Crimean-Congo haemorrhagic fever

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Summary

Crimean-Congo haemorrhagic fever (CCHF) is one of the most widespread arboviroses in the world. It is present in Africa, south-east Europe, the Middle East and Asia. It is caused by a nairovirus (Bunyaviridae family) transmitted by several species of ticks. The geographical distribution of the disease coincides with the distribution of *Hyalomma* ticks. While infected livestock do not show signs of illness, humans are severely affected, with a high mortality rate. The most common symptoms are high fever, dizziness, headache, vomiting and haemorrhages. Pathogenesis studies in interferon-receptor-deficient mice indicated that the interferon response is crucial in controlling virus propagation and in protecting against the disease. Detection of the virus in biological material is currently performed by reverse-transcription polymerase chain reaction. Enzyme-linked immunosorbent assay and indirect immunofluorescence are used to detect the presence of CCHF virus-specific antibodies. In the 1970s, a formalin-inactivated vaccine prepared from suckling mouse brain was used in Eastern Europe and the former Soviet Union, but its efficacy remains to be proven. Treatment of patients with ribavirin is recommended by the World Health Organization, but it should be administered as early as possible. Although important progress has been made over the last few decades, many questions about the pathogenesis and epidemiology of the disease are still to be addressed and there is a need to develop efficient vaccines and antivirals.

Keywords


Historical aspects

The disease now known as Crimean-Congo haemorrhagic fever (CCHF) was first reported in the 12th Century in humans living in a region that is presently Tajikistan. The disease was described as a haemorrhagic syndrome, with blood in the rectum, gums and abdominal cavity, and in urine, vomit and sputum (1, 2). The first documented outbreak of a disease known as Crimean haemorrhagic fever was described in 1944–1945, when hundreds of military personnel from the former Soviet Union were infected while helping peasants in Crimea. From 1953 to 1969 annual outbreaks of this disease, including many fatal cases, occurred in the south-west of the former Soviet Union, in the Astrakhan area. The aetiology was demonstrated in 1967 when the virus was isolated from blood and tissues of patients after intracerebral inoculation of newborn mice (2). The Crimean haemorrhagic fever virus was later shown to be antigenically indistinguishable from Congo virus, which had been isolated in 1956 from a febrile patient in what is now the Democratic Republic of the Congo (3). Therefore, the virus was renamed Crimean-Congo haemorrhagic fever virus (CCHFV) (1, 3). Nowadays, outbreaks of CCHF are documented in Africa, the Middle East, Eastern Europe, and Western Asia (2).

Biological properties

Crimean-Congo haemorrhagic fever virus belongs to the *Nairovirus* genus, a group of enveloped RNA viruses approximately 100 nm in diameter. It belongs to the *Bunyaviridae* family, which also comprises the genera *Hantavirus*, *Phlebovirus*, *Orthobunyavirus* and *Tospovirus* (4). The nairovirus genome consists of three segments of single-stranded, negative-sense RNA, designated large (L), medium (M) and small (S) (5). These genome segments encode four structural proteins: the L segment codes
for the L protein, which is an RNA-dependent RNA polymerase, the M segment encodes the two structural membrane glycoproteins Gn and Gc, and the S segment encodes the nucleocapsid protein N. Non-structural proteins encoded by the M segment were synthesised as products of the processing of the glycoprotein precursor (6, 7). Different protein domains were identified within the L protein, including an ovarian tumour protease (OTU) domain which appears to be unique to nairoviruses and functions as a core element of a cysteine protease capable of deconjugating proteins modified with ubiquitin or ubiquitin-like proteins (8, 9). Like the other members of the Bunyaviridae family, the 3' and 5' terminal sequences of each genome segment are conserved and complementary to each other, forming a pan-handle structure which possesses conserved polymerase binding sites. Viral multiplication occurs in the cytoplasm of infected cells, and viral particles bud principally through the Golgi apparatus (10).

**Organisation of the viral genome**

The S segment is approximately 1.6 kilobases (kb) in size and contains one open reading frame (ORF) that codes for the viral N protein in the antigenomic orientation (5). Numerous N molecules encapsidate the viral RNA genome into ribonucleoprotein particles present in the virion. In infected cells, the N protein is found primarily in the perinuclear region and it has been suggested that actin filaments are involved in the targeting of N to that region, limiting virus assembly and the generation of infectious virions (11). The N protein is cleaved by a caspase-3 protease which is activated during CCHFV infection, the sequence of the cleavage site being conserved among CCHFV strains (12). The N protein forms oligomers with itself, actin and the L protein, the binding domains as well as the amino- and carboxy-terminal regions of the L protein necessary for the formation of the N-L complexes have been identified (13). When the S ORF is over-expressed in insect cells, the N protein is able to self-assemble, forming virus-like particles (14). Although the S segment of several members of the *Bunyaviridae* family expresses an NSs protein involved in antagonism of host defence mechanisms (15, 16), to date the *Bunyaviridae* family expresses an NSs protein involved in antagonism of host defence mechanisms (15, 16), to date, no evidence of L protein autoproteolytic processing was found, and the OTU protease activity was found to be unnecessary for virus RNA replication in a minigenome system (8).

The L segment of CCHFV comprises approximately 12 kb and contains a single ORF encoding a 448 kilodalton protein (17, 18). The viral RNA-dependent RNA polymerase encoded by the L segment is responsible for RNA replication and messenger RNA (mRNA) synthesis. The OTU domain located in the N terminus of the viral L protein was shown to be a functional protease. However, no evidence of L protein autoproteolytic processing was found, and the OTU protease activity was found to be unnecessary for virus RNA replication in a minigenome system (8).

**Transmission and epidemiology**

Crimean-Congo haemorrhagic fever virus usually circulates in an enzootic tick–vertebrate–tick cycle. It is mainly transmitted by ticks of the *Hyalomma* genus. The geographical distribution of the disease coincides with the global distribution of *Hyalomma* ticks (19, 20). Although CCHFV has also been isolated from other ticks of other genera (*Amblyomma, Rhipicephalus, Ornithorhynchus, Boophilus, Dermacentor* and *Ixodes* spp.), their role in virus transmission is yet to be determined (21). The virus has been isolated from both eggs and unfed immature stages of ticks, suggesting both transovarial (20) and transstadial transmission (22, 23, 24). In areas with a temperate climate CCHF cases normally occur from spring to early autumn, when the ticks are at their most active.

Although the virus persists in ticks, vertebrates are needed to provide blood meals for the ticks. A variety of livestock (cattle, goats, sheep, horses, pigs, hares, ostriches, camels, donkeys, mice and domestic dogs) can become infected with the virus. In fact, numerous domestic and wild vertebrates have been reported to mount an antibody response and/or develop viraemia (21). In contrast to CCHFV-infected humans, infected livestock generally exhibit no sign of disease (20, 23, 25, 26).

It has been shown that the majority of birds are resistant to infection (20); however, migratory birds can carry infected ticks, therefore facilitating virus dissemination from one endemic country to a new one (2, 27, 28). Although no antibodies were detected, tick-infested ostriches were shown to have caused a serious outbreak of CCHF during slaughtering in South Africa. Interestingly, experimentally infected ostriches can develop viraemia (28).

Humans can be infected mainly through direct contact with blood or tissues from infected material and livestock, through tick bites or, possibly, via aerosol generated from infected animal excreta. CCHFV cases are mainly found in farmers, abattoir workers, healthcare workers and veterinarians (1). The potential for human-to-human transmission of CCHFV puts healthcare workers at risk when caring for
patients: exposure to infected blood or needle-stick injuries have accounted for several cases of nosocomial outbreaks, including fatalities (1). Healthcare workers are advised to wear protective barrier clothing (29) and it is recommended that infectious CCHFV should be manipulated only in laboratories with biosafety level 4 facilities (30).

Consuming cooked meat is not a risk factor since the post-slaughter acidification of the tissues inactivates the virus. Recreational activities such as hiking, camping and other rural activities in CCHF-endemic areas have been proposed as risk factors for tick exposure and for disease acquisition (1).

Emergence of Crimean-Congo haemorrhagic fever virus

Crimean-Congo haemorrhagic fever is the second most widely spread arbovirus (after dengue virus) and it has the greatest geographical distribution of all tick-borne viruses (1). Currently, CCHFV is known to be present in more than 30 countries, including countries in Africa (e.g. Democratic Republic of the Congo, Uganda, Mauritania, Nigeria, South Africa, Senegal), south-east Europe (e.g. Russia, Bulgaria, Kosovo, Turkey, Greece), the Middle East (e.g. Iraq, Iran, Saudi Arabia, Oman) and Asia (e.g. China, Kazakhstan, Tajikistan, Uzbekistan, Pakistan, India (31)).

During the last decade, CCHFV has caused human disease in previously unaffected countries, including Turkey, Iran, Greece, Georgia and Albania (32, 33, 34, 35) and, more recently, in India (36). The virus has also re-emerged in south-western regions of the Russian Federation (37) and in Central Africa, after an absence of nearly 30 years. Moreover, some recent data suggest that CCHFV has extended its zone of circulation in Europe, for example:

- serological evidence of CCHFV in humans has been reported in Portugal and Hungary (37, 38)

- antibodies against CCHFV have been detected in livestock in Romania, with prevalence values similar to those observed in other regions where the disease is endemic

- the circulation of CCHFV in *Hyalomma lusitanicum* ticks collected from indigenous deer in Spain has also been reported (39).

It has been suggested that global warming and climate changes may increase the incidence and geographical range of CCHF. Such changes may alter the tick growth patterns and redirect the migration routes of birds hosting the infected ticks, i.e. to areas newly warmed by increased earth temperature patterns. Anthropogenic factors, such as changes in land use, agricultural practices, hunting activities and movement of livestock may also influence CCHFV epidemiology dynamics (37).

Clinical features

Humans are the only species in which CCHFV is known to cause a severe disease (2). The progression of the disease can be divided into four distinct phases: the incubation, the pre-haemorrhagic, the haemorrhagic, and the convalescence phases (2). The incubation phase ranges from three to seven days after exposure to the virus and is followed by the pre-haemorrhagic phase, which lasts on average for three days (40). The haemorrhagic phase starts with the sudden onset of fever, headache, myalgia, dizziness, vomiting and increasing viraemia (2, 40, 41) and is characterised by haemorrhagic manifestations ranging from petechiae to large haematomas on the mucosal membranes and skin. The most common bleeding sites are the nose (epistaxis), the gastrointestinal system (haematemeses, melena, and intra-abdominal bleeding), the urinary tract (haematuria) and the respiratory tract (haemoptysis) (1, 42). Hepatomegaly and splenomegaly are reported to occur in one-third of patients (2). Without treatment, the average mortality rate is 30–50%, with most deaths occurring from 5–14 days after the onset of the illness (2, 5). For those who survive, the convalescence phase begins about 10–20 days after the onset of illness (1).

In a study of 12 patients in South Africa, immunohistochemistry and *in situ* hybridisation showed that mononuclear phagocytes, endothelial cells and hepatocytes are the main targets of infection. The association of parenchymal necrosis in the liver with viral infection suggested that the cell damage might be a direct effect of the virus (43). In bone marrow biopsy of patients, reactive haemophagocytosis by histiocytes was detected, which suggested that haemophagocytosis can play a role in the pathogenesis of the disease.

Pathogenesis

Studies *in vitro* and *in vivo* demonstrated the susceptibility of CCHFV to type I interferons (IFNs): both type I IFN receptor knockout (IFNAR/-/-) mice and STAT-1 knockout (STAT-1/-/-) mice were susceptible to CCHFV infection and developed a clinical disease leading to death, showing that the IFN response is crucial in controlling CCHFV and protecting against liver damage in mice (44, 45). In IFNAR/-/- mice, the liver and the spleen showed the highest levels of CCHFV RNA. In STAT-1/-/- mice, the white blood cells were the first site of CCHFV RNA detection and the virus also replicated extensively in the liver and the spleen
Furthermore, CCHFV was shown to multiply *in vitro* in human peripheral blood mononuclear cells, including monocyte-derived dendritic cells (DCs) (46, 47) and its supernatants have been shown to activate human endothelial cells (48). The later study concluded that CCHFV has both direct and indirect effects on endothelial cells. Other studies showed that CCHFV multiplies *in vitro* in hepatocyte cell lines (49, 50). The proapoptotic direct effect of CCHFV was demonstrated in hepatocyte cell lines (50) together with the alteration of inflammation and oxidative stress pathways (51).

In *vitro*, CCHFV was shown to delay the up-regulation of IFN-stimulated gene 56, and possibly interfere with the IFN regulatory factor 3 pathway (49). The type I IFN-inducible protein MxA, recombinant or IFN-induced, was reported to reduce the yield of CCHFV progeny by up to a thousand-fold by interacting with a component of the nucleocapsid (52, 53).

Crimean-Congo haemorrhagic fever virus was shown to have preferential basolateral entry and basolateral release in polarised epithelial cells (54). Moreover, CCHFV was shown to enter cells via a clathrin-, pH- and cholesterol-dependent mechanism (55). It was also demonstrated that viral internalisation relies on the presence of intact microtubules, as it was shown that, within the first hour after infection, CCHFV moves along microtubules to reach the cellular sites of viral transcription and multiplication (56). The human cell surface nucleolin was identified as a putative CCHFV entry factor, as were multivesicular bodies (57, 58). Components of the endosomal sorting complex were required for viral transport (58).

**Diagnosis and prognosis factors**

The usual approach for CCHF diagnosis combines the detection of the viral RNA genome and/or the antigen during the viraemic phase and the detection of specific immunoglobulin M (IgM) and then immunoglobulin G (IgG) antibodies in human serum or blood during the haemorrhagic and convalescent phases.

Detection of viral genome is by far the easiest method of diagnosis to implement. The quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR) is the current gold standard; several assays have been developed in order to enhance the specificity and sensitivity of this diagnostic tool (59, 60, 61). Recently, a highly specific and sensitive RT-PCR test was developed, allowing the detection of up to 18 strains of CCHFV (62). DNA chips were also used to detect several CCHFV isolates in different endemic zones (63, 64). CCHFV can also be isolated from blood samples or tissue suspensions after intracerebral inoculation of newborn mice or by infection of different cell lines (Vero, VeroE6, BHK21, SW13, LLC-MK2) (1, 20). Although cell culture is easier, it is not as sensitive as virus isolation in newborn mice (65). After isolation, CCHFV identification is performed using direct immunofluorescence or RT-PCR. Direct antigen detection tests can also be used, e.g. inverse passive haemagglutination and enzyme-linked immunosorbent assay (ELISA) immunocapture (65). Immunohistochemistry is also useful for post-mortem diagnosis (43).

In a later stage of the disease, IgM and IgG antibodies directed against CCHFV can be detected by direct immunofluorescence or ELISA (66). However, it is important to notice that in fatal cases antibodies are rarely observed (67).

Several authors have tried to identify criteria that can be measured in the course of disease and could predict disease severity (68, 69, 70, 71). A severity grading score (SGS) system has been established using the variables which, in the literature, are assumed to be associated with mortality and have been considered to be of clinical importance. These variables are listed in Table I.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Elevated levels of IL-6 and TNF-α</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Elevated levels of plasminogen activator receptor</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Elevated levels of soluble urokinase plasminogen activator receptor</td>
<td>Increased mortality</td>
</tr>
</tbody>
</table>

Histopathological studies and clinical features indicate that CCHF resembles other haemorrhagic fevers such as Ebola haemorrhagic fever. In addition to having a similar incubation period, they also share common clinical symptoms and generate similar results in standard laboratory tests (neutropenia, thrombocytopenia, lymphocytopenia, atypical lymphocytes and increasing numbers of immature neutrophils). They also have similar immune responses to infection (elevated levels of IL-6 and TNF-α) and similar patterns of tissue damage (1, 20, 74, 75, 76, 77). Furthermore, Ebola virus and CCHFV share the same target cells: MPs, DCs, endothelial cells and hepatocytes (78). High mortality is another common feature of these diseases.

**Prophylaxy and treatment**

In the 1970s, a formalin-inactivated vaccine based on suckling mouse brain, developed in the Soviet Union and licensed in Bulgaria, was used in several parts of Eastern Europe and the Soviet Union for protection from CCHFV infections. Vaccinated people showed a high frequency of
detectable antibodies (79). More recently, another study showed that vaccinated individuals developed a robust anti-CCHFV-specific T-cell activity and high levels of CCHFV antibodies following the first dose (80). However, the vaccine efficacy remains to be proven. A DNA vaccine containing the CCHF genome M segment has been developed and was shown to elicit neutralising antibodies in mice. However, the authors were unable to evaluate the vaccine protective efficacy due to the lack of an animal model at that time (81). An attempt was made to evaluate an oral vaccine in plants expressing CCHFV glycoprotein (82). More recently, a modified vaccinia virus Ankara expressing the CCHF virus glycoproteins was developed as a recombinant vaccine candidate and was shown to protect 100% of IFNAR−/− mice (83).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;60</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>13.2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>No</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13.6</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>No</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>33.3</td>
</tr>
<tr>
<td>Organ failure</td>
<td>No</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>100</td>
</tr>
<tr>
<td>Aspartate aminotransaminase</td>
<td>&lt;5 × ULNV</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>&gt;5 × ULNV</td>
<td>14.9</td>
</tr>
<tr>
<td>Alanine aminotransaminase</td>
<td>N</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>&gt;ULNV</td>
<td>10.8</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>&lt;3 × ULNV</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>&gt;3 × ULNV</td>
<td>20</td>
</tr>
<tr>
<td>Leukocyte (cells/μl)</td>
<td>&lt;10,000</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>&gt;10,000</td>
<td>42.9</td>
</tr>
<tr>
<td>Prolongation of prothrombin time</td>
<td>&lt;3 sec</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;3 sec, &lt;6 sec</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>&gt;6 sec</td>
<td>46.2</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>&gt;100</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>0</td>
</tr>
<tr>
<td>D-dimer</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;10 × ULNV</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;10 × ULNV</td>
<td>19.4</td>
</tr>
<tr>
<td>Platelet (cells/μl)</td>
<td>&gt;100,000</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;50,000, &lt;100,000</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000</td>
<td>12.5</td>
</tr>
</tbody>
</table>

ULNV: upper limit of normal value; N: normal value

Other therapies have also been tested. A very high dose of methylprednisolone was administered to five patients and it had a beneficial effect (97). The effects of Roferon A, Intron A (recombinant interferon) and Multiferon (natural interferon) against CCHFV were also demonstrated in vitro (98). Currently, the use of ribavirin administered as early as possible, together with supportive treatments, remains one of the best choices for CCHF patients (96). Haematological and neurological abnormalities are common side effects induced by ribavirin treatment. During the treatment of CCHF patients with ribavirin, adverse effects were described, but the severe adverse effects were not reported in a randomised study (42, 90, 94, 95).

### Concluding remarks

Although many efforts have been made in recent years to better understand the biology, transmission and epidemiology of CCHFV, it remains a very dangerous virus, as it has a high mortality rate and there is a risk of emergence in still-unaffected areas. Even if ribavirin appears to be
efficient if provided early on after the onset of the clinical symptoms, other drugs, as well as vaccines, are needed. Pharmaceutical industries and laboratories carrying out basic studies should combine their efforts to develop new molecules and efficient vaccines.

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Fièvre hémorragique de Crimée-Congo

C. Peyrefitte, P. Marianneau, N. Tordo & M. Bouloy

Résumé

La fièvre hémorragique de Crimée-Congo (FHCC) est l’une des arboviroses les plus répandues dans le monde. Elle est présente en Afrique, dans le sud-est de l’Europe, au Moyen-Orient et en Asie. Elle est due à un nairovirus (de la famille des Bunyaviridae) transmis par plusieurs espèces de tiques. La distribution géographique de cette maladie coïncide avec celle des tiques du genre *Hyalomma*. Chez les animaux d’élevage l’infection est asymptomatique tandis que chez l’homme elle provoque une maladie grave associée à une mortalité élevée. Les symptômes les plus courants sont une forte fièvre, des vertiges, des maux de tête, un vomissement et des hémorragies. Des études pathogéniques sur des souris dont le gène du récepteur de l’interféron est déficient ont montré que la réponse induite par l’interféron joue un rôle crucial dans le contrôle de la propagation du virus et dans la mobilisation d’une protection contre la maladie. La méthode utilisée actuellement pour détecter la présence du virus dans du matériel biologique est l’amplification en chaîne par polymérase couplée à une transcription inverse. L’épreuve immuno-enzymatique et l’immunofluorescence indirecte sont utilisées pour la détection d’anticorps spécifiques contre le virus de la FHCC. Un vaccin à virus inactivé par le formol préparé à partir d’encéphale de souriceaux non sevrés était utilisé dans les années 1970 en Europe orientale et dans l’ex-Union soviétique, mais son efficacité n’est toujours pas démontrée. L’Organisation mondiale de la santé préconise de recourir à la ribavirine en administration précoce pour le traitement des patients atteints. Malgré les progrès remarquables accomplis au cours des dernières décennies, un grand nombre de questions demeure sans réponse concernant la pathogénie et l’épidémiologie de cette maladie ; en outre, il est nécessaire de mettre au point des vaccins et des antiviraux efficaces.

Mots-clés


Fièbre hemorrágica de Crimea-Congo

C. Peyrefitte, P. Marianneau, N. Tordo & M. Bouloy

Resumen

La fiebre hemorrágica de Crimea-Congo es una de las arbovirosis más extendidas por el mundo, pues está presente en África, el sudeste de Europa, el Oriente Medio y Asia. Su agente causal es un nairovirus (familia Bunyaviridae) que
transmiten varias especies de garrapatas. El área de distribución geográfica de la enfermedad coincide con la distribución de las garrapatas del género *Hyalomma*. Mientras que el ganado infectado no exhibe signo alguno de enfermedad, el ser humano se ve afectado de gravedad y sufre una tasa de mortalidad elevada. Los síntomas más frecuentes son fiebre alta, mareo, cefalea, vómitos y hemorragias. Los estudios sobre la patogénesis realizados con ratones carentes del receptor del interferón ponen de manifiesto que la respuesta del interferón es crucial para controlar la propagación del virus y ofrecer protección contra la enfermedad. Actualmente, para detectar el virus en muestras biológicas se utiliza la reacción en cadena de la polimerasa (PCR) acoplada a transcripción inversa. Para determinar la presencia de anticuerpos específicos contra el virus se emplea el ensayo inmunoenzimático o la técnica de inmunofluorescencia indirecta. En los años setenta, en Europa Oriental y la ex Unión Soviética se utilizaba una vacuna inactivada con formalina preparada a partir de cerebro de ratón lactante, pero aún está por demostrar que resulte eficaz. La Organización Mundial de la Salud recomienda tratar a los pacientes con ribavirina, pero es preciso administrar el fármaco lo antes posible. Aunque en los últimos decenios se ha avanzado notablemente, aún quedan por estudiar muchos aspectos de la patogénesis y la epidemiología de la enfermedad y por obtener vacunas y fármacos antivirales eficaces.

**Palabras clave**

**References**


