<50 and who are unresponsive to conventional support. Lethality rates remain at ~30–40% even with good management, but most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days with no apparent long-term residua. The antiviral drug ribavirin inhibits hantaviruses in vitro but did not have a marked effect on patients treated in an open-label study.

VIRAL HEMORRHAGIC FEVER

VHF is a constellation of findings based on vascular instability and decreased vascular integrity. An assault, direct or indirect, on the microvasculature leads to increased permeability and (particularly when platelet function is decreased) to actual disruption and local hemorrhage (a positive tourniquet sign). Blood pressure is decreased, and in severe cases shock supervenes. Cutaneous flushing and conjunctival suffusion are examples of common, observable abnormalities in the control of local circulation. Hemorrhage occurs infrequently. In most patients, hemorrhage is an indication of widespread vascular damage rather than a life-threatening loss of blood volume. In some VHFs, specific organs may be particularly impaired. For instance, the kidneys are primary targets in hemorrhagic fever with renal syndrome (HFRS), and the liver is a primary target in yellow fever and filovirus diseases. However, in all of these diseases, generalized circulatory disturbance is critically important. The pathogenesis of VHF is poorly understood and varies among the viruses regularly implicated in the syndrome. In some viral infections, direct damage to the vascular system or even to parenchymal cells of target organs is an important factor; in other viral infections, soluble mediators are thought to play a major role in the development of hemorrhage or fluid redistribution.

The acute phase in most cases of VHF is associated with ongoing virus replication and viremia. VHFs begin with fever and myalgia, usually of abrupt onset. (Arenavirus infections are the exceptions as they often develop gradually.) Within a few days, the patient presents for medical attention because of increasing prostration that is often accompanied by abdominal or chest pain, anorexia, dizziness, severe headache, hyperesthesia, photophobia, and nausea or vomiting and other gastrointestinal disturbances. Initial examination often reveals only an acutely ill patient with conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension, perhaps with tachycardia. Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital edema, and proteinuria are common. AST concentrations are usually elevated at presentation or within a day or two thereafter. Hemoconcentration from vascular leakage, which is usually evident, is most marked in HFRS and in severe dengue. The seriously ill patient progresses to more severe clinical signs and develops shock and other findings typical of the causative virus. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, seizures) are all poor prognostic signs.

One of the major diagnostic clues to VHF is travel to an endemic area within the incubation period for a given syndrome. Except in infections with Seoul, dengue, and yellow fever viruses, which have urban hosts/vectors, travel to a rural setting is especially suggestive of a diagnosis of VHF. In addition, several diseases considered in the differential diagnosis—falciparum malaria, shigellosis, typhoid fever, leptospirosis, relapsing fever, and rickettsial diseases—are treatable and potentially lethal.

Early recognition of VHF is important because of the need for virus-specific therapy and supportive measures. Such measures include prompt, atraumatic hospitalization; judicious fluid therapy that takes into account the patient's increased capillary permeability; administration of cardiotonic drugs; use of pressors to maintain blood pressure at levels that will support renal perfusion; treatment of the relatively common secondary bacterial (and the more rare fungal) infections; replacement of clotting factors and platelets as indicated; and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. DIC should be treated only if clear laboratory evidence of its existence is found and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. The available evidence suggests that VHF patients have decreased cardiac output and will respond poorly to fluid loading as it is often practiced in the treatment of shock associated with bacterial sepsis. Specific therapy is available for several of the VHFs. Strict barrier nursing and other precautions against infection of medical staff and visitors are indicated when VHFs are encountered except when the illness is due to dengue viruses, hantaviruses, Rift Valley fever virus, or yellow fever virus.

Novel VHF-causing agents are still being discovered. Besides the viruses listed below, the latest addition may be the unclassified rhabdovirus Bas-Congo virus, which has been associated with three cases of VHF in the Democratic Republic of the Congo. However, Koch's postulates have not yet been fulfilled to prove cause and effect.

Arenaviruses The most important arenaviruses causing VHF are Junín virus, Lassa virus, and Machupo virus. Chapare, Guanarito, Lujo, and Sabiá viruses have caused limited and/or infrequent outbreaks or individual cases.

JUNÍN/ARGENTINIAN AND MACHUPO/BOLIVIAN HEMORRHAGIC FEVERS These severe diseases (with fetal lethality rates reaching 15–30%) are caused by Junín virus and Machupo virus, respectively. Their clinical presentations are similar, but their epidemiology differs because of the distribution and behavior of the viruses' rodent reservoirs. Junín/Argentinian hemorrhagic fever has thus far been recorded only in rural areas of Argentina, whereas Machupo/Bolivian hemorrhagic fever seems to be confined to rural Bolivia. Infection with the causative agents almost always results in disease, and all ages and both sexes are affected. Person-to-person or nosocomial transmission is rare but has occurred. The transmission of Junín/Argentinian hemorrhagic fever from convalescing men to their wives suggests the need for counseling of patients with arenavirus hemorrhagic fever concerning the avoidance of intimate contacts for several weeks after recovery. Compared with the pattern in Lassa fever (see below), thrombocytopenia—often marked—is the rule, hemorrhage is common, and CNS dysfunction (e.g., marked confusion, tremors of the upper extremities and tongue, and cerebellar signs) is much more common in disease caused by Junín virus and Machupo virus. Some cases follow a predominantly neurologic course, with a poor prognosis.

The clinical laboratory is helpful in diagnosis since thrombocytopenia, leukopenia, and proteinuria are typical findings. Junín/Argentinian hemorrhagic fever is readily treated with convalescent-phase plasma given within the first 8 days of illness. In the absence of passive antibody therapy, IV ribavirin in the dose recommended for Lassa fever is likely to be effective in all the South American VHFs caused by arenaviruses. A safe, effective, live attenuated vaccine exists for Junín/Argentinian hemorrhagic fever. After vaccination of more than 250,000 high-risk persons in the endemic area, the incidence of this VHF decreased markedly. In experimental animals, this vaccine is cross-protective against Machupo/Bolivian hemorrhagic fever.

LASSA FEVER Lassa virus is known to cause endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, and Liberia, although it is probably more widely distributed in western Africa. In countries where Lassa virus is endemic, Lassa fever can be a prominent cause of febrile disease. For example, in one hospital in Sierra Leone, laboratory-confirmed Lassa fever is consistently responsible for one-fifth of admissions to the medical wards. In western Africa alone, probably tens of thousands of Lassa virus infections occur annually. Lassa virus can be transmitted by close person-to-person contact. The virus is often present in urine during convalescence and is suspected to be present in seminal fluid early in recovery. Nosocomial spread has occurred but is uncommon if proper sterile parenteral techniques are used. All ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission takes place year-round.

Among the VHF agents, only arenaviruses are typically associated with a gradual onset of illness, which begins after an incubation period of 5–16 days. Hemorrhage is seen in only ~15–30% of Lassa fever patients; a maculopapular rash is often noted in light-skinned patients. Effusions are common, and male-dominant pericarditis may develop late. Maternal lethality is higher than the usual 15–30% and is especially increased during the last trimester. The fetal death rate