reaches 90%. Excavation of the uterus may increase survival rates of pregnant women, but data on Lassa fever and pregnancy are still sparse. These figures suggest that interruption of the pregnancy of Lassa virus–infected women should be considered. White blood cell counts are normal or slightly elevated, and platelet counts are normal or somewhat low. Deafness coincides with clinical improvement in ~20% of patients and is permanent and bilateral in some patients. Reinfection may occur but has not been associated with severe disease.

High-level viremia or a high serum AST concentration statistically predicts a fatal outcome. Thus, patients with an AST concentration of >150 IU/mL should be treated with IV ribavirin. This antiviral nucleoside analogue appears to be effective in reducing case–fatality rates from those documented among retrospective controls. However, possible side effects, such as reversible anemia (which usually does not require transfusion), dependent hemolytic anemia, and bone marrow suppression, need to be kept in mind. Ribavirin should be given by slow IV infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg every 6 h for 4 days and then by 8 mg/kg every 8 h for 6 days. Inactivated Lassa virus vaccines failed in preclinical studies.

Bunyaviruses The most important VHF-causing bunyaviruses are Crimean-Congo hemorrhagic fever virus, hantaviruses, Rift Valley fever virus, and "severe fever with thrombocytopenia syndrome virus." Other bunyaviruses—e.g., the Garissa variant of Ngari virus and Ilesha virus—have caused sporadic VHF outbreaks in Africa.

CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF) This severe VHF has a wide geographic distribution, potentially emerging wherever virus-bearing ticks occur. Because of the propensity of CCHF virus–transmitting ticks to feed on domestic livestock and certain wild mammals, veterinary serosurveys are the most effective mechanism for the monitoring of virus circulation in a particular region. Human infections are acquired via tick bites or during the crushing of infected ticks. Domestic animals do not become ill but do develop viremia. Thus, there is risk of acquiring CCHF during sheep shearing, slaughter, and contact with infected hides or carcasses from recently slaughtered infected animals. Nosocomial epidemics are common and are usually related to extensive blood exposure or needlesticks.

Although generally similar to other VHFs, CCHF causes extensive liver damage, resulting in jaundice in some patients. Clinical laboratory values indicate DIC and show elevations in concentrations of AST, creatine phosphokinase, and bilirubin. Patients who do not survive generally have more distinct changes than survivors in the concentrations of these markers, even in the early days of illness, and also develop leukocytosis rather than leukopenia. In addition, thrombocytopenia is more marked and develops earlier in patients who do not survive than in survivors. The benefit of IV ribavirin for treatment remains hotly debated, but clinical experience and retrospective comparison of patients with ominous clinical laboratory values suggest that ribavirin may be efficacious. No human or veterinary vaccines are recommended.

HEMORRHAGIC FEVER WITH RENAL SYNDROME HFRS is the most important VHF today, with more than 100,000 cases of severe disease in Asia annually and milder infections numbering in the thousands in Europe. The disease is widely distributed in Eurasia. The major causative viruses are Puumala virus (Europe), Dobrava-Belgrade virus (the Balkans), and Hantaan virus (eastern Asia). Amur/Soochong, Gou, Kurkino, Muju, Saaremaa, Sochi, and Tula viruses also cause HFRS but much less frequently and in more geographically confined areas determined by the distribution of reservoir hosts. Seoul virus is exceptional in that it is associated with brown rats (*Rattus norvegicus*); therefore, the virus has a worldwide distribution because of the migration of these rodents on ships. Despite the wide distribution of Seoul virus, only mild or moderate HFRS occurs in Asia, and human disease has been difficult to identify in many areas of the world. Most cases of HFRS occur in rural residents or vacationers; the exception is Seoul virus infection, which may be acquired in an urban or rural setting or from contaminated laboratory-rat colonies. Classic Hantaan virus infection in Korea and in rural China is most common in the spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in rodent saliva and feces. Patients with HFRS are not infectious.

Severe cases of HFRS evolve in four identifiable stages. The *febrile stage* lasts 3 or 4 days and is identified by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back is characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate DIC is present. Other laboratory findings of HFRS include proteinuria and active urinary sediment. The *hypotensive stage* lasts from a few hours to 48 h and begins with falling blood pressure and sometimes shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Kinin activation is marked. The rising hematocrit reflects increasing vascular leakage. Leukocytosis with a left shift develops, and thrombocytopenia continues. Atypical lymphocytes—which in fact are activated CD8+ and, to a lesser extent, CD4+ T cells—circulate. Proteinuria is marked, and the urine's specific gravity falls to 1.010. Renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria. During the *oliguric stage*, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. Oliguria persists for 3–10 days before the return of renal function marks the onset of the *polyuric stage* (diuresis and hyposthenuria), which carries the danger of dehydration and electrolyte abnormalities.

Mild cases of HFRS may be much less stereotypical. The presentation may include only fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria. Infections with Puumala virus, the most common cause of HFRS in Europe (*nephropathia epidemica*), result in a much-attenuated picture but the same general presentation. Bleeding manifestations are found in only 10% of patients, hypotension rather than shock is usually documented, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma followed by polyuria and hyposthenuria in recovery. The lethality rate is <1%.

HFRS should be suspected in patients with rural exposure in an endemic area. Prompt recognition of the disease permits rapid hospitalization and expectant management of shock and renal failure. Useful clinical laboratory parameters include leukocytosis, which may be leukemoid and is associated with a left shift; thrombocytopenia; and proteinuria. HFRS is readily diagnosed by an IgM-capture ELISA that is positive at admission or within 24–48 h thereafter. The isolation of hantaviruses is difficult, but RT-PCR of a blood clot collected early in the clinical course or of tissues obtained postmortem should give positive results. Such testing is usually undertaken if definitive identification of the infecting virus is required.

Mainstays of therapy are management of shock, reliance on vasopressors, modest crystalloid infusion, IV human serum albumin administration, and treatment of renal failure with prompt dialysis to prevent overhydration that may result in pulmonary edema and to control hypertension that increases the possibility of intracranial hemorrhage. Use of IV ribavirin has reduced lethality and morbidity in severe cases, provided treatment is begun within the first 4 days of illness. Lethality may be as high as 15% but with proper therapy should be <5%. Sequelae have not been definitively established.

RIFT VALLEY FEVER The natural range of Rift Valley fever virus was previously confined to sub-Saharan Africa, with circulation of the virus markedly enhanced by substantial rainfall. The El Niño Southern Oscillation phenomenon of 1997 facilitated subsequent spread of Rift