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Review Article

An Emerging Threat of Crimean Congo Hemorrhagic Fever: Call for Preparedness

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ABSTRACT

In poor–resource countries, most of the population depends on primary health centers, which are run by public sector. Recently, emerging and re–emerging diseases cause a great threat to human as well as animals. One of such diseases is the Crimean–Congo hemorrhagic fever (CCHF), which is affecting few human beings (with ensuing death) in the Gujarat state and is considered an additional challenge before the medicos. The disease is one of the deadly hemorrhagic fevers that are endemic in most parts of the world, and is caused by genus *Nairovirus* of Bunyaviridae family. Ticks either of genus *Ixodid* or *Argasid* can transmit this virus. Humans become infected either due to tick bite or by contact with blood or other fluids of body of another infected human being. The persons like veterinarians, animal health professionals, medicos and paramedical staff, livestock and agriculture industry workers are at risk to this infection. For diagnosis of the disease, virus isolation, enzyme–linked immunoassay (ELISA) and polymerase chain reaction (RT–PCR) are the most common and specific assays. The mainstay is intensive monitoring and supportive treatment. Ribavirin is found to be effective but it is controversial. In the absence of any effective vaccine, the effective preventive and control measures are control of vector (tick) population, hygienic measures, and awareness among health professionals. The present review attempts to summarize the knowledge on the disease in terms of etiology, public health concern, vectors involved in transmission, pathology and pathogenesis, clinical signs, diagnosis, treatment, prevention and control.

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INTRODUCTION

About 80% of Indian populations are depending upon the primary health care centers supported by general medical practitioner to avail the medical facility. Presently, the medical professionals are standing at a cross road to tackle the newly emerging diseases, which have never been taught nor even included in their course curriculum. One of such diseases is the Crimean–Congo hemorrhagic fever (CCHF) affecting few human beings (with ensuing death) in the Gujarat state as reported recently is an additional challenge before the medicos (Bajpai and Nadkar, 2011; Lahariya et al., 2012). National Institute of Virology at Pune and High Security Disease Investigation Laboratory of Indian Veterinary Research Institute located at Bhopal are presently involved for isolation and confirmation of virus from the clinical sample. Being a zoonotic disease, the situation is more alarming for the farmers and other workers of livestock, agricultural and slaughterhouses; including veterinarians, those are more closely associated with animal husbandry practices due to their occupation; especially in poor–resource countries (Leblebicioglu, 2010; Appannanavar and Mishra, 2011; Bajpai and Nadkar, 2011). Humans and young mice are the only known host species that build up clinical disease with CCHF virus. At this juncture, the medical professionals need to update themselves with recent information about this deadly virus so that they can take appropriate precaution to save them and minimize the spread of disease to susceptible individuals. The possible factor responsible for emergence and re–emergence of CCHF is climate, environmental and economic changes that significantly affect the reproduction rate of ticks and other human activities in agriculture, human mobility (Maltezou and Papa, 2010; Mertens et al., 2010; Estrada–Pena et al., 2012). The present review attempts to summarize the knowledge on the disease in terms of etiology, public health concern, vectors involved in transmission, pathology and pathogenesis, clinical signs, diagnosis, treatment, prevention and control.

Causative Agent

The causative agent of Crimean–Congo hemorrhagic fever (CCHF) is a RNA virus of the genus *Nairovirus*, family *Bunyaviridae* (Flusin et al., 2010; Appannanavar and Mishra, 2011; Bajpai and Nadkar, 2011). The virus is a spherical, single–stranded RNA virus having envelope and the genome contains three segments [small (S), medium (M), large (L)] (Zhou et al., 2013) encoding for the virus nucleocapsid protein, the two envelope proteins (Gn and Gc), and the viral transcriptase proteins, respectively (Schmaljohn, 1996). The CCHF virus structure as well as replication strategy is similar to other Bunyaviruses. Virus enters inside the cells due to receptor–dependant endocytosis using viral glycoproteins (Gn and Gc)

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as ligands that binds with specific receptor present on susceptible host cells. Following entry, virus replicates in the cytoplasm (Nichol, 2001). Phylogenetically, on the basis of the sequences of viral small segments, CCHFV strains can be divided into seven clusters (clades). The virus is one of the most genetically diverse arboviruses, with nucleotide sequence differences ranging from 20% (in S segment) and 31% (in M segment) (Morikawa et al., 2007; Bente et al., 2013). Virus shows genetic diversity via reassortment and recombination events that may happen amongst CCHFV strains during co–infection of ticks or vertebrates (Anagnostou and Papa, 2009; Bente et al., 2013). Virus strains from different geographic regions may show a high degree of genetic diversity, while closely related viruses have also been isolated in far distant regions (Bente et al., 2013). The virus is susceptibility to disinfectants like 1% hypochlorite and 2% glutaraldehyde and can be physically inactivated at 56°C for 30 min and it is stable in blood outside the host for up to 10 days at 40°C. The virus is highly susceptible to the drug ribavirin.

Host Range and Vector Involved

Though the CCHFV can infect animals, however cattle, sheep, goats, camels and hares may not show clinical signs due to asymptomatic stage. The causative virus has been isolated from all these animals as well as virus specific antibodies have been demonstrated in sera, without any clinical disease. Ixodid (hard ticks) or Argasid (soft ticks) can play role in transmission of the disease (Heyman et al., 2010; Leblebicioglu et al., 2012; Gargili et al., 2013). The principal vector of CCHFV comprises of the ticks of genus *Hyalomma* (*H. marginatum marginatum*), probably because both immature and adult stages actively seek hosts for the blood meals, which is required for maturation (Bente et al., 2013) but the non *Hyalomma* tick species can also transmit the virus to humans. Depending on the geographical area, apart from *Hyalomma* species; Ixodes species, (*Boophilus microplus*, *Dermacentor niveus*, *Rhipicephalus bursa*) have also been involved in the transmission of CCHF (Hoogstraal, 1981). Transstadial transmission of CCHFV in the ticks during their life stages (larvae to nymph to adult) helps the virus to persist in host ticks. Transovarial route of transmission can also be observed with this virus (Gonzalez et al., 1992; Turell, 2007). The highest titers of CCHFV can be recovered from salivary glands and reproductive tissues from the experimentally infected ticks, positively linked with blood feeding. CCHFV can also show venereal transmission (male to female) in *H. truncatum* ticks. An enzootic tick–vertebrate–tick cycle plays crucial role in circulation of the virus and wherein sheep, goats, and cattle are thought to be the amplifiers of the virus. Antibodies have been reported in horses, donkeys, pigs, rhinoceroses, giraffes and buffalo (CFSPH, 2007). Infestation of the immature stages of the ticks by small animals such as rabbits, hares, hedgehogs and rodents assist the maintenance of the virus in the lifecycle of the ticks (Gonzalez et al., 1992; Gargili et al., 2013). Feeding on the ground–dwelling birds, hares and hedgehogs drives larval and nymphal ticks to become infected with CCHFV, (Gale et al., 2010), while the adult ticks become infected while feeding on infected sheep, goats, cattle and pigs (Gale et al., 2010). Most species of birds play role as mechanical vectors in transportation of infected ticks, and appear to be refractory to CCHFV infection; but experimental studies in Ostriches have revealed the presence of the virus in for up to 1 to 4 days in blood and 5 days in visceral organs (Center for Food Security and Public Health (CFSPH), 2007). In experimentally infected blue–helmeted guinea fowl (*Numidia meleagris*), low viremia was reported and antibodies have been reported in a magpie. Experimentally infected red–beaked hornbill and a glossy starling became seropositive but with no viremia. In tortoise, antibodies to CCHF virus have been reported from Tadzhikistan (CFSPH, 2007). Expertise from either parasitologist or entomologist is very much required for the identification of ticks and isolation of virus in laboratory having adequate biosafety facilities.

Mode of Transmission

Although ticks are often involved in the transmission of CCHFV (Elston, 2010), transmission from animal to human as well as from human to human may also occur (Vorou et al., 2007). Fortunately, virus cannot survive in a sound way outside the body of host. CCHFV infection in humans is acquired by direct contact with infected blood or other tissues of the infected individuals or livestock animals or from the bite of a tick (Flusin et al., 2010; Bajpai and Nadkar, 2011). Most of the CCHF cases have been reported to occur in persons involved with the livestock and animal husbandry industry like agricultural/farm workers, slaughterhouse personnel's and veterinarians (WHO, 2001; Bente et al., 2013). Farmers, veterinarians and health professional/workers can be infected by exposure to CCHFV infected blood and other body fluids, or via contaminated needle injuries through direct contact of their broken skin or mucous membranes (Bente et al., 2013). Infection may also occur during post–mortem examination in an abattoir or during treatment of an apparently healthy animal, which is harboring the virus. Apart to this, exposure to the bloody vomits, body fluids or aerosol from patients with advanced disease stages can also lead to human–to–human transmission of the virus (Chinikar et al., 2010). Out of all these possible ways of acquiring infection, the bite of an adult tick or mashing of an infected tick on exposed skin play primarily role in making humans infected.

Epidemiology

CCHF was first identified in the Crimea of Russia in 1944–1945 (Casals et al., 1970). The disease was associated with the bite of the tick *H. marginatum* in humans and the etiological agent was detected in the larvae, adult ticks and blood of patients during the fever. Subsequently, in the year 1956 this disease was seen in Congo of Zaire in Africa from the blood of febrile patients (Casals, 1970; Whitehouse, 2004). In 1969, it was recognized that the pathogen causing the Crimean haemorrhagic fever and the Congo haemorrhagic fever were serologically indistinguishable and linkage of these two place names resulted in the current name for the disease and the virus (Casals, 1969; Whitehouse, 2004; Gao et al., 2010; WHO, 2011; Wu et al., 2013). CCHF is one of the deadly hemorrhagic fevers that are endemic in Africa, Asia, Russia, Europe, and the Middle East and being zoonotic, it is of public health concerns in many countries of the world (Mardani and Keshtkar–Jahromi, 2007; Flusin et al., 2010; Leblebicioglu, 2010; Chinikar et al., 2010; Appannanavar and Mishra, 2011; Ergonul, 2012; Leblebicioglu et al., 2012; Lobermann et al., 2012; Bente et al., 2013; Oncu, 2013; Nemeth et al., 2013). The surveillance of the virus is difficult in Africa, due to limited sanitary facilities. Nearly 100 cases were reported in Africa especially in South Africa in the last decade (Grard et al., 2011). In 2003, outbreak occurred in Mauritania (Nabeth et al., 2004) and a nosocomial outbreak was reported in Sudan in 2008 (Aradaib et al., 2010; Grard et al., 2011). CCHF is endemic in Europe and Bulgaria however outbreaks have been recorded in other countries like Kosovo, Turkey, Albania, Ukraine and South–west of the Russian Federation with increased number of cases (Maltezou et al., 2010). In Bulgaria, totally 159 CCHF cases were identified between 1997 and 2009 (Vescio et al., 2012). Between 2002 and 2009 increased numbers of CCHF cases were reported from Turkey (Ozdarendeli et al., 2010). During 2010, Pakistan notified to World Health Organization (WHO) about 26 suspected CCHF cases, including 3 deaths. In 2012, similar outbreak occurred in

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Pakistan with 61 suspected cases, including 17 deaths (case fatality rate 27.8%). The last outbreak was reported from Pakistan with 16 suspected cases, including 6 deaths in July 2013 (Chinikar et al., 2010; WHO, 2010; WHO, 2013a). CCHF is a notifiable disease to the World Organization for Animal Health (OIE) and the WHO due to the risk of its zoonotic potential.

The first outbreak of CCHF in India was reported from Ahmedabad, Gujarat province of western India in January 2011 (NCDC, 2011; Patel et al., 2011). In this outbreak among 76 reported cases, four human deaths were occurred in which the first death was of a 32–year old housewife on 3rd January, 2011 in a Korat village of Sanand, and on 13th January, 2011 a 35–year old doctor treating her died, and on 18th January, 2011 an accompanying nurse also died (Mourya et al., 2012). The following villages were affected seriously during outbreak of CCHF in Gujarat – Moraiya (13 cases), Shela (6 cases), Changodhar (23 cases), Navapur–Vaghajipuar (13 cases), Dholeshwar (5 cases), Kolat (9 cases), Motidevti (1 case) and Telav (6 cases) (Ministry of Health and Family Welfare, 2011). The entomologists collected the ticks from the affected village and Ahmadabad Municipal Corporation area and sent these to National Institute of Virology (NIV), Pune and High Security Animal Disease Laboratory (HSADL) in Bhopal, Madhya Pradesh for viral investigations. Rodent samples were also sent to the HSADL laboratory in Bhopal. The CCHF virus was found in high quantities in ticks (Mourya et al., 2012). National Centre for Disease Control, New Delhi developed the polymerase chain reaction (PCR) primers for the testing of the samples. To tackle the infection, the Gujarat government supplied the Ribavirin tablets (Sinha, 2011).

A seasonal pattern of disease is observed with the highest activity time of ticks during spring and early autumn (Vorou, 2009). Till date, this disease has been reported as an endemic in our neighboring countries like Tazakistan, Pakistan, Russia, Iran and Turkey (Maltezou and Papa, 2010; Tishkova et al., 2012; Atkinson et al., 2013; Keshtkar–Jahromi et al., 2013). Therefore, there is a need to take precautionary measures to combat the threat nip it in the bud, before it spreads to a greater extent. Outbreaks reported in Africa and Eurasia indicates that one should be careful about migrating birds infested by immature ticks. Indeed, the birds may play significant role in the spread of CCHF virus. Ostrich is the only known susceptible bird for CCHFV infection; two disease outbreaks of CCHF have been documented in South Africa with slaughtering of these birds.

Public Health Importance

Only humans and new–born mice readily succumb to disease. However, domestic animals and non–human primates are either refractory or undergo mild infection with transient viremia sometimes, but they act as a main source of infection for humans (Prajapati et al., 2011). Persons living in close contact with animals are at the high risk of getting CCHF. Veterinarians and farmers may castrate, dehorn, attach ear tags and immunise the young animals, and thus expose themselves through getting infected blood onto broken skin. Animals are sometimes co–infested with tick–borne diseases like babesiosis or anaplasmosis and at the same time with CCHF virus, and are thus viraemic at a time when they are treated, autopsied or butchered by veterinarians, farmers and farm workers, wherein these may get the CCHF infection. In urban areas, consumption of CCHF infected animals meat is a potential threat to public (Ergonul, 2006). CCHF harbouring tick infested animals pose an additional threat to abattoir workers, as partially engorged ticks tend to detach from their hosts after slaughter, or from the hides and skins of the hosts, and may then attach to any humans in the vicinity. Droplet exposures to mucous membrane from the infective blood, aerosols, and accidental parenteral inoculation are the primary hazards (WHO, 2013).

Potential Bioterrorism Agent

CCHF virus can be transmitted from person to person with a case–fatality rate of 5–50%. It is transmissible by small–particle in aerosol. The highly pathogenic nature of the CCHF virus has created the fear that it might be used as an agent of bioterrorism or bio–warfare (Ergonul, 2006). According to WHO classification CCHF virus comes under risk group IV and requires BSL–4 for limiting the number of researchers with access to this pathogen (Bronze et al., 2002; Keshtkar–Jahromi et al., 2011). There is possibility of usage of CCHF virus as a mass casualty bioterrorism weapon (Borio et al., 2002). However, all possibilities need to be kept in the mind and research in this virus should be continued.

Pathology and Pathogenesis

The strategy adapted by the virus in disease progression involves deregulation of host immune responses by combating and attacking cells involved in initiation of antiviral responses, which results in delay in synthesis of interferon (Andersson et al., 2008; Weber and Mirazimi, 2008). The exact mechanism for hemorrhages is unclear but may be due to damage to endothelial cells that leads to deregulated stimulation of platelet aggregation, resulting into coagulopathy. This further stimulates the intrinsic coagulation cascade, which eventually results into the deficiency of blood coagulation factor and subsequent hemorrhages. Increased vascular permeability occurs due to destruction of endothelial cells or due to disruption of the tight junctions of the endothelial barrier, but the later event as well as necrosis or apoptosis of cells was not observed in epithelial cell lines with CCHF virus. These results indicate that the hemorrhages and coagulation disorders are the indirect effects of CCHF virus, probably with high proinflammatory cytokine levels. Excessive release of cytokines may lead to vasodilatation, higher vascular permeability and hypotension with failure of vital organs, shock and ultimately death (Akinci et al., 2013). CCHF virus also impairs the innate as well as adaptive immune system, which cause poor clearance of CCHFV from the body.

Bente et al. (2010) established a new mouse model to study CCHFV pathogenesis that exhibits key features of fatal human CCHF, without adaptation of the virus to the host. They reported mice deficient in the STAT–1 signaling molecule were highly susceptible to virus infection, succumbing within 3 to 5 days post infection. CCHF virus challenged mice showed fever, leukopenia, thrombocytopenia and highly elevated liver enzymes. Main histopathological changes were noticed in liver and spleen. Proinflammatory cytokine levels were significantly increased in the blood of the affected animals, suggestive of a cytokine storm. Immunologic analysis revealed delayed immune cell activation and intensive lymphocyte depletion, which may be responsible for pathogenesis of CCHFV.

Clinical Signs in Humans

The incubation period of CCHF virus ranges from a few days up to 1 week depending on the route of transmission the load of viral inoculum. The development of disease is rapid with the course of four stages: incubation, pre–hemorrhagic, hemorrhagic and the convalescence period with a case fatality rate of 2–50% (Chinikar et al., 2010). The symptoms of pre–hemorrhagic phase are non–specific and usually initiates with fever, myalgia, dizziness, headache, sore eyes, photophobia, neck pain and stiffness, backache, all of which may disappear on an average after 3 days of appearance (Ergonul, 2012). There may be fever, malaise, nausea, vomiting and aching throat, arthralgia, myalgia, diarrhoea and generalised abdominal pain (Mardani and Keshtkar–Jahromi, 2007; Leblebicioglu, 2010). After 2–4 days, all these symptoms may be substituted by

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sleeping sickness, depression and lethargy/exhaustion, and pain in the abdomen may get precipitated to the right upper quadrant with noticeable hepatomegaly. Hepatitis may be seen in few patients, which might lead to jaundice. Septicemia affects nearly all of the body organs including liver, lungs and lymphoid tissues (Weber and Mirazimi, 2008).

The hemorrhagic fever stage is of shorter duration, characterized by epistaxis, bleeding from the gastrointestinal, urinary and respiratory tract, skin bleeding with petechiae to ecchymoses. Hepatorenal and pulmonary failure occurs in severe cases along with faulty coagulation causing haemorrhages. Contrary to it, less severe febrile cases with no hemorrhages can also be observed. In surviving patients, improvement starts 10 to 20 days after the onset of illness. However, generalized weakness, a weak pulse and tachycardia are observed in the convalescent phase. Usually a complete but slow recovery is seen which may take even a year or so.

Clinical Signs in Animals

CCHF virus infections are asymptomatic in animals. Experimentally infected sheep and cattle show only transient and mild elevation in body temperature and become viremic for one week (CFSPH, 2007). But viremic mammals can transmit CCHF virus in their blood and tissues. No postmortem lesions have been reported in animals except newborn rodents.

Sample Collection

The important specimens for virus isolation are venous blood, serum, midstream of urine, and throat swab (Whitehouse, 2004). In postmortem liver, spleen and kidney tissue are desirable for virus isolation (WHO, 2011).

Diagnosis

The timely diagnosis of CCHF is important for the patients, nosocomial infections and to prevent outbreaks so that mortality rate can be reduced (Mardani et al., 2010; Ergonul, 2012). The serum levels of aspartate and alanine aminotransferase (AST and ALT) gets increased, prothrombin is extended, thromboplastin times are incomplete, and anemia, leucopenia and thrombocytopenia have also been observed (Mardani and Keshtkar–Jahromi, 2007). Complete blood and platelet counts, prothrombin and activated partial thromboplastin time as well as liver function test provide presumptive diagnosis for this fatal disease (Flusin et al., 2010). In clinical cases, the levels creatinine phosphokinase and lactate dehydrogenase liver enzymes are elevated and bleeding markers gets delayed (Ergonul, 2006). The disease can be diagnosed in laboratory by virus isolation, antigen detection, molecular techniques (RT–PCR), and detection of antibodies against CCHFV (Mardani and Keshtkar–Jahromi, 2007; Flusin et al., 2010; Ergonul, 2012; Oncu, 2013). Recently, immunofluorescence assay and enzyme linked immunosorbant assay (ELISA) have been found useful to detect virus specific antibodies (IgM and IgG) using recombinant virus N protein antigen as a test antigen. Identifying IgM specific antibodies or a fourfold increase of IgG antibodies in clinical sera by ELISA test is considered to be a positive indicator of disease (Saijo et al., 2005; Bajpai and Nadkar, 2011). On the other hand, the antibody responses show considerably high inverse correlation with load of virus. Unfortunately, many times fatal cases have slight substantiation of antibody responses against CCHF virus. Therefore, the revealing CCHFV DNA in the blood with reverse transcription–polymerase chain reaction (RT–PCR) test is a sensitive diagnostic alternative having greater accuracy. Improvement in RT–PCR test has gone further to differentiate strain variation incorporating different primers instead of using single primer (Duh et al., 2006). Isolation of virus in newborn mice through intracranial or intraperitoneal inoculation of clinical samples (blood from the human patient or ground tick pools) is the traditional method used but it is more sensitive than cell culture isolation technique. But these methods can be carried out only in biosafety level–4 (BSL–4) laboratory, which are available only in limited areas. For isolating virus from blood and organ suspensions a variety of cell lines (LLC–MK2, Vero, BHK–21, SW–13) can be used for good yield of virus. Only elevated concentrations of CCHFV can be detected in cell cultures, considered to be most helpful during initial five days of sickness. A non–cytopathic persistent infection of the cells, based on the viral strain and cell line, is generally seen, with little or no cytopathic effect (CPE) may be seen in some cases. Therefore, virus isolation in cell culture is generally less sensitive. CCHFV can be detected by immunofluorescence assay (IFA) using virus specific monoclonal antibodies (MAbs). RT–PCR assay being highly sensitive can be well employed for CCHFV positive screening of culture negative samples and the test has also added advantage of screening stored clinical samples, retrospectively. Recently, reverse transcription loop–mediated isothermal amplification (RT–LAMP) has been reported to be highly useful for quick detection and differentiation of the virus in distant locations as well as rural hospitals (Osman et al., 2013).

Treatment

The therapy of CCHF is thorough surveillance and supportive treatment (Bajpai and Nadkar, 2011; Ergonul, 2012; Oncu, 2013). Red blood cells, platelets, plasma transfusions and maintenance of normal blood pressure are necessary as part of supportive treatment (Mardani and Keshtkar–Jahromi, 2007; Leblebicioglu et al., 2012). Currently, no specific antiviral treatment exists for CCHF in humans (Flusin et al., 2010) so the supportive treatment becomes more essential (Leblebicioglu et al., 2012). However, scientific reports indicate that intravenous injection of ribavirin is effective for therapeutically controlling CCHF infections (Soares–Weiser et al., 2007; Bajpai and Nadkar, 2011; Ascioglu et al., 2011; Ergonul, 2012; Oncu, 2013) but it is controversial (Flusin et al., 2010; Keshtkar–Jahromi et al., 2011). Few reports suggest for both oral and intravenous formulations of Ribavirin (Ozkurt et al., 2006; Mardani and Keshtkar–Jahromi, 2007). Contrary to it, recent report indicated no clear benefit from Ribavirin therapy in suspected and confirmed cases of CCHF patients (Ergonul, 2008; Soares–Weiser et al., 2010). Novel and emerging therapeutic modalities like cytokine, herbal, gene silencing, virophages and others need to be explored for CCHFV (Mahima et al., 2012; Dhama et al., 2013 a, b).

Prevention and Control

In the absence of any effective vaccine, the only preventive and control measures are control of vector (tick) population, hygienic measures, and awareness among health professionals (Flusin et al., 2010; Bajpai and Nadkar, 2011). Measures need to be taken to counter the problem of global warming and emergence of tick borne diseases (Dhama et al., 2013c). In absence of full proof technique to eradicate the tick population (vector), it is suggested that complete prevention of CCHF is quite impossible. However, in CCHF endemic areas, acaricide treatment of livestock and protective measures against tick bite are effective in reducing the prevalence of disease (Bajpai and Nadkar, 2011). The virus has been classified as a WHO Risk Group IV pathogen and appropriate animal models are lacking. These reasons are the major blocks in development of prophylactic and therapeutic measures (Keshtkar–Jahromi et al., 2011). The most important ways to protect humans from the disease is having a check on the tick population and avoiding contact with virus infected materials. A strict isolation practice needs to be implemented in hospitals for a suspected case so that healthcare persons and other workers are protected well in time before confirmatory diagnosis or negative results (Leblebicioglu, 2010). A risk of nosocomial transmission and

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spread of viral infection from patients with CCHF in hospital is of major public health concern (Mertens et al., 2010). Adequate disease control measures are needed to avoid grave outbreaks of CCHF. For reducing the danger of virus spread to healthcare personnels, awareness and follow up of safer practices does have high value. High–risk persons like veterinarians, farmers, shepherds, butchers, slaughterhouse employees and people in endemic areas need to be aware about CCHF and must avoid themselves in contacting contaminated substances viz., infected ticks, blood, saliva and infected animal tissue. They should use appropriate protective clothing and preventive repellents. Using 1% hypochlorite or 2% glutaraldehyde solution can disinfect affected area. A critical element for preventing of CCHFV is to monitor the livestock movements by creating a tracking and registration system (Vorou, 2009), which is practically not possible in our country due to many inherent reasons. Awareness should be made regarding safe animal slaughtering and management of virus contaminated meat and skins. In spite of all such precautionary measures, prevention of this disease is a very difficult task to be achieved and rather preparedness to face the challenge and to minimize the spread of CCHFV before it affects large population.

Vaccines

An inactivated/killed vaccine using mouse brains has been utilized in some countries but without much success. However, in Bulgaria, other parts of Eastern Europe and the former Soviet Union formalin inactivated brain tissue preparation from newly born mice is somewhat efficacious vaccine (Keshtkar–Jahromi et al., 2011; Papa et al., 2011). Dose required is 1 ml and initially two doses are to be given subcutaneously at an interval of 4 weeks. Re–vaccination is required at 1 year after the first vaccination and subsequently after every 5 years (Tkachenko et al., 1971; Vasilenko et al., 1972). Effective antibody response is initiated 14 days after the vaccination. The drawback of vaccine is genetic variability among the viral stains found in European, Asian, Africa and Bulgarian region (Yashina et al., 2003; Seregin et al., 2004).

Conclusion and Future Perspectives

In 21st century, emerging and re–emerging diseases are the most critical public health challenges. The possible factors responsible for emergence and re–emergence of CCHF are climate, environmental and economic changes that significantly affect the reproduction rate of ticks and other human activities in agriculture, human mobility etc. Recently, the outbreak of this infection in Gujarat state knocks the door in India. The population under serious risk of this infection is human and animal health professional, workers of livestock and agriculture industries etc. The emergence of disease poses a significant economic and social challenge As effective prophylactic and therapeutic measures are lacking, urgent and long–term investments are need of today for quick diagnosis, timely and effective response with ultimate goal to reduce disease impact. Health care units should have easy access to blood bank and must possess state–of–art intensive care units. To control the chances of CCHFV exposure, proper precautions should be taken for disposal of blood and other body fluids. There is urgent need of effective control strategies for tick population control so that this type of tick borne infections can be controlled.

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