

# An Update on Crimean Congo Hemorrhagic Fever

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## ABSTRACT

Crimean Congo hemorrhagic fever (CCHF) is one of the deadly hemorrhagic fevers that are endemic in Africa, Asia, Eastern Europe, and the Middle East. It is a tick-borne zoonotic viral disease caused by CCHF virus of genus *Nairovirus* (family Bunyaviridae). CCHF not only forms an important public health threat but has a significant effect on the healthcare personnel, especially in resource-poor countries. India was always a potentially endemic area until an outbreak hit parts of Gujarat, taking four lives including the treating medical team. The current review is an attempt to summarize the updated knowledge on the disease particularly in modern era, with special emphasis on nosocomial infections. The knowledge about the disease may help answer certain questions regarding entry of virus in India and future threat to community.

**Key words:** Crimean Congo hemorrhagic fever, Nosocomial, Update

## INTRODUCTION

Crimean Congo hemorrhagic fever (CCHF) is one of the severe forms of hemorrhagic fever endemic in Africa, Asia, Eastern Europe and the Middle East with a near fatal mortality rate. CCHF not only forms an important public health threat but has a significant effect on the healthcare personnel, especially in resource-poor countries. India was always under the potential threat of CCHF viral infection until an outbreak hit parts of Gujarat, taking four lives including the treating medical team in recent past. With regard to questions on the importation of virus in the region, acquisition of virus by the index case and the viral status in India are yet to be revealed. The endemic potentiality of the country poses a challenge in controlling the CCHF viral infection not only for India but also for its neighboring countries. The present review is an attempt to summarize the updated knowledge on the disease.

CCHF is a zoonotic viral disease caused by tick-borne virus *Nairovirus* (family Bunyviridae). The disease has a wide distribution that correlates with the global distribution of *Hyalomma* tick, the vector responsible for viral transmission. The disease is generally asymptomatic in infected animals

but highly fatal in humans. The disease in humans begins as non-specific febrile symptoms, which progress to hemorrhagic syndrome. Although tick is a major vector in transmission of the disease, further secondary cases are frequently seen due to human to human transmission via percutaneous or per mucosal exposure to blood and body fluids containing the virus. This uncommon transmission takes place most often among healthcare workers in hospital settings, thus posing a significant nosocomial hazard.<sup>[1]</sup> Adhering to universal precautions while caring for patients, timely infection-control measures, and administration of prophylactic therapy to healthcare workers after exposure can serve as important measures in limiting the spread of infection.<sup>[2,3]</sup> However, additional community-based control measures such as use of pesticides to control tick population are necessary to decrease disease transmission and prevent further spread in the community.

## HISTORY OF CCHF

The first evidence of CCHF dates back to the 12<sup>th</sup> century, where a description of a hemorrhagic syndrome in Tajikistan and the description of the arthropod that caused the disease appears similar to the modern-day CCHF.<sup>[4]</sup> In the modern era, CCHF was described for the first time among Soviet Union military personnel in Crimea during World War II (1944-45) and was named Crimea hemorrhagic fever. The virus was isolated from blood and tissues of patients using intracerebral inoculation of suckling mice.<sup>[5]</sup>

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Subsequently, it was shown that the virus responsible for Crimea hemorrhagic fever was indistinguishable from Congo virus that caused febrile illness in Belgian Congo. Hence, linking the two names led to new nomenclature of the CCHF virus.<sup>[6]</sup>

## EPIDEMIOLOGY

The geographic range of CCHF virus is the most extensive one among the tick-borne viruses that affect human health, and the second most widespread of all medically important arboviruses, after dengue virus.<sup>[5,7]</sup> Since its discovery in 1967, nearly 140 outbreaks involving more than 5,000 cases have been reported all over the world. A total of 52 countries have been recognized as endemic or potentially endemic regions, reporting substantial number of cases every year. The distribution of *Hyalomma* spp., the principal tick vector, also has wide distribution. CCHFV is mainly seen in the Middle East and Asia and parts of Europe including southern portions of the former Union of Soviet Socialist Republics (USSR).

In the initial years after the virus was first described in 1967, a majority of cases were reported from the former Soviet Union (Crimea, Astrakhan, Rostov, Uzbekistan, Kazakhstan, Tajikistan) and Bulgaria.<sup>[4,5]</sup> In the years that followed, outbreaks were reported from parts of Africa such as the Democratic Republic of the Congo, Uganda, and Mauritania.<sup>[8,9]</sup> A significant number of cases were also reported from Middle Eastern countries such as Iraq,<sup>[10]</sup> the United Arab Emirates (UAE),<sup>[11]</sup> and Saudi Arabia.<sup>[12]</sup> In the previous decade, most cases have been reported from Pakistan,<sup>[13]</sup> Iran,<sup>[14]</sup> Bulgaria,<sup>[15]</sup> Turkey,<sup>[16-18]</sup> and also India (from the outbreak in Gujarat). A majority of these outbreaks are seen in the community; also, contact with livestock animals infested with ticks is noted. However, in some outbreaks, nosocomial spread was documented where contact with blood and other body fluids from patients have been the main mode of transmission. Between 1953 and 2005, nearly 80 cases of CCHF infection have been described among healthcare personnel.<sup>[7]</sup> Table 1 shows

the nosocomial outbreaks of CCHF observed during the past few years. Individuals who come in direct contact with the patient, such as clinicians, nurses and other hospital staff, are at a greater risk. This happens more when the knowledge about the disease is lacking. Thus, it becomes essential to train healthcare personnel in endemic and potentially endemic regions to manage such situations in order to minimize the nosocomial spread of the infection. Emphasis on standard and universal precautions should be given, especially in resource-poor countries.

India: CCHF viral infection had not been reported in humans from India before, though previous seroprevalence studies have shown viral antibodies both in animals and humans.<sup>[26]</sup> In 1973, Shanmugam *et al.*, in their study, tested a total of 643 human sera from all over India; of these, nine samples from Kerala and Pondicherry were positive for anti-CCHF virus antibody. In the same study, 34 of 655 serum samples collected from sheep, horse, goat, and domestic animals from all over India showed evidence of CCHF virus. Subsequently, in 1977, Kaul *et al.*, conducted a survey of ixodid ticks to determine the Crimean hemorrhagic fever (CHF) virus activity in Jammu and Kashmir state of India, but CCHF virus was not isolated in any of the 138 pools comprising eight species under six genera of ticks.<sup>[27]</sup> However, a related species of the genus *Nairovirus* – Ganjam virus – that belongs to the Nairobi Sheep group is transmitted locally by *Hemaphysalis* ticks. This virus has veterinary importance in India and has been demonstrated in mosquitoes, man, and sheep.<sup>[28]</sup> The recent outbreak of CCHF viral infection in Gujarat is the first notable report from India.<sup>[25]</sup> The striking feature of this outbreak was high fatality and rapid spread among treating medical team.

## MODES OF TRANSMISSION

Humans are infected by the bite of or by crushing an infected tick of the *Hyalomma* spp., against bare skin. The infection can also be acquired by percutaneous and permucosal route by contact with animal blood or tissues

**Table 1: Recent outbreaks of nosocomial Crimean Congo hemorrhagic fever infections**

Year of outbreak	Location	Number of cases	Fatal cases	Setting	Reference
2008	Bulgaria	5 (1)	1 (0)	Community (Nosocomial)	[19]
2008	Sudan	10 (3)	6 (3)	Community (Nosocomial)	[20]
2008	Turkey	688 (1)	40 (1)	Community (Nosocomial)	[21]
2009	Iran	2 (4)	2 (2)	Community (Nosocomial)	[22]
2009	Kazakhstan	19 (3)	5 (3)	Community (Nosocomial)	[23]
2009	Tajikistan	4 (1)	2 (1)	Community (Nosocomial)	[24]
2011	India	2 (3)	1 (3)	Community (Nosocomial)	[25]

Number in brackets indicates the number of nosocomial cases

and drinking unpasteurized milk. The possibility of aerosol transmission is suspected in few cases in Russia, but no definite evidence exists.<sup>[5]</sup> Human-to-human transmission is possible and is an important route in a nosocomial set up when skin or mucous membranes are exposed to blood and body fluids of patients with hemorrhage [Figure 1]. In addition, possible horizontal transmission from a mother to child has been reported.

**RESERVOIRS AND VECTORS**

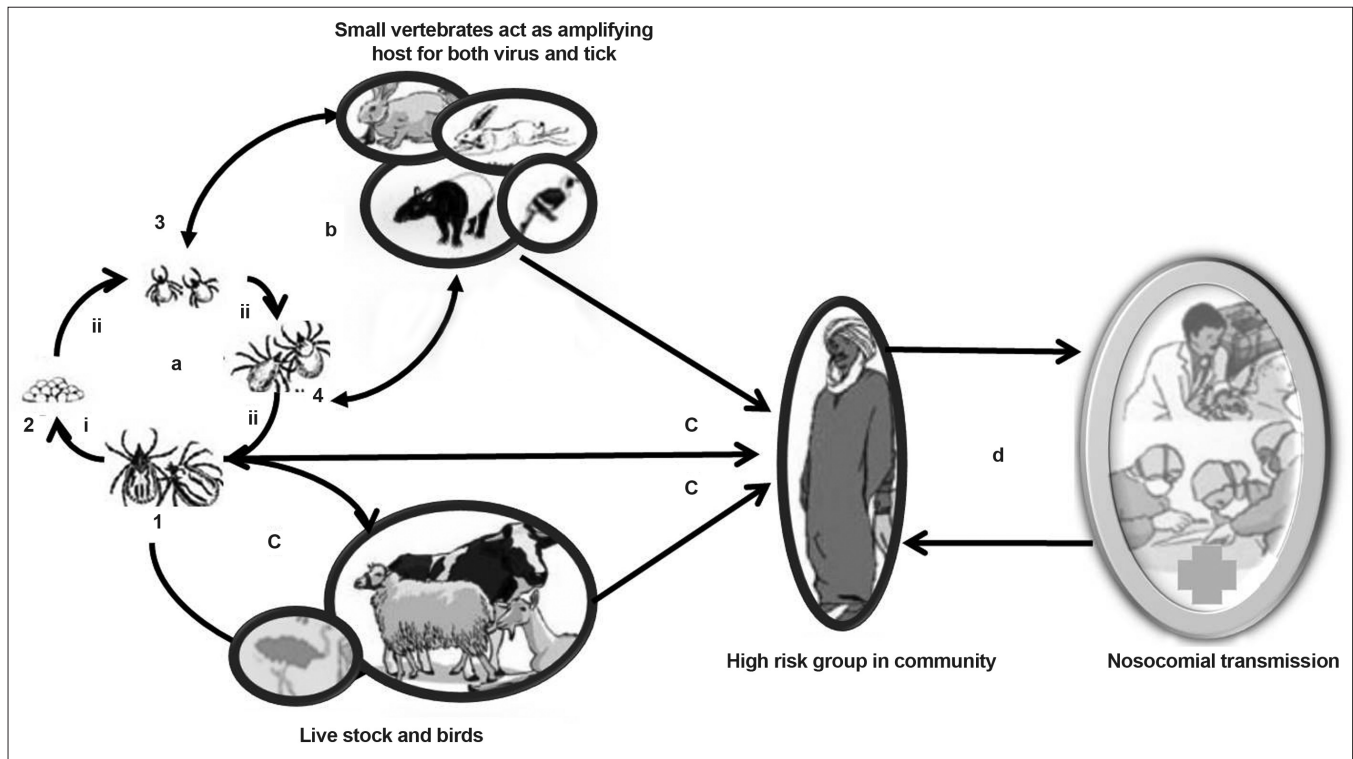
The CCHF virus circulates in an enzootic tick–vertebrate–tick cycle. However, there is no evidence that the virus causes disease in animals. Wide range of domestic and wild animals may get CCHF virus infection. The virus infection has been commonly demonstrated among smaller wildlife species—eg, hares and hedgehogs that harbor the tick vectors that are at immature stages.<sup>[4,5]</sup> These small animals are believed to act as amplifying hosts and maintain the virus in nature. This virus has been found in around 31 species of ticks in seven genera of the family Ixodidae (hard ticks). Among the various genera of family Ixodidae, the most efficient and common vectors for CCHF appear to be members of the *Hyalomma* genus. Other ixodid ticks including members of the genera *Rhipicephalus*, *Boophilus*, *Dermacentor*, and *Ixodes* may also transmit the virus.

These vectors have both trans-ovarial and trans-stadial transmission of virus, thus contributing to circulation of the virus in nature by remaining infected throughout their developmental stages and also by passing to the next generation. Immature ticks (nymphs) generally inhabit smaller animals, while mature ticks transmit the infection to large vertebrates such as livestock.

**AGENT**

**Taxonomy**

The CCHF virus is a member of the *Nairovirus* genus under family Bunyaviridae, which has four other genera, namely, *Hantavirus*, *Phlebovirus*, *Orthobunyavirus*, and *Tospovirus*. Genus *Nairovirus* has approximately 34 described tick-borne viruses that are grouped into seven serogroups.<sup>[29]</sup> Among these, only three members are known to cause disease in humans and they are CCHF, Nairobi sheep disease virus, and Dugbe virus. CCHF virus is a spherical enveloped virus with approximately 100-nm diameter and has glycoprotein spikes 8-10 nm in length. Under electron microscopy, the virion of CCHF can be distinguished from other members within the Bunyaviridae family, as they possess small morphologic surface units with no central holes arranged in no obvious order.<sup>[30]</sup>



**Figure 1:** Modes of transmission of CCHF virus, (a) Tick cycle, 1- adult, 2- eggs, 3- larvae, 4- nymph; (i) Trans-ovarian, (ii) Trans-stadial; (b) Tick- Small vertebrate cycle; (c) Tick- Large vertebrate/bird/human cycle; (d) Human- Human cycle (community/nosocomial)

## Genetic diversity in CCHF

The genome of family Bunyaviridae is tripartite and consists of three segments of negative-sense, single-stranded RNA, small (S), medium (M), and large (L), which encode the nucleocapsid protein, glycoproteins (Gn and Gc), and viral polymerase, respectively. Additionally, an M segment-encoded nonstructural protein, NSM, has recently been identified in the Nairovirus-Crimean-Congo Hemorrhagic Fever Virus (CCHFV). Initially, the antigenic structures of CCHF viruses from various geographical regions were thought to be indistinguishable. With the availability of nucleotide and amino acid sequence information, extensive genetic diversity has been shown in these viruses. Most nucleic acid sequence analyses are based on the S segment of the genome and, according to these studies, the CCHF virus comprises eight genetically distinct clades [Table 2].<sup>[7]</sup> The knowledge of various clades of CCHF virus has great epidemiological implications. These can provide clue regarding the source of infection during an outbreak in an endemic region and also help in tracing the path of spread of imported cases. The significant antigenic differences among various clades should be considered while choosing the target for vaccine.

## CLINICAL FEATURES IN HUMANS

Human beings are the only host of CCHFV in whom the disease manifestations are visible. The typical course of CCHF infection has four distinct phases—incubation period, prehemorrhagic phase, hemorrhagic phase, and convalescent phase. The incubation period for CCHF virus is in the range of 3-7 days. The mean duration is largely influenced by the route of infection, viral load, and source of infection—blood or tissue from livestock. The minimum viral load required for transmission of disease is 1-10 organisms.<sup>[35]</sup> The disease begins with the prehemorrhagic phase characterized by nonspecific prodromal symptoms during which it mimics other

viral diseases. The major symptoms include high fever, myalgia, headache, nausea, abdominal pain, and non-bloody diarrhea. This is accompanied by hypotension, relative bradycardia, tachypnea, conjunctivitis, pharyngitis, and cutaneous flushing or rash.<sup>[4]</sup> The prehemorrhagic phase lasts for 4-5 days and in a majority of the patients it progresses to hemorrhagic phase. The hemorrhagic phase is generally short and has a rapid course with signs of progressive hemorrhage and diathesis. These include petechiae, conjunctival hemorrhage, epistaxis, hematemesis, hemoptysis, and melena. Certain patients may also have hepatosplenomegaly.<sup>[16,18,36]</sup> The disease is fatal in 40-60% of the cases. In severe cases, death occurs as a result of multiorgan failure, disseminated intravascular coagulation, and circulatory shock. Acute respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage, accompanied by systemic inflammatory reaction, have also been reported during hemorrhagic manifestations.<sup>[37,38]</sup> In the survivors, the convalescent period begins 10-20 days after the onset of illness. During this phase, patients may have feeble pulse, tachycardia, loss of hearing, and loss of memory and hair. However, these after effects have been reported only in few outbreaks.<sup>[4,11,16,17]</sup>

## PATHOGENESIS

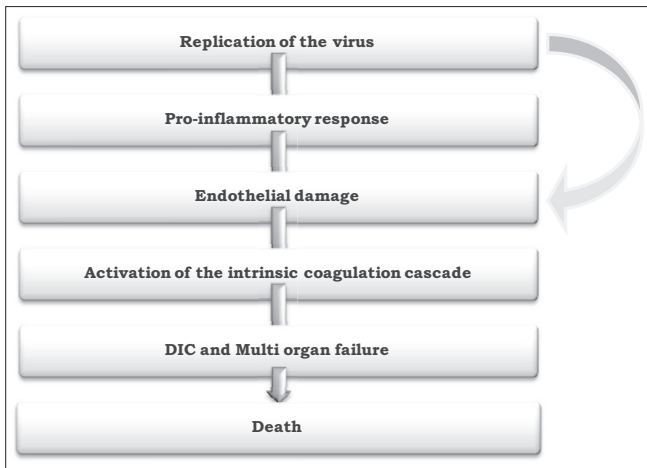
The pathogenesis of CCHF is not well understood. A common pathogenic feature of hemorrhagic fever viruses is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response. This damage is characterized by rapid replication of the virus along with dysregulation of the vascular system and lymphoid organs. As seen in other viral hemorrhagic fevers, damage to the endothelium plays an important role in CCHF pathogenesis. This further leads to hemostatic failure by stimulating platelet aggregation and degranulation, with subsequent activation of the intrinsic coagulation cascade [Figure 2]. Marked pro-inflammatory response disproportional to the extent of lesion is a striking feature seen in these patients. The proinflammatory cytokines are key regulators in the pathogenesis and mortality of patients with CCHF. Levels of Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)- $\alpha$  are shown to be significantly higher in patients with fatal CCHF as compared to those with non-fatal infection.<sup>[39]</sup>

## LABORATORY DIAGNOSIS

Early diagnosis is an essential requirement, not only for patient management but also for prevention of further transmission of disease, as it has the potential for nosocomial spread. A high index of suspicion is necessary in the early

**Table 2: Clades of Crimean Congo hemorrhagic fever virus and their geographic distribution**

Clades	Geographic location	References
Clade 1	European, Southeast Russian, and Turkish strains	15, 31-33
Clade 2	AP92-isolated from <i>Rhipicephalus bursa</i> ticks from Greece	15, 31
Clade 3	Central Asia—Kazakhstan, Tajikistan, Uzbekistan, and China	34
Clade 4	Group 1 from Iran, Madagascar, and Pakistan	15
Clade 5	Group 2 from Iran, Senegal, and Mauritania	15
Clade 6	Senegal, Mauritania, and South Africa	7
Clade 7	Nigeria and Central African Republic	7
Clade 8	Uganda	7



**Figure 2:** Pathogenesis of CCHF viral infection

phase because the clinical presentations are nonspecific. History of travel to endemic areas, tick bite, and exposure to blood or tissues of livestock or human patients are key pointers to suspect CCHF viral infection. The important differential diagnoses for CCHF viral infection are bacterial infections such as rickettsiosis (tick-borne typhus and African tick bite fever), leptospirosis, and borreliosis (relapsing fever) as well as other infections, which present as hemorrhagic disease such as meningococcal infections, Hantavirus hemorrhagic fever, malaria, yellow fever, dengue, Omsk hemorrhagic fever, and Kyasanur Forest disease. Knowledge of endemicity of these infections should be kept in mind to proceed with further diagnostic modalities.

### Viral isolation

The most definitive way of diagnosis is the demonstration of virus or viral genome. Isolation by cell culture is simpler and rapid as compared with traditional methods of intracerebral inoculation of a sample in newborn mice. Viral isolation is done by using cell lines such as LLC-MK2, Vero, BHK-21, and SW-13.4 and can be achieved in 2-5 days. CCHF virus generally produces no or little cytopathic effect and can be identified by immunofluorescence assay with specific monoclonal antibodies. However, viral isolation is useful only in the early phase of infection when the viral load is high but suffers from poor sensitivity; moreover, this can be done only if the biosafety level 4 containment facilities are available.

### Molecular methods

Demonstration of viral genome is by far the most definitive form of diagnosis. Reverse-transcriptase PCR (RT-PCR) is the method of choice for rapid laboratory diagnosis of CCHF virus infection. Another benefit to molecular

diagnostic assays is their rapidity as compared to virus culture, and a presumptive diagnosis can be made within 8 hour. Further improvisation of this technique requires automated real-time assay. The real-time PCR assay has various advantages like lower contamination rate, higher sensitivity, and specificity and provides results in a few minutes. Drosten *et al.*, developed a one-step real-time RT-PCR assay for detecting CCHFV using primers to the nucleoprotein gene; using DNA-intercalating dye, SybrGreen I.<sup>[40]</sup> Later, a real-time RT-PCR assay was developed using TaqMan-Minor Groove Binding Protein (MGB) probe, which had higher specificity and a shorter probe length.<sup>[30]</sup>

### Serological assays

Serological tests are useful in the second week of illness. Serological tests formerly used for the detection of antibody to the virus, such as complement fixation, hemagglutination inhibition and reverse passive hemagglutination inhibition, lacked sensitivity and reproducibility, but indirect Immunofluorescence (IF) could detect IgG and IgM antibody responses by days 7-9 of illness in all survivors of the infection.<sup>[41-43]</sup> Enzyme-Linked Immunosorbent Assay (ELISA) to detect specific IgM and IgG have largely replaced these conventional serodiagnostic tests. Specific IgM persists for up to 4 months post-infection, while IgG remains detectable for at least 5 years. Recent or current infection is confirmed by demonstrating IgM, using IgM antibody capture (MAC)-ELISA in a single sample, or a fourfold or greater increase in antibody titer in paired serum samples.<sup>[44]</sup> Recently, a recombinant nucleoprotein (rNP)-based IgG ELISA was developed for serological diagnosis of CCHF virus infections; this was shown to be a valuable tool for diagnosis and epidemiological investigations of CCHFV infections.<sup>[45]</sup> Similarly, CCHFV rNP-based IgM-capture ELISA has shown to be a useful method for diagnosis of CCHFV infections.<sup>[46]</sup>

### TREATMENT

The general approach in treatment of patients with CCHF viral infection depends on the severity of the clinical manifestation and is done by managing fluid and electrolyte imbalances. The early diagnosis and supportive care in the form of blood, platelet, and plasma replacement has proven to be life-saving, especially in patients with hemorrhagic manifestation. There is no consensus on the role of specific antiviral therapy in the management of these patients. Tasdelen *et al.* have shown the beneficial effect of ribavirin if given at an early phase of the CCHF.<sup>[47]</sup> However, a systematic meta-analysis showed no change in

mortality rate with the use of ribavirin in the randomized control studies, while pooled observational studies showed reduction in mortality by 44%. In addition, no difference in length of hospital stay was reported. Thus, no clear message of benefit is available from the current data on ribavirin, as observational data are heavily confounded. These results clearly indicate the need for randomized control studies in a setting with optimal supportive care.<sup>[48]</sup> According to World Health Organization (WHO), ribavirin is the anti-viral medication of choice for CCHF and the recommended dose is an initial dose of 30 mg/kg followed by 15 mg/kg for four days and then 7.5 mg/kg for six days for a total of 10 days.

Apart from the specific antiviral therapy, the role of immunotherapy in the form of immunoglobulin has also been studied. A new specific immunoglobulin CCHF-Venin that contains antibodies to CCHF virus was prepared from the plasma pool of boosted donors by a combined ethanol-polyethylene glycol fractionation method with an ion-exchange purification step.<sup>[49]</sup> However, unlike that on Ebola virus, limited studies are available, which show the beneficial effects of immunotherapy in CCHF.<sup>[30,50]</sup>

### PROPHYLAXIS

In case of known direct contact with blood or secretions of a probable or confirmed case such as needlestick injury or contact with mucous membranes such as eye or mouth, the recommended procedure is to carry out baseline blood studies and start the patient on oral ribavirin. The direct or indirect contacts of cases should be monitored for 14 days from the date of last contact with the patient or other source of infection by recording the temperature twice daily. If the patient develops a temperature of 38.5°C or higher, headache, and muscle pains, he/she must be considered a probable case, admitted to hospital, and started on ribavirin treatment. Experience with ribavirin in the prevention of CCHF is substantially limited, as compared to other viral hemorrhagic fever, eg, Lassa fever. According to Centers for Disease Control and Prevention (CDC), the *in vitro* susceptibility data of ribavirin in CCHF and other Bunyaviridae supports the use of ribavirin both for treatment and prophylaxis in high-risk contacts. The CDC recommends that similar procedures for care, including isolation and body fluid precautions and therapy, recommended for Lassa fever be followed for patients with CCHF and their contacts; however, additional study and experience is required.

### PREVENTION AND CONTROL MEASURES

The mainstay of prevention and control of CCHF viral

infection should target both at the community level and in the nosocomial set up. At the community level, care should be taken to prevent human contact with livestock and minimize the tick burden in these vertebrate hosts. Measures such as avoidance of tick habitat, regular examination of clothing and skin for ticks, and use of tick repellents should be taken to prevent tick bites. Fully covered clothing is recommended to prevent tick attachment to body parts. While handling livestock or domesticated animals, appropriate acaricidal agents should be used to control tick population. Protective clothing and gloves should be used whenever there is chance of contact with skin or mucous membranes of viremic animals, particularly when blood and tissues are handled. Consumption of unpasteurized milk and uncooked meat should be avoided. Human-to-human transmission of CCHF virus is seen when direct contact with blood and body fluids occurs, especially in a healthcare setup when appropriate infection control measures are not taken. Strict universal precautions are necessary when caring for patients and this can be achieved by barrier nursing, isolation, and use of protective gears such as gloves, gowns, face-shields, and goggles with side shields. Safe burial practices, including the use of liquid bleach solution as a disinfectant, and covering the body in polythene bags have been published. Laboratory workers must follow stringent biosafety precautions and viral isolation techniques should be carried out in laboratories where biosafety level 4 is available. CCHFV can be inactivated by disinfectants including 1% hypochlorite and 2% glutaraldehyde; these can be destroyed by heating at 56°C (133°F) for 30 min. Prophylactic treatment with ribavirin has occasionally been used after high-risk exposures but its role is controversial.<sup>[51]</sup>

### Vaccine

The major hindrance in developing vaccine against CCHF virus is the great genetic variation noted in different strains. Despite this genetic variability, Ahmed *et al.* have shown that some epitopes are conserved, and CCHFV vaccines may have to be either immunogens derived from several CCHFV strains, or can target the immune response on conserved neutralizing epitopes.<sup>[52]</sup> An inactivated vaccine derived from mouse brain has been used in the former Soviet Union and Bulgaria.<sup>[53]</sup> However, in most of the countries vaccine is not available.

### CONCLUSION

CCHF was always an impending threat to India, which has now become a reality with the current outbreak in Gujarat. The vector and reservoir animals were already present. The

related species of the genus *Nairovirus*, eg, Ganjam virus of Nairobi sheep disease, is also transmitted by same vector as CCHF virus and has been reported previously. The emergence of this deadly viral infection in a huge country like India having all ecological suitability for the virus is a challenge for the entire medical fraternity. This emphasizes the need for active surveillance not only for existing pathogens in any geographic location but also for those that pose future threat. The use of molecular techniques even for surveillance is of paramount importance for preventing further spread of this highly pathogenic virus.

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