International Journal of Infectious Diseases 55 (2017) 118–121

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

# An Unexpected Fatal CCHF Case and Management of Exposed Health Care Workers

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ARTICLE INFO

*Article history:*
Received 30 October 2016
Received in revised form 4 December 2016
Accepted 23 December 2016
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

*Keywords:*
Crimean-Congo Hemorrhagic Fever
prophylaxis
health care workers
ribavirin

ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is a tick borne viral disease which can also be transmitted by direct contact with blood or tissue specimens of infected animals or humans. We present a fatal case of CCHF, who was diagnosed after death, and describe the post-exposure management plan for the health care workers (HCWs) involved in her care. In total of 52 HCWs were involved in the patient's care and they were stratified into risk groups. Overall, 20 HCWs were grouped in high and intermediate risk groups, including the HCW with needle stick injury. High and intermediate risk groups were offered post exposure prophlaxis (PEP) with ribavirin. Fourteen of 20 HCWs started PEP, however 10 ceased after negative CCHF-PCR results. Negative CCHF-PCR results were reported for all HCWs at the 5th day of exposure. Side effects with PEP developed in 5 of HCWs and were mainly gastrointestinal complaints which reversed after drug discontinuation. All HCWs were followed for 14 days both clinically and with laboratory tests. None of the HCWs developed CCHF. PEP with ribavirin can be considered as a safe option in protection.
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## INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a tick-born disease of humans with a wide geographical distribution from western China to the Balkans, from South Africa to Middle East.[1] CCHF virus (Bunyaviridae Family and Nairovirus Genus) was first isolated from Russian soldiers in the Crimea in 1944 and source of transmission was described in 1967 by a Russian virologist.[2] CCHF is endemic in Greece, Bulgaria, Kosovo, Albenia, Russia, South Africa, Iran and Turkey. There has been a rapid increase in its incidence in Turkey and Iran within the last decade.[3–5] Recently an autocthonous fatal case of CCHF, and an infected HCW were reported in Spain.[6]

CCHF is a fatal disorder and the clinical picture may range from subclinical disease to multiple organ failure and shock.[2,7,8] Mortality is reported to be 3-30% depending on the route of transmission, host immunologic factors, viral load, time to diagnosis and administration of post-exposure prophylaxis (PEP).[9,10] Since the first report of CCHF in 2002, over 9000 cases have been declared with a case fatality rate of 4.7% in Turkey.[3] After the first nosocomial outbreak of CCHF in 1976 in Pakistan, many countries reported case series of nosocomial outbreaks including Turkey.[9–19] Direct contact with ticks or infected materials, needle stick injuries and aerosols were the most commonly reported transmission routes of nosocomial CCHF.[12–21] Strict adherence to barrier precautions is of pivotal importance in the prevention of infection.

Post-exposure use of ribavirin in CCHF is controversial. Despite some low quality studies failing to show benefits of PEP with ribavirin; there are multiple case reports and animal studies encouraging its use.[9,10,19–26] Moreover, a predefined algorithm for post exposure management of HCWs is not present, despite presence of strong recommendations by experts.

In this study, we aimed to describe the post-exposure management plan for the HCWs who had contact with a highly infectious case of CCHF.

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http://dx.doi.org/10.1016/j.ijid.2016.12.026
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## INDEX CASE

A 39-year-old woman with hepatorenal failure was transferred from an intensive care unit (ICU) to Ankara University Medical ICU as a candidate for liver transplantation. Hepatic failure was assumed to be due to ingestion of high amounts of herbal tea within the last 6 months. She had no underlying disease other than migraine. No fever was noticed till her admission to the current ICU. She denied exposure to ticks. On admission she was hypotensive, hypothermic, anuric and had severe metabolic acidosis and hypoxia. She had bleeding from nose, gastrointestinal system and previous puncture sites. She was intubated, and hemorrhagic secretions were aspirated. Pulse index continuous cardiac output (PICCO) catheters for hemodynamic monitorisation were inserted. Continuous renal replacement therapy was started. On the 17th hour of admission arteriovenous extracorporeal membrane oxygenation (ECMO) cannulation was performed during cardiopulmonary resuscitation (CPR), and she was lost on the 29th hour of admission. During her stay, frequent suctioning, bag-valve-mask ventilation, multiple arterial and venous punctures were performed.

Two days following her loss, her 2-year-old nephew was hospitalized with the tentative diagnosis of CCHF. They had a picnic together, one week prior to onset of her symptoms. Thereupon the sera of our patient, which was stored at −20 °C for further studies, was sent to national reference laboratory for viral diseases of Turkey. PCR results revealed extremely high viral copies of CCHF.

### *Practice Routines in the Medical Intensive Care Unit (ICU)*

ICU of Ankara University is a third level unit with 9 bed. In average, one nurse cares 2-3 patients. Standard precautions for infection control, such as hand hygiene with alcohol based solutions and using gloves are part of the routine. When contamination with patient body fluids (including physical examination) is possible, surgical mask, glove and gown are used unless the procedure is an emergent one. Wearing goggles was not a common practice, until report of the presented case.

### *Post-exposure follow-up plan and ribavirin prophylaxis*

Immediately after the positive result for CCHF was obtained, i.e. two days after the patient died, all the contacts were listed. They were all informed about the situation and their exposure to the patient's body fluids was questioned.

HCWs were grouped into three depending on their risks. Group 1 (high risk) comprised of HCWs who had direct skin or mucosa contact with contaminated blood or body fluids, participated in CPR and did not comply with barrier precautions. Needle stick injury and splash of blood or body fluids were included in the first group. Group 2 (intermediate risk) included HCWs who were present at the bedside, participated during the above mentioned events, but reported compliance with barrier precautions, thus had no direct contact with contaminated blood or body fluids. Group 3 (low risk) included HCWs who were in the room but did not have any direct contact with the patient and did not get closer than 1 m to the patient. Group 1 and 2 HCWs were offered ribavirin prophylaxis at a dose of 2 g per day divided in four doses. Group 3 was followed for clinical signs and symptoms. All HCWs were informed about clinical signs and symptoms of CCHF and the follow-up plan was discussed with all groups. All contacts were followed daily with fever control, complete blood count and liver enzyme levels for 14 days. CCHF RT-PCR tests were performed for all on the 4-5th days of exposure.

## RESULTS

In total 52 HCWs participated in the care of the patient. PEP was offered for 20 of the HCWs who were cathegorized as high and intermediate risk groups. The details of HCWs who were offered PEP are shown in Table 1. CCHF-PCR studies were performed from all contacts and were negative. However, ribavirin prophylaxis was continued for the high risk HCWs with the concern that viral load

**Table 1**
Characteristics of HCWs under high and intermediate risk group.

| No | Age | Sex | Risk Group | Occupation | Exposure | Ribavirin use (day) | Reasons for PEP non-compliance and/or cessation |
|---|---|---|---|---|---|---|---|
| 1 | 39 | M | 1 | Physician | ECMO | N/A | Unable to access drug |
| 2 | 38 | F | 1 | Physician | Secretions on hair and face | 1 | Severe enteritis, flu like symptoms |
| 3 | 31 | M | 1 | Physician | ECMO | 10 | – (Had mild abdominal pain that did not cause treatment cessation) |
| 4 | 42 | F | 1 | Physician | ECMO | 10 | – |
| 5 | 36 | M | 1 | Physician | ECMO | 10 | – |
| 6 | 29 | F | 1 | Nurse | Needlestick injury | 10 | – |
| 7 | 28 | M | 2 | Physician | CPR | N/A | Presence of underlying health problems, self-reported proper |
| 8 | 25 | F | 2 | Physician | CPR | N/A | usage of PPE, absence of exposure to blood and secretions |
| 9 | 41 | F | 2 | Physician | CPR | 1 | Self-reported proper usage of PPE |
| 10 | 26 | M | 2 | Physician | CPR | 1 | Severe enteritis, mild hepatitis |
| 11 | 25 | M | 2 | Physician | CPR | 2 | Flu like symptoms, mild hepatitis |
| 12 | 31 | M | 2 | Physician | CPR | 1 | Self-reported proper usage of PPE |
| 13 | 28 | F | 2 | Nurse | Patient care | 1 | Self-reported proper usage of PPE |
| 14 | 37 | F | 2 | Nurse | Patient care | 1 | Self-reported proper usage of PPE |
| 15 | 30 | F | 2 | Nurse | Patient care | N/A | Self-reported proper usage of PPE |
| 16 | 32 | M | 2 | Nurse Assistant | Patient care | 7 | * |
| 17 | 42 | M | 2 | Nurse Assistant | Patient care | 7 | * |
| 18 | 31 | M | 2 | Nurse Assistant | Patient care | 7 | *Baseline liver enzymes mildly elevated, progressed with PEP, quit treatment on 7th day. |
| 19 | 48 | F | 2 | Burial Officer | care of the corpse | N/A | Self-reported proper usage of PPE |
| 20 | 49 | F | 2 | Burial Officer | care of the corpse | N/A | Self-reported proper usage of PPE |

CPR: Cardiopulmonary ressuscitation, PPE: Personal Protective Equipment, ECMO: Extracorporeal Membrane Oxygenation, NA: Not Applicable, F: Female, M: Male.
*Despite cessation is offered, he preffered to continue.

may not be high enough to be detected on PCR. Ending PEP was recommended for the intermediate risk group after negative PCR results.

Two of six doctors who were present during cardiopulmonary ressuscitation (CPR) did not accept PEP, because of underlying health problems, absence of gross contamination and the reported proper use of mask, gown and gloves (HCW 7,8). Two quit PEP after negative PCR results (HCW 9,12). One had to quit within 48th hour of therapy due to severe enteritis and mild hepatitis (HCW 10). The other quit ribavirin after 48 hours because of flu-like symptoms that increased after ribavirin intake and mild hepatitis (HCW 11).

A 29-year-old nurse had incurred a needle stick injury (HCW 6). She was offered PEP with high dose ribavirin (4 gr in 4 divided doses for 14 days). She did not have any side effects other than mild elevation of bilirubin levels (highest values total bilirubin: 1.7 mg/dL, direct bilirubin: 0.5 mg/dL) and completed PEP. She did not develop CCHF.

During placement of nasogastric feeding tube, bloody oral secretions had splashed over one of the doctor's hair and face (HCW 2). She had washed her face and hair with chlorhexidine containing soap and water. She was offered PEP as well. However, after she received the first three doses she had severe diarrhea and stopped PEP. On follow-up, she did not have any further complaints.

Three cardiovascular surgeons (HCW 1,3,5) and an interventional radiologist (HCW 4) performed the ECMO catheterization during CPR. All were offered PEP. All, but one (HCW 1), started PEP and completed the course of drugs. One of the surgeons was abroad, and did not have access to drug (HCW 1).

Three nurse assistants were offered PEP until PCR results were available, because of their close contact with the patient and her body fluids, with adequate barrier precautions (HCW 16,17,18). However, they continued PEP for 7 days on their own personal decision (HCW 16,17,18). One had mild elevation of the liver enzymes prior to treatment (HCW 18), and it increased over the course of PEP. After cessation of treatment enzyme levels returned to baseline levels within weeks.

One HCW from Group 3 and two HCWs from Group 2 (HCW 8,19) developed fever and malaise within the first week of follow-up. Since repeated PCR testing results were negative, no treatment was offered.

Overall, 52 HCWs had contact with the patient, and 20 (6 from Group 1, 14 from Group 2) were offered PEP. Of these HCWs, 14 (5 from Group 1, 9 from Group 2) received PEP. Most common side effects of ribavirin were gastrointestinal complaints. Adverse reactions precluded continuation of prophylaxis in 3 HCWs (severe enteritis and mild hepatitis). After cessation of treatment, all side effects reversed within a few days. Four HCWs completed the recommended course of PEP. None of the HCWs developed CCHF.

## DISCUSSION

CCHF is a highly contagious disease with well known nosocomial infection risk and high fatality rate.[1] Since the initial report of transmission to HCWs in 1976, many occupational transmissions have been reported from Pakistan, South Africa, Iran, India, Tajikistan, Germany, Russia, Turkey, and Spain.[6,9–19] Rate of CCHF after blood exposure and needlestick injury were reported as 8.7% and 33%, respectively, from the incident at Tygerberg Hospital in 1985.[15] As with all other diseases atypical presentation is possible, such in this case, and diagnosis may be a dilemma. Therefore, not all patients may be under strict isolation during their stay in the hospital.

Although well-planned, controlled, randomized trials are missing, ribavirin is consistently being reported as a safe and effective drug for both treatment and post exposure prophylaxis.[7,12] Randomized-control trials may be unethical given the severity of the disease.[27] Yet, trials on mice demonstrate its efficacy, emphasizing early administration for favorable results. Bente et al.,[28] have reported a study on mice in order to indicate the importance of ribavirin administration time. They showed that the mice to which ribavirin were administered on 24th hour of inoculation had higher mortality than the mice to which ribavirin was administered within 1 hour.

Similar to other incidents reported, the contacts in this case were grouped according to their risk and ribavirin PEP was offered to groups under high risk.[9,10,17,19] Case series reveal that, ribavirin is generally well-tolerated without severe side-effects. Anemia, fatigue, myalgia, allergic skin reactions, nausea, vomiting, and hemolysis are the most reported adverse effects of ribavirin.[9,10,22–24] In our series three HCWs had severe gastrointestinal problems and/or mild elevation of the liver enzymes that caused cessation of ribavirin (Table 1).

Direct skin or mucosal contact with blood or body fluids has been a well documented route of infection.[5,12] Transmission by aerosol inhalation was suggested by several case reports.[10,11,17] In the reported case, during the aerosol generating multiple procedures, surgical masks and N95 masks were frequently used.

In conclusion, a post-exposure plan should be developed and the plan should stratify the contacts depending on their risks. Ribavirin is the drug of choice for PEP and its use is safe. As well, all HCWs should be aware of potential contagious diseases in critically ill patients and be educated to adhere strictly to standard, contact and droplet precautions.

## Declaration of Interest

This paper was granted by Turkish Society for Febrile Neutropenia and Society For Appropriate Drug Usage. There is no commercial relationship or potential conflict of interest related to the submission including all authors.

## Ethical Consideration

This study was approved by the local ethical committee of Ankara University with protocol number 46004091-302.14.06/E.19478

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