## c FOCUS FEATURE: Crimean-Congo haemorrhagic fever (CCHF)

**Case report**

A 39-year-old previously well female resident of Elgin in Western Cape Province was hospitalised on 5 January 2014, presenting with haematemesis and a petechial rash for investigation. Along with her husband and children, she had travelled to Free State Province from 21 to 29 December 2013 to stay with family on a cattle and sheep farm in the Welbedacht Dam area. On 29 December 2013 she became ill with fever, headache and influenza-like symptoms whilst travelling back to Elgin. She consulted a doctor and began doxycycline therapy for suspected tick bite fever; however, she did not improve on treatment and her illness progressed. On admission she was noted to have extensive petechiae and purpura, haematemesis, and a tendency to bleed from venepuncture sites. Initial laboratory investigations showed leukopenia (2 x $10^9$/L), thrombocytopenia (24 x $10^9$/L), transaminasemia (AST 13 000 IU/L, ALT 3 000 IU/ L), and a coagulation profile suggestive of DIC. The patient reported that although she had not noticed any tick bites, she had found a 'bontpoot' tick lodged in her navel a few days earlier. CCHF was confirmed by positive RT-PCR and serology testing at the Centre for Emerging and Zoonotic Diseases, NICD-NHLS. The patient developed numerous complications and required supportive care in ICU, but has improved meanwhile.

Epidemiology

The first modern description of CCHF was of an outbreak in the West Crimea region of southern Ukraine during World War II. At that time, agricultural activities were disrupted, pastures were overgrown, and hares with ticks proliferated. During the summer of 1944 about 200 cases of fever with haemorrhage occurred among farmers and soldiers assisting with the harvest. In 1967, an identical virus was isolated from a blood sample taken in 1956 from a patient in the Belgian Congo.

CCHF infection is the most widespread tick-borne viral infection of humans, and occurs across a vast area from Western China through southeastern Asia and the Middle East to southeastern Europe and throughout most of Africa. Since 2000, the incidence and geographic range of confirmed CCHF cases have markedly increased, with disease being reported for the first time in Turkey, Iran, India, Greece, Georgia, and some Balkan countries.

*Hyalomma* spp. are the only known vectors of CCHF. These ticks transmit the virus to a variety of wild and domestic mammals, which develop an asymptomatic transient viraemia, and therefore also act as reservoirs. Tick larvae and nymphs prefer feeding on small animal hosts (including hares, hedgehogs, rodents and ground-feeding birds e.g. guinea fowl). Adults feed on large mammals, either wildlife (including antelope and buffalo) or domestic livestock (including sheep, cattle, pigs, horses and ostriches). Humans are infected either by tick bites or by exposure to contaminated blood/excreta of the reservoir animals, and human cases often occur during spring and summer months, when the spread of CCHF virus between ticks and mammals is highest. Person-to-person transmission can occur through contact with virus-containing body fluids of a patient; nosocomial outbreaks are well described and have been associated with high mortality rates. The life cycle of *Hyalomma* spp. ticks and transmission pathways of CCHF virus to humans are shown in Figure 1.

**FOCUS ON CCHF**

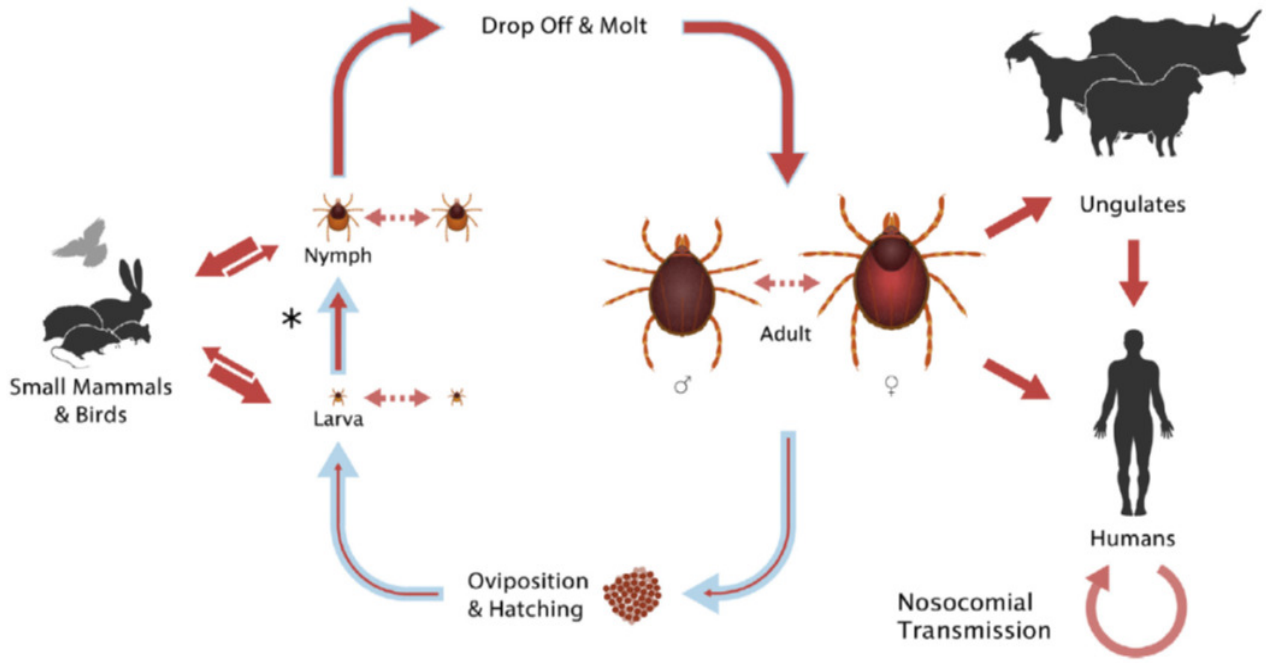


**Figure 1. Life cycle of *Hyalomma* spp. ticks, and transmission pathways of CCHF virus to humans.**

Reproduced from: Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo haemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. *Antiviral Res* 2013 Oct; 100

Clinical features

Although most infections with CCHF virus result in a mild, nonspecific febrile illness, some patients do develop severe haemorrhagic disease. The course of CCHF infection is divided into four phases: incubation, prehaemorrhagic, haemorrhagic, and convalescence. The incubation period varies according to the mode of transmission: following a tick bite, it ranges 1-5 days and following contact with infected blood/tissues it usually ranges 5-7 days, with a maximum of 13 days. The prehaemorrhagic phase is characterised by the abrupt onset of fever, malaise and a variety of nonspecific symptoms (including headache, neck pain and stiffness, sore eyes, photophobia, dizziness, somnolence and depression). Examination may reveal a flushed appearance with injected conjunctivae or chemosis; hepatomegaly with right upper quadrant tenderness; lymphadenopathy; and enanthema/petechiae of the throat, tonsils or buccal mucosa. The haemorrhagic phase usually begins on day 3-6 of illness and most often is heralded by a petechial rash appearing first on the trunk and limbs. This may rapidly progress to cutaneous purpura and ecchymoses (particularly in the antecubital fossae, upper arms, axillae and groin) and bleeding from the gastrointestinal and urinary tracts. Hepato-and splenomegaly are common findings. Internal bleeding (including retroperitoneal and intracranial haemorrhage) and vaginal bleeding may also occur. Severely ill patients develop hepatorenal failure and ARDS from about day 5 onwards, with progressive drowsiness, stupor and coma; jaundice may develop during the second week of illness. In fatal cases, death is usually as a result of haemorrhage and DIC, multi-organ failure and shock. The convalescence period in survivors begins about 10-20 days after the onset of illness, and full recovery may take up to a year.

Laboratory findings

Haematology testing shows an early leukopenia, with the development of thrombocytopenia during the first week of illness. Coagulation abnormalities develop, with prolonged prothrombin time (PT) and activated partial prothrombin time (APTT), and detection of fibrin degradation products (FDP) and D-dimers indicative of DIC. Progressive hepatic involvement results in increased transaminasemia

(ALT and AST). As patients become hypotensive, increased urea and creatinine reflect renal insufficiency. During the first five days of illness, any of the following clinical laboratory features are highly predictive of a fatal outcome: leucocyte count ≥10 x $10^9$/L; platelet count ≤20 x $10^9$/L; AST ≥200 IU/L; ALT ≥150 IU/L; APTT ≥60 seconds; and fibrinogen ≤110 mg/dL. After day five of illness, all clinical laboratory values may be grossly abnormal without necessarily being indicative of a poor prognosis.

Diagnosis

CCHF should be suspected when a person with an appropriate exposure history becomes acutely ill with fever, malaise and other nonspecific signs and symptoms, together with physical findings suggestive of vascular leak and abnormal coagulation. Swanepoel, Mynhardt and Harvey devised a scoring system for the clinical diagnosis of CCHF based on a set of clinical, laboratory and exposure criteria (see appendix). This tool can assist the healthcare worker in deciding whether the patient should be regarded as a suspected CCHF case. Testing for CCHF is done at the NICD-NHLS. CCHF virus RT-PCR is usually positive during the first 7-10 days of illness, with IgM detectable by the end of the first week, followed shortly by the appearance of IgG.

Management

General supportive measures are the mainstay of management. Volume replacement (with careful monitoring to prevent pulmonary oedema) and administration of blood products (platelets, fresh frozen plasma, packed red blood cells) as needed is critical. Prophylactic therapy for stress ulcers with H2-receptor antagonists is advised. If tick bite fever is also a differential diagnosis, empiric doxycycline treatment must be given until the diagnosis is confirmed. The role of the antiviral drug ribavirin in treatment of CCHF is controversial. Randomised controlled trials have not been performed, but some case series and studies reported apparent benefit. It appears that ribavirin is most beneficial when initiated within the first 5 days of illness. Although antibody therapy has been tried, there are no controlled trials or objective data that support its use.

Case fatality rate

The reported case fatality rate of CCHF has varied widely from 3 – 30%, depending on the number of cases in the respective case series/studies, and whether mild illness was included. The case fatality rate in the largest case series described to date (Turkey, >6 000 cases since 2002) has been about 5%, which suggests that the higher rates reported in earlier outbreaks reflect a failure to recognise less severe infection.

Infection prevention and control considerations

All patients with suspected CCHF should be presumed infectious and isolated until a specific diagnosis is made. Although experience with CCHF has shown that routine standard precautions are protective in most cases, specific viral HF isolation precautions are advised (use of surgical mask, double gloves, gown, protective apron, face shield and shoe covers) in order to prevent contact and droplet exposure to blood and bodily fluids. Percutaneous exposure (via needle-stick or sharps injuries) carries a particularly high risk for transmission; safe use and disposal of needles and sharps must be emphasised, and the use of needles/sharps limited as far as possible.

Contact tracing and monitoring

Persons having unprotected direct contact with a CCHF patient during the symptomatic phase of illness should be identified and monitored for 14 days following last contact with the CCHF patient. Temperature should be measured and recorded 12-hourly, and persons who develop fever or other signs/symptoms suggestive of CCHF should be immediately isolated until the diagnosis can be excluded.

Post-exposure prophylaxis (PEP)

Although oral ribavirin has been used as PEP for contacts of CCHF cases, there are no data on efficacy, dose, or duration. The consideration of ribavirin as PEP should be reserved for definitive high-risk exposures, for example needle-stick injuries or mucous membrane exposures.

CCHF in South Africa

CCHF is the commonest viral haemorrhagic fever occurring in South Africa. The first human CCHF

case was reported in 1981: a 13-year-old boy spent a week camping in a nature reserve in the Bloemhof area (North West Province), and on return developed an acute illness with sudden onset of fever and nonspecific symptoms; a *Hyalomma* spp. tick was found attached to his scalp. On the third day he developed a cutaneous petechial rash with profuse gastrointestinal and mucous membrane bleeding; he died on day 6 of illness. Since then, up to 20 CCHF cases have been reported annually, with a total of 194 laboratory-confirmed cases documented to date. Although cases have been reported from all nine provinces, more than half the cases originate from the semi-arid areas of Northern Cape Province and Free State Province (Figure 2), with exposure predominantly in rural farming areas. Although CCHF cases have been reported throughout the year, more than half the cases in the last decade have occured between December and March. In South Africa, the virus is transmitted by *Hyalomma* spp. ticks which have distinctive brown and white bands on their legs; they are known as 'bont-legged ticks' or 'bontpootbosluise' (Figure 3). There are three species of *Hyalomma* genus ticks in South Africa, and although they are widely distributed, the ticks tend to be most numerous in the drier north-western parts of the country – the Karoo, western Free State, Northern Cape, and North West provinces.

Males account for 91% of South African cases, most being farmers and other agriculture-related workers; the occupational risk groups include farmers, herders, abattoir workers, veterinarians/animal health workers, hunters, and persons informally slaughtering domestic/wild animals. Approximately two-thirds of cases have been associated with tick bite exposures, the remainder reporting direct exposure to infected animals. The majority of cases have been sporadic and isolated; however, outbreaks have also occurred, including an outbreak at an ostrich abattoir in Oudsthoorn affecting 17 persons, and a nosocomial outbreak in Cape Town where six healthcare workers contracted disease (one doctor and five nurses, with one fatality) from a single patient. The case fatality rate of South African CCHF cases has been 24%, but this data is biased since only severe cases are tested and detected.

Detailed information for healthcare workers regarding CCHF can be found on the NICD website http://www.nicd.ac.za/ (see FAQ).

**Source:** Source: Division of Public Health Surveillance and Response, and Centre for Emerging and Zoonotic Diseases, NICD-NHLS; Western Cape Department of Health

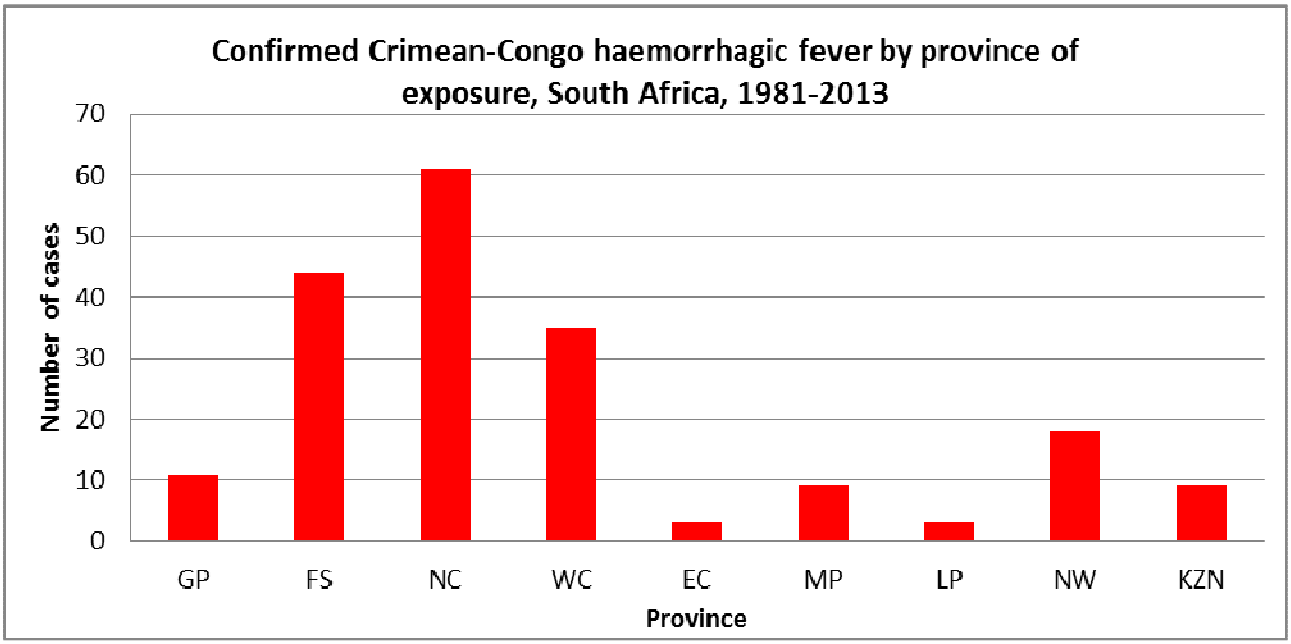


**Figure 2. Confirmed Crimean-Congo haemorrhagic fever cases by province of exposure, South Africa, 1981-2013.**

**Figure 3. *Hyalomma* spp. ticks ('bont-legged' ticks/'bontpootbosluise')**
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