluent has a low infectious risk but should be considered contaminated because a small dialyser leak may go unnoticed. Due to the risk of DIC in Ebola patients, the subclavian site for catheter insertion should not be used because compression is difficult if bleeding occurs. The choice for the femoral vein or internal jugular depends on patient characteristics and the experience of the user. One study suggests the right internal jugular vein and the left internal jugular vein as back-up site and that femoral access sites should be avoided secondary to bleeding risks (retroperitoneal bleeding).[40] A retrospective study (no Ebola patients) suggested that for temporary dialysis catheters the femoral site (filter run-time 17.1 h) should be favoured in ICU patients. If an extended CRRT period is foreseen, an IJ line (filter run-time 25.2 h) should be considered.[43] Portable X-ray or ultrasound equipment may be required within the isolation room. During CRRT, it is to be ensured that patients receive appropriate nutrition support as recommended by clinical guidelines (total daily protein intake of approximately 2 g/kg per day).[44,45] More information on how to safely perform acute haemodialysis in Ebola patients is provided by the Centers for Disease Control and Prevention (CDC).[42]

Psychological aspects of care

Apart from the physical suffering, the impact of being faced with a diagnosis of Ebola virus disease is expected to be devastating. Being isolated and subjected to care in isolation by healthcare professionals in full personal protective equipment, and being separated from (potentially also infected) next of kin adds to the multiple challenges faced by suspect and confirmed patients alike. It should go without saying that all professional support should be offered to counterbalance these challenges as far as possible.

Specific therapy/adjuvant therapeutics under development

To date, there is no specific antiviral therapy for Ebola virus disease. However, the World Health Organization has compiled, and regularly updates, a list of potential therapies and their state of development on their website.[46,47] At the time of writing, therapeutic options currently undergoing clinical trials are convalescent blood and plasma and several drugs: favipiravir,

Table 1. New treatments for Ebola virus disease currently under investigation.

Treatment	Mechanism	Key notes	Clinical trial status
Convalescent whole blood	Transfusion of blood products of EVD survivors containing antibodies	Cost-effective, easily obtained Efficacy has not been proven Improvement of blood transfusion safety and services are being developed	Phase II/III underway
Convalescent plasma			Phase II/III underway
Favipiravir	Virus RNA polymerase inhibitor	Good results in mice and in vitro In phase III trials for other viruses	Phase II started December 2014 Preliminary data inconclusive, trial continues
ZMapp	Cocktail of three human-mouse chimeric monoclonal antibodies	Promising clinical effect in NHPs, initial low availability but with up-scaled production available	Phase II started early February 2015
TKM-100802	siRNA molecule	Promising clinical effect in NHPs, but adverse effects seen in earlier phase I clinical trial	Phase II started March 2015
BCX-4430	Nucleoside analogue	Effective in mouse studies	Phase I trial underway
AVI-7537	Phosphorodiamidate morpholino oligonucleotide	Very specific for this strain Limited doses	Phase I completed No further trials planned

ZMapp, TKM-100802 and BCX-4430. A clinical study is planned for interferons.[47] Several other drugs have been used compassionately in Ebola virus disease patients, but so far no studies are planned to further determine their possible use in Ebola virus disease therapy. Table 1 summarises current treatment studies. In the following, we provide a concise overview on the most relevant recent developments. For a broader view including very early developments, De Clercq recently conducted a very comprehensive review.[48]

Human convalescent blood

The use of human convalescent blood or derived products to treat Ebola virus disease was prioritised as a potential treatment by the WHO in September 2014.[49] The rationale behind this approach is that patients who survived Ebola virus disease developed a protective immune response against the virus, potentially via the generation of neutralising antibodies. If these antibodies are administered to patients by transfusion, they could aid patients in clearing the virus. An important prerequisite is that the safety of transfusions is guaranteed in order to prevent infection with blood-borne diseases, which is standard in Western countries but poses formidable challenges in endemic areas. The WHO mentions that national capacities for safety are being assessed and transfusion services will be strengthened.[47]

There is no strong evidence for the efficacy of convalescent blood therapy yet. Convalescent blood has been used in the past to treat various infectious diseases[50] and evidence that it may be effective in Ebola virus disease comes from animal studies and uncontrolled studies in humans, reviewed extensively by Chippaux and colleagues.[51] For endemic areas, it is important to assess the efficacy of plasma and serum transfusions: although various advanced products can be made from convalescent blood that may be more effective, the means to produce these advanced blood products may not be available in endemic areas.[52] There are currently phase II/III trials underway for convalescent whole blood in Sierra Leone and convalescent plasma in Guinea and Liberia.[47]

Favipiravir (T-05/Avigan)

Favipiravir inhibits virus RNA polymerase and has been shown to successfully treat Ebola virus disease in mice and suppress virus replication in vitro. Interferon-I receptor knockout mice were used as a model and were treated six days post-infection, leading to reduced symptoms and increased survival of mice.[53] Immunodeficient mice were able to survive virus exposure after being treated with favipiravir shortly after inoculation.[54] Favipiravir has reached phase III trials for influenza,[54] giving it a head start in future trials. In January 2015, trials were started in MSF (Médécins Sans Frontières) Ebola treatment centres in Guinea.[55] Preliminary data were inconclusive.[47] The study completion is expected for September 2015.

ZMapp

ZMapp is a cocktail of three chimeric mouse-human monoclonal antibodies produced in plants and has shown promising results in nonhuman primates. When administered within five days after exposure to the Ebola virus, six out of six nonhuman primates treated with ZMapp survived, even though some of these animals showed advanced disease symptoms.[56] Seen as a very promising candidate to end the Ebola epidemic since late 2014, its clinical evaluation was delayed by the rapid exhaustion of ZMapp supplies.[57] After scale-up of the production there is currently sufficient ZMapp available for clinical trials.[58] A phase I trial has recently been completed and a phase II trial to determine efficacy started in February 2015.[47]

TKM-100802 (TKM-Ebola) and TKM-Ebola-Guinea

TKM-100802 is a small interfering RNA (siRNA) molecule that prevents virus replication by impeding the viral RNA polymerase. A small study with nonhuman primates showed

that six macaques that were infected with Zaire Ebola virus and that were subsequently treated with up to seven TKM-100802 doses survived, whereas two control subjects and one subject with a shorter treatment regimen died [59]. The phase I trial finished in May 2014 for a single ascending dose, although for the multiple ascending dose the phase I trial was put on hold after registering cytokine elevations.[60] However, this complete hold was changed to a partial hold by the FDA, allowing compassionate use.[60] A variant of the drug, TKM-Ebola-Guinea, was developed to specifically target the virus responsible for the current outbreak and showed comparable efficacy results (unpublished data).[60] A phase II clinical trial (RAPIDE-TKM) apparently started in early March 2015.[61]

BCX-4430

BCX-4430 inhibits viral RNA polymerase through RNA-chain termination as a nucleoside analogue. Early studies show effective protection when administered within two hours post-infection in mice.[62] A phase I trial is currently underway and if the drug is found to be safe, an efficacy trial may follow.[47]

AVI-7537

AVI-7537 targets specific viral mRNA sequences and prevents their translation through an antisense phosphorodiamidate morpholino-oligonucleotide. It is highly specific for the Ebola virus strain of the current outbreak.[46] Rodent animal model studies showed 50-60% survival rates.[63] Although a phase I safety study was completed, there are no clinical trials planned at the moment.[46]

Vaccine development

The development of a disease-preventing vaccine is a major public health priority, and research efforts to move candidates from animal models to early clinical development stages have been scaled up massively during the current outbreak. However, to date there are no working (i.e. effective and safe) vaccines registered, and it remains to be seen whether this effort will be sustained during the upcoming post-outbreak phase and whether development of at least one of those candidates will be seen through. The most promising candidates are a chimpanzee adenovirus 3 (ChAd3-ZEBOV) vaccine, and a recombinant vesicular stomatitis virus (rVSV-ZEBOV) vaccine. Preliminary data of the phase I trial for the ChAd3-ZEBOV vaccine (NCT02240875) and of various phase I clinical trials of the rVSV-ZEBOV vaccine were recently published.[64-66] No safety concerns were identified and an immune response was seen, albeit lower than was observed in animal studies. In the PREVAIL trial (NCT02344407), both vaccines will be studied simultaneously in a combined phase II/III study of the two vaccines.[67]

Also under development and progressing rapidly towards clinical testing is a heterologous prime-boost vaccine which uses Ad26 (Adenovirus 26) EBOV (Ebola virus), and MVA (Modified smallpox vaccine virus) EBOV antigens consecutively. With the rapid progress made at the time of writing, a reliable up-to-date source on the newest developments is the WHO web page on vaccine development.[47]

Infection prevention

The care of Ebola virus disease suspect and confirmed patients – as of patients with other viral haemorrhagic fevers – offers formidable infection control challenges and requires major logistic, material and, consequently, financial efforts both inside and outside endemic areas. The primary goal must be to prevent secondary cases. Detailed guidelines and protocols, as recently reviewed by Missair and colleagues who assessed risks of exposure particularly in view of anaesthetic/intensive care,[68] have been developed, from a supranational down to an individual healthcare facility level to minimise nosocomial infection. By implementing an adequate surveillance system at the entrance plus implementing hospital hygiene protocols, security personnel, cleaning personnel and health personnel can stay to support the patients, without fear of getting infected. Thorough education at all levels and daily awareness for all healthcare workers is important. If an Ebola contact has occurred, specific monitoring measures of staff are needed and should be implemented according to supranational and national guidelines. Of note, shedding of viable viral material, e.g. from urine,[29] sweat[29] and semen[10], may persist for a prolonged period after recovery and require appropriate hygiene measures. Whilst it is the task of the attending healthcare team to provide optimal care for suspect and confirmed cases, contact tracing and interacting with the public involves a multidisciplinary team outside the actual point-of-care setting.

In most academic (and many non-academic) medical centres outside endemic areas around the world, situation-specific protocols have been implemented and trained. Public health authorities of global significance (WHO, CDC) have developed detailed guidelines and sources of detailed information on Ebola virus disease and all aspects of how to handle individual patients and outbreaks. Most countries have implemented their own guidelines through their national public health institutions. In the case of the Netherlands, for example, this is the National Institute for Public Health and the Environment (RIVM).[69] Since the beginning of the outbreak, the RIVM has continuously updated and expanded its online guideline on viral haemorrhagic fevers, containing background information on the diseases and very specific schemes for patient triage and management, with links to a whole range of documents extensively describing handling of suspect and confirmed cases and the interaction of all stakeholders involved in managing such a situation in a coordinated and professional approach.

Conclusions

For the medical specialist being confronted with an Ebola suspect or a confirmed case, understanding of the routes

of transmission and profound knowledge of the necessary infection prevention measures in immediate patient care and handling of laboratory material are vital. Whilst containment and avoidance of nosocomial spread are paramount, it has been clearly shown that even the most severely ill patients do have a fair chance of survival if they have access to intensive care. The current outbreak massively boosted progress in the development of specific therapeutics and vaccines; however, to date these are not readily at hand because phase II/III stages of clinical development have not yet been accomplished. Common basic intensive care treatment strategies of circulatory and vital organ function support with focus on counterbalancing fluid and electrolyte loss and treating concomitant bacterial infections are essential for patient survival.

Disclosure

All authors declare no conflict of interest. No funding or financial support was received.

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