A case of Crimean-Congo haemorrhagic fever imported in Greece: Contact tracing and management of exposed healthcare workers

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Abstract

Background: Nosocomial transmission is a major mode of infection of Crimean-Congo haemorrhagic fever (CCHF). In May 2018, a patient with CCHF was hospitalised in Greece.

Objective: Our aim was to present the management of healthcare workers (HCWs) to the CCHF case.

Methods: Contact tracing, risk assessment and follow-up of exposed HCWs were performed. Testing (RT-PCR and/or serology) was offered to contacts. Post-exposure prophylaxis (PEP) with ribavirin was considered for high-risk exposures.

Results: Ninety-one HCWs were exposed to the case. Sixty-six HCWs were grouped as high-risk exposures. Ribavirin PEP was offered to 29 HCWs; seven agreed to receive prophylaxis. Forty-one HCWs were tested for CCHF infection; none was found positive. Gaps in infection control occurred.

Discussion: CCHF should be considered in patients with compatible travel history and clinical and laboratory findings. Early clinical suspicion and laboratory confirmation are imperative for the implementation of appropriate infection control measures. Ribavirin should be considered for high-risk exposures. Infection control capacity for highly pathogenic agents should increase.

Keywords

Crimean-Congo haemorrhagic fever, infection control, healthcare workers, contact tracing, ribavirin

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Background

Crimean-Congo haemorrhagic fever (CCHF) is an acute, life-threatening disease transmitted to humans primarily by ticks of the genus *Hyalomma*, but also through direct contact with blood or tissues of viremic patients or animals (Maltezou and Papa, 2011). Nosocomial transmission is a major mode of infection and healthcare workers (HCWs) are second only to farmers as a risk-group (Ftika and Maltezou, 2013; Leblebicioglu et al., 2016). The disease at late stage manifests as a rapidly progressing acute febrile syndrome with profound haemorrhagic manifestations and case fatality rates up to 50% (Maltezou and Papa, 2011). CCHF virus (CCHFV) has the widest geographic distribution among all tick-borne viruses. Over the past two decades, new CCHF foci emerged or re-emerged; nowadays CCHFV is endemic in more than 30 countries in Southern Europe, the Middle East, Central and Southwest Asia, and Africa (Maltezou and Papa, 2011; Negredo et al., 2017). Imported CCHF cases have been occasionally reported (Ftika and Maltezou, 2013).

A 47-year old Greek man presented at Xanthi General Hospital on 31 May 2018. He had a history of fever, severe headache, fatigue, photophobia and myalgias which commenced three days previously; he had been working in bridge construction in a forested area in Blagoevgrad, Southwestern Bulgaria for the past 23 days before his admission. He had severe thrombocytopenia ($10,000$ platelets/ mm^3) and impaired coagulation parameters. On 1 June 2018, the patient was transferred to the University Hospital of Alexandroupoli, where he deteriorated rapidly, experiencing lethargy, severe ecchymoses, extensive haematomas and multiorgan failure (Figure 1). He underwent a bone marrow biopsy which showed haemophagocytosis. On day 9, the patient mentioned that on May 26 he removed a tick from his abdomen. CCHF was suspected and ribavirin was administered. The diagnosis was confirmed at the National Reference Center for Arboviruses and Hemorrhagic Fever Viruses, Thessaloniki by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and by detection of CCHFV-specific IgM antibodies in serum. The patient improved and on 21 June he was discharged (Papa et al., 2018).

We present the contact tracing and management of exposed HCWs to prevent nosocomial CCHFV transmission, including the administration of post-exposure prophylaxis (PEP) with ribavirin.

Methods

Infection control

Before CCHF was suspected, gloves, surgical masks and semi-permeable gowns were available for HCWs. Starting from clinical suspicion of CCHF (June 4, 12:00),

Figure 1. Ecchymoses and haematoma of the CCHF patient (day 10).

the patient was strictly isolated in a single room (not under negative pressure) under contact and respiratory precautions and personal protective equipment (PPE; gloves, FFP3 respiratory masks, waterproof gowns and goggles) was used. Handling of samples, management of apparel and waste, and cleaning procedures were performed in accordance with the national guidelines for the management of viral haemorrhagic fevers (World Health Organization, 2018).

Contact tracing and surveillance of exposed HCWs

Guidelines for contact tracing and active surveillance of HCWs exposed to CCHFV were immediately sent to both hospitals. The date(s), shift(s), duration and type of contact, and the use of PPE were recorded. Direct contact was defined as contact with the patient's body, biological fluids, tissues, apparel or waste. The criteria used for risk assessment of exposed HCWs are shown in Table 1.

Management of exposed HCWs

HCWs with a history of contact were followed for the development of symptoms and with daily temperature measurement for 14 days after the last contact. Testing (RT-PCR and/or serology) was offered to contacts regardless of symptoms. Ribavirin at $600 \text{ mg} \times 4$ for 7–10 days per os was offered to HCWs with high-risk exposure.

Table 1. Risk assessment of HCWs potentially exposed to CCHFV.*

Level of risk	Description of risk
High	Direct contact with the patient, his mucous membranes, biological fluids, tissues, apparel and/or waste or being in a distance of < 1 m without barrier precautions; diagnostic or therapeutic interventions without PPE
Intermediate	Direct contact with skin or mucous membranes, tissues, apparel or waste with barrier precautions; being in the same room but in a distance of > 1 m
Low	Contact with the patient, his mucus membranes, biological fluids, tissues, apparel and/or waste wearing PPE

*Exposure to the CCHF patient, his mucus membranes, biological fluids, tissues, apparel or waste.

HCW, healthcare worker; CCHFV, Crimean-Congo haemorrhagic fever virus; PPE, personal protective equipment (gloves, gowns, FFP3 respiratory mask and goggles).

Results

Ninety-one HCWs were exposed to the patient, his biological fluids, tissues, apparel or waste (Table 2). In the first hospital, 42 HCWs had a history of any contact. Of them, 37 were considered as having high-risk exposure, including: two internists (A1, A2) and one haematologist (A3) who examined the patient; one radiologist (A4) who performed abdominal ultrasound; one radiology technician (A32) who performed chest X-ray in close proximity; one microbiologist (A5), two residents (A7, A9) and two laboratory technicians (A33, A34) who performed blood sampling and/or handled blood samples; one resident (A8) who spent 1 h with the patient in the ambulance; 13 nurses (A10, A11, A14–A22, A25, A26) and four nurse students (A28–A31) who had direct contact with the patient or his apparel, performed blood sampling and/or measured vital signs; two paramedics (A39, A40) who transferred the patient; four cleaners (A35–A38) and one nurse assistant (A27) who cleaned the room and/or disposed the waste; and two ambulance drivers (A41, A42) who came in close proximity with the patient during his transportation to the second hospital.

One nurse (A11) developed a non-haemorrhagic rash, myalgias and lumbar pain three days after caring for the patient for 2 h and after blood sampling wearing gloves. Complete blood count on day 6 of her illness was within normal range (264,000 platelets/mm³). She was tested negative by RT-PCR; she stayed home until the result was available. In addition, no CCHFV IgM and IgG antibodies were detected in a serum sample taken 10 days after onset of her symptoms and CCHFV infection was excluded. The remaining 41 HCWs were asymptomatic during the 14-day

follow-up. The radiologist (A4) and a medical resident (A8) considered as having the highest-risk contact also tested negative by RT-PCR. In total, 27 HCWs agreed to get tested for CCHFV infection, including the symptomatic nurse (A11), 25 HCWs (one already found negative by RT-PCR) who tested negative for specific CCHFV IgM and IgG antibodies 21 days after the last contact, and one who tested negative by RT-PCR only. No HCWs received ribavirin PEP.

In the second hospital, 49 HCWs had a history of any contact with the case (Table 2). Of them, 29 were considered as having high-risk exposure. There were: one internist (B2) who spent 1 h with the patient at admission; two residents (B8, B9) and one nurse (B20) who contacted the patient while he was sweaty; four radiologists (B11–B14) who conducted chest X-rays and CT in close proximity with the patient; four haematologists (B4–B7) and a haematology resident (B10) who examined blood microscopy slides (including one who performed the BM biopsy); one laboratory technician (B28) who prepared blood stains and handled blood samples; 14 laboratory technicians (B29 through B42) who handled blood samples; and one paramedic (B49) in close proximity with the patient. Ribavirin PEP was offered to the 29 HCWs with high-risk exposure but only seven received it. One HCW who received ribavirin developed a fever < 38.4 °C three days after her contact with the patient; cystitis was laboratory-diagnosed and ciprofloxacin was prescribed. Three HCWs reported fatigue and gastrointestinal complaints attributed to ribavirin. Laboratory tests showed a reduction of haematocrit in two ribavirin-treated HCWs, while a third also noted an elevation of bilirubin and ribavirin was discontinued. None of the 49 HCWs with a history of contact developed any symptom other than those described above. Of the 29 HCWs with high-risk exposure, 14 agreed to get tested for CCHFV infection; all were tested negative by CCHFV IgM and IgG antibodies (4–6 days after last contact and three weeks later). In addition, the internist who examined the patient at admission and the laboratory technician who prepared blood stains were considered having the highest-risk contact and tested negative by RT-PCR.

Discussion

CCHF cases challenge healthcare facilities in terms of prompt suspicion and infection control preparedness and response (Conger et al., 2015; Fletcher et al., 2017; Ftika and Maltezou, 2013; Lumley et al., 2014; Roy et al., 2016; Yadav et al. 2017). An unsuspected CCHF case admitted with massive haemorrhage has been the source of infection in most nosocomial epidemics (Ftika and Maltezou, 2013). Interventions for gastrointestinal haemorrhage, emergency operations, needle-stick injuries, percutaneous exposure to blood and mouth-to-mouth resuscitation are high-risk activities (Ftika and Maltezou, 2013; Leblebicioglu et al.,

Table 2. HCWs with contact with the CCHF case* until clinical suspicion (4 June, 12:00).†

No.	Profession	Direct contact/ risk level	Description of contact
A/1	Internist	Yes/H	Examination of the patient for 2 h (mask: no, gloves: no)
A/2	Internist	Yes/H	Examination of the patient (mask: no, gloves: no)
A/3	Haematologist	Yes/H	Examination of the patient (mask: no, gloves: no)
A/4	Radiologist	Yes/H	Abdominal ultrasound (mask: no, gloves: no)
A/5	Microbiologist	Yes/H	Handled blood samples (mask: no, gloves: yes)
A/6	Medical resident	Yes/I	Examination of the patient for 2 h (mask: yes, gloves: yes)
A/7	Medical resident	Yes/H	Blood sampling (mask: no, gloves: yes)
A/8	Medical resident	No/H	With the patient in the ambulance for 1 h (mask: no, gloves: no)
A/9	Microbiology resident	Yes/H	Handled blood samples (mask: no, gloves: yes)
A/10	Nurse	Yes/H	Direct contact with the patient/bed linen, blood sampling (mask: no, gloves: no)
A/11	Nurse	Yes/H	Blood sampling, monitoring of vital signs, 2 h with the patient (mask: no, gloves: yes)
A/12	Nurse	Yes/I	Blood sampling (mask: yes, gloves: yes)
A/13	Nurse	Yes/I	Blood sampling (mask: yes, gloves: yes)
A/14	Nurse	Yes/H	Blood sampling, measurement of vital signs, 2 h with the patient (mask: no, gloves: yes)
A/15	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/16	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/17	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/18	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/19	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/20	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: yes)
A/21	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: no)
A/22	Nurse	Yes/H	Administration of i.v. medications (mask: no, gloves: no)
A/23	Nurse	Yes/I	Attended the rounds (mask: no, gloves: no)
A/24	Nurse	Yes/I	Attended the rounds (mask: no, gloves: no)
A/25	Nurse	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/26	Nurse assistant	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/27	Nurse assistant	Yes/H	Cleaned the room (mask: no, gloves: yes)
A/28	Nurse student	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/29	Nurse student	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/30	Nurse student	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/31	Nurse student	Yes/H	Monitoring of vital signs (mask: no, gloves: no)
A/32	Radiology technician	Yes/H	Chest X-ray in close proximity (mask: no, gloves: no)

(continued)

Table 2. (Continued)

No.	Profession	Direct contact/ risk level	Description of contact
A/33	Laboratory technician	Yes/H	Blood sampling (mask: no, gloves: yes)
A/34	Laboratory technician	Yes/H	Blood sampling (mask: no, gloves: yes)
A/35	Cleaner	Yes/H	Cleaned the room, waste disposal (mask: no, gloves: yes)
A/36	Cleaner	Yes/H	Cleaned the room, waste disposal (mask: no, gloves: yes)
A/37	Cleaner	Yes/H	Cleaned the room, waste disposal (mask: no, gloves: yes)
A/38	Cleaner	Yes/H	Cleaned the room, waste disposal (mask: no, gloves: yes)
A/39	Paramedic	No/H	Transportation of the patient in close proximity (mask: no, gloves: no)
A/40	Paramedic	No/H	Transportation of the patient in close proximity (mask: no, gloves: no)
A/41	Ambulance driver	No/H	Transportation of the patient, in close proximity (mask: no, gloves: no)
A/42	Ambulance driver	No/H	Transportation of the patient, in close proximity (mask: no, gloves: no)
B/1	Professor of ID	Yes/L	Examination of the patient (PPE: yes)
B/2	Internist	Yes/H	Examination of the patient for 1 h (mask: no, gloves: no)
B/3	ID specialist	No/I	Attended the rounds (mask: no, glove: no)
B/4	Haematologist	Yes/H	Contact with blood on microscope slide (mask: no, gloves: no), performed BM biopsy (mask: yes, gloves: yes)
B/5	Haematologist	Yes/H	Contact with blood on microscope slide, present in BM biopsy (mask: no, gloves: no)
B/6	Haematologist	Yes/H	Contact with blood on microscope slide (mask: no, gloves: no)
B/7	Haematologist	Yes/H	Contact with blood on microscope slide (mask: no, gloves: no)
B/8	Medical resident	Yes/H	Examination of the sweaty patient for 20 min (mask: no, gloves: yes)
B/9	Medical resident	Yes/H	Examination of the sweaty patient for 20 min (mask: no, gloves: yes)
B/10	Haematology resident	Yes/H	Contact with blood on microscope slide, present in BM biopsy (mask: no, gloves: no)
B/11	Radiologist	No/H	Chest X-ray, in close proximity (mask: no, gloves: no)
B/12	Radiologist	No/H	CT scan, in close proximity (mask: no, gloves: no)
B/13	Radiologist	No/H	CT scan, in close proximity (mask: no, gloves: no)
B/14	Radiologist	No/H	CT scan, in close proximity (mask: no, gloves: no)
B/15	ID nurse	No/L	Attended the rounds (PPE: yes)
B/16	Nurse	No/I	Attended the rounds (mask: no, gloves: yes)
B/17	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/18	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/19	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)

(continued)

Table 2. (Continued)

No.	Profession	Direct contact/ risk level	Description of contact
B/20	Nurse	Yes/H	I.V. medications, monitoring of vital signs of the sweaty case (mask: no, gloves: yes)
B/21	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/22	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/23	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/24	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/25	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/26	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/27	Nurse	Yes/I	Administration of i.v. medications, monitoring of vital signs (mask: yes, gloves: yes)
B/28	Laboratory technician	Yes/H	Prepared blood stains, handled blood samples (mask: no, gloves: no)
B/29	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/30	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/31	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/32	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/33	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/34	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/35	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/36	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/37	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/38	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/39	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/40	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)

(continued)

Table 2. (Continued)

No.	Profession	Direct contact/ risk level	Description of contact
B/41	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/42	Laboratory technician	Yes/H	Handled blood samples of the patient (mask: no, gloves: no)
B/43	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/44	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/45	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/46	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/47	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/48	Cleaner	Yes/I	Cleaned the room, waste disposal (mask: yes, gloves: yes)
B/49	Paramedic	No/H	Transportation of the patient, in close proximity (mask: no, gloves: no)

*The patient, his biological fluids, mucous membranes, tissues, apparel or waste.

†Starting from clinical suspicion, HCWs used PPE.

‡Mask: surgical mask.

A, General Hospital of Xanthi; B, University Hospital of Alexandroupoli; L, low risk; I, intermediate risk; H, high risk; HCW, healthcare worker; CCHF, Crimean-Congo haemorrhagic fever; ID, infectious diseases; PPE, personal protective equipment; BM, bone marrow; CT, computed tomography; i.v., intravenous.

2016). Airborne transmission has also been reported as a risk (Pshenichnaya et al. and Nenadskaya, 2015). Our patient did not have any apparent haemorrhage and the bone marrow biopsy was the only risky intervention. It has been estimated that the CCHFV RNA is detectable at up to 16–18 days of illness (Burt et al., 1998; Wolfel et al., 2007). The absence of apparent haemorrhages may explain the absence of nosocomial transmission. Our patient's viral load on day 9 was 3.33×10^7 copies/mL of plasma which is relatively high; it was probably even higher on day 6 (Papa et al., 2018). However, CCHFV is less easily transmitted from person to person than previously thought and the respective risk may be overstated, as shown by recent seroprevalence studies among HCWs caring for CCHF patients in endemic countries (Maltezou et al., 2009; Weidmann et al., 2016). This is in contrast to the risk of transmission to other viral haemorrhagic fevers such as Ebola haemorrhagic fever (Ftika and Maltezou, 2013).

The use of ribavirin for CCHF treatment or PEP remains an issue of controversy (Maltezou and Papa, 2011). Almost all data about ribavirin efficacy are limited to small studies and methodological concerns have been raised (Maltezou and Papa, 2011). Currently, ribavirin is used in most CCHF-endemic countries (Maltezou et al., 2010). We offered ribavirin PEP to HCWs with high-risk exposure, following risk-assessment. Ribavirin was generally well-tolerated and most probably had a protective impact as PEP, in accordance with other studies (Güven et al., 2017; Leblebicioğlu et al., 2016; World Health Organization, 2018). However,

several HCWs refused prophylaxis. We identified gaps in infection control before CCHF was suspected. There is a need to increase infection control capacity and to address issues of HCW compliance through education (Fletcher et al., 2017). Well-designed studies about the efficacy of ribavirin PEP are urgently needed (Maltezou and Papa, 2011).

Our patient was working outdoors in Blagoevgrad, an area where since 2008 several CCHF cases have occurred (Christova et al., 2009). Currently, CCHF is endemic in south-eastern Europe including Bulgaria, Albania, Kosovo and Russia. This information, in association with the patient's compatible clinical and laboratory findings and the history of a recent tick bite (a major route of CCHF infection), established the clinical suspicion of CCHF on the third day after admission in the second hospital (day 9 of his illness). By that time, 91 HCWs from two hospitals had been exposed. Contact-tracing, surveillance and management of exposed HCWs was highly demanding in terms of human resources and costs and was time-consuming. Communication of evidence-based knowledge about ribavirin PEP and risk assessment were also a challenge.

In conclusion, our report illustrates the challenges of managing a CCHF case in terms of prevention of nosocomial transmission. CCHF should be considered in patients with compatible travel history as well as clinical and laboratory findings. Clinical awareness, early suspicion and prompt laboratory confirmation are imperative not only for the optimum treatment of the patient, but

also to trigger timely proper infection control measures for disease spread containment. Contact tracing, surveillance and management of exposed HCWs were demanding. Infection control capacity against highly pathogenic agents should increase.

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