Original article

IMPORTED VIRAL HAEMORRHAGIC FEVER WITH A POTENTIAL FOR PERSON-TO-PERSON TRANSMISSION : REVIEW AND RECOMMENDATIONS FOR INITIAL MANAGEMENT OF A SUSPECTED CASE IN BELGIUM

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ABSTRACT

Viral haemorrhagic fevers are caused by a wide range of viruses. There are 4 types of viruses well known to spread from person to person and able to cause nosocomial outbreaks with a high case fatality rate : an arenavirus (Lassa fever and more exceptionally the Junin and Machupo virus), a bunyavirus (Crimean-Congo haemorrhagic fever) and the *Filoviridae* (Ebola and Marburg viruses). So far there have been only a limited number of imported cases of viral haemorrhagic fever in industrialized countries. In recent years an increasing number of outbreaks of filovirus infections have occurred in Africa and in 2000 5 cases of Lassa fever were brought from Sierra Leone to Europe. Therefore European physicians should consider the possibility of a viral haemorrhagic fever in an acutely ill patient just returning from Africa or South-America with fever for which there is no obvious cause. Such patients should be questioned for risk factors for viral haemorrhagic fever. Using universal precautions for handling blood and body fluids and barrier nursing techniques there is little risk that if a patient with viral haemorrhagic fever arrives in Belgium there will be secondary cases.

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INTRODUCTION

Viral haemorrhagic fevers (VHF) are often life-threatening. They are caused by a wide range of viruses that are endemic in certain parts of Africa, South America and some rural parts of the Middle East and Eastern Europe (1,2) . The agents causing VHF with a potential for person-to-person transmission are all RNA viruses, but they belong to distinct families. Most of them are zoonoses, some are transmitted by rodents, others by ticks, others by mosquitoes (2). For the *Filoviridae* (Ebola and Marburg virus) the reservoir and possible vectors are unknown (3). Most of these viruses are highly virulent and are associated with a high mortality rate (2) with the exception of the dengue virus, that causes usually only a mild disease, especially in travellers (4). Only after acquiring a second dengue virus infection with a new serotype there is a risk for dengue shock syndrome (4,5). Moreover with dengue there is no direct person to person spread (the infection is only transmitted by mosquitoes which are absent in Belgium).

There are 4 types of HF viruses well known to spread from person to person, able to cause nosocomial outbreaks and with a high case fatality rate : *Arenaviridae* (Lassa fever virus and more exceptionally the Junin and

Machupo viruses), a bunyavirus [Crimean-Congo haemorrhagic fever (CCHF) virus] and the *Filoviridae* (Ebola and Marburg viruses) (1). Except for CCHF there is no known animal reservoir for these infections in Europe. So far there have been only a limited number of imported cases of VHF in industrialized countries. With the exception of the Marburg epidemic in 1976 (6), for nearly all other VHF patients imported in Europe no person to person spread has occurred because universal precautions were used. In only one person who had been in contact with a patient with Lassa fever in Germany were antibodies detected (7).

In this paper we will review only Lassa fever, Ebola haemorrhagic fever (HF), Marburg HF, and CCHF in more detail as well as the initial diagnostic approach when confronted in Belgium with a patient suspected to have VHF.

Four highly infectious viruses able to cause nosocomial outbreaks

Lassa fever

Epidemiology

Lassa virus infection has been demonstrated in numerous West African countries (8). The reservoir of Lassa fever is the rat *Mastomys natalensis* (9). Infected animals remain infected throughout their life and excrete large amounts of virus in urine. In rural West African villages transmission occurs probably through contamination of broken skin or mucous membranes, either through direct contact with the urine of infected rats or through indirect contact with materials or food contaminated by rat urine. Person to person spread may occur through the use of contaminated needles or instruments, the administration of infected blood, and by close personal contact through exposure to pharyngeal secretions (infection can also occur following airborne transmission). Patients may continue to excrete virus in body fluids up to a few months after recovery (8).

Clinical manifestations

Lassa virus causes disease that may vary in severity from subclinical to fatal. In Sierra Leone the case fatality rate among hospitalized cases of Lassa fever was 16% (8). However the estimated overall case fatality rate for Lassa fever in the eastern part of Sierra Leone is 1 – 2% (7). The incubation period of Lassa fever is usually 7 to 10 days. The onset of the illness is insidious, initially with non-specific symptoms including fever. Predictors for Lassa fever are facial oedema, conjunctivitis, purulent pharyngitis, vomiting, proteinuria and abdominal tenderness (10).

Treatment

Ribavirin is able to reduce mortality by 60% in severe cases particularly if intravenous treatment is started early in the course of infection (11). However, antiviral treatment does not abolish either viraemia or viruria in convalescent patients. The prophylactic use of oral ribavirin may prevent or delay disease in exposed contacts (11). The optimal dose of ribavirin remains to be determined. Doses between 1000 and 2400 mg a day have been proposed (11,12). In all persons treated with ribavirin a complete blood count, aspartate aminotransferase concentration and drug levels should be monitored (12).

Ebola

Ebola outbreaks have now been reported from Sudan, the Democratic Republic of Congo, Gabon, Ivory Coast and Uganda (13-15). The natural reservoir of the Ebola virus is unknown. Monkeys have been involved in outbreaks among human beings but are probably not the reservoir because they also frequently die of Ebola infection. They may however transmit the infection to humans. This was the case in Ivory Coast where a Swiss zoologist was infected, while conducting an autopsy on a wild chimpanzee (14). In Gabon children became infected by cutting a dead chimpanzee into pieces (15). So far ecological studies never have been able to detect any animal reservoir (16-17). In the National Institute of Virology in South Africa a large variety of animals were injected experimentally with the Ebola virus, only bats were found to support replication and circulation of high titers of virus, without developing disease (18). Therefore bats could be a potential reservoir for the Ebola virus but this still has to be documented. Ebola virus is transmitted through blood and body fluids from infected patients or monkeys. The risk of transmission increases if the contact with a patient has occurred in the later stages of illness (19-20). The most likely route of infection is through contact of contaminated fingers with the oral mucosa or conjunctiva. Aerosol transmission has been observed among monkeys infected with the Reston and the Zaire subtype of Ebola virus (21-23). Ebola virus has also been identified in alveoli of experimentally infected monkeys and in human lung specimens (24).

Therefore transmission through aerosolised particles cannot be excluded completely. The Ebola virus has been isolated from vaginal and seminal fluids, therefore sexual transmission is also theoretically possible (20,25). Infectious virus was detected in seminal fluid of a convalescent patient, 82 days after onset of the disease (25). In general convalescent patients are considered to be non infectious but they should continue to use condoms as long as the Ebola virus can be isolated from vaginal or seminal fluids.

Clinical manifestations

The incubation period of Ebola virus infections is usually around 7 days (between 3 and 21 days). It is an acute infection with a rapid rise in temperature often associated with headache and muscle and joint pains. Gastrointestinal manifestations such as anorexia, nausea, vomiting and diarrhoea are also often early symptoms. After 3 to 8 days patients may develop a morbilliform rash (difficult to recognize on a black skin). The throat and conjunctiva may be inflamed and 50% of the patients will develop haemorrhagic manifestations (26,27). In the end stage of the disease patients often present with extreme lethargy and neurological abnormalities such as confusion, epilepsy, etc... Death generally occurs during the second week of illness. Patients die in shock, in metabolic acidosis and renal insufficiency (26).

Treatment

There is no specific treatment for Ebola haemorrhagic fever. Whether transfusions of blood or serum from convalescent patients may reduce case fatality rates remains controversial (27,28).

Marburg

Epidemiology

Marburg infection was discovered in 1967 during an outbreak among laboratory workers in Marburg and Frankfurt, Germany and Belgrade, Yugoslavia (6). This outbreak was a consequence of direct contact with blood, organs and cell cultures from African green monkeys that had been caught in Uganda. Since then a few isolated cases of Marburg infection have been reported from Africa : from Kenya and Zimbabwe (29-31). In Durba, in the north east province of the Democratic Republic of Congo, several outbreaks of Marburg infection probably occurred already since many years (32,33). The infection was first identified in 1999 (32,33). The infection occurs mainly in mine workers working in the Gorumbwa goldmine (previously the Kilo Moto mines). These mineworkers work deep under the ground in very bad hygienic conditions. They often stay several days under the ground and eat, drink and sleep in the mine. This mine is also inhabited by rodents and thousands of bats. So far however from none of the bats and rodents captured in the mines has Marburg virus been isolated. Marburg virus infection seems to be transmitted in a similar way to that of Ebola virus. However, it could be that the Marburg virus is less virulent. Case fatality rates among European patients with Marburg infection were only 22% and among confirmed African cases in Durba 56 % (34). It is also possible that Marburg infection is less infectious than Ebola haemorrhagic fever. Indeed there were less secondary cases of Marburg HF in Durba compared to Ebola HF in Kikwit.

Clinical manifestations

Similar to Ebola HF.

Treatment

There is no specific treatment for Marburg infection.

Crimean/Congo haemorrhagic fever (CCHF)

Epidemiology

CCHF is a tickborne haemorrhagic fever. Initially this infection was documented during an outbreak in the USSR in 1944-1945 in the Steppe region of the Western Crimea (35). Later it was realized that the infection occurred also in the Central Asian republics, and in countries bordering the Black and Caspian Seas, Bulgaria and Yugoslavia (36). In 1956 an antigenically and biologically closely related virus was isolated in the Belgian Congo (37). Since then it has been shown that the virus is widespread in Eastern, Western and Southern Africa, Asia and Eastern Europe (38-42). Both domestic [sheep, goats, cattle and ostriches (in South-Africa)] and wild animals are involved in the maintenance cycle of the virus. Agricultural workers, campers and the military are the groups at highest risk.

Clinical manifestations

After an infective tick bite the incubation period is about 5 to 12 days. The illness begins abruptly with fever, chills, malaise, irritability, headache and severe pains in limbs and back, followed by nausea, vomiting and abdominal pain. The fever is usually continuous but may be biphasic. The face and neck are flushed and oedema-

tous, the conjunctiva and pharynx are congested and there may be oedema of the soft palate. Patients may be depressed and somnolent. In most cases a fine petechial rash begins on the back and then covers the entire body. The liver is enlarged in 50% of the cases. Bleeding manifestations were reported in about 75% of patients (42-43). Involvement of the central nervous system is seen in 10-25% of cases, this may include neck rigidity, excitation and coma. Case fatality rates between 30-50% have been reported in nosocomial outbreaks (39-43). Nosocomial infections with high levels of mortality have been reported from Dubai, Iraq and Pakistan (39-41).

Treatment

Ribavirin may reduce both the duration of the fever and the severity of the haemorrhagic manifestations (44).

DIAGNOSIS OF VIRAL HAEMORRHAGIC FEVER

Clinical diagnosis

Certainly in an early stage, when an influenza-like illness is present, it is impossible to make a diagnosis of VHF only on clinical grounds. But even in the later stages, a relatively large percentage of patients infected with Lassa fever virus, *Filoviridae* or CCHF virus might not develop haemorrhagic manifestations. On the other hand the presence of fever together with bleeding manifestations can also be seen in patients suffering from malaria, typhoid fever, other bacterial infections such as pyelonephritis, pneumonia, septicaemia, meningococcal meningitis, leptospirosis, rickettsial infection, plague, etc... (28). It is therefore essential to take into account epidemiological criteria when assessing the risk of a patient to be infected with VHF. When a patient has visited exclusively cities, the diagnosis of Lassa fever, a filovirus infection or CCHF is improbable. The diagnosis of VHF can also be excluded if the interval between the onset of symptoms and the last possible exposure exceeds 3 weeks. The patient should be questioned about possible exposure to symptomatic persons in areas endemic for VHF. A history of yellow fever vaccination during the last 10 years eliminates the diagnosis of yellow fever (45).

Laboratory investigations

Laboratory investigations have the objective to confirm the suspected diagnosis of VHF and to exclude more likely diseases. The most important examinations for the latter objective are the thickfilm to exclude malaria and blood cultures to exclude typhoid fever and other septicaemias. Experience has shown that most ill patients suspected of VHF will be suffering from malaria. Laboratory tests to exclude or confirm malaria should be performed as soon as possible in order to start antimalarial treatment urgently if necessary. However, multiple infections are not uncommon in the tropics and the finding of malaria parasites does not absolutely exclude one of the haemorrhagic fevers.

The diagnosis of VHF is performed by PCR, virus isolation, antigen detection and by the demonstration of IgM antibody or by a fourfold rise in IgG antibody titer in serum.

IgG and IgM antibodies are usually not detectable in the early phase of a VHF infection (46) hence the need for PCR or viral cultures. Since there is variation in the RNA sequence of different VHF virus strains (up to 27% for Lassa virus), PCR tests carry a certain risk of false negative results (47). Therefore virus isolation, for which a biosafety level 4 is required, remains the golden standard for the diagnosis of VHF. Such a biosafety level 4 laboratory is not available in Belgium but the Institute of Tropical Medicine, Antwerp (tel. 03 247 64 37) will provide laboratory assistance to diagnose other tropical diseases able to cause haemorrhagic fever and will be responsible for the transport of specimens to a European biosafety 4 level laboratory in order to confirm or exclude the diagnosis of VHF within 48-72 hours.

Leucocytosis is generally present in cases of bacterial infections, while during Lassa fever, CCHF, Marburg or Ebola virus infection leucopenia is generally found, certainly in the early course of the infection (48). Severe liver abnormalities can be seen during Lassa, CCHF, Marburg and Ebola virus infection but also occur during viral hepatitis, leptospirosis and malaria. Thrombocytopenia is often present in patients with VHF but is also nearly always present during severe *Plasmodium falciparum* infection (49) and also may occur during leptospirosis and hantavirus infection.

Because of the potential risk associated with handling infectious material, laboratory testing should be the minimum necessary. Blood films are not infectious after fixation in solvents.

Initial management of patients suspected of VHF

(adapted from the guidelines proposed by the Advisory Committee on Dangerous Pathogens, United Kingdom) (50).

Persons will be classified according to risk category.

Minimum risk

Febrile patients who

- have not been in known endemic areas before the onset of illness or
- have been in an endemic area, or been in contact with a known or suspected source of VHF, but in whom the onset of illness was definitely more than 21 days after their last contact with any potential source of infection.

Over 95% of seriously ill patients in the minimum risk category will have malaria. Only severely ill patients should be hospitalized. No special VHF precautions are needed. If a patient is suspected to have VHF it is recommended to contact the physician on call of the Institute of Tropical Medicine, Antwerp (tel. 03 247 64 05, weekdays 9 am - 5 pm, (tel. 03 821 30 00, other hours and during weekends) or the department of infectious diseases St.-Pierre Hospital, Brussels (tel. 02 535 31 11).

Moderate risk

Febrile patients

- who have been in an endemic area during the 21 days before the onset of illness, but who have no additional risk factor
- or have not been in a known endemic area but who may have been in an adjacent area or country during the 21 days before the onset of the illness, and who have evidence of severe illness with organ failure and/or haemorrhage which could be due to VHF and for which no alternative diagnosis is currently evident.

Such patients should be followed closely and isolated in a hospital if severely ill. A high level of infection control for patient care and particularly for laboratory procedures is needed. Virological tests for VHF may not be needed. Also in this category 95% of the cases will have malaria.

More details about the management and control of VHF can be found on the website of the European Network for diagnostics of Imported Viral Diseases (51).

High risk

Febrile patients who

a) have been in an endemic area during the 3 weeks before illness and
- have lived in a house or stayed in a house for more than 4 hours where there were ill, feverish persons known or strongly suspected of having VHF,
- or took part in nursing or caring for ill feverish patients known or strongly suspected to have VHF,
- or had contact with body fluids, tissue or the dead body of such a patient,
- or are laboratory or other (health) worker who has or has been likely to have come into contact with the body fluids, tissues or the body of a human or animal known or strongly suspected to have VHF,
- or were previously categorized as moderate risk, but who have developed organ failure and/or haemorrhage.

b) have not been in an endemic area but during the 3 weeks before illness they
- cared for a patient or animal known or strongly suspected to have a VHF or came into contact with the body fluids, tissues or dead body of such a patient or animal,
- or handled clinical specimens, tissues or laboratory cultures known or strongly suspected to contain the agent of VHF.

Such patient should be isolated in a hospital. Virological tests for VHF are indicated. As soon as the diagnosis of VHF is confirmed, patients should be transferred to the isolation unit of the Belgian Military Hospital Queen Astrid (unit 13). This is a unit specifically equipped for the care for persons with VHF (figure 1 and 2). The Belgian Military Hospital will also organize the transport of the patient to this unit. Cases should be reported to the Institute of Hygiene and Epidemiology.

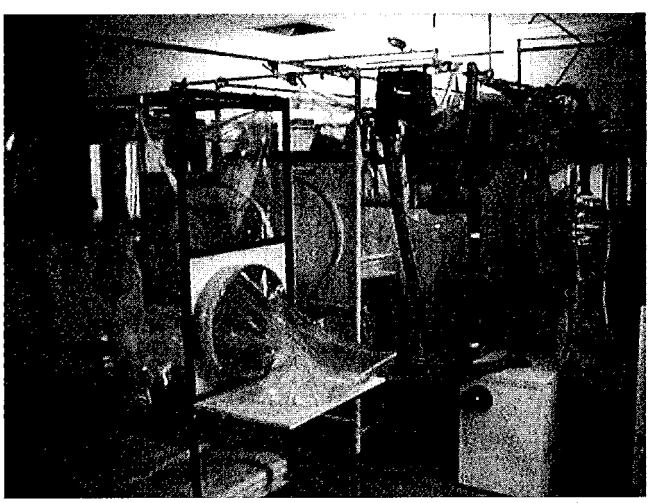

Figure 1
The isolation unit at the Military Hospital : the bed of the viral haemorrhagic fever patient, inside a plastic «cocoon», is completely isolated from the environment

Figure 2
How a nurse/physician outside the plastic cocoon is able to care for the viral haemorrhagic fever patient.

HANDLING LABORATORY SPECIMENS

Blood and urine specimens should be taken by experienced staff. For moderate and high risk patients, protective measures including wearing a protective gown, a waterproof protective apron, latex gloves, HEPA face mask and eye protection are recommended.

To obtain blood specimens dry cotton-wool balls or gauze swaps (not disposable alcohol swaps) should be used to apply pressure to the venepuncture wound. Specimen tubes should be labelled with patient identification before being filled. Blood collection by fingerprick or making direct blood films should not be undertaken. Blood films should be made only by an experienced person, using an EDTA sample. They should be dried and fixed before examination. Thickfilms should not be prepared. All equipment used for blood taking should be placed into a dedicated sharps box for immediate sealing and disposal. Gloves, disposable gowns, materials used to clean up spillage and empty specimen containers should be placed in waste bags which are immediately tied or sealed and then double bagged into a second waste bag for immediate disposal by incineration.

TABLE 1 : DIFFERENTIAL DIAGNOSIS OF HAEMORRHAGIC FEVER (HF)

Viruses	Disease
Arenaviruses	Argentinian HF (Junin virus), Bolivian HF (Machupo virus), Lassa fever, Venezuelan HF (Guanarito virus), Brazilian HF (Sabia virus)
Bunyaviruses	Rift Valley fever, Crimean-Congo HF, HF with renal syndrome (Hanta viruses : Hantaan, Puumala, Seoul, Dobrava-Belgrade virus), Hantavirus pulmonary syndrome
Flaviviridae	Yellow fever, Dengue HF, Omsk HF, Kyasanur Forest HF,
Filoviruses	Ebola , Marburg
Other viruses	Measles, rubella, hepatitis (A, B, C, D, E), human immune deficiency virus, Chikungunya, Sindbis, herpes, influenza, infectious mononucleosis
Rickettsia	Rocky Mountain spotted fever, tick bite fever, epidemic typhus, Q fever
Bacteria	Various septicaemias (e.g. meningococcal, staphylococcal, streptococcal, typhoid, plague), shigellosis, leptospirosis, relapsing fever
Protozoa	Falciparum malaria, visceral leishmaniosis, trypanosomiasis
Miscellaneous	Acute leukaemia, especially promyelocytic, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura

HF = haemorrhagic fever

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