



## REVIEW ARTICLE

# Crimean-Congo Hemorrhagic Fever: What Do We Know about Pulmonary Injury? A Compilation of Evidence

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## Introduction

Crimean-Congo Haemorrhagic Fever (CCHF) is a lethal vector-borne viral infection produced by a Nairo virus, a genus of the Bunyan viridae family. Crimean-Congo Haemorrhagic Fever Virus (CCHFV) is a single-stranded RNA virus with three segments (large, medium, and small), two envelope proteins (Gn and Gc) and an RNA-dependent RNA polymerase [1-3]. Studies have found the GC protein to be the target-binding protein as well as an important mediator for virus entry [4]. Variations in small segments of RNA help to group the virus into seven different genotypes designated Africa-1, Africa-2, Africa-3, Europe-1, Europe-2, Asia-1 and Asia2 [5-7]. CCHF is endemic in Asia, Europe, Middle East and Africa. The spread of the disease has increased in recent years with approximately 140 outbreaks and more than 5000 cases have been registered worldwide [8]. More than 1000 cases are reported from southeastern Europe and western Asia each year [9].

The virus can be transmitted to humans in different manners. One of them is through tick bites of the Hyalomma genus, although it can be transmitted by other tick species. The tick may transmit the infection to livestock such as goats, sheep and cattle, resulting in the development of viremia and antibodies. Therefore, people who work with these animals (eg: butchers) are considered to be at risk. Livestock and bird migratory patterns can also affect spread of infection [1,2,5,10-15]. Person to person transmission can occur through contact with

blood and bodily fluids of affected patients. Because of this, healthcare workers are considered subjects at risk, particularly during the haemorrhagic stage of disease [10,11].

The human is considered the dead-end host of the virus [11]. The course of CCHF includes four stages: incubation, pre haemorrhagic, haemorrhagic, and convalescence [16]. The incubation period varies depending on how infection occurs. It can last up to 9 days when the disease is acquired through a tick bite and a maximum of 13 days when transmission occurs by infected tissues or blood [3]. Next, the pre-haemorrhagic period involves a broad-albeit non-specific range of symptoms such as fever, chills, severe headache, photophobia, myalgia, abdominal pain, nausea, flushing, hypotension, and bradycardia [17,18]. The haemorrhagic stage can develop as soon as 3 days into the disease [3]. Evidence of haemorrhage can be as subtle as small petechiae, through large ecchymosis, all the way up to mucosal (eg: gums) and internal organs (eg: lungs and GI tract) haemorrhage [18,19]. Fatality rates in hospitalized patients are as high as 50% and death occurs mainly due to disseminated intravascular coagulation and multi organ failure [11,20]. The convalescent period starts after about 20 days of illness. It can take up to a year for survivors to be fully recovered. Some of the symptoms of this stage include loss of memory, hair loss, headache, and poor vision [5-8].

There is still little understanding and knowledge on

how does CCHFV affect the pulmonary system because only a handful of studies have been conducted in this regard [21]. Therefore, the purpose of this article is to exhibit what is known so far about CCHF from a pulmonary point of view. We try to make a compilation that reasonably depicts the degrees in which the disease can affect the respiratory tract, and how does previous pulmonary disease alter severity of disease and its prognosis. Additionally we found a case report in which ribavirin was given and successfully improved the patient both clinically and radiologically.

## Evidences

According to Sannikova IV, et al. in 2007, the pulmonary lesion caused by CCHF may behave as Acute Respiratory Distress Syndrome (ARDS). Also, during the haemorrhagic stage of the disease haemoptysis, pulmonary haemorrhage, and bleeding into the pleural cavity could be manifestations of the disease. In their study, they found that severity of disease correlates with elevation of pro inflammatory cytokines [22].

A case report published by Doganci L, et al. in 2008, exposed the case of a young adult Turkish man who presented with non-productive cough and bilateral crackles, fever, skin rashes, myalgia, nausea, diarrhoea, and occasional epistaxis. They diagnosed him with CCHF and then performed a CT-scan of the chest, which confirmed what they saw in a previous chest radiograph. The patient had bilateral patchy alveolar infiltrates, in relation with a diffuse alveolar haemorrhage. Ribavirin therapy was initiated with successful clinical and radiological results. Emphasis was placed on the contagious nature of the virus and the high-risk probability for nosocomial spread in bronchoscopes contaminated with patient blood [23].

There is a study published in 2009 in which Abadoglu O, et al. conducted a questionnaire that reveals history of diagnosed symptoms of asthma, non-specific bronchial hyper reactivity, allergic rhinitis, and history of other familial allergic diseases. They applied the questionnaire to 114 diagnosed CCHF cases, and to 122 healthy controls. The study found that there was no relation between self-reported allergic diseases and CCHF. They did, however, find that some symptoms could be more or less severe depending on pre-existing conditions or history of disease [24].

In 2011 Dogan OT, et al. published a study to determine common symptoms, clinical signs, and radiological changes. It was a retrospective study of 108 patients who had laboratory confirmation of CCHF. For each patient they studied the clinical history, and analysed the patient's age, sex, occupation, city of residence, history of tick bite or of tick removal, smoking history, chest X-ray results, outcome, and clinical and laboratory findings. They realized that dyspnoea and cough were common symptoms, but haemoptysis was only present in

six cases. Patients also presented productive coughing, dyspnoea, and chest pain. In chest radiography they noticed 19 cases with parenchymal infiltration, 15 cases with hilar pathology, and 7 with pleural thickening, 6 with interstitial pathology, and 1 with mediastinal pathology. Interestingly (albeit not statistically significant), pathologic radiographs were more common in patients who eventually died from the disease than among survivors. The rest of them had no pulmonary affection reported by chest X-ray. Seven patients died because of severe pulmonary infection, and haemorrhage [25].

In a similar study from 2014, Bilgin G, et al. analysed the medical histories of 128 patients who had laboratory confirmation of CCHF. They focused wanted to correlate disease with patient's age, sex, occupation, place of residence, contact with ticks, smoking history, laboratory findings, and pulmonary radiological changes. The pulmonary radiographs revealed infiltration, hilar and interstitial pathology, pleural thickening and effusion in 25% of the patients. The rest of them were normal. 9.4% of patient's presented bilateral pulmonary affectation, they didn't detect acute respiratory distress syndrome signs. They didn't find statistically significant differences between survivors and non-survivors in terms of sex, contact with ticks, place of residence, smoking, symptoms and physical examination findings related to the respiratory system. They saw that haemoptysis, chest pain, dyspnoea, and pulmonary infiltration or haemorrhages are indicative factors of worse prognosis and mortality. Patients also presented cough, sputum, rales and rhonchi. Pleural effusion was presented in only one patient without a clear cause. Another interesting finding in this study was the elevation in C-reactive protein. In this regard, they found that patients who eventually died from CCHF were higher than in patients who survived the disease. This finding was found to be statistically significant [26].

Finally in 2016, a retrospective study by Aktas T, et al. examined CCHF viral infection and its consequences at systemic inflammation, pulmonary vascular beds, and lung tissue. They designed a retrospective study of 45 patients. They included patients who were diagnosed by laboratory analysis with CCHF and with a thoracic computer tomography for evaluation of the lungs (measurement of pulmonary trunk, main pulmonary arteries, atria, and ventricles). These measurements were compared with the control group (patients with normal thoracic CT). They found that the study groups average pulmonary artery diameter was larger than that of the control group ( $p < 0.001$ ). This is important because pulmonary hypertension may appear in these conditions and could affect the clinical course of the illness. To add up, patients with CCHF could present alveolar haemorrhage, pleural effusion, acute respiratory distress syndrome and shock, with an increased systemic inflammatory response affecting the lungs. However, pathophysiological changes in CCHF are still unknown [22].

## Discussion

CCHF incidence and prevalence have increased recently with more than 1000 cases reported from south-eastern Europe and western Asia each year [9]. This is important because fatality rates in hospitalized patients have reached approximately 50% and death occurs mainly due to disseminated intravascular coagulation and multi organ failure [11-21]. There are no specific treatment or vaccine prophylaxes at this moment.

This study describes respiratory disease caused by CCHF virus. The mentioned articles conclude that the virus can cause haemoptysis, cough, dyspnoea, chest pain, hilar and interstitial pathology, pulmonary haemorrhage, bleeding into the pleural cavity, acute respiratory distress syndrome, shock, and may lead to pulmonary hypertension.

Some of the evidence suggests that prompt identification of pulmonary injury due to CCHF could benefit from treatment with ribavirin, but efficacy of ribavirin is still debatable. Further clinical trials are needed.

A more thorough study and deeper reviews of pulmonary lesions and disease caused by CCHF could help us to better understand the progress of disease and to better focus management and treatment of certain patients.

## Conclusion

CCHF is a severe disease that causes important multi systemic failure. There are no specific reviews of respiratory disease caused by CCHF virus. The virus can cause haemoptysis, cough, dyspnoea, chest pain, hilar and interstitial pathology, pulmonary haemorrhage, bleeding into the pleural cavity, acute respiratory distress syndrome, shock, and may lead to pulmonary hypertension. Some of the evidence suggests that prompt identification of pulmonary injury due to CCHF could benefit from treatment with ribavirin. Further studies are needed.

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