Editorial

Crimean Congo haemorrhagic fever: an overview

Of the medically significant tick-borne viruses' induced diseases, Crimean Congo haemorrhagic fever (CCHF) has the most extensive geographic distribution. CCHF is a severe haemorrhagic fever with a case fatality rate ranging from 9% to as high as 50% in hospitalised patients. Nosocomial and community outbreaks have been described. The fact that there is a potential for human to human transmission coupled with high mortality rates associated with this disease, the fears that the virus can be used as a bioterrorism agent and the increase of incidence and geographic range of the Crimean Congo haemorrhagic fever make the virus an important human pathogen. Therefore, it is pertinent to be aware of this disease so as to be able to recognise, manage and prevent transmission of disease among humans. In fact, the first human case of CCHF was described from Ahmedabad, India in January 2011. The tests conducted at National Institute of Virology (ICMR, Pune) confirmed the presence of CCHF virus in blood as well as urine samples of the patient. Moreover, the doctor and the nurse attending to the patient also died of similar illness; and this created a panic all over the country. Of the four deaths reported from Kolat village, Ahmedabad, two were confirmed and two were suspected cases. All villages in the 5 km radius and a total of 37,589 people were checked, and 300 blood samples were taken and tested [1].

Nomenclature

Crimean Congo haemorrhagic fever (CCHF) was first described in the 12th century as a haemorrhagic syndrome in the present day Tajikistan. During that era, it was speculated that the disease's transmission was associated to louse or ticks that normally parasite black birds. In the modern era, the first outbreak of the disease was characterised in the Crimea region in 1944-1945 when more than 200 cases occurred and the disease was given the name Crimean haemorrhagic fever. Ten years later and specifically in 1956, a similar illness was defined in Belgian Congo and in 1969, it was recognised that the isolated pathogen had the same antigenic structure as the Crimean strains. Thus, resulted the current name of the disease, Crimean-Congo haemorrhagic fever [2,3].

Epidemiology

Crimean Congo haemorrhagic fever is found in Eastern Europe, particularly in the former Soviet Union. It is also distributed throughout the Mediterranean, in north-western China, central Asia, southern Europe, Africa, the Middle East, and the Indian subcontinent.

The causative agent of Crimean Congo haemorrhagic fever is a negative-sense, single-stranded RNA virus of the family *Bunyaviridae*, genus *Nairovirus*. The virus is transmitted mainly through direct contact with bles and outbreaks of CCHF affecting humans do occur. Fortunately, human disease is infrequent.

Clinical features

The typical course of CCHF infection in humans has four distinct phases: incubation, prehaemorrhagic, haemorrhagic and convalescence period.

The length of the incubation period for the illness relates to the mode of acquisition of the virus. Following infection via tick bite, the incubation period is usually one to three days, with a maximum of nine days. The incubation period following contact with infected blood or tissues is usually five to six days, with a documented maximum of 13 days.

The pre-haemorrhagic phase is characterised by sudden onset of symptoms. The symptom onset is sudden, with fever, myalgias, dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia (sensitivity to light). Nausea, vomiting and sore throat may be present early, accompanied by diarrhoea and generalised abdominal pain. Sharp mood swings, along with confusion or aggressiveness may be noticed in the next few days. Hypotension may also be evident. After two to four days, the agitation may be replaced by drowsiness, depression and lassitude, and the abdominal pain may localise to the right upper quadrant, with

detectable hepatomegaly. There is usually evidence of hepatitis. After the fifth day of illness, in severe cases, hepatorenal failure and pulmonary failure may ensue.

The haemorrhagic phase is short and lasts for 2-3 days. Haemorrhagic manifestations may be witnessed from variable sites- petechiae, ecchymoses, melaena haematuria, epistaxis and gum bleed.

In those patients who recover, improvement generally begins on the ninth or tenth day after the onset of illness. During the convalescence phase, tachycardia, polyneuritis, temporary complete hair loss, xerostomia, poor vision, anorexia, loss of memory and hearing may be present. There is no known relapse of the illness.

Laboratory abnormalities may include leucopenia or leucocytosis, thrombocytopenia, and raised levels of aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase and creatinine phosphokinase. Prothrombin time and activated partial thromboplastin time are prolonged and fibrinogen is decreased, whereas fibrin degradation products are elevated.

Diagnosis

Diagnosis of suspected CCHF should be performed in specially-equipped, high biosafety level laboratories. IgG and IgM antibodies may be detected in serum by enzyme-linked immunoassay (ELISA) from about day six of illness. IgM remains detectable for up to four months, IgG levels decline but remain detectable for up to five years.

Patients with fatal disease may not develop a measurable antibody response and in these individuals, as well as in patients in the first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples- by growing in cell culture or detecting viral antigens using immunofluorescence or ELISA. The method of choice for rapid laboratory diagnosis is the reverse transcriptase polymerase chain reaction (RT-PCR) which is sensitive, specific and rapid.

Case Definitions are enlisted below [4] for purposes of brevity-

Suspected Case- Patient with sudden onset of illness with high-grade fever over 38.5°C for more than 72 hours and less than 10 days, especially in CCHF endemic area and among those in contact with sheep or other livestock (shepherds, butchers, and animal handlers). It is important to note that fever is usually associated with headache and muscle pains and does not respond to antibiotic or antimalarial treatment.

Probable case- Suspected case with acute history of febrile illness 10 days or less,
and Thrombocytopenia less than 50,000/mm^3
and any two of the following:

Petechial or purpuric rash, Epistaxis, Haematemesis, Haemoptysis, Blood in stools, Ecchymosis, Gum bleeding, Other haemorrhagic symptom
and No known predisposing host factors for haemorrhagic manifestations

Confirmed case- Probable case with positive diagnosis of CCHF in blood sample, performed in specially equipped high bio-safety level laboratories (as outlined above)

Treatment

If the case meets the criteria for probable CCHF, isolation precautions should be initiated, health facility staff alerted, the case should be immediately reported, blood samples drawn for CCHF diagnostic confirmation, and treatment protocol started without waiting for confirmation.

General supportive therapy is the mainstay of patient management in CCHF. The WHO recommends that intensive monitoring to guide volume and blood component replacement is required. No specific drug has been approved by the FDA (Food and Drug Administration of USA) for use in CCHF. The antiviral drug ribavirin has been used in treatment of established CCHF infection with some apparent benefits. Both oral and intravenous formulations seem to be effective, although intravenous preparations are not yet available in India. The efficacy of ribavirin has been shown in vitro studies, in mice animal models and treatment with ribavirin was shown to be effective in CCHF patients. However, ribavirin efficacy for CCHF treatment cannot be unequivocally established since controlled studies are lacking in this regard [5]. If the patient meets the case definition for probable CCHF, ribavirin treatment protocol needs

to be initiated immediately with the consent of the patient/ relatives and the attending physician. (It is important that the patient should not conceive within 6 months of ribavirin therapy). High dose oral ribavirin therapy is to be administered as- 2 gm loading dose, then 4 gm/day in 4 divided doses for 4 days followed by 2 gm/day in 4 divided doses for 6 days.

The value of immune plasma from recovered patients for therapeutic purposes has not been demonstrated, although it has been employed on several occasions.

Suspected or diagnosed patient with CCHF should be isolated in a private room, preferably in a negative-pressure room; the subjects should be treated and cared for, using barrier-nursing techniques that include disposable gloves, masks, shoe covers and goggles. The patient should be attended only by designated medical/para-medical staff and all used material such as syringes, gloves, tubing etc., should be collected in autoclave-able bag and autoclaved before incinerating. All instruments should be autoclaved before re-use and all surfaces should be decontaminated with liquid bleach. The patients' samples should be collected, labelled, sealed and decontaminated from outside with liquid bleach and packed in triple container packing. After the patient is discharged, all room surfaces should be treated with liquid bleach and the room should be fumigated. By using these measures transmission in the nosocomial setting can be prevented. In case of death of the CCHF patient, the dead body should be sprayed with 1:10 liquid bleach solution and then placed in a plastic bag which should be sealed with adhesive tape and the vehicle used for the body's transportation should be disinfected with 1:10 liquid bleach solution. The clothing of the deceased should be burned.

In case of direct contact with the patient’s blood or secretions the recommended procedure is the rigorous daily follow-up of the person that came in contact by checking white blood cell counts and biochemical tests for at least 14 days after exposure and the administration of oral high-dose ribavirin (as above). In this regard, prophylactic ribavirin was administered in a health care worker who had a needle-stick injury and it has been shown that the subject did not develop CCHF.

The long-term effects of CCHF infection have not been studied well enough in survivors to determine whether or not specific complications exist. However, recovery is slow.

Prevention and control

- Although an inactivated, mouse brain-derived vaccine against CCHF has been developed and used on a small scale in Eastern Europe, there is no safe and effective vaccine widely available for human use.
- The tick vectors are numerous and widespread and tick control with acaricides (chemicals intended to kill ticks) is only a realistic option for well-managed livestock production facilities.
- Persons living in endemic areas should use personal protective measures that include avoidance of areas where tick vectors are abundant and when they are active (Spring to Fall); regular examination of clothing and skin for ticks, and their removal; and use of repellents. Light-coloured clothing should be worn to facilitate easy tick identification and clothing should cover legs and arms.
- Persons who work with livestock or other animals in the endemic areas (butchers, farmers and veterinarians) can take practical measures to protect themselves. These include the use of repellents on the skin (e.g. DEET, N, N-diethyl-m-toluamide) and clothing (e.g. permethrin) and wearing gloves or other protective clothing to prevent skin contact with infected tissue or blood.
- When patients with CCHF are admitted to hospital, there is a risk of nosocomial spread of infection. In the past, serious outbreaks have occurred in this way and it is imperative that adequate infection control measures be observed to prevent this disastrous outcome.
- Patients with suspected or confirmed CCHF should be isolated and cared for using barrier nursing techniques. Specimens of blood or tissues taken for diagnostic purposes should be collected and handled using universal precautions. Sharps (needles and other penetrating surgical instruments) and body wastes should be safely disposed of using appropriate decontamination procedures.

- Healthcare workers are at risk of acquiring infection from sharps injuries during surgical procedures and, in the past, infection has been transmitted to surgeons operating on patients to determine the cause of the abdominal symptoms in the early stages of (at that moment undiagnosed) infection. Healthcare workers who have had contact with tissue or blood from patients with suspected or confirmed CCHF should be followed up with daily temperature and symptom monitoring for at least 14 days after the putative exposure.

- Use of acaricides on animals before slaughter or export is recommended. Human outbreaks have been reported after exposure to infected ostriches during slaughter. These infections seem to be preventable by keeping the birds free of ticks 14 days before slaughter. In CCHF-endemic areas, it has been suggested to have a 30-day quarantine period for ostriches before slaughter.

There is a need to study the prevalence in animals and in at-risk humans in endemic areas, and a useful animal model needs to be developed. Research also needs to explore the efficacy of specific treatment with ribavirin and other anti-viral drugs, and development of a safe and effective vaccine for human use.

In India and other tropical countries a number of viral haemorrhagic fevers may be endemic. It is important to entertain the possibility of CCHF whenever a viral haemorrhagic fever is encountered, specially when sudden onset fever of 3 to 10 days duration along with myalgias is reported in persons having close contact with livestock; and which does not respond to antibiotics or antimalarials. An informed and vigilant practitioner can help contain such illnesses in the long run.

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