CHAPTER 12

Epidemiology and Pathogenesis of Rift Valley Fever and Other Phleboviruses

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I. INTRODUCTION

Rift Valley fever (RVF) virus is unique among the phleboviruses in its pathogenicity for humans and domestic animals, its various routes of infection, and its wide host range. Since the first isolation and detailed description of the disease following an epizootic in sheep in the Rift Valley of Kenya in 1930 (Daubney *et al.*, 1931), there have been significant epizootics in South Africa (Swanepoel and Coetzer, 1995), Egypt in 1977–1979 (Meegan and Hoogstraal, 1979; Meegan, 1979), West Africa in 1987 (Digoutte and Peters, 1989), Madagascar in 1990 (Morvan *et al.*, 1992), and most recently a reintroduction into Egypt in 1993 (Arthur *et al.*, 1993). Presently, virologic and serologic evidence suggests that the virus exists throughout sub-Saharan Africa and Madagascar and, in light of its recurrence in Egypt, may be extending its range even farther though, to date, no outbreaks have been reported outside Africa.

Modern transportation provides a potential means for global transmission via infected animals and humans incubating the virus as well as infected

The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense.

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R. M. Elliott (ed.), *The Bunyaviridae*

vectors carried as stowaways. Hence, international travelers to endemic areas should be aware of the disease and its public health and agricultural importance.

Typically the virus is associated with pastoral regions where habitat conducive to the maintenance of arthropod vectors is present. Natural hosts for RVF virus include mosquitoes, sheep, cattle, buffalo, camels, goats, other ruminants, and humans. Newborn lambs, calves, and puppies are highly susceptible. Mice, lambs less than 7 days old, and baby hamsters are the most susceptible experimental animals. Several species of wild rodents are susceptible to RVF but the epidemiologic significance of their role in virus maintenance and transmission is not known. Various avian and reptilian species have been tested for susceptibility and are refractory to RVF virus.

Epidemics of RVF typically center around regions where there are large concentrations of sheep and cattle. Explosive epidemics occur periodically and are associated with periods of heavy rainfall producing localized flooding and dense or expanding vector populations (Davies *et al.*, 1985). Transovarially infected floodwater *Aedes* eggs hatch producing infected adults which feed extensively on cattle (Linthicum *et al.*, 1985). Other mosquito species feeding on the infected livestock ingest viremic blood meals and, if those mosquitoes are efficient vectors, develop disseminated infections and become competent secondary vectors. Secondary vectors include mosquitoes of many species of the genera *Aedes*, *Anopheles*, *Culex*, *Eretmapodites*, and *Mansonia*. *Culicoides* spp. and sand flies may play limited roles in biological transmission and, along with other arthropods, mechanical transmission. *Culex pipiens* was an important mosquito vector in the Egyptian epizootic in 1977 (Meegan *et al.*, 1980).

In the absence of epidemics, a cycle of enzootic circulation exists in many regions of Africa. Livestock infections, probably acquired by the bite of infected mosquitoes, result in low rates of disease and abortion that are undiagnosed because of confusion with other livestock diseases as well as a lack of diagnostic capabilities. Reservoirs for RVF virus are unidentified, though there is strong evidence of interepidemic maintenance via transovarial transmission in certain *Aedes* mosquitoes (Logan *et al.*, 1991). The infected eggs are deposited and may remain dormant in depressions, called "dambos" in East Africa or "pans" in South Africa, that are subject to inundation. When flooding occurs, the eggs hatch and infected larvae emerge and develop into infected adults. Through monitoring of changes in vegetation, satellite remote sensing is being used to identify areas of flooding which may trigger hatching of floodwater *Aedes* and provide breeding sites for secondary vectors (Linthicum *et al.*, 1987).

Though aerosol transmission between infected and susceptible livestock appears less important than mosquito transmission, humans may be infected by aerosol in the laboratory and during slaughter of viremic animals (Hoogstraal *et al.*, 1979). Blood, serum, and the products of abortion from RVF virus-infected animals are sources for infection of humans in at-risk occupa-

tions such as abattoir workers, farmers, veterinarians, and laboratory technicians (Peters and Meegan, 1981). The major natural means of RVF transmission is by bite of infected mosquitoes, though mechanical transmission by arthropods is possible. Consumption of milk or meat from infected animals does not appear to be a common means of transmission.

High concentrations of virus may be found in amniotic fluid and the serosanguinous fluid in the thorax of aborted lamb carcasses and may provide a source of environmental contamination as well as diagnostic material.

II. CLINICAL SIGNS

In Africa, the disease in animals seems to be limited to domestic ruminants, with imported European animals being more severely affected than native African breeds. Sheep and cattle are the primary domestic ruminant species affected by RVF virus, with goats being involved to a lesser extent.

Clinical signs vary considerably and are related to the species and age of the animal involved. Disease progression and severity of disease are generally inversely proportional to age (Easterday *et al.*, 1962a,b; Coackley *et al.*, 1967; Kaschula, 1957; McIntosh *et al.*, 1973). Adult cattle and sheep may suffer mortality rates of 10–30% or higher, depending on the nutritional state of the animal; but in animals less than 7 days old, fatality rates may approach 100%. The disease is characterized by a short incubation period, fever, hepatitis, abortion, and death. Widespread abortion, infertility, and rapidly fatal neonatal disease are typical of outbreaks among cattle and sheep. Fulminant neonatal disease may be the first indication of RVF in areas where abortion rates are high as a result of other abortogenic agents. Newborn lambs and kids are highly susceptible to infection with RVF virus and may suffer 90–100% mortality rates. Experimentally infected calves and lambs experience an acute febrile response, often exceeding 42°C, accompanied by viremia, followed by collapse and death within 24 to 48 hr. Experimentally infected pregnant ewes experience a fever of up to 42°C for 1 to 4 days, followed by recovery or prostration and death; abortion occurs 5 to 20 days later in survivors. Other overt signs are inconsistent, but include congestion of mucous membranes, injected conjunctiva, hyperemia of the oral mucosa, mucopurulent nasal discharge, salivation, vomiting, anorexia, general weakness, an unsteady gait, fetid diarrhea, and a rapid decrease in milk production. A definite leukopenia, most severe in younger animals, which corresponds to maximal viremia and temperature response, is seen, often followed by leukocytosis in later stages of the disease. Elevated serum AST, GGT, and LDH values are common. Experimentally infected animals are viremic for 2 to 5 days with titers often in excess of 10^8 PFU/ml. No long-term carrier state in animals has been identified. Central nervous system involvement, evidenced by encephalitis, occurs periodically in experimentally infected rodents surviving a week or more after experiencing a brief episode of low

viremia or in animals with high viremias that have been treated with antiviral drugs or passive antibodies (Peters *et al.*, 1986). Weanling gerbils, *Meriones unguiculatus*, appear to be refractory to liver disease and uniformly develop fatal encephalitis, providing a unique model to study RVFV-induced encephalitis (Anderson *et al.*, 1988). While the incidence of encephalitis in cattle naturally infected with RVF virus is not known, there is a single report of RVF viral encephalomyelitis in an experimentally infected calf (Rippy *et al.*, 1992). The animal appeared to recover after viremia and pyrexia but became moribund and was euthanized 9 days after virus inoculation. The calf was no longer viremic but RVF virus was isolated from the brain and multifocal necrotizing encephalitic lesions were observed on pathologic examination.

The disease in humans is usually a temporarily incapacitating illness. Infection results in fever, malaise, headache, and myalgia, often with other constitutional symptoms developing, followed by complete recovery. Probably 1% or less of human infections progress to the more severe and often fatal complications of hemorrhagic disease, encephalitis, or retinal disease (Jouan *et al.*, 1989; McIntosh *et al.*, 1980; Peters and LeDuc, 1991; Van Velden *et al.*, 1977). The determinants of these different syndromes are unknown. However, during the RVF virus outbreak in Egypt in 1993, a presumptive case definition of ocular disease characterized by macular and paramacular retinal lesions, frequently with hemorrhage and edema, following a febrile episode was established (Arthur *et al.*, 1993). This clinical presentation was quite different from the previous outbreak in 1977–1978 in which the hemorrhagic form was frequently seen and accounted for nearly 600 human deaths (Laughlin *et al.*, 1979; Meegan, 1979).

The introduction of RVF virus into Egypt in 1977 produced the largest recorded RVF epidemic. Prior to this epidemic, only 4 human deaths attributable to RVF had been reported. The sudden and unexpected appearance of this previously geographically limited sub-Saharan virus and the unprecedented numbers of encephalitic, ocular, and fatal hemorrhagic disease remain an enigma. Introduction via importation of diseased animals from the south or wind-borne arthropods are unproven possibilities. The epidemic centered in the fertile Nile Delta region harboring an essentially naive population of human, livestock, and arthropod hosts and vectors. The demography of the region coupled with an alteration in virulence of the virus, perhaps through reassortment, and the presence of endemic hepatotropic organisms, like *Schistosoma mansoni*, may have contributed to this devastating epizootic. Although extensive epidemiologic data could not be collected, an estimated 18,000 to > 200,000 clinical cases in humans occurred with 598 fatalities and about 800 cases of ocular disease associated with RVF virus infection (Meegan, 1979). Animal losses resulting from abortion and mortality were high and impacted significantly on the availability and cost of animal protein in Egypt.

The hemorrhagic fever syndrome seen in an estimated 1% of human

cases has a case fatality of approximately 50% and is manifested during the course of acute illness. Complications of encephalitis and retinal disease usually develop as the acute illness fades or during the recovery period.

The presence of serum antibody to RVF virus seems to be the major immunologic defense mechanism in recovery. In rodents and monkeys the outcome of RVF virus infection appears to be regulated by serum antibody and interferon and the early appearance of serum interferon may be a contributory factor in limiting viremia and preventing clinical disease (Peters *et al.*, 1986; Morrill *et al.*, 1989, 1990).

III. PATHOLOGY

The most consistent pathologic changes in all species affected involve the liver. The liver appears to be the primary site of virus replication and initial mild hepatocellular changes rapidly progress to final massive necrosis. As the disease progresses in neonates, the necrotic foci may enlarge to 2 mm in diameter and the liver becomes friable, irregularly congested, and may become mottled brown or yellow in color. As these necrotic areas enlarge, extensive destruction of normal hepatic architecture occurs. Hepatic lesions in adult ruminants are not as severe as those found in neonates, but multiple necrotic areas may be present. In some animals, only small, microscopic necrotic areas with varying degrees of visceral and serosal hemorrhages are seen. Coagulated blood may be found in the lumen of the gallbladder in those cases with marked hemorrhage in the liver. Hemorrhages are seen infrequently in the abomasum and intestinal tract.

The rhesus monkey provides a realistic model for human infection with hepatic lesions occurring in the characteristic midzonal pattern seen in humans and other animals. Experimentally infected rhesus monkeys experience a transient viremia, often exceeding 10^7 PFU/ml serum. Usually the viremic phase is followed by an uncomplicated recovery though a variety of clinical symptoms including diminished food intake, lethargy, cutaneous petechiae, and occasional vomiting may be observed. The disease, in approximately 20% of infected monkeys, progresses to a fatal hemorrhagic form which is thought to be mediated by disseminated intravascular coagulation (Cosgriff *et al.*, 1989; Peters *et al.*, 1989). Death is preceded by epistaxis, petechial to purpuric cutaneous lesions, anorexia, and vomiting. Microscopically, extensive moderate to severe centrolobular and midzonal coagulative necrosis occurs in all lobes of the liver.

IV. DIAGNOSIS

An epidemiologic pattern suggestive of RVF includes: short incubation period; high mortality in lambs, calves, and kids that are less than 1 week of

age; illness in adult sheep and cattle; high abortion rate among cows and ewes; liver lesions at necropsy; an acute febrile disease in humans; and the presence of dense populations of arthropod vectors.

In the laboratory, a characteristic histopathologic finding of liver necrosis in all susceptible animals often provides the first clue that the disease is RVF. A definitive diagnosis of RVF is accomplished by isolating and identifying the virus or by observing a fourfold rise in specific, neutralizing antibody titer between acute and convalescent sera (Peters and Meegan, 1981). During past epizootics, the most common material used for virus isolation included whole blood or serum collected from animals at the peak of pyrexia. Fresh specimens of liver from animals dying of the illness and the products of abortion are also excellent diagnostic materials. Infected humans are also a source of diagnostic material; and, if possible, suspected mosquito vectors should be collected for virus-isolation studies.

RVF virus may be isolated in laboratory rodents as well as in a number of common cell culture systems; however, virus isolation should not be attempted unless adequate personal protection, such as vaccination, can be assured or Biosafety Level 3 (BSL-3) containment facilities are available (Peters and Meegan, 1981; Eddy *et al.*, 1981). Laboratory animals of choice for isolation are suckling mice, adult mice, and hamsters. RVF virus is one of the few viruses that will kill adult mice and hamsters within 1 to 4 days after intraperitoneal inoculation (Wood *et al.*, 1990).

Serologic techniques used to demonstrate RVF virus antibody in domestic animals and humans include HI, CF, IFA, agar gel diffusion, plaque-reduction neutralization, and ELISA tests. A quick and practical means of diagnosis is the simultaneous application of the IgM and IgG antibody ELISA to human and animal sera (Ksiazek *et al.*, 1989). The IgM response provides a measure of recent infection since IgM antibodies decline within several months after infection and the IgG response is a measure of lifetime exposure. The ELISA is also used to demonstrate viral antigen in suspect tissue and serum. Nucleic acid hybridization and enzyme immunochemistry techniques for detection of viral antigen have been useful but are less sensitive than virus isolation. Polymerase chain reaction (PCR) methodology is exquisitely sensitive and specific and its utility as a diagnostic tool for RVF virus is being evaluated.

V. TREATMENT AND CONTROL

No specific treatments are currently available. RVF virus is sensitive to several antiviral agents and interferon *in vitro*. Experimental studies in RVF virus-infected rhesus macaques show that ribavirin and recombinant interferon alpha are effective prophylactic drugs; however, chemotherapeutic efficacy for the disease has not been demonstrated (Peters *et al.*, 1986; Morrill *et al.*, 1989). Passive antibody therapy, by administration of immune plasma

or serum, may be effective but impractical in an epizootic. Neonatal calves have been shown to be completely protected against experimental challenge with virulent virus through ingestion of colostrum from immune dams (Mebus, 1992).

Relocation of animals to an altitude where mosquitoes are absent or application of residual insecticides to animals and their pens and barns has been suggested, though movement of animals during an epizootic is undesirable and rarely practical, and effectiveness of residual insecticides in animal holding areas is dependent on vector habits. Limiting amplification of virus in domestic animals will probably block extensive human disease and mass vaccination is the method of choice in controlling RVF during an epizootic.

Effective live attenuated and killed veterinary vaccines for RVF are in use in many African countries (Assad *et al.*, 1983). The live attenuated Smithburn strain provides long-lasting immunity but is abortogenic in pregnant ewes. The live-virus vaccines should be used only in enzootic areas of Africa or to control an epizootic.

Killed vaccines are recommended for use outside enzootic areas of Africa. A formalin-inactivated vaccine is safe for pregnant ewes but provides only short-term immunity and requires booster inoculations to maintain a durable immunity. Stringent production controls are necessary to ensure the absence of residual live virus.

The only vaccine cleared for human use is a killed product available only from the United States Army Medical Research and Materiel Command (USAMRMC). This vaccine is in limited supply and requires an initial three-dose series for protective immunity with annual booster inoculations required to maintain that immunity.

A live attenuated vaccine (MP-12) developed for use in livestock and humans is being tested (Caplen *et al.*, 1985). Extensive laboratory studies have shown this vaccine to be safe and efficacious against virulent virus challenge in pregnant cows and ewes as well as neonatal calves and lambs (Morrill *et al.*, 1987, 1991; Hubbard *et al.*, 1991; Mebus *et al.*, 1989). Under experimental conditions, the vaccine does not induce fetal damage in sheep or cattle. Limited field studies in Senegal have shown the MP-12 vaccine to be safe, immunogenic, and nonabortogenic (R. Lancelot, 1993, personal communication). More extensive field studies are anticipated in the future. The MP-12 vaccine is less neurovirulent than Smithburn strain in rhesus monkeys and, since the genome of this virus has at least one attenuating lesion on each of the three segments, reversion to virulence is unlikely and reassortment with wild-type virus would produce attenuated progeny. The American Committee on Arthropod-Borne Viruses' (ACAV) Subcommittee on Arbovirus Laboratory Safety (SALS) has determined that the MP-12 vaccine strain may be handled at BSL-2, providing additional safety to humans involved in vaccine production and vaccination procedures (*Biosafety*, 1993). Presently the current lot of MP-12 vaccine is undergoing human testing at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID).

If MP-12 proves to be a safe and effective immunogen, it would provide a measure of protection to those in high-risk professions with the advantages of single-dose immunization providing a rapid and durable immunity and a low cost per dose.

Suggested specific measures to control an RVF epidemic include:

1. Implement an animal vaccination program using a live attenuated RVF vaccine (inactivated vaccine for pregnant animals and neonatal lambs).
   a. Establish a vaccine barrier between known affected areas and unaffected areas.
   b. Positively identify vaccinated animals with an ear tag, tattoo, or other means of identification not easily counterfeited or duplicated.
   c. Prohibit the use of common needles to immunize herds or flocks.
   d. Prohibit the movement of nonvaccinated animals from affected areas.
   e. Employ integrated vector control measures in the areas of active virus transmission and elsewhere as practical and appropriate. Use caution when using insecticides to prevent destruction of mosquito predator species as well as contamination of water and food supplies.
   f. Use personal protective measures such as insect sprays, repellents, and bednets.
2. Implement active surveillance for human and animal disease as well as seroprevalence outside the area of active virus transmission.
   a. Inform human health care providers and veterinarians of the present epizootic/epidemic and be alert for cases exhibiting common signs and sequelae of the disease.
   b. Alert those in high-risk occupations (farmers, herdsmen, and abattoir workers) to the potential hazard of aerosol and parenteral infection through the slaughtering of sick animals and assisting with abortions or handling of products of abortion from ruminants.
   c. Public awareness of the threat through radio, newspaper, and television broadcasts and instructions in personal protective measures. This information should be truthful, accurate, and informative and care must be taken to instruct and not induce panic or over reaction.
3. Vaccination should be sought for certain professionals such as veterinarians, physicians, health care providers, biomedical researchers, and laboratory technicians who are at greatest risk of infection through their attendance to patients or processing of laboratory specimens.

VI. OTHER PHLEBOVIRUSES

Sandfly fever (SF) is a self-limited febrile viral illness transmitted by biting insects of the genus *Phlebotomus* (Sabin, 1952). It occurs in Africa,

Europe, and Asia with seasonal incidence peaking between April and October (Tesh *et al.*, 1976). The virus is transovarially transmitted in sand flies (*Phlebotomus papatasi*), a phenomenon that is important to the maintenance of endemic disease. Humans may also serve as viremic vertebrate hosts in a human–*Phlebotomus*–human cycle. Although serosurveys have suggested that small mammals may have antibody to certain viral strains, the significance of this finding to the maintenance of the disease is uncertain (Le-Lay-Rogues *et al.*, 1983).

SF has a wide geographic distribution in those parts of Europe, Africa, and Asia between 20 and 45° north latitude, reflecting the range of *P. papatasi* (Tesh *et al.*, 1976; Saidi *et al.*, 1977). The disease persists mainly in the lower altitudes of these subtropical and tropical countries in which there are long periods of hot, dry weather. Its occurrence is distinctly seasonal, with the highest incidence occurring during the late spring and summer months, depending on the prevailing temperatures and timing of the rainy season (Sabin, 1944). There are more than 20 viral isolates from phlebotomine flies in both hemispheres that are antigenically related to SF viruses, and which cause rare cases of human disease (Tesh *et al.*, 1974a,b, 1982). However, sandfly fever Sicilian (SFS) and sandfly fever Naples (SFN) are the most important epidemiologically.

Field isolates of SF virus have demonstrated poor infectivity and lack of pathogenicity for various laboratory animals, hence undermining attempts to understand the pathogenic mechanisms of disease (Sabin, 1952). These studies have consisted of the inoculation of hamsters, mice, rats, rabbits, guinea pigs, and monkeys. Pathogenicity for suckling mice has been demonstrated only after serial blind passage and adaptation to mouse brain.

The clinical illness is well-defined by human volunteer studies as self-limited (hence the eponym three-day fever), with no mortality or sequelae and a very predictable clinical course (Hertig and Sabin, 1964). After intravenous inoculation of human volunteers with the virus, the incubation period has been shown to be $1\frac{1}{2}$ to 2 days, followed by a temperature of $> 102°F$ in two-thirds of subjects. The duration of fever is from 1 to 4 days and is accompanied by a frontal or retroorbital headache, malaise, myalgias, anorexia, and lymphopenia. In addition, many patients will also have low back pain, photophobia, and nausea. A small percentage may suffer from arthralgias, odynophagia, and/or vomiting. Infrequently, a patient may experience abdominal pain lasting 1–2 days. On physical examination, persons with SF appear flushed, and often have conjunctival injection. The heart rate is usually elevated early in the course of the disease in association with the fever.

The most distinctive laboratory feature of SF is leukopenia, which occurs in approximately 90% of infected subjects within 2–3 days of resolution of fever (Hertig and Sabin, 1964). Slight decrements in volunteers' platelet counts are occasionally noted, but never below normal limits and always with spontaneous recovery. Mild elevations of the liver transaminases and alkaline phosphatase (2–3× normal values) may also occur during the febrile period, and routinely return to normal within the following week.

Diagnostic techniques for SF are similar to those employed for RVF and include the isolation of the virus from febrile patients or the demonstration of a fourfold increase in neutralizing antibody. Enzyme immunoassays have also been used to detect IgM and IgG antibodies in serum.

Other phleboviruses have been discovered which are serologically related to Naples and Sicilian types, and which are broadly distributed in Eurasia and the Americas (Tesh *et al.*, 1974b; Travassos da Rosa *et al.*, 1983; Shope *et al.*, 1980). These viruses have been recovered from phlebotomine flies and mosquitoes. Several of these phleboviruses appear to cause a disease in humans similar to SF: Chagres, Alenquer, Candiru, and Punta Toro viruses. Toscana virus represents a strain that is distinct albeit related to SF Naples, and which has been reported as a cause of aseptic meningitis in the Tuscany region of Italy and in Portugal (Verani *et al.*, 1980, 1984; Ehrnst *et al.*, 1985). Although transovarial transmission of viruses in *Phlebotomus* spp. has been demonstrated, decline of virus infection rates in successive generations suggests that these agents may not be maintained indefinitely by such a mechanism (Ciufolini *et al.*, 1985, 1989; Endris *et al.*, 1983).

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