# Bunyaviridae

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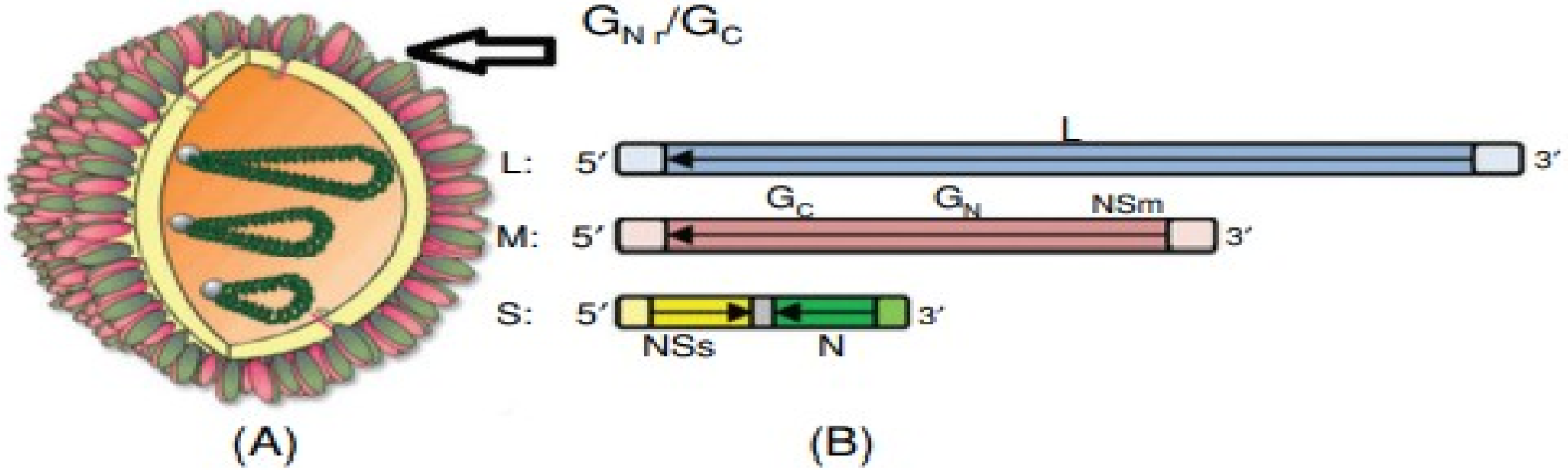
# Bunyaviruses

The family Bunyaviridae is the largest family of viruses and includes the generaOrthobunyavirus,Hantavirus,Nairovirus, Phlebovirus, and Tospovirus.
There are several hundred bunyaviruses, and viruses of veterinary significance are classified within the genera Bunyavirus—California encephalitis serogroup viruses and Akabane virus (as well as Aino and Cache Valley viruses); Phlebovirus—Rift Valley fever virus (RVFV); Nairovirus—Nairobi sheep disease virus; and Hantavirus.
Many of the bunyaviruses are arboviruses that are transmitted by arthropods such as mosquitoes, ticks, and biting flies, and thus have the capacity to alternately replicate in vertebrate animals and insects.
Several bunyaviruses are important zoonotic pathogens, including hantaviruses (the cause of hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome in people); RVFV; Crimean–Congo hemorrhagic fever virus; and Nairobi sheep disease virus.

# General Family Properties

Bunyaviruses are enveloped, pleomorphic viruses that are 80–120 nm in diameter with surface projections (spikes) emanating from the envelope surface of mature virions (Figure 59.1).
The virions consist of four structural proteins, including two external glycoproteins in the envelope, a nucleocapsid protein that encapsidates the genome, and a transcriptase protein (L).
The envelope glycoproteins are responsible for neutralization and hemagglutination. A variety of nonstructural proteins are also encoded by the viral genome.
The nucleic acid is helical and included in three distinct segments—large (L), medium (M), and small (S)—each comprised of single-stranded, negative-sense, or ambisense RNA. The organization and structure of the genomes determine the genera of these viruses. In addition, serological methods are used to provide further classification. However, many epitopes on envelope and capsid proteins a lenges for taxonomic efforts.
There is considerable genetic diversity and serological cross-reactivity among viruses within the various genera of the Bunyaviridae

**FIGURE 59.1.** *Representations of bunyavirus structure and genomic organization including the structure of the surface glycoproteins, $G_C$ and $G_N$. (A) The two glycoproteins $G_N$ and $G_C$ are incorporated into the lipid bilayer during the budding process. The three encapsidated genome segments (associated with the nucleoprotein N and the polymerase L) are incorporated into the virion. (B) Schematic representation of the three RVFV RNA genome segments and coding strategy. The arrow indicates the open reading frames in each segment, which are flanked by noncoding regions. (Courtesy of Mandell and Flick 2011.)*



Genetic reassortment may occur when cell cultures or insects are simultaneously infected with multiple, but closely related, bunyaviruses. The bunyaviruses undergo genetic drift and selection, especially in arthropod hosts.

**Antigenic drift**, random genetic mutation of an infectious agent resulting in minor changes in proteins called antigens, which stimulate the production of antibodies by the immune systems of humans and animals. Genetic diversity plays a prominent role in viral evolution, pathogenesis, immune escape, and drug resistance.
The bunyaviruses are generally susceptible to drying, heat, acids, bleaches, detergents, and most common disinfectants.

**Crimean–Congo hemorrhagic fever virus**

Crimean-Congo haemorrhagic fever (CCHF) in humans is a disease caused by CCHF virus (CCHFV). CCHFV is transmitted by bites from infected ticks (mainly of the *Hyalomma* genus) or by direct contact with blood or tissues of infected ticks, viraemic patients or viraemic livestock

Due to the involvement of ticks and vertebrates in the life cycle of the virus, and the environmental factors that influence the virus's reservoirs, hosts and vectors,

Infected individuals present a variety of symptoms, ranging from asymptomatic or mild febrile illness to severe disease characterised by haemorrhagic manifestations, multiorgan failure and shock. The case fatality rate is approximately 30% among hospitalised patients.

In survivors, improvement is seen 9–10 days after symptom onset, at which time they are discharged from the hospital. Recovery may be slower in a small proportion of patients. Hematological and biochemical abnormalities include thrombocytopenia, leukopenia, transaminasemia, prolonged coagulation times, elevated D-dimers, decreased fibrinogen levels, and elevated levels of creatine phosphokinase and lactate dehydrogenase. High viral load, severe thrombocytopenia, elevated liver enzymes and prolonged bleeding times are predictors of severe disease and fatal outcome .

Currently, there is no specific antiviral drug for CCHF treatment or approved vaccine available. Therefore, prevention, early diagnosis and barrier nursing of patients are the only means to avoid viral spread. Work with infectious CCHFV particles requires a maximum biocontainment laboratory.

# The pathogen

CCHFV belongs to the genus *Orthonairovirus* (family *Nairoviridae*, order *Bunyavirales*). The disease was first identified in 1944 in Crimea (Crimean haemorrhagic fever), while the virus was first isolated in 1956 in Congo (Congo virus), resulting in the current name of the virus and the disease.

The virion is spherical with an approximate diameter of 80–100 nm. The CCHFV genome consists of three segments of single-stranded negative sense RN — the small (S), medium (M) and large (L) segments — which encode the viral nucleocapsid, the glycoprotein precursor (which is cleaved into two envelope glycoproteins, GN and GC, and various non-structural proteins) and the polymerase, respectively.

Based on the S segment sequences, the currently identified CCHFV strains can be classified into seven genotypes (genotypes I to VII), with genotype IV divided further into two subgenotypes (IVf and IVg).

# Diagnostics

Early and accurate diagnosis of CCHF is critical for the patient's life and for timely response and control measures. Laboratory diagnosis in the acute phase of the disease is achieved mainly by detection of CCHFV RNA using molecular methods, but also by detection of CCHFV antigen and isolation of the virus (in high containment facilities).

Prolonged detection of CCHFV RNA has been reported, but — in general — molecular methods are helpful during the first week of illness. The high genetic variability of CCHFV strains may diminish the efficacy of molecular tests, affecting their diagnostic potential .

Metagenomic next generation sequencing can support pathogen identification, especially in cases with complicated symptomatology.

CCHFV-specific IgM and IgG antibodies are detectable after the fifth day of the disease using serological methods (ELISA or indirect immunofluorescence). CCHFV infection is confirmed by detection of IgM antibodies or seroconversion, or four-fold increase in IgG antibody titres in serial serum samples. It should be noted that antibody response is often absent or delayed in severe or fatal cases.