

## Crimean Congo Hemorrhagic Fever in Pakistan

Crimean-Congo hemorrhagic fever (CCHF) is a widespread tick-borne viral disease that is endemic in Africa, the Balkans, the Middle East and Asia. It is a zoonotic disease carried by several domestic and wild animals.<sup>1</sup> Crimean-Congo Haemorrhagic Fever (CCHF) virus belongs to genus *Nairovirus* within the family Bunyaviridae with a triple-segmented RNA genome.<sup>2</sup> The first evidence of CCHF like illness dates back to the 12<sup>th</sup> century, where a description of hemorrhagic syndrome in Tajikistan and the description of the arthropod that caused the disease appears similar to the modern-day CCHF.<sup>3</sup> The disease was first described in Crimea in 1944 and was called Crimean Hemorrhagic fever and then later in Congo, hence it was named Crimean-Congo Hemorrhagic fever. The virus infects wild as well as domestic animals like sheep and cattle through tick bites, while there is contradicting evidences on transmission by migratory birds.<sup>4,5</sup>

Humans are infected when they come in direct contact with blood or tissues from infected animals or bites of infected ticks. Crushing of infected ticks could also result in infection. The people who work in close contact with livestock such as those working in agriculture, slaughter-houses and veterinary hospitals are at a higher risk of acquiring the disease. Once a human is affected, the infection spreads to other people if they come in contact with the patient's infected blood or body fluids.<sup>6,7</sup>

The incubation period for CCHF virus is 3-7 days. The minimum viral load required for transmission of disease is 1-10 organisms.<sup>8</sup> The major symptoms include high fever, myalgias, headache, nausea, abdominal pain and non-bloody diarrhea. This is accompanied by hypotension, relative bradycardia, tachypnea, conjunctivitis, pharyngitis and cutaneous flushing or rash.<sup>9</sup> The pre-hemorrhagic 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>10-12</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 (DIC) 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>13</sup> The important differential diagnoses of CCHF are the viral and bacterial infections which present as hemorrhagic disease.<sup>14</sup>

Viral isolation is definitive but only useful for diagnosis in the early phase of infection with high viral load; moreover, this can be done only if the biosafety level 4 containment facilities are available.<sup>15</sup> Demonstration of viral genome is another definitive form to diagnose this disease. Reverse-transcriptase PCR (RT-PCR) and real-time PCR are the tools to help the physicians in this context.<sup>16</sup> Enzyme-Linked Immunosorbent Assay (ELISA) to detect specific IgM and IgG has largely replaced the conventional serodiagnostic tests. A recombinant nucleoprotein (rNP)-based IgG ELISA has also been developed for serological diagnosis of CCHF viral infections.<sup>17</sup>

Pakistan is considered as an endemic country for Crimean-Congo Hemorrhagic fever with numerous outbreaks and sporadic cases reported during the past few decades. Few studies revealed that all CCHF viruses from Hamadan province of Iran clustered together with the CCHFV strains of Pakistan<sup>18,19</sup> proving evidence that the unchecked and uncontrolled animal movements between these countries remain a source of sustained and constant introductions of CCHFV to naive populations.<sup>20</sup> In the same way, animal trade between Pakistan and Middle Eastern countries also provide sources for the importation of CCHF virus between these countries including UAE as evidenced by an outbreak in Dubai and was found linked to the transportation of cattle from Pakistan.<sup>21</sup> Likewise, unlawful animal trade and uncontrolled population movements occur between Pakistan and Afghanistan through Quetta city due to the very similar cultural and tribal civilizations inherent across the bordering areas of both countries. Baluchistan province is a major source of animal's skin and hides production and also serves as a corridor for receiving skins and hides from Southern Afghanistan and Southeastern parts of Iranian Baluchistan via the Taftan gateway.<sup>22</sup>

In Pakistan, 74 deaths have been reported due to CCHF during the last 3 years.<sup>23</sup> The first CCHF case in Pakistan was reported in 1976 from a patient who underwent laparotomy at Rawalpindi General Hospital.<sup>24</sup> Majority of the cases were reported from Baluchistan province with subsequent transmissions to non-endemic regions mainly through infected animals directly or via infested ticks. Molecular investigations confirmed the cases of CCHF reported during 2008 in Quetta city of Baluchistan province and it had been revealed that out of forty four study subjects, sixteen (36%) samples were found positive for CCHF IgM. Similarly, viral RNA was detected in six (16%) samples. Phylogenetic analysis revealed that all study viruses belong to genotype Asia-1 with closest similarity (99-100%) to the documented strains from Pakistan, Afghanistan and Iran.<sup>25</sup> A recent outbreak of this deadly infection has been reported in Southern Punjab, Pakistan. The deaths of the two health care providers has been reported and it convinced the health professionals to stress on the need of strict preventive measures while fearing the outbreak of the fatal infection in the country. In order to prevent the transmission of CCHF, Ministry of National Health Services, Pakistan, issued an updated awareness news letter no. 33 in June 2015, in which control of the spread of CCHF was focused.

On the religious occasion of Eid-ul-Adha almost 5 million animals have been slaughtered across the country in every year<sup>26</sup> and this holy festival of Eid-ul-Adha is in the next month (September 2016). The festival is susceptible for CCHF outbreak in Pakistan as the recent events are on record. Given the upcoming feast of Eid-ul-Adha, the risk of CCHF transmission may increase if policies are not revised for the slaughter of animals and suitable personal protective measures are not ensured. The higher authorities should start the awareness campaigns on the prevention and control of CCHF through electronic and print media without wastage of time so that further losses of precious lives can be avoided.

## REFERENCES

1. Hewson R, Chamberlain J, Mioulet V, Lloyd G, Jamil B, Hasan R, Gmyl A, Gmyl L, Smirnova SE, Lukashev A. Crimean-Congo haemorrhagic fever virus: sequence analysis of the small RNA segments from a collection of viruses world wide. *Virus Res* 2004;102(2):185-189.
2. Flick R, Flick K, Feldmann H, Elgh F. Reverse genetics for Crimean-Congo hemorrhagic fever virus. *J Virol* 2003;77(10): 5997-6006.
3. Hoogstraal H. The epidemiology of tick borne Crimean-Congo hemorrhagic fever in Asia, Europe and Africa. *J Med Entomol* 1979;15:307-417.
4. Nabeth P, Cheikh DO, Lo B, Faye O, Vall IO, Niang M. Crimean-Congo hemorrhagic fever, Mauritania. *Emerg Infect Dis* 2004;10:2143-9.
5. Jameson LJ, Morgan PJ, Medlock JM, Watola G, Vaux AG. Importation of *Hyalomma marginatum* vector of Crimean-Congo haemorrhagic fever virus into the United Kingdom by migratory birds. *Ticks Tick Borne Dis* 2012;3:95-9.
6. Lacy MD, Smego RA. Viral hemorrhagic fevers. *Adv Pediatr Infect Dis* 1996;12:21-53. <http://www.hamariweb.com/articles/article.aspx?id=37884>
7. Franz DR, Jahrling PB, Friedlander AM, McClain DJ, Hoover DL, Bryne WR, et al. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA* 1997;278:399-411.
9. Hoogstraal H. The epidemiology of tick borne Crimean-Congo hemorrhagic fever in Asia, Europe and Africa. *J Med Entomol* 1979;15:307-417.
10. Ergonul O, Celikbas A, Dokuzoguz B, Eren S, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in turkey and impact of oral ribavirin therapy. *Clin Infect Dis* 2004;39:284-7.
11. Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, Tasyaran MA, Vahaboglu H, et al. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: A multicentre study of clinical features and outcome measures. *J Med Microbiol* 2005;54:385-9.
12. Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in Eastern Turkey: Clinical features, risk factors and efficacy of ribavirin therapy. *J Infect.* 2006;52:207-15.
13. Sannikova IV, Pacechnikov VD, Maleev VV. Respiratory lesions in Crimean-Congo hemorrhagic fever. *Ter Arkh* 2007;79:20-3.
14. Hoogstraal H. The epidemiology of tick borne Crimean-Congo hemorrhagic fever in Asia, Europe and Africa. *J Med Entomol* 1979;15:307-417.
15. Drosten C, Kummerer BM, Schmitz H, Gunther S. Molecular diagnostics of viral hemorrhagic fevers. *Antiviral Res* 2003;57:61-87.
16. Shepherd AJ, Swanepoel R, Leman PA. Antibody response in Crimean-Congo haemorrhagic fever. *Rev Infect Dis* 1989;11:801-6.
17. Saijo M, Qing T, Niikura M, Maeda A, Ikegami T, Prehaud C, et al. Recombinant nucleoprotein-based enzyme-linked immunosorbent assay for detection of immunoglobulin G antibodies to Crimean-Congo hemorrhagic fever virus. *J Clin Microbiol* 2002;40:1587-91.
18. Tahmasebi F, Ghiasi SM, Mostafavi E, et al. Molecular epidemiology of Crimean-Congo hemorrhagic fever virus genome isolated from ticks of Hamadan province of Iran. *J Vector Borne Dis* 2010; 47(4): 211- 216.
19. Chinikar S, Ghiasi SM, Hewson R, Moradi M, Haeri A: Crimean-Congo hemorrhagic fever in Iran and neighboring countries. *J Clin Virol: the official publication of the Pan American Society for Clinical Virology* 2010;47(2): 110-114.
20. Izadi S, Holakouie-Naieni K, Majdzadeh SR, Chinikar S, Nadim A, Rakhshani F, Hooshmand B. Seroprevalence of Crimean-Congo hemorrhagic fever in Sistan-va-Baluchestan province of Iran. *Jpn J Infect Dis* 2006; 59(5): 326-328.
21. Suleiman MN, Muscat-Baron JM, Harries JR, Satti AG, Platt GS, Bowen ET, Simpson DI: Congo/Crimean haemorrhagic fever in Dubai. An outbreak at the Rashid Hospital. *Lancet* 1980; 2(8201): 939-941.
22. Raziq MYZR. Prospects of Livestock Production in Baluchistan. *Pakistan Vet J* 2010; 30(3): 181-186.
23. World Health Organization (WHO), Eastern Mediterranean Regional Office (EMRO). Crimean-Congo Hemorrhagic Fever in Pakistan. Cairo, Egypt: *Weekly Epidemiological Monitor* 2014;7:44.
24. Jomezai GSPEK. Crimean-Congo Hemorrhagic Fever: a survey of cases of CCHF in Baluchistan. *Prof Med J* 2007;14(1): 17-20.
25. Muhammad Masroor Alam, Adnan Khurshid, Salmaan Sharif, Shahzad Shaukat, Muhammad Suleman Rana, Mehar Angez, Syed Sohail Zahoor Zaidi. Genetic analysis and epidemiology of Crimean Congo hemorrhagic fever viruses in Baluchistan province of Pakistan. *BMC Infectious Diseases* 2013; 13:201.
26. Rehman A, Baloch NU, Awais M. Eid-ul-Azha festival in Pakistan: a vulnerable time for Crimean-Congo hemorrhagic fever outbreak. *Am J Infect Control* 2014;42:939-40.

**Dr. Muhammad Bilal Ghafoor**

Assistant Professor (Hematology Division)

Department of Pathology

Sheikh Zayed Medical College/Hospital

Rahim Yar Khan

Cell: 0333 3303300

Email: drbilal01@hotmail.com