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ENDEMIC ERRATIC INFECTION CRIMEAN-CONGO HAEMORRHAGIC FEVER (CCHF) NOW IN MAHARASHTRA: AN EPHEMERAL REVIEW

Syed Ayesha Fatema*[1], Dr. Jaleel Ahmed Siddiqui[2] and Jyoti Pathare Randil

[1]*Professor, PG Dept. of Medicine (Moalijat), ZVM Unani Medical College and Hospital Azam Campus Pune Maharashtra INDIA.

[2]HOD and Professor, PG Dept. of Basic Principles Medicine (Kulliyat), ZVM Unani Medical College and Hospital Azam Campus Pune Maharashtra INDIA.

[3]Vice Principal St Andrews College of Nursing Pune. Maharashtra INDIA.

***Corresponding Author: Dr. Syed Ayesha Fatema**

Professor, PG Dept of Medicine (Moalijat), ZVM Unani Medical College and Hospital Azam Campus Pune Maharashtra INDIA.

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ABSTRACT

Rationale and Objectives: Although in India Maharashtra remains sternly affected by the Covid-19 infection since March 2020; anxiety of spread of another disease, Crimean-Congo haemorrhagic fever (CCHF), in Palghar district of Maharashtra, has put the stakeholders of health sciences on its toes. Hence present Research has been accomplished as a way aboard to explore the standpoint of the disease CCHF into the scientific intuition of the epidemic diseases with the focus to uncover concrete information and solution to control the CCHF endemic in Maharashtra, India. **Methodology:** Present descriptive study, accomplished at ZVMUMC Hospital, Pune. Several classical and Modern texts then published papers in various legendary indexed journals have been reviewed to understand CCHF's epidemiology, pathogenesis, clinical standpoints, management, complication and vector facts etc. **Review of Literature:** CCHF is a fatal, acute, tick-borne viral, zoonotic infection associated with high mortality, having diagnostic features of haemorrhage, myalgia, and fever, thrombocytopenia, leukopenia, anemia, increased hematocrit, elevated liver biochemicals, and findings consistent with disseminated intravascular coagulation, eminently diagnosed with IgG ELISA an IgM serology, immunofluorescence and quantitative reverse transcription Polymerase chain reaction. Isolation is mandatory and Oral ribavirin is the first line of treatment. Live attenuated vaccines are still under study for CCHF. **Conclusion:** Defining Strategies for understanding and treatment protocols for the diagnosis and management, Isolation, and Intensive care of CCHF patients, is pronounced utmost necessity of present time.

KEYWORDS: Crimean-Congo Haemorrhagic Fever (Cchf), Endemic, Maharashtra, India, Palghar, Congo Fever, Vector Born Disease.

INTRODUCTION

According to Ministry of Health and Family Welfare, GOI, since the outbreak, of COVID-19 global pandemic, on March 11, 2020, presently at the end of September 2020, total cases 940441 were active and 5187825 were cured, also 97497 were dead globally besides at Maharashtra, total 260789 cases were active and 1069159 were cured, and 36181 were dead.[1] Although Maharashtra remains sternly affected by the Covid-19 infection in recent months; spread of another disease has put the stake holders of health sciences and government on its toes. Authorities have been forewarned about a probable spread of Congo fever in Palghar district of Maharashtra.[2,3,4,5]

Congo fever or Crimean-Congo Hemorrhagic Fever (CCHF) is a dire, tick-borne viral, zoonotic disease with hemorrhagic manifestations and substantial mortality in humans, which was firstly witnessed in Crimea in 1944 and then was first isolated in Africa (Congo) from a febrile patient in 1956[6], then and there, this virus is far and widely distributed around the world.[6] CCHF is a fatal viral infection pronounced in parts of Africa, Asia, Eastern Europe, and the Middle East.[7] By 2000, new outbreaks had been reported from India too along with other countries, but the virus was not isolated from India's samples.[8, 9] However, the presence of CCHF in India was firstly documented in 2011 during a nosocomial outbreak in Gujarat.[10] In addition, a cross-sectional serosurvey of CCHF among livestock in 22 States in India done by ICMR during 2013-2014 has submitted occurrence of CCHFV infection among castles in different states.[11] Afterwards, at Gujrat in August 2019, few confirmed CCHF cases, detected including animal caretakers and medical personnel treating Congo fever patients.[12] From this time forth, it's been evaluated that Secondary infections commonly can occur due to human-to-human transmission through either

percutaneous or mucosal contact to infected blood and body fluids. At present after Gujrat, because of the current outbreak at Palghar Maharashtra, present Research has been done as a way aboard to explore the standpoint of the disease Crimean-Congo haemorrhagic fever (CCHF) into the scientific intuition of the epidemic diseases with the focus to uncover concrete information and solution to control the disease CCHF endemic in Maharashtra and India.

METHODOLOGY

Present research is of descriptive observational study Design, done at dept of General Medicine, at ZVMUMC and Hospital Pune in the middle of September – October 2020. Many classical texts, books and published research papers in various reputed indexed journals like *NEJM, Lancet, BMJ, ICMR journals* etc. have been reviewed to understand about the disease CCHF, its epidemiology, pathogenesis, clinical standpoints management and complication. It's been found that the disease CCHF is so rare that it has not been mentioned in many famous books of medicine i.e. Harrisons, Davidsons, Robbins pathology, harsh Mohan, API. It's been found that annual book Current medical diagnosis and treatment 2018 and 2019 has mentioned the details of the disease CCHF in it, where Garnes JMDN and Shandera XW has mentioned as one of several single-stranded RNA viruses (members of the family of Bunyaviridae infection) under headings of haemorrhagic fevers.as The bunyaviruses include the Crimean-Congo hemorrhagic fever (transmitted by infected animal exposure or tick bite and possibly by sexual intercourse), the Rift Valley fever (transmitted by exposure to infected animal products or bite of an infected mosquito or other infected insect), and the Hantaviruses (associated with rodent exposure and discussed separately below). The search strategy followed to retrieve data, as key words i.e. *epidemic, pandemic, CCHf, Crimean-Congo hemorrhagic fever, bunyaviruses, Congo fever, tick-borne diseases, viral diseases, zoonotic diseases, haemorrhagic fever.* References has been written in Vancouver referencing styles and generated through, Queen's University Belfast cite 2 write website of reference generator.[13]

REVIEW OF LITERATURE

Etiology: CCHFV is the single-stranded, enveloped, RNA virus, belongs to the genus Nairovirus and family Bunyaviridae, holding tripartite, negative polarity.[14] The bunyaviruses consist of CCHFV, the Rift Valley fever virus and the Hantaviruses, and they infect by disease-ridden animal exposure or tick bite, possibly by sexual intercourse, bite of an infected mosquito or other infected insect and rodent exposure subsequently.[15] Particularly the CCHFV is transmitted to humans through tick saliva during blood feeding by infected tick bites or from direct contact with viremic animals or humans.[16] Ticks are utmost vital vectors and reservoirs of CCHFV and human beings may get infected if they intrude normal life cycle of the diseased ticks, which is happening, on animals as their host.[17] Hyalomma species of Ticks as the main vector, and others like Rhipicephalus, Haemaphysalis and Dermacentor species also play role of important vectors of CCHFV infections, who reservoir this virus; thus, in view of geographical dissemination, type of host and environmental conditions, diverse range of ticks responsible for the incidence of CCHF disease.[17] Main vectors are Hyalomma marginatum, D. marginatum and several species of Rhipicephalus bursa, and Boophylus annulatus potentially serves as secondary vectors.[18] Another way of spread of CCHFV among tick vector is an interesting mechanism called "co-feeding behavior" in which viral transmission occurs between feeding ticks on the host.[17] Apart from tick bite, the other route for transmissions of virus to human being (nosocomial infections and the direct contact with infected blood or tissue).[17] The extent of the incubation period duration depends on the mode of acquirement of the virus,[19] so it may varies between species, ranging from 2 to 21 days.[15, 20, 21]

Diagnosis: Although viral hemorrhagic fevers are an imperative etiology to contemplate in pyrexia of unknown origin (PUO) in children in predominant areas, but due to deficiency of accurate presenting symptoms, it becomes challenging to reach the diagnosis.[21]

The clinical symptoms in the early phase of a viral hemorrhagic fever, be similar to a flu-like illness or gastroenteritis or Hepatitis and in late phase is more specific like Exanthemas, mucosal lesions, organ failure, persistent leukopenia, altered mental status, and hemorrhage can occur.[15,20,21] Onset of symptoms could be sudden, with fever, myalgia, (muscle ache), dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia (sensitivity to light). With some differences among different regions suggested but not well studied.[22] sharp mood swings and confusion could be there initially followed by nausea, vomiting, diarrhoea, abdominal pain and sore throat, Subsequently two to four days, the anxiety may be replaced by sleepiness, depression and lassitude, with detectable hepatomegaly.[22] Prominent hemorrhagic manifestations like red eyes and throat, flushed face, and petechiae on internal mucosal surfaces (that may go to advancement as ecchymoses or uncontrollable bleeding) tachycardia and lymphadenopathy,.[19,21,23] There is usually an evidence of hepatitis, and rigorously ill patients may experience rapid kidney worsening, sudden liver failure or pulmonary failure after the fifth day of illness.[19,23] The range of pathology described for Crimean-Congo hemorrhagic fever continues to grow and include cardiac failure, bilateral alveolar hemorrhages, and retinal hemorrhages.[15,20]

According to CMDT "Laboratory features usually include thrombocytopenia, leukopenia anemia, increased hematocrit, elevated liver biochemical tests, and findings consistent with disseminated intravascular coagulation, proteinuria and hematuria in urine analysis." CCHF is pre-eminently diagnosed with an IgM and IgG serology

or immunofluorescence and quantitative reverse transcription Polymerase chain reactions test. Viral load in Crimean-Congo hemorrhagic fever virus infection is associated with mortality. These viruses can be isolated in culture, but this testing should be done at a biosafety level 4 laboratories.[15,20,21] Intra-abdominal free fluid, hepatomegaly, gallbladder wall thickening, thickening of the duodenal and colonic wall, and splenomegaly are reported with Crimean-Congo fever.[15,20,21]

Differential diagnosis: CCHF can be differentiated with Septic infections (i.e. meningococcemia), Rocky Mountain spotted fever, dengue, typhoid fever, and malaria.[15,20,21]

Prognosis: In CCHF infections there is a 5% to 30% the fatality rate and Risk factors for complications are advanced age, thrombocytopenia, prolonged clotting factor parameters, and hepatitis, also patients with altered sensorium and prolonged international normalized ratio having threat for mortality.[15,20,21]

Treatment:[15,20,21] Patients with CCHF required to get hospitalization, in private rooms with utmost standard care for contact, droplets and Barrier precautions to prevent contamination of skin or mucous membranes, especially in patients with significant pulmonary involvement or patients undergoing procedures. Supportive therapy is the mainstay of therapy. There is no approved antiviral medication, but ribavirin is shown to be effective in vitro and in vivo against certain viruses (Lassa virus, Crimean-Congo hemorrhagic fever, and Rift Valley fever pathogens). Early diagnosis and management can reduce mortality.

The efficacy for post exposure ribavirin in the management CCHF remains circumstantial. An inactivated vaccine is available for Rift Valley fever but is not licensed and is not commercially available. There are no vaccines approved for other viruses causing viral hemorrhagic fever. A DNA vaccine against Crimean-Congo hemorrhagic fever is established and spectacles high humoral immune responses with noteworthy protection in mouse models. For the reason that the disease is extremely communicable to health care workers, Isolation is required to people having warning sign of any hemorrhagic fever and habitat in possible endemic area for diagnosis and management.[15,20,21]

Basic and Applied Aspects of Vector Biology: Ticks are primordial group of coerce pest which are parasitically sucking the blood, existing over a number of centuries. According to Estrada-Peña, Cupp and Eddie, "Two general types of ticks are evident today: argasid or soft ticks, and ixodid or hard ticks. Each lineage exhibits distinct patterns of host coevolution and preference. However, about 10% of the approximately 850 species are of medical importance because of their indiscriminate host selection and catholic feeding behavior. Consequently, a number of diseases have begun to emerge in the temperate zones, including Lyme borreliosis and several others presumed to be associated with ticks. Ticks may serve as both pathogens and disease vectors. Because of the unique physiology of the salivary glands and the contents in tick saliva of toxins, feeding alone may cause disease. Ticks also transmit a number of different types of pathogens (viruses, rickettsiae, spirochetes and bacteria, fungi, protozoa, filarial nematodes) and even exceed mosquitoes in this regard. Abatement and control of ticks emphasizes a broad approach because of the differing types of habitats in which pest species may be found. The use of repellents and acaricides as well as cultural and management practices are of primary importance. Other approaches (ivermectin) may be beneficial; with the advent of molecular genetics and its usefulness in immunology, the development of tick vaccines for common pest species appears promising."[24,25]

Vector genetics: The familiar one among the most significant livestock's and human pathogen's, vector list, is Hyalomma, and its wide range, scattered in all over the topographical flora and fauna. Not only the Taxonomy and nomenclature of the Hyalomma ssp. is dubious, but also identification is challenging.[26] In addition, for two times the CCHFV has been isolated from Culicoides species flies, but it's not a sufficient evidence, to verify that, these flies also transmit and spread CCHFV.[27]

Bionomics: In cattles, it has been documented that the uppermost incidence of Hyalomma ticks and lowermost incidence of Rhipicephalus ticks is there.[28] As mentioned by Durrani et. al.,[28] "Ticks were considered parasites of domestic animals as early as 400 B.C. Aristotle in his famous Historia Animalium" stated that the ticks were disgusting parasites and that were generated from grass. Ticks are cosmopolitan in distribution, but occur principally in tropical and subtropical regions and harm by tick bites and blood sucking. Estimates of the amount of blood removed vary according to the species under consideration. A single adult female tick may remove 0.5 — 2.0 ml. of blood. If an animal carries numerous ticks a substantial loss of blood may occur. Heavy infections do occur in nature, it is more usual for animals to carry a few hundred ticks. These produce what is generally known as "tick worry".[28] Hyalomma ticks, as vectors of tropical theileriosis are widespread in North Africa, southern Europe, Middle East, Central Asia and China." According to studies, moderate temperature and humidity greatly enhanced the developmental stages of Hyalomma ticks, and the temperatures above 40°C and below 12°C prevented moulting.[28]

Life cycle of Hyalomma ticks and vertical and horizontal transmission of CCHFV is shown in figure 1 below. Spengler says "The course of the tick life cycle is indicated with arrows. Upon hatching, larvae find a small animal host for their first blood meal (hematophagy).

Depending on the tick species, the larvae either remain attached to their host following engorgement and molt in place (two-host ticks) or drop off to molt (three-host ticks); this transition is marked by an asterisk. The nymphs, then either continue to feed on the animal on which they molted (two-host ticks) or attach to a new small vertebrate host (three-host ticks). Nymphs of all species drop off their host and molt into adults, upon engorgement. Adult ticks then find a large animal for hematophagy, and mate while attached to the host. After taking a blood meal, the engorged females drop off and find a suitable location for ovipositioning. During the tick life cycle, CCHFV can be transmitted between ticks and mammals (solid red arrows), and directly between ticks through co-feeding (dashed arrows). For each kind of virus transfer, the thickness of the arrow indicates the efficiency of transmission. Humans can become infected through the bite of an infected tick or through exposure to the body fluids of a viraemic animal or an infected person."[29]

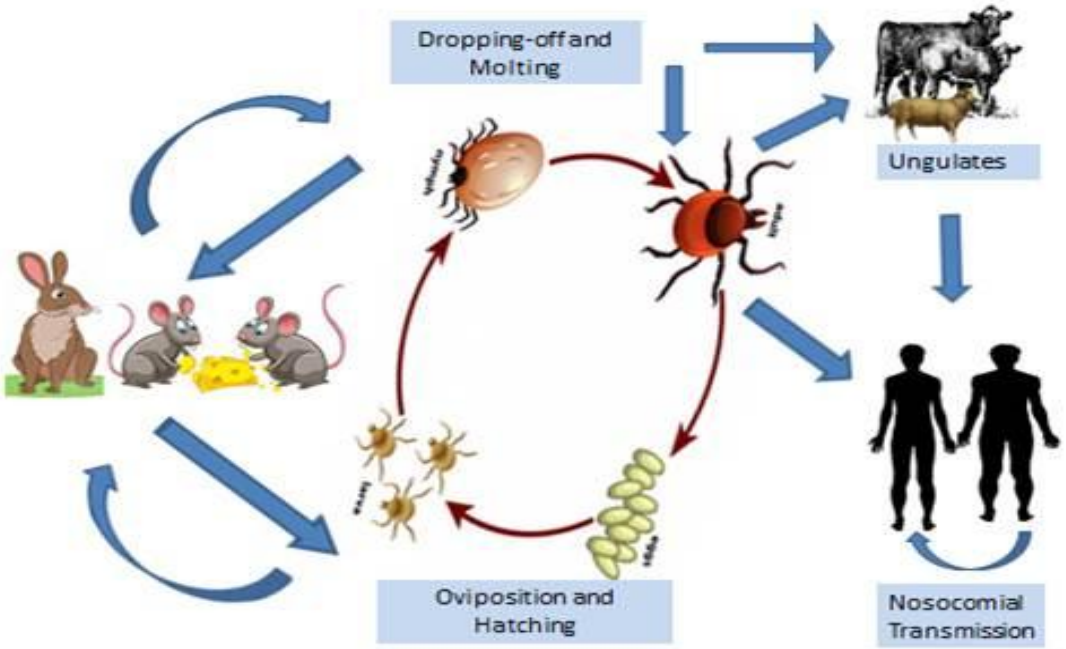

Figure 1: Life cycle of Hyalomma ticks and vertical and horizontal transmission of Crimean-Congo hemorrhagic fever virus (CCHFV)

Hyalomma marginatum tick's preoviposition period is 7 days; average number of eggs they lay is max. 13,180 and min. 3,184, greatest egg production rate is average 1,170 egg/female, observed feeding time of larvae and nymphs are 22/23 days, a nymph produces a male weighed less than 23 mg, and females of 26 mg; and the combined larval-nymphal feeding time is of 22 and 23 days subsequently.[30] The premolting period of transformation of nymphs to adults of both genders is similar.[30] The entire life-cycle gets completed within 147 days.[31]

As Mourya writes "Mostly CCHF vectors are two-host ticks and they have need of two hosts to complete their life cycles, so the adults lay eggs and emerging larvae, attach to the vertebrate host. Hyalomma anatolicum parasitizes mainly cattle. The detachment and dropping rhythms of the species are so adjusted that these occur only at a time when the cattle is resting in the sheds normally at night time. The engorged ticks that drop in the sheds find suitable niche in the cracks and the crevices, where the female ticks oviposit, and the larvae, and the nymph moult to the next stage. The questing larvae, the unfed nymphs and adults that have moulted from the previous stage can easily find their hosts in the cattle sheds. The humans acquire infection when they come in close contact of this environment. CCHFV vector Hyalomma spp. remains confined to resting shades of the animals and accidental bites occur to human residing in close proximity to the animals, thus only sporadic cases occur. Therefore, only sporadic cases occur for CCHF, though the virus is widely prevalent in various geographical areas."[32]

Vector/parasite resistance: Animals are extensively susceptible to CCHFV contagion, but proneness is not universal among all animal species that the vast majority of avian species scrutinized and examined gave the impression as they are headstrong towards the infection; and their serological studies shows the absence of CCHFV antibodies in them (like i.e. some birds), and no viremia was identified in almost all experimentally infected bird species.[29]

Indeed, Birds, on the other hand, may be a very operational source of transporting ticks over wide-ranging geographic zones during their migratory flights.[29]

Beside the fact that about 500 females may simultaneously feed on a single animal, and each female may lay around 5000 eggs, the data concerning the efficiency of transovarial infection from the female to the egg is unclear, but found that transovarial transmission efficiency of is ~1%; this scenario would generate 25,000 infected larvae from only one host that is not a reservoir, but just the food source for the females.[29]

Interestingly, it has been evaluated that immunity is not acquired against all species of ticks, may be because of Immunosuppressive components in tick saliva.[33] Jongejan mentioned "Also significant systemic effect of the tick on the progression of the disease was found, measured by reduced cell-mediated and humoral immune responses. The mechanisms involved are not yet known, but components in tick saliva of adult A. variegatumare mediators in the development of severe forms of dermatophilosis in animals infested by this tick. However, this apparent immunosuppressive effect appears to be specific for dermatophilosis, there being no evidence that this tick induces similar effects where other diseases are concerned.[33] The immune response under arena regarded as more like immune suppression than immune protection.[34]

CCHFV and Ticks: CCHFV circulates in an "enzootic tick-vertebrate-tick cycle" in which ticks deed as vectors and reservoirs. CCHFV has been found in ticks of >30 species; among them, Hyalomma marginatum ticks are deliberated as the most corporate vectors.[35] Birds are considered as the foremost hosts for the immature stages of this tick species and Migratory species could carry infected ticks over protracted distances and thus propagate the virus.[35]

Epidemiology: The geographic distribution of CCHF, like that of its tick vector, is widespread with cases reported in Asia, the Middle East, and Eastern Europe. Although In 2002, Turkey experienced the largest reported outbreak with over 2500 cases. Hospital associated transmission of CCHF is well documented.[20]

The terrestrial series of CCHF virus is the second most widespread among the tick-borne viruses that affect anthropoid well-being, after dengue viruses.[7] As per manuscript of Dr Önder Ergönül in his publication with lancet at 2006 that the signs of this disease CCHF were found in 12th century at Tazakistan, afterwards it was firstly described as a quantifiable clinical entity in 1944 and 45, at Sovioat Union (Crimea, Astrakhan, Rostov, Uzbekistan, Kazakhstan, Tajikistan) at World War II. Former of 1970, maximum cases were testified from the former Soviet Union and Bulgaria, as well as from parts of Africa such as the Democratic Republic of the Congo and Uganda, hence the virus named as Crimean haemorrhagic fever-Congo virus, and then Crimean-Congo haemorrhagic fever virus.[7]

"An outbreak in 1965 in China with a case fatality rate of 80% was noted, but not presented in detail. The initial recognition of haemorrhagic cases in Africa occurred in the 1960s, resulting in a series of in-depth studies in South Africa and reports of additional outbreaks from Congo, Mauritania, Burkina Faso, Tanzania, and Senegal. A substantial number of cases were also reported from Middle Eastern countries such as Iraq, the United Arab Emirates (UAE) Saudi Arabia and Oman, and from Pakistan and China. By 2000, new outbreaks had been reported from Pakistan, Iran, Senegal, Albania, Yugoslavia, Bulgaria, Turkey, Kenya, and Mauritania. Serological evidence for CCHF virus has been reported from Greece, India, Egypt, Portugal, Hungary, France, and Benin, although the virus was isolated only in Greece and the only reported human case was a Greek laboratory infection."[7] Now CCHF virus is widespread in the Balkans, including Bulgaria, the former Yugoslavia, and Albania. It is of interest that the strain that caused the laboratory-related infection in Greece was exceedingly mild, possibly reflecting chance variation; however, the virus has the greatest phylogenetic change from other CCHF viruses.[7] Mortality rates are between 4–20% depending on the geographical region and the quality of health care services.[36]

CONCLUSION

After the extensive analysis of dynamic documents and manuscripts from reputed books, websites and printed and e- version of various articles from indexed journals, it's been evaluated that, CCHF is an acute, tick-borne viral, zoonotic disease with hemorrhagic exhibitions and substantial mortality in humans. Defining Strategies for treatment protocols for the diagnosis and management, Isolation, and Intensive care of CCHF patients, is pronounced utmost necessity of present time. Although Vector born Infectious diseases still play a significant role in shaping the morbidity and mortality patterns in the developing countries. Appreciative generous concern of vectors, causal infection sources of virus, vector etc. and their bionomics must be taken on utmost precedence so that better interferences and medications can be prepared and provided to control such zoonotic contaminations and infections. Increasing cognizance, approachability in the midst of rural and urban inhabitants and practicing anti-tick practice and protections would definitely support in reducing the prevalence of these ailments, in Maharashtra, India.

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