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Two-Decade Experience of Crimean-Conge Hemorrhagic Fever (CCHF) Management in Iran

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Crimean-Conge hemorrhagic fever (CCHF) is endemic in many countries in Africa, Southeastern Europe, and Asia. It is a tick-borne disease caused by genus Norovirus. It was first described in 1994. Then, in 1969, it was recognized that the same pathogen was responsible for an illness identified in 1956 in the Congo; linkage of the two place names resulted in the current designation of Crimean-Congo hemorrhagic fever virus (CCHFV) (1).

In Iran, CCHFV was first identified in livestock sera and ticks in the 1970s, but the first human infection was not diagnosed until 1999. Since then, the incidence of CCHF has been on a significant rise in Iran (1). By the end of July 2019, Iran Ministry of Health reported 1501 confirmed cases of CCHF with 195 deaths, giving a case fatality rate (CFR) of 13% more commonly in Sistan Baluchestan, Razavi Khorasan, Kerman, Isfahan, and Fars, in sequence. The rise in CCHF in Iran was similar to that in a neighboring country, Turkey, although the incidence was much higher in Turkey, with a total CFR of around 5%. It seems that the feature of CCHF in Iran including most updated number of cases and its distribution and our experience is as a result of treating this disease with Ribavirin (2).

In response to CCHF in Iran, the National Expert Committee of Viral Hemorrhagic Fevers (NECVHFs) was created by the Iranian Center for Disease Control (CDC), the Pasteur Institute, and the National Veterinary Organization. This committee, consisting of clinicians, epidemiologists, entomologists, veterinarians, and virologists, is to identify and investigate CCHF cases and is responsible for monitoring and prevention programs (1).

Activities are conducted at two levels. At the domestic level, the committee is mainly engaged in the development of rules for case identification, therapy, prevention, research, and information collection. Level II activities include local reaction to CCHF, mainly through universities and health centers, including diagnosis and therapy, measures to isolate suspected cases, prevention of secondary transmission, and reporting of new cases to the CDC through comprehensive questionnaires. Phylogenetic analysis of all recognized CCHFV strains showed that they could be divided into 7 lines with distinct names by separate researchers. There is a cumulative temperature requirement for molting of Hyaloma ticks, climate change appears to be only one of many factors. Alterations in habitat and in small mammal populations, migratory birds, and other factors are also being investigated in studies focusing on the potential for CCHF to spread within Europe. At the beginning of an outbreak, the published literature on CCHF ribavirin treatment was restricted to an observational study in South Africa and another in Pakistan. Based on these reports and WHO suggestions for viral hemorrhagic fever therapy, the NECVHF decided to include ribavirin as part of therapy for patients suspected to CCHF. Unless the diagnosis is ruled out, patients are provided with a complete 10-day course (1).

The findings of the 1999 - 2002 ribavirin therapy were published in 2003. The death rates of 139 suspected and 69 confirmed CCHF patients were compared based on oral ribavirin therapy. For those with confirmed infection, the survival rate was 69.8% for treated patients and 41.7% for untreated patients, while the rates were 88.4% and 54.2%, respectively, for those with suspected disease. The overall efficacy of therapy with ribavirin was 80% among confirmed cases and 34% among others considering the fact that many of them did not have CCHF (1).

Although in a systematic review by Soares-Weiser et al. the ineffectiveness of ribavirin in the treatment of CCHF was emphasized, due to the lack of CCHF effective treat-

ment, supportive care including blood, platelet, and electrolyte administration and oral and IV administration of ribavirin, especially in the first three days of disease onset, have shown to slow the progression of the disease (3). Recently, Favipavir, used in Japan for the treatment of influenza, has been used as an adjunct drug in animal models and could achieve successful results. Therefore, examining the efficacy of this drug in clinical trials is proposed to depict the exact efficacy of this drug (4).

Recently, a systematic review and meta-analysis by Arab-Bafrani et al. examined 24 studied and found that ribavirin administered to CCHF patients reduced the mortality rate considerably (by 1.7 folds) compared to those who did not receive this medication. In addition, ribavirin prescription was discovered to be more efficient in the initial stage of the disease and a delay in starting therapy resulted in a 1.6-fold rise in mortality rate. Additionally, the interventional treatment led to a 2.3-fold decrease in mortality rate among those receiving ribavirin along with corticosteroids compared to those receiving ribavirin monotherapy (5).

To sum up, CCHF's worldwide distribution and re-emergence underline the significance of further groundwork to combat the pathogen that poses severe threats to human and animal health. Future studies require to concentrate, in particular, on prevention and treatment agents including IVIG, steroids, and monoclonal antibodies. Also, further research is needed to determine pathophysiology, the route of transmission, and efficacy of drugs such as favipiravir in double-blind randomized clinical trials.

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