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Review article

Therapeutic management of Crimean-Congo haemorrhagic fever☆

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ABSTRACT

Crimean-Congo haemorrhagic fever has been reported in more than 30 countries in Africa, Asia, the Middle East and Eastern Europe, with an increasing incidence in recent years, especially in Europe. Because no specific treatments have demonstrated efficacy, supportive treatment is essential, as well as the provision of a centre with the appropriate means to guarantee the safety of its healthcare professionals. Laboratory monitoring of thrombocytopenia, severe coagulopathy or liver failure is of critical importance. Patients with Crimean-Congo haemorrhagic fever should be admitted to High Level Isolation Units where appropriate biocontainment procedures can prevent nosocomial transmission through infected fluids or accidents with contaminated material. In case of high-risk exposures, early administration of ribavirin should be considered.

Manejo terapéutico de la fiebre hemorrágica de Crimea-Congo

Palabras clave:
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RESUMEN

La fiebre hemorrágica de Crimea-Congo afecta a más de 30 países de África, Asia, Europa oriental y Oriente Medio, con una creciente incidencia durante los últimos años, especialmente en Europa. Sin un tratamiento específico eficaz, las medidas terapéuticas de soporte son fundamentales, así como disponer de un centro con los medios adecuados para garantizar la seguridad de los trabajadores. La monitorización analítica es esencial para el manejo de la trombocitopenia, la coagulopatía grave o el fallo hepático. La atención a los pacientes con fiebre hemorrágica de Crimea-Congo debe llevarse a cabo en Unidades de Aislamiento de Alto Nivel, capaces de aplicar procedimientos de biocontención que eviten la transmisión nosocomial a través de fluidos infectados o accidentes con material contaminado. En caso de exposiciones de alto riesgo podría plantearse la administración precoz de ribavirina.

Introduction

Crimean-Congo haemorrhagic fever (CCHF) virus has a broad global distribution.[1,2] In 2010, ticks belonging to the genus *Hyalomma* infected with CCHF virus, whose lineage matched virus strains from Mauritania and Senegal, were identified in Extremadura.[3] However, until the first two cases of CCHF were diagnosed in August 2016 in Spain,[4] no human cases of autochthonous acquisition had been reported in western Europe.[5]

CCHF virus belongs to the family *Bunyaviridae* and the genus *Nairovirus*. Its main vectors are ticks belonging to the genus *Hyalomma*.[1] Different animals, both domesticated and wild, act as reservoirs for the virus (cats, sheep, goats, horses, donkeys, pigs, hares, hedgehogs, etc.).[6] Livestock is one of the most important hosts. Human beings may be infected by either a tick bite or direct handling of infected meat or fluids.[6] Nosocomial transmission has been reported by healthcare staff with accidental needle sticks or unprotected exposure to blood, bodily fluids or droplets from patients diagnosed with CCHF.[6,7] Infection has also been reported in healthcare workers involved in the care of ill patients, without the exact route of transmission having been identified (in some articles, these cases of infection with no clear source account for up to 10–15% of nosocomial cases).[7–9]

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The spectrum of seriousness of CCHF is highly variable. Seroprevalence studies in endemic areas have suggested that up to 80% of cases are asymptomatic.[6,10] The classic clinical course of CCHF has been divided into four periods: incubation, pre-haemorrhagic phase, haemorrhagic phase and convalescence.[6,11] Reported mortality ranges from 3% to 30%, depending on the outbreak studied. Mortality is primarily caused by fulminant hepatitis, thrombocytopenia and massive bleeding.[6,10,12] In Turkey, since the first cases were identified in 2002, more than 9700 cases have been reported with a mortality rate of approximately 5% which has remained stable over the years.[13]

CCHF virus is classified as a biosafety level 4 pathogen[14] capable of interpersonal transmission. It is advisable to manage patients with a suspected or confirmed diagnosis of CCHF using strict precautions for contact under which the patient is isolated in an individual room, preferably with a separate entrance and exit. Viruses are to be isolated in biosafety level 4 high-containment laboratories, and patients with CCHF are to be managed in high-level isolation units.[14,15]

Supportive therapy is essential, since there is no effective specific aetiological treatment. Although its use is controversial as no conclusive studies have demonstrated its efficacy, in the most serious cases, it is advisable to use high-dose ribavirin. Other treatments, such as hyperimmune serum from convalescent patients, have not been shown to be useful. Furthermore, there are no vaccines with proven efficacy or safety in humans.[2]

Protective measures in a hospital setting against Crimean-Congo haemorrhagic fever

The CCHF virus is a biosafety level 4 pathogen that is transmissible and capable of causing nosocomial outbreaks with a high mortality rate.[7] Contact with contaminated materials and fluids, contact with blood from gastrointestinal bleeding, accidental needle sticks and surgical operations in patients with an unknown diagnosis have been reported as the main routes of infection in a healthcare setting. Close interpersonal contact with the patient and manipulation of the respiratory tract are routes of transmission that are still subject to debate[16]; however, nosocomial outbreaks of CCHF have indeed been reported during orotracheal intubation.[8] The virus's limited repercussions for domestic settings shows that invasive procedures and unprotected contact in the haemorrhagic phase cause most secondary cases.

Ideally, patients with CCHF should receive care in high-level isolation units equipped for critical care, as CCHF may progress with rapid deterioration. The room should be equipped with negative pressure systems should procedures that generate droplets need to be performed.[14,15]

Healthcare staff should be well informed about the disease and its possible mechanisms of infection. They should also be suitably educated and have regular training in putting on and taking off personal protective equipment (PPE).[6,17] Emergency departments in endemic regions should receive instruction in upholding strict contact precautions and ensuring isolation of any suspected case from the start.[16] Some retrospective studies have found that around 50% of cases of nosocomial infection originate in patients not yet diagnosed with CCHF.[7]

Although universal basic protective barriers could suffice to prevent most cases of nosocomial infection, it should be noted that hospital care is provided to more seriously ill patients with greater viraemia. Existing evidence on nosocomial outbreaks and World Health Organisation (WHO) recommendations for other highly lethal haemorrhagic fevers justify the use of PPE comprising at least the following items: a waterproof gown, gloves, a mask and goggles (or a face screen).[8,16] For clinical management of confirmed cases, it is advisable to use the same PPE used to manage Ebola virus disease: a waterproof body suit, double layers of footwear and gloves, a hood, a mask and airtight goggles. PPE must always be suited to the type of healthcare to be provided, as the risk of infection may vary.[2,18]

Therapeutic management

Symptomatic treatment

Drugs should not be administered via intramuscular injection so as to prevent haematomas and local bleeding at puncture sites.[6]

It is advisable to administer paracetamol as an antipyretic and to avoid non-steroidal anti-inflammatory drugs to the extent possible due to their potential repercussions for clotting.[6]

Proton pump inhibitors may be used to prevent gastrointestinal bleeding, which may occur due to either disease complications or stress.[6,17,19] In women, inhibition of menstrual bleeding through administration of progesterone may be indicated.[17]

Antibiotics

Although antimicrobials should not be used in a confirmed case of CCHF, unless superinfection is suspected,[17] they must be considered in an investigational case by assessing the different entities included in the differential diagnosis and the patient's geographic origin.[2] The differential diagnosis of CCHF is broad. If the patient's geographic origin is taken into account, it includes Alkhurma haemorrhagic fever and Rift Valley fever in the Middle East; Omsk haemorrhagic fever in Russia; Kyasanur forest disease in India; hantavirus in Europe and Asia; Lassa virus, Ebola virus, Marburg virus, Rift Valley fever and yellow fever in Africa; and dengue fever mainly in Asia and central Africa. In tropical and subtropical countries, malaria is the most important alternative diagnosis to be ruled out. If the transmission vector is taken into account, the following must also be included: *Rickettsia* spp., *Ehrlichia* spp., *Borrelia, Anaplasma* and *Babesia*. In addition, many other infectious diseases may feature a similar initial clinical picture: tularaemia, Q fever (*Coxiella burnetii*), viral hepatitis, influenza virus infection, meningococcal meningitis, leptospirosis, typhoid fever, sepsis due to staphylococci or Gram-negative bacilli, toxic shock syndrome, salmonellosis, shigellosis, psittacosis, trypanosomiasis, septic infection due to *Yersinia pestis*, rubella and measles.[2]

Glucocorticoids

The efficacy of glucocorticoids for the treatment of CCHF has not been confirmed.[19] Studies dedicated to evaluating their usefulness are limited and consist of small case series in both adults and paediatric patients. They have found that administration of high-dose methylprednisolone (20–30 mg/day) seems to promote early haematological recovery, reverse haemorrhagic lesions and decrease the need for transfusion of blood products. Their results have been inconclusive due to patients simultaneously receiving ribavirin.[20,21] Should a patient develop a haemophiliac syndrome secondary to CCHF, treatment with corticosteroids would be more clearly indicated, since this does have demonstrated efficacy in cases secondary to infections by other microorganisms.[22,23]

Supportive therapy

Care for patients with CCHF requires careful monitoring of vital signs to detect organ failure early and start the necessary supportive care immediately.[6]

CCHF requires close laboratory monitoring: complete blood count, alanine non-transferable (ALT), aspartame non-transferable