FOCUS ON: TROPICAL DISEASES

Viral haemorrhagic fevers—implications in intensive care

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KEYWORDS
Haemorrhagic fever; Viral; Ebola; Lassa; Marburg; Crimean-Congo; Identification; Management

Summary The viral haemorrhagic fevers are a group of potentially lethal infections, for which limited therapy is available and for which early diagnosis is desirable in order that meticulous isolation, contact tracing and public control measures can be instituted. It is important in these days of widespread foreign travel and integration that all clinicians especially intensivists be aware of this rare potential diagnosis in patients with organ failure, haemorrhage and a pyrexia of unknown origin. In addition these organisms have been considered to have a potential use as biological weapons. It is intended that this article will provide aid in the diagnosis, management and public health/ infectious control procedures required in the event of a patient presenting with a possible diagnosis of viral haemorrhagic fever.

Introduction

The 20th century developed the promise that we were entering an era of antibiotics and drug therapy capable of combating and even eradicating serious infectious diseases. As we enter the next millennium we are increasingly aware of a range of viral infections with easy transmission and potentially devastating outcomes that do not have obvious treatment regimens. This article aims to review a group of such pathogens, the viral haemorrhagic fevers (VHF), of which, despite technology, we know surprisingly little and for which no cure (beyond supportive care) and few vaccines exist. Although the risk they pose to western countries may at first seem small, increasing foreign travel, a heightened risk of bioterrorism, environmental changes and the ability for organisms to adapt have made VHF an important public health issue.

The viral haemorrhagic fevers are a group of highly infectious and often fatal diseases with similar clinical presentations that are caused by several distinct families of viruses: arenaviruses, filoviruses, bunyaviruses and flaviviruses. The United Kingdom (UK) Health Department’s guidance from the Advisory Committee on Dangerous Pathogens highlights four VHF viruses as cause for concern in the UK due to possible person-to-person spread. These are Lassa (an arenavirus), Crimean-Congo haemorrhagic fever (CCHF—a bunyavirus), Ebola and Marburg (filoviruses). It is these viruses, their epidemiology, presentation and treatment that will be reviewed in this article. Information
was gathered by searching Medline, Pubmed and Cochrane databases and from a number of public health and government websites.

### General management guidelines for patients with suspected VHF

The UK Health Department guidelines recommend categorization of febrile patients into minimum, moderate or high risk of being infected with VHF (Table 1). In all cases, malaria is an important alternative diagnosis that must be excluded at an early stage. The local Infection Control Team should be informed ideally prior to patient admission or as soon as VHF is considered a potential diagnosis. Local procedure may require the Consultant in Communicable Disease Control (CCDC) to be informed though in moderate- or high-risk patients this is a mandatory action. Public health precautions are unlikely in minimum risk patients but are most effective when instituted early and in moderate- and high-risk patients may severely limit disease spread. Patients in the moderate- and high-risk groups should be admitted or transferred to either of the Department of Health designated High Security Infectious Disease Units (HSIDUs) at Coppel's Wood hospital, London or Newcastle General Hospital, Newcastle upon Tyne (appendix). Movement of these patients requires Ambulance Category III transportation to ensure that infection control issues are maintained at all times.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>UK Department of Health Advisory Committee on Dangerous Pathogens (ACDP) guidance on risk stratification for febrile patients** (reproduced by kind permission of the ACDP).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimum Risk</strong></td>
<td>This category includes febrile patients who have:</td>
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<td></td>
<td>• Not been in known endemic areas before the onset of illness;</td>
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<td>or</td>
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<td></td>
<td>• been in endemic areas, (or 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.</td>
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<tr>
<td><strong>Moderate Risk</strong></td>
<td>This category includes febrile patients who have:</td>
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<td></td>
<td>• Been in an endemic area during the 21 days before the onset of illness, but who have none of the additional risk factors which would place him or her in the high risk category;</td>
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<td></td>
<td>or</td>
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<td></td>
<td>• not been in a known endemic area but who may have been in adjacent areas or countries during the 21 days before the onset of illness, and who have evidence of severe illness with organ failure and/or haemorrhage which could be due to a VHF and for which no alternative diagnosis is currently evident.</td>
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<tr>
<td><strong>High risk</strong></td>
<td>This category includes febrile patients who:</td>
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<td>(a)</td>
<td>Have been in an endemic area during the 3 weeks before illness and:</td>
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<td></td>
<td>• Have lived in a house or stayed in a house for more than 4 h where there were ill, feverish persons known or strongly suspected to have a VHF;</td>
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<td>or</td>
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<td></td>
<td>• took part in nursing or caring for ill, feverish patients known or strongly suspected to have a VHF, or had contact with the body fluids, tissue or dead body of such a person.</td>
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<td></td>
<td>or</td>
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<tr>
<td></td>
<td>• are a laboratory, health or other worker who has, or has been likely to have come into contact with the body fluids, tissues or dead body of a human or animal known or strongly suspected to have a VHF;</td>
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<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• were previously categorized as ‘moderate’ risk, but who have developed organ failure and/or haemorrhage.</td>
</tr>
<tr>
<td></td>
<td>(b)</td>
</tr>
<tr>
<td></td>
<td>• 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;</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• Handled clinical specimens, tissues or laboratory cultures known or strongly suspected to contain the agent of a VHF.</td>
</tr>
</tbody>
</table>

**Details reproduced by kind permission of Ms. H. Lewis, member of the ACDP UK Health Department, given on 20th January 2004.
Contacts of the patient will be highlighted and placed under surveillance by the CCDC and the Communicable Disease Surveillance Centre (CDSC). Tissue and body fluid samples may contain high levels of virus and will need to be sent to the High Security Infectious Disease Laboratories (HSIDL) (appendix). Prior to dispatch, the receiving units should be contacted to ascertain the exact manner in which the samples should be labelled, packaged and delivered. If samples have already been dispatched the CCDC or Infection Control Consultant must be identified as the individual responsible for locating them with subsequent labelling and packaging as appropriate. A summary of the actions required from the clinician initially caring for a patient considered to be at risk of being infected by a VHF is detailed below:

- Inform the Infection Control Consultant immediately.
- Isolate the patient and ensure strict infection control precautions.
- Minimize all contact with patient body fluids including excreta and unnecessary phlebotomy.
- Contact a HSIDL to ascertain what samples will be required and how they should be labelled, packaged and dispatched.
- Send a blood film to the local laboratory for examination for malaria parasites.
- Send all other samples as instructed by the HSIDL.
- Reusable equipment should be disinfected using 0.5% sodium hypochlorite solution or 0.5% phenol with detergent, and wherever possible by autoclaving, incineration or boiling. Fortunately, the viruses involved in the haemorrhagic fevers are not highly resistant to chemicals or heat.
- Provide medical support as required while awaiting advice from the CCDC or HSIDU. If the diagnosis is still uncertain consider early ribavirin therapy.

**General treatment measures**

Supportive therapy should be commenced with early admission to a critical care unit if patient condition is deteriorating. Patients are usually fluid-replete and resuscitation with intravenous fluids should be considered early. Choice of fluid should be considered carefully as excessive crystalloid therapy may exacerbate peripheral and pulmonary oedema. Peripheral oedema may make intravenous cannulae insertion difficult and central venous cannulation should be undertaken cautiously given the risks from coagulopathy. In addition, careful attention should be given to the management of pressure areas and areas of skin breakdown. Careful monitoring of coagulation is required as coagulopathy is a significant feature of the viral haemorrhagic fevers and liver dysfunction may occur. Correction of disseminated intravascular coagulopathy should be performed if haemorrhage is problematic though mild-to-moderate haemorrhage may be tolerated if it is not associated with significant organ dysfunction. Heparin therapy has been used in the management of coagulopathy although its use remains controversial. Both liver and renal dysfunction may occur and appropriate monitoring should take place with adjustment of drug and treatment regimes accordingly. Renal replacement therapy may be required in severe cases. Pleural effusions, pulmonary haemorrhage, pulmonary oedema and acute lung injury may occur in any combination and may necessitate invasive mechanical ventilation. The goals of the intensivist should be those usually employed in the management of patients with systemic inflammatory response syndrome and multiple organ dysfunction including surveillance for secondary bacterial and fungal infections.

**Lassa fever**

**Background and presentation**

The Lassa fever virus is a member of the Arenaviridae family. It is a single-stranded RNA virus and is zoonotic (carried by animals) with the multi-mammate rat the main vector for disease spread. The disease was first identified in Nigeria and several hundred thousand cases still present annually in West Africa. Areas particularly affected include Guinea, Liberia, Sierra Leone and regions of Nigeria. Of the cases that require hospitalization 15% (1% of the total case load) will die as a result of the illness though outbreaks have been reported with mortalities nearer 60%. This amounts to about 5000 deaths per year emphasizing the serious impact the disease has in affected parts of the world.

Lassa fever presents between 7 and 21 days following exposure to the virus. The virus is carried by rats from which it is shed in the urine and faeces, and it is direct or indirect contact with these sources that results in disease transmission to humans. Transmission has been reported as a result of inhalation of tiny particles contaminated by rat excretions. Once contracted by a human, person-to-person spread...
can occur through direct contact with body fluids (including sexual contact) or with equipment contaminated with such fluids. Significantly the virus may be excreted in patients' urine for up to nine weeks. Skin-to-skin contact does not result in spread, however by the nature of the transmission characteristics, spread of the disease can and does occur commonly amongst healthcare workers caring for patients with the disease. This has been a particular problem due to many of the hospitals in endemic regions lacking disposable gowns, gloves and masks and having inadequate sterilization equipment. Presentation is often non-specific with fever, malaise, arthralgia, and diarrhoea and vomiting, cough, sore throat and bleeding from mucosal membranes. In severe cases multiple organ dysfunction may ensue with hypotension, pleural effusions, convulsions and head and neck oedema occurring commonly. The presence of symptoms and signs such as these in a patient who has visited an endemic country or been in contact with someone with similar symptoms (dead or alive) during the previous three weeks should prompt the clinician to consider Lassa fever in the differential diagnosis. Laboratory diagnosis is most commonly made using enzyme-linked immunosorbent assay (ELISA) although immuno-histochemistry may reveal post-mortem diagnoses.

**Treatment**

As with all the life-threatening VHF's treatment is predominantly supportive although, in the case of Lassa fever, Ribavirin therapy has been used successfully with the greatest benefit achieved with early therapy. Multi-organ dysfunction can occur with severe cases and such patients will require management in the critical care unit as detailed above.

**Prevention**

The mainstay of disease prevention is rodent control to reduce the vector transmission and meticulous infection control and isolation of moderate to high-risk patients once they have been identified. Prophylactic ribavirin should be considered in any close contacts of patients including care workers. Attempts have been made at producing vaccines, however clear knowledge of the immune responses triggered by natural infection are lacking and this has made it difficult to predict whether or not exposure to recombinant Lassa protein would confer protection. At the time of writing no vaccine is available as prophylaxis against Lassa fever.

**Ebola haemorrhagic fever**

**Background and presentation**

The Ebola virus has resulted in 50–90% mortality during outbreaks making it one of the most virulent and dangerous viruses known to mankind. It first appeared during simultaneous outbreaks in Sudan and Zaire in 1976 but has since been reported in Gabon, Sudan, the Ivory Coast, Uganda and the Republic of the Congo though transmission in humans has not been maintained. It is one of the two known members of the Filoviridae family, the other being the equally virulent Marburg virus. Despite progress in the understanding of the virus, neither the natural reservoir nor the trigger for its re-emergence during human outbreaks has been identified. Given the zoonotic nature of similar viruses, it seems likely that the virus is maintained in nature by an animal host native to the African continent. Of interest, a seasonal emergence of the virus has been found in the great apes, civet cats and several other bush species. Such animals are a source of bush meat for local hunters who acquire the meat during the rainy seasons. Some of this meat is used for local consumption however there is an increasing international market for such meat that may travel long distances and could potentially act as a viral reservoir.

Transmission may occur by contact with body fluids or tissue from living or dead carriers of the virus. Healthcare staff have been involved in significant numbers during past outbreaks, with two-thirds of the deaths during the 1995 outbreak in Kikwit being amongst health workers. Contaminated needles have been implicated in a number of these cases. Airborne spread has not been reported and those living in close quarters to infected individuals have not been shown to be at increased risk.

The incubation period for the human disease is between 2 and 21 days, with most cases presenting between 1 and 2 weeks after initial exposure. Symptoms include sudden onset of fever, myalgia, weakness, sore throat and headache followed by vomiting, bloody diarrhoea, rash, renal and liver dysfunction, and both internal and external bleeding. Laboratory diagnosis requires specialized equipment that detects viral antigens or genes, isolates the virus in cell culture or identifies antibodies.
Management

In the event of a patient exhibiting symptoms or signs of haemorrhagic fever the general measures detailed above should immediately be instituted. In the meantime detailed history of possible exposure including foreign travel and contact with other hospitalized patients should be ascertained in order to assess the likelihood that the patient may have contracted a viral haemorrhagic fever. Treatment is based on organ support as detailed above.

Prevention

Ebola virus presents a number of problems with regards disease prevention. Firstly, the natural reservoir for the virus is still to be identified. Secondly, various strains of the virus have been identified with differing levels of virulence. Quite why these viral agents should have the ability to cause such extreme pathogenicity is again unclear. It is known, however that patients who die from the disease usually have not mounted a significant immune response to the virus at the time of death. The last problem that extends to all of the viruses discussed in this article is that, at the time of writing, no vaccine or specific treatment exists at present though work to solve this problem is ongoing.

Marburg haemorrhagic fever

Background and presentation

Marburg virus was the first of the filoviridea family to be recognized. It was identified in 1967 when a number of laboratory workers in Germany developed haemorrhagic fever following the handling of tissues from green monkeys. It is a rare type of haemorrhagic fever that, like Ebola, has appeared sporadically over the past four decades and for which the natural reservoir has yet to be identified. Although the initial identification of the virus was made in Europe, the monkeys who had acted as the vector had been transported from Uganda, and all the outbreaks since have been in Africa with cases reported in Kenya, Uganda, Zimbabwe, South Africa, Durba and the Democratic Republic of the Congo.

As with Ebola virus, the animal host for Marburg is unknown however once human infection has occurred, person-to-person spread can occur through contact with body fluids and tissue. Droplets of body fluids have been suspected as the source of spread in some cases. The reported mortality is less than with Ebola though still significant at about 25%. Those at risk of the illness include those in close contact with infected patients, including health care workers, and laboratory and quarantine facility workers who have handled non-human primates associated with the disease. Once infected, the incubation period is between 5 and 10 days following which symptoms of fever, malaise, and nausea and vomiting, abdominal pain, sore throat, diarrhoea and a rash may develop. As with the other severe haemorrhagic fevers, the disease may progress to fulminating multiple organ failure. Laboratory diagnosis is usually by ELISA however several techniques are available for post-mortem diagnosis.

Management and prevention

Meticulous attention should be given to the general measures detailed above and supportive care should be provided. Ribavirin has not been shown to be of benefit though given the difficulties differentiating the haemorrhagic fevers clinically and the time that can lapse before definitive diagnosis, therapy should be considered for the patient and close contacts. A number of complications following recovery from Marburg virus have been reported including hepatitis, transverse myelitis and orchitis. No vaccine exists at the time of writing.

Crimean–Congo haemorrhagic fever (CCHF)

Background and presentation

CCHF is caused by a tick-borne virus belonging to the Nairovirus family. It is endemic in many countries throughout Africa, Europe and Asia and has produced sporadic cases in humans since it was first reported in the Crimea in 1944 (at which time it was referred to as Crimean haemorrhagic fever). The most common and efficient vectors for the virus are ticks belonging to the Hyalomma genus, which cause infection in animals and humans through their bite. Humans may also become infected through contact with blood or tissue from infected animals and a wide range of both domestic and wild animals have been implicated. If infected by a tick bite, the incubation period ranges from 1 to 9 days however infection following contact with blood or tissue results in an incubation...
period of between 5 and 13 days. Symptoms may occur suddenly with headache, photophobia, neck stiffness, myalgia and fever. Neurological features may then ensue with confused, agitated and aggressive behaviour being followed by reduced conscious level after about 2–4 days. Abdominal tenderness with hepatomegaly may develop. The disease may progress to cause cardiovascular instability, coagulopathy, hepatic and renal dysfunction and respiratory failure. The mortality is about 30%.

As with the other viral haemorrhagic fevers, diagnosis is usually by ELISA with postmortem diagnosis being possible by a number of means.

Management and prevention

General treatment and management should be guided as detailed above. Ribavirin therapy is recommended and this may be orally administered if intravenous preparations are unavailable. There are several reports of the use of immune plasma from recovered patients for therapeutic purposes though the efficacy of this therapy has not been substantiated. Prevention is aimed at control of the tick vectors and by the use of repellents to reduce the incidence of tick bites. A vaccine has been developed and used on a small scale in Eastern Europe however no vaccine has been made available for widespread human use at the time of writing.

Appendix

High Security Infectious Disease Units:

Coppetts Wood Hospital
Contact the on-call Infectious Disease Doctor at: The Royal Free Hospital
London NW3 2QG, UK
Tel: 020-7794-0500
Newcastle General Hospital
Newcastle upon Tyne
Tyne & Wear, UK
Tel.: 0191-273-8811

High Security Infectious Disease Viral Diagnostic Laboratories:

Public Health Laboratory Service, Virus Reference Division
Central Public Health Laboratory
Colindale Avenue
London NW9 5HT, UK
Tel.: 020-8200-4400

Center for Applied Microbiology and Research
Porton Down
Salisbury SP4 0JG, UK
Tel.: 01980-612100

References