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CLINICAL EVALUATION OF METHODS OF THERAPY FOR CRIMEAN-CONGO HEMORRHAGIC FEVER

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Abstract. We initiated the retrospective study of 81 patients with Crimean-Congo hemorrhagic fever in the Republic of Uzbekistan for a period from June 2013th to June 2018th. This article presents the results of a comparison of mortality depending on etiological antiviral treatment. The comparison groups included four types of therapy: a) patients who received ribavirin according to WHO standards; b) those who received ribavirin+convalescent blood plasma; c) patients who received only convalescent blood plasma; and d) only supportive treatment without the use of ribavirin and convalescent blood plasma. Considering the limitations of observational studies, we concluded that the type of therapy did not play a role in reducing CCHF mortality.

Keywords: CCHF; hemorrhagic fever, ribavirin, convalescent blood plasma, treatment

Introduction. Crimean Congo hemorrhagic fever (Latin Febris haemorrhagica crimiana, synonym for Central Asian hemorrhagic fever) is an acute human infectious disease transmitted through tick bites, contact with the blood of a tick or a patient with Crimean Congo hemorrhagic fever (CCHF) [1]. The CCHL was first described in 1944-1945 as an independent human disease based on research conducted in Crimea under the leadership of Chumakov M.P. In the summer of 1944 and 1945 in the steppe regions of Crimea, over 200 cases of severe acute febrile illness with pronounced hemorrhagic manifestations were recorded. Cases of the disease were observed among the rural population and the soldiers who helped the farmers to harvest. At first, this disease was called "acute infectious toxicosis", then, by the suggestion of Chumakov, it received the official name "Crimean hemorrhagic fever". In 1967 in Russia by Chumakov, the CHF virus was isolated by the method of intracerebral infection of newborn white mice [2].

The viral strains causing Crimean hemorrhagic fever were later shown to be antigenically and biologically closely related to the Congo fever virus isolated and registered in 1969 in the Congo. Therefore, in 1970, at the suggestion of D. Casals, the disease was named Crimean-Congo hemorrhagic fever (CCHF), and the virus was assigned to the genus Nairovirus of the Bunyaviridae family [3]. Crimean-Congo hemorrhagic fever is found very widely in the world - in 16 countries of Europe, Asia, and Africa. Since the mid-90s of the last century, there has been a certain activation of the natural foci of the CCHF in several regions of the planet, including

the Near and Middle East, Central Asia, and southern Europe. So, in 1998, the World Health Organization (WHO) noted two outbreaks: in Pakistan - four patients with two deaths and Afghanistan - 19 patients with a mortality rate of 63%. In May 2000, an outbreak of CCHF was re-reported in one of the provinces of Afghanistan with a fatality rate of 60%. Also, epidemic complications took place in the South African Republic in 1996, in the Sultanate of Oman in 1995-1996. and in 2000. In the spring and summer of 2001, 8 patients with CCHF were registered in Kosovo. From 1997 to 2003 in Bulgaria 138 people fell ill with CCHF, of which 19 died. According to the WHO, in 2002 and 2003, 19 patients with CCHF were identified in Turkey, and in February 2003, CCHF diseases were noted in Mauritania (30 patients with six deaths) [4, 5]. The disease is varied, with a large number of different symptoms depending on the severity of the disease. Sometimes the stages of the disease are less pronounced, and the disease remains undetected since the initial symptoms are similar to those in acute respiratory infections. As a result, mortality from the disease ranges from 10 to 40%.

The mechanism of infection is predominantly transmissible - through the bite of an infected tick, contaminated - when ticks are crushed with unprotected hands. Possible air-dust transmission (in laboratory conditions) and infection through contact with the blood of sick people and pets, as well as parenteral - in the provision of medical care.

As it is the central part of Asia, the territory of Uzbekistan is endemic for arboviruses of CCHF. Many Uzbek scientists conducted studies on the epidemiology and prevalence of natural foci of CCHF. For example, Saktaganov et al. (1989), studying the characteristics of natural foci of arbovirus infections in the Southern Aral Sea region, showed the existence of natural foci of CCHF pathogens in the surveyed area, ecologically associated with mites Hyalommo asiaticum [6]. Until 2002, Komilov et al. studied the clinical course of CCHF without hemorrhagic manifestations and the structural distribution of clinical forms. Also, using the model of the Surkhandarya region, they studied the landscape confinement of some arboviruses, including the CCHF [7]. Nematov et al in 2002-2004, by serological methods, established the fact of the circulation of the CCHF virus in the territory of the Kyzylkum natural plague focus. [8] Narziev et al. (2006) studied changes in platelet-vascular homeostasis and clinical manifestations of CCHF based on materials from the Bukhara region [9]. In 2005, Shermatov et al. gave epidemiological characteristics of CCHF in the southern region of Uzbekistan. According to the above data, in the natural conditions of the southern region of Uzbekistan, CCHF is more widespread in the foothill zone than in the mountainous and lowland zones [10].

Materials and methods.

***Study design and patients*.** We conducted a retrospective analysis of the medical data of all (81 patients) infected patients with the CCHF virus and received treatment in specialized medical centers in the regions of the Republic of Uzbekistan

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from June 2013th to June 2018th, to assess the effectiveness of standard, non-standard therapy and the use of convalescent blood plasma. By medical data, patients suspected of having CCHF were defined as those who had clinically observed signs and symptoms (e.g., fever, muscle pain, and bleeding), epidemiological risk factors (a receipt of a tick bite, exposure to tick splashing [i.e., crushing a tick between 2 exposed body parts], travel to or residence in an area of endemicity for CCHF, contact with persons with suspected cases of CCHF, or contact with animals) (Table 1).

Table 1. Clinical and epidemiologic features of patients

Groups	**Ribavirin**		**Ribavirin + Convalescent plasma**		**Convalescent plasma only**		**No antiviral therapy**	
Result	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
Demographic characteristics								
Sex								
Male	9 (39%)	3 (13%)	17 (42.5%)	6 (15%)	4 (67%)	1 (16.5%)	8 (67%)	1 (8%)
Female	8 (35%)	3 (13%)	14 (35%)	3 (7.5%)	1 (16.5%)	-	1 (8%)	2 (17%)
Age	41.1±13.1	33.5±16	36.7±11.4	32.2±7.57	32±20.8	45	27.9±8.3	41.6±4.9
City area	2	1	2	-	1	1	-	-
Rural area	15	5	29	9	4	-	9	3
Clinical features								
Moderate	9	-	8	-	-	-	6	-
Severe	6	5	23	3	5	-	3	2
Critical	-	1	-	6	-	1	-	1
Epidemiology								
Tick bite	13	1	12	1	0	1	4	0
Crushing a tick	1	0	5	5	1	0	2	0
Contact with animal blood	0	1	0	0	1	0	0	0
Animal care	1	2	2	0	3	0	2	2
Patient's care	2	2	11	2	0	0	1	1
Other	0	0	2	0	0	0	1	0

The research participants were mainly represented by residents of the rural population - 73 people (90%), 7 people were from cities (8.5%), 1 person (1.5%) - a resident of the capital city – Tashkent. The age of the patients ranged from 14 to 66 years, with a mean of 35.9±12.4 years. 39.5% (32 people) of the participants were female, the remaining 60.5% (49 people) were men. When analyzing the history of the transmission of infection, we drew attention to the fact that the majority of the infected (60 people - 74%) were not closely associated with animal husbandry

(shepherds, workers of livestock farms). Among the rest, shepherds made up 11% (9 people), and 12 (15%) study participants were medical workers. Only one of the participants was initially misdiagnosed as a patient with a disease of the genitourinary system due to uterine bleeding and was admitted to the gynecology department, which was later transferred to a specialized infectious diseases hospital. All lethal outcomes (19 participants, 23% of the total number of participants) were noted up to the 7th day of hospitalization, with the largest number of fatality at the initial four days (90% of all death cases).

Laboratory diagnosis of virus included serological (ELISA) and qualitative molecular genetic methods (detecting viral RNA in real-time PCR). To assess the general condition of the patient, medical centers used a complete blood count (CBC), chemistry (complete metabolic) panel, ultrasound, and others methods on demand.

The mainstay of treatment of CCHF was supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. As an antiviral therapy were used ribavirin and convalescent blood plasma.

For comparison the effectiveness of therapy, we divided patients into four groups according to received antiviral therapy: a) patients, who received standard-dose ribavirin by WHO recommendation (30 mg/kg as an initial loading dose, then 15 mg/kg every 6h for 4 days, and then 7.5 mg/kg every 8h for 6 days) – 23; b) patients, who received standard-dose ribavirin+convalescent blood plasma - 40; c) only convalescent blood plasma – 6; and d) patients without antiviral therapy – 12.

In Uzbekistan, the following practice of using the serum of convalescents for CCHF [7] is recommended. The serum of convalescents should be administered in the first 10 days of illness, preferably in case of fever in the patient; when the patient's temperature is below 36°C, serum administration is not recommended. It is indicated that the volume of plasma to be administered by the titer of antibodies in the serum and the severity of the disease: with a titer of up to 1: 100, it is administered 3-4 times, with a titer of 1: 150 - 2-3 times, with 1: 200 - 1 time. Despite the above-mentioned recommendations, all the patients who was in our study received convalescent fresh frozen plasma, 200-250 ml each dose. We did not find any guidelines on using fresh frozen plasma of convalescents to CCHF patients.

The study was conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and was approved by local ethics committees and appropriate regulatory authorities.

Statistics. Continuous data were compared using Student's *t-test*. If the outcome variable was continuous but had a distribution that was not normal, Mann–Whitney U-test was used for the comparison of groups. Categorical data were compared with the chi-squared test or Fisher's exact test when appropriate. For survival analysis, Kaplan–Meier method (log-rank test) was used. The SPSS program, version 26.0 (SPSS Inc., Chicago, IL), was used for statistical data analysis.

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Results. Demographically, most of the patients were rural residents. We did not note the difference in morbidity and mortality rates by place of residence, by sex, and by profession. The age of the patients also did not matter according to the above criteria. The dependence of the outcome of the disease on the type of therapy was analyzed (patients, who received the standard dose of ribavirin; patients, who received the standard dose of ribavirin + convalescent blood plasma; patients with only convalescent blood plasma; and patients without antiviral therapy). However, the statistical tests Pearson Chi-Square (p-0.96), Likelihood Ratio (p-0.96), Linear-by-Linear Association (p-0.76) did not find a statistically significant difference between the groups affecting patient survival. Consequently, the type of therapy did not affect the outcome of the disease.

Logistic regression was performed to assess the survival of patients receiving ribavirin (standard dose ribavirin; standard dose ribavirin + convalescent blood plasma) with those who did not receive treatment according to WHO recommendations (only convalescent blood plasma; without antiviral therapy). Against the fact that the relative risk of survival is 1.925 times higher when taking ribavirin according to the WHO recommendations compared with the regimen without ribavirin, the data did not show a statistically significant difference between the abovementioned groups (p-0.278).

An independent-samples t-test was performed to determine the relationship between the day of hospitalization after the first symptoms and mortality of patients. Even though patients with a subsequent lethal outcome were admitted at 4.0 ± 1.49 days from the onset of the disease, compared with 3.29 ± 2.38 days in survivors from the disease during the observation period, the difference is not statistically significant (p-0.22). All deaths after hospitalization were recorded up to 6 days inclusive, despite the absence of a significant difference between the day of hospitalization from the onset of clinical manifestations and death.

Discussion. Our study had several limitations. The study is primarily observational, which reduces its evidence-based effectiveness. Second, there is a lack of data on patients with mild disease, which increases the likelihood of bias in applying the results to all patients with CCHF. Thirdly, in some cases, we noted (in our personal opinion) the use of unreasonable drugs in the absence of clear indications and guidelines for the management of patients, which could cause the deterioration of the patient's condition.

CCHF is a rare but dangerous disease. In this regard, in endemic regions, the hospital should have theoretically trained medical personnel for timely diagnosis, isolation of the patient, and providing him with the necessary medical care. The main treatment for CCHF is still supportive therapy since until now there is no advice on a specific therapy, there is no certified vaccine. The development of new treatment approaches is significantly complicated by the lack of a laboratory model of CCHF. The virus is difficult to maintain in a laboratory. Although currently used in several

methods of etiotropic treatment of Crimean Congo hemorrhagic fever, they do not have a solid evidence base.

The first drug tested and approved for CCHF was ribavirin. Ribavirin is an antiviral drug, nucleoside analog (WHO http://www.who.int/csr /disease/crimean_congoHF/en/). Based on its in vitro antiviral efficacy [12], it has been tested in patients with CCHF, and these observational studies have shown positive results from its use [13, 14, 15], especially if used in the early stages of the disease. It has also been shown that ribavirin inhibits the release of many viruses both in vivo and in vitro [16], and has a direct and indirect effect on viruses. Ribavirin was supposed to be used for various viral infections - from influenza to Lassa fever, Ebola, and hepatitis C.

In 2006, WHO approved the use of ribavirin for the treatment of CCHF and included it in the list of essential medicines based on its effect in vitro [17]. However, recently, scientific materials have accumulated that dispute the therapeutic effect of ribavirin in CCHF. The FDA has not approved ribavirin as an anti-viral agent for CCHF.

The clinical research [13, 14, 15]. done by Turkish scientists have shown the effectiveness of early initiation of the use of ribavirin. Early prescribing of ribavirin treatment to patients was often used in Iran, Pakistan, Turkey, Greece, Bulgaria, Russia, and other countries. However, there is no reliable scientific evidence to support its effectiveness. Furthermore, there are some ethical considerations for conducting randomized clinical trials with a control group to evaluate the efficacy of ribavirin [18].

Duygu et al. (2012) reported 400 cases of CCHF admitted to a hospital in Tokat (Turkey) in 2007-2009. All patients underwent supportive treatment without the use of ribavirin and convalescent blood plasma. The mortality rate was 5%.

A randomized study by Koksal et al. [19], which involved 64 patients with CCHF (the first group - they received ribavirin and maintenance therapy) and 72 patients with CCHF (the second group - they received only maintenance therapy without ribavirin). Demographically the groups did not differ. The duration of clinical manifestations, the need for transfusion of platelet suspensions, the time of normalization of the platelet count, and mortality did not differ in these groups. In patients who received ribavirin, more time was required for the normalization of the number of leukocytes. However, in this test group there were patients who started taking ribavirin late after the onset of the disease, which is known to be less effective in the later stages of ribavirin [20].

It should be noted that in 2004-2007 the use of ribavirin in the treatment of patients with CCHF in Turkey fell from 68% to 12%, but the mortality rate remained stable at 5-7% (19,21,22,23). Based on the above scientific studies, since 2008 in Turkey, ribavirin has been removed from the recommendations for the treatment of

CCHF due to the lack of evidence of its effectiveness. Despite this, ribavirin is used in some hospitals in Turkey.

However, it was found [20] that if a patient starts taking ribavirin in the first 3 days from the onset of the disease, the death rate from CCHF was significantly lower (3%) than in those who started taking the drug later than the specified period. (22%). Dokuzoguz B et al [24] followed 281 patients with a confirmed diagnosis of CCHF. The average age of the patients was 47 + \ - 16. The mortality rate was 8%. Patients were admitted to the hospital on average 4 + \ - 2 days of illness. Of these patients, 44 received ribavirin and steroid therapy. Among patients with a moderate course of infection and receiving ribavirin, mortality was statistically significantly lower (1.49%) compared with patients who did not receive this drug (17%). At the same time, as the authors note, among patients with severe infection, ribavirin was ineffective in reducing mortality.

Johnson S et al. conducted a systematic review of articles evaluating the effectiveness of ribavirin, which included one randomized clinical trial with 136 patients and four non-randomized clinical trials with 612 patients with CCHF. The authors concluded that ribavirin has a very low level of evidence, in reducing mortality from CCHF, reducing bed-days, and improving disease outcomes [25].

Anti-CCHF immune globulin, prepared from the plasma of disease survivors, was suggested as therapy by Chumakov et al. [27] at the time of the 1944–1945 Crimean outbreak, but later assessments in the Soviet Union found little indication of advantage. However, immune globulin therapy was initiated in Bulgaria, later in Uzbekistan, Kazakhstan, and some other post-Soviet Union republics, where it continues in use. Intramuscular and intravenous anti-CCHF immunoglobulin showed rapid improvement in CCHF infected patients in 1990, but its random clinical trials for efficacy were not carried out. Hyperimmune globulin therapy has been associated with the clinical improvement of patients in South Africa and Turkey.

Leshchinskaya et al. [26] tested convalescent serum with i / m administration of 80 ml 1 or 2 times a day 4 days after the onset of hemorrhagic syndrome in 61 patients with CCHF. There were 88 patients in the control group. This study did not show a therapeutic effect for convalescent serum. In a clinical study by Aydin et al 2007 with 22 CCHF patients, specific immunoglobulin had a rapid positive effect in 8 patients.

Hyperimmune serum prepared from convalescent plasma reduces viral load [23]. When it was used in a study conducted without a control group of patients, 13 (86.6%) of 15 patients with CCHF with a high viral load survived. Experience with the use of “human convalescent serum” is also available in Bulgaria [27]. However, it is difficult to evaluate the results of these studies, as they were conducted without using the case-control method [28]. At the same time, positive experience with the use of immune sera may indirectly indicate that immunogenetic mechanisms play an important role in the pathogenesis of CCHF [29].

The existing in Uzbekistan practice of using the CCHF convalescent serum recommended by Komilov and approved by the Ministry of Health of the Republic of Uzbekistan has no scientific justification due to the lack of an analysis of the world literature in it and the lack of study of the effectiveness of the previous experience of its use in the country.

Conclusions. Considering the limitations of observational studies, we concluded that the type of therapy did not play a role in reducing CCHF mortality. The use of blood plasma from convalescents has taken place in many states, but there are no unambiguous conclusions on the application of this method. Further well-organized research is needed.

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