Rinderpest (Cattle Plague)

Rinderpest was the first animal disease to be globally eradicated. Because it was such a scourge and re-emergence remains a possibility, it is vital to maintain current information. Rinderpest was a viral disease of cattle and other ruminants (domestic and wild) **characterized by fever, erosive stomatitis, diarrhea, and high morbidity and mortality.** In the post-eradication era, testing for rinderpest, preferably using molecular methods, should be considered when an etiologic agent cannot be determined for an infectious disease with characteristic signs of rinderpest.

Historically, rinderpest virus was a scourge that wrought economic havoc throughout Africa, Asia, and Europe. The need to combat rinderpest provided the impetus for the establishment of the first modern veterinary school in Lyon (France) in 1762. After several decades of success in eradicating rinderpest from Europe, the disease recurred unexpectedly in Belgium in 1920, and renewed efforts to eradicate it resulted in the creation of the World Organization for Animal Health (OIE) in 1924. After the creation of the Food and Agriculture Organization (FAO) of the United Nations in 1946, the OIE and FAO signed a cooperation agreement in 1952. Thereafter, the two organizations (FAO and OIE) were major participants in several worldwide campaigns to combat rinderpest, which culminated in global eradication of the disease in 2011. In fact, the last reported rinderpest outbreak occurred in Kenya in 2001, but a 10-year active surveillance period was necessary before global eradication could be declared. Rinderpest is only the second viral disease, after smallpox, to have been successfully eradicated worldwide.

The successful eradication of rinderpest shows that smallpox eradication in 1980 was not an unrepeatable feat and should provide a certain degree of confidence to the international community that concerted, science-based efforts can result in future successes.

Rinderpest virus is biologically similar to the virus of peste des petits ruminants (PPR), which has been targeted by the OIE and FAO as the next animal disease for global eradication.

Rinderpest was a disease of cloven-hoofed animals characterized by fever, necrotic stomatitis, gastroenteritis, lymphoid necrosis, and high mortality. In epidemic form, it was the most lethal plague known in cattle. All wild and domesticated species of the order Artiodactyla were variably susceptible to rinderpest, although dissemination of the virus largely depended on continual transmission among domesticated cattle, buffalo, and yaks. The virus also infected goats and sheep, leading to underdiagnosis of the clinically similar peste des petits ruminants in regions where the two diseases coexisted.

Etiology, Epidemiology, and Transmission of Rinderpest

Rinderpest virus is a *Morbillivirus*, closely related to the viruses causing peste des petits ruminants, canine distemper, and measles. Strains of varying virulence for cattle occurred and could be differentiated genetically. However, a single serotype of the virus existed, and a vaccine prepared from any strain could protect against all strains.

Rinderpest virus is shed in nasal and ocular secretions and can be transmitted during the incubation period (1–2 days before onset of fever). Transmission required direct or close indirect contact between susceptible animals and sick animals

shedding the virus. The role of fomites in transmission was negligible, because the virus is fragile, being inactivated within 12 hours of exposure to atmospheric heat and light. There was no carrier state, and recovered animals acquired lifelong immunity. In endemic areas, young cattle became infected after maternal immunity disappeared and before vaccinal immunity began, with possible auxiliary cycles in wild ungulates.

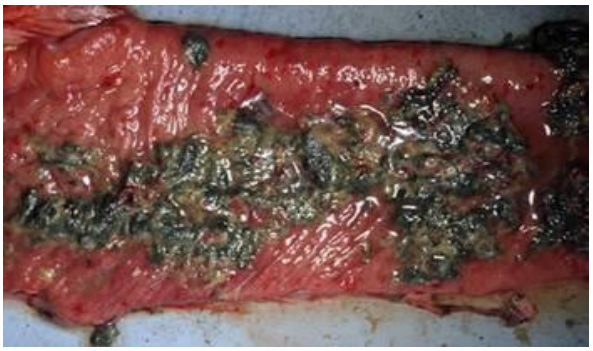
Clinical Findings of Rinderpest

After an incubation period of 3–15 days, fever, anorexia, depression, and oculonasal discharges developed, followed by necrotic lesions on the gums, buccal mucosa, and tongue. The hard and soft palates were often affected. The oculonasal discharge became mucopurulent, and the muzzle appeared dry and cracked.

Diarrhea, the final clinical sign, could be watery and bloody. Convalescence was prolonged and could be complicated by concurrent infections due to immunosuppression. Morbidity was often 100% and mortality was up to 90% in epidemic areas, but in endemic areas morbidity was low and clinical signs were often mild.

Lesions

Rinderpest, necrosis and fibronecrotic exudate



Gross pathologic lesions occurred throughout the GI and upper respiratory tracts, either as areas of necrosis and erosion, or congestion and hemorrhage, the latter creating classic "**zebra-striping**" in the rectum.

Lymph nodes could be enlarged and edematous, with white necrotic foci in the Peyer's patches. Histologic lesions included lymphoid and epithelial necrosis with viral-induced syncytia, and intracytoplasmic and intranuclear inclusions were often seen.

Diagnosis of Rinderpest

- It is recommended that post-eradication laboratory diagnosis of rinderpest focus on molecular techniques (such as RT-PCR), which are not only accurate but also allow for phylogenetic analysis to pinpoint the source of any re-emerging virus strain.

Clinical and pathologic findings were sufficient for diagnosis of rinderpest in endemic areas and after initial laboratory confirmation of an outbreak. In areas where rinderpest was uncommon or absent, laboratory tests had to be used to differentiate it from bovine viral diarrhea in particular, as well as East Coast fever, foot-and-mouth disease, infectious bovine rhinotracheitis, and malignant catarrhal fever. Virus isolation and detection of specific viral antigens in affected tissues using an immunodiffusion test was the standard, but simpler, more rapid and more discriminating tests, such as antigen-capture ELISA and reverse transcription PCR (RT-PCR), were favored toward the end of the eradication campaign. The RT-PCR technique allowed phylogenetic characterization of the virus and helped trace the origin of strains in new outbreaks. A simple lateral flow pen-side test for field use also proved useful in the final stages of the eradication campaign. In the 10-year

period between occurrence of the last outbreak and the official declaration of eradication, active rinderpest surveillance in recent endemic areas included the testing of all susceptible cloven-hoofed animals presenting with erosive stomatitis.

Control of Rinderpest

Active immunity to rinderpest was lifelong, whereas maternal immunity lasted 6–11 months. Control in endemic areas was by immunization of all cattle and domestic buffalo >1 year old with an attenuated cell culture vaccine. In these areas, outbreaks were controlled by quarantine and "ring vaccination" and sometimes by slaughtering. In epidemics, the disease was best eliminated by imposing quarantine and by slaughtering affected and exposed animals. Control of animal movements was paramount to control rinderpest; many outbreaks were due to the introduction of infected cattle to hitherto uninfected herds. The lessons learned from this huge success will be instrumental in the fight against peste des petits ruminants.

BOVINE EPHEMERAL FEVER

ETIOLOGY

Bovine ephemeral fever (BEF) is associated with an arthropod-borne rhabdovirus that is the type species of the genus Ephemerovirus. There are a number of strains that vary antigenically. Other antigenically related but nonpathogenic species of Ephemerovirus occur in the same environment in Australia. The BEF virus is closely associated with the leukocyte–platelet fraction of the blood, and it can be maintained deep frozen or on tissue culture and chick embryos.

EPIDEMIOLOGY

Occurrence A disease of cattle, ephemeral fever is enzootic in the tropical areas of Africa, in most of Asia, the Middle East, the East Indies, and in much of Australia, with extensions into the subtropics and some temperate regions. In these areas the disease presents as episodic epidemics. Area outbreaks can last several months, with the spread of infection following prevailing winds, and during this period most herds within a region will be infected. The proportions of herds affected in outbreaks in the Jordan Valley in Israel in 1990 and 1999 were 79% and 98% respectively.

The morbidity rate in outbreaks is usually between 25% and 45%, but if the population is highly susceptible or the infecting strain virulent, the morbidity rate may reach 100%. In enzootic areas, only 5% to 10% will be affected. A rate of 1% for case fatality and loss from involuntary culling is usual with low virulence strains but can approach 10%. Source of Infection The source of infection is the animal affected with the clinical disease and biological vectors (hematophagous biting insects).

Method of Transmission A great deal of work in recent years has not clearly defined the vector list, which probably includes the mosquitoes Aedes spp., Culex annulirostris, Anopheles bancroftii and A. annulipes, and the biting midge Culicoides brevitarsis. Culex annulirostris has been identified as a biological vector in Australia.

This mosquito can transmit infection within a week of feeding on an infected animal, and the epidemiology of the disease in Australia supports transmission by mosquitoes rather than Culicoides spp. The reservoir host, other than cattle, has not been identified. This is of particular importance when the epidemiologic pattern of occurrence of the disease changes, as it has done in Australia after being introduced in approximately 1936. The disease now occurs annually in areas where it used to occur only once each decade, probably because of establishment of the virus in indigenous vectors. Spread by wind-borne carriage of vectors has been documented.

Epidemiologic studies suggest that outbreaks in Japan originate from Korea, and those in Israel originate from Turkey. Transboundary movement can also occur by animal transport, although transmission does not occur through contact with infected animals or their saliva or ocular discharge. The disease is not spread through semen, nor is intrauterine administration of the virus a suitable route of transmission.

Experimental Reproduction

The disease can be transmitted by the injection of whole blood or the leukocyte fraction of it. Experimental reproduction in cattle requires IV administration, and viremia lasts 3 days with a maximum of 2 weeks. There is no carrier state.

Environment Risk Factors

The disease occurs in the summer months, outbreaks are clustered and relatively short lived, and spread depends largely on the insect vector population and the force and direction of prevailing winds. The disease tends to disappear for long periods to return in epizootic form when the resistance of the population is diminished. Recurrence depends primarily on suitable environmental conditions for increase and dissemination of the insect vector and the degree of population immunity, as indicated by neutralizing antibody titers and immunity coverage. During periods of quiescence the disease is still present, but the morbidity is reputed to be very low. However, in many enzootic areas the degree of surveillance is less than intense, and clinical cases may occur without being observed. Temporary protection against infection is provided by subclinical infections by other unrelated arboviruses (e.g., Akabane, Aino, and others).

Animal Risk Factors

Among domestic animals, only cattle are known to be naturally affected, but antibodies can be found in African ruminant wildlife. All age groups of cattle are susceptible, but calves less than 3 to 6 months old are not affected by the natural disease. With experimental infections calves as young as 3 months old are as susceptible as adults to experimental infection but do not show clinical disease. In dairy cattle, higher-producing cows are at greater risk, and clinical disease may be minimal in cows under 2 years of age. A recent Israeli study in 10 beef herds found average morbidity and mortality rates of 46.2% and 4.8%, respectively, with higher rates in bulls than cows and a higher morbidity in cows 2 to 5 years of age than in heifers less than 2 years of age. In natural outbreaks there is no breed susceptibility. In Africa, based on serologic results, the virus is thought to be cycling in populations of wild ruminants between epidemics in domestic cattle. Buffalo (Bubalus bubalis)

are susceptible to experimental infection, but it is unlikely that they play any part as a reservoir host. After experimental infection of cattle there is solid immunity against homologous strains for up to 2 years. Immunity against heterologous strains is much less durable, which probably accounts for the apparent variations in immunity following field exposure.

Economic Importance

Although the case-fatality rate is very low, considerable loss occurs in dairy herds as a result of the depression of milk flow—up to 80% in cows in late lactation. In an Israeli study of eight infected dairy herds, the decline in milk yield from preinfection levels varied between cows and ranged from 30% to 70%, with the highest-yielding cows having the greatest drop. Following recovery from disease, milk production was still less than that of preinfection levels. There is also a lowered resistance to mastitis. Reproductive inefficiency is associated with a significant delay in the occurrence of estrus, abortion in cows, and temporary sterility in bulls. Occasional animals die of intercurrent infection, usually pneumonia, or prolonged recumbency. Bovine ephemeral fever can have a serious effect on the agricultural economy in countries where cattle are used as draught animals. For cattle-exporting countries such as Australia, BEF causes interference with movement of cattle when receiving countries insist on evidence of freedom from the disease.

PATHOGENESIS

Experimental production of the disease requires the IV route of transmission. Virus multiplication probably occurs primarily within the vascular system. The BEF virus alters cellular biology in cattle to enhance virus entry and replication. This includes activation of intracellular signaling pathways to up-regulate clathrin and dynamin 2 expression and activation of COX-2-mediated E-prostanoid receptors 2

and 4 to enhance clathrin-mediated endocytosis of the virus. After an incubation period of 2 to 10 days, there is a biphasic fever with peaks 12 to 24 hours apart. The fever lasts 2 days, and increased respiratory rate, dyspnea, muscle trembling, limb stiffness, and pain are characteristic at this time. There is generalized inflammation with vasculitis and thrombosis, serofibrinous inflammation in serous and synovial cavities, and increased endothelial permeability at the same sites. The virus can be detected in circulating neutrophils and plasma, the serosal and synovial fluids, the mesothelial cells of synovial membrane and epicardium, and in neutrophils in the fluids. Clinical signs are thought caused by the expression of mediators of inflammation coupled with a secondary hypocalcemia.

CLINICAL FINDINGS

Calves are least affected, with those less than 3 to 6 months of age showing no clinical signs. Overweight cows, high-producing cows, and bulls are affected the most. Deaths are relatively uncommon and are usually less than 1% of the herd. In most cases the disease is acute. After an incubation period of 2 to 4 days, sometimes as long as 10 days, there is a sudden onset of fever (40.5°–41°C), which may be biphasic or have morning remissions. Anorexia and a sharp fall in milk yield occur. There is severe constipation in some animals and diarrhea in others. Respiratory and cardiac rates are increased, and stringy nasal and watery ocular discharges are evident. The animals shake their heads constantly, and muscle shivering and weakness are observed. There may be swellings about the shoulders, neck, and back. Muscular signs become more evident on the second day, with severe stiffness, clonic muscle movements, and weakness in one or more limbs. A posture similar to that of acute laminitis, with all four feet bunched under the body, is often adopted. On about the third day, the animal begins eating and ruminating, and the febrile reaction disappears, but lameness and weakness may persist for 2 to 3 more days. A common

name of **"3-day sickness"** is applied because animals typically progress through onset of disease to severe illness and recovery within 3 days. Some animals remain standing during the acute stages, but the majority go down and assume a position reminiscent of parturient paresis, associated with hypocalcemia, with the hindlegs sticking out and the head turned into the flank. Occasionally, animals adopt a posture of lateral recumbency. Some develop clinically detectable pulmonary and subcutaneous (SC) emphysema, possibly related to a nutritional deficiency ofselenium. In most cases recovery is rapid and complete unless there is exposure to severe weather or unless aspiration of a misdirected drench or ruminal contents occurs. Some cases have a second episode of clinical disease 2 to 3 weeks after recovery. Occasional cases show persistent recumbency and have to be destroyed, and abortion occurs in a small proportion of cases. Affected bulls are temporarily sterile. Milder cases, with clinical signs restricted to pyrexia and lack of appetite, may occur at the end of an epizootic.

CLINICAL PATHOLOGY

Blood taken from cattle in the febrile stage clots poorly. Marked leukocytosis with a relative increase in neutrophils occurs during the acute stage of the disease. There is a shift to the left and lymphopenia. Plasma fibrinogen levels are elevated for about 7 days, and there is a marked increase in creatine kinase activity. In natural cases, but not experimentally produced ones, significant hypocalcemia occurs.8 Available serologic tests include a complement fixation test, serum neutralization, fluorescent antibody test, agar gel immunodiffusion (AGID) test, and a blocking ELISA, which is reported to be simple and the preferred test.

NECROPSY FINDINGS

Postmortem lesions are not dramatic. The most consistent lesions are a serofibrinous polyserositis, involving the synovial, pericardial, pleural, and peritoneal cavities, with a characteristic accumulation of neutrophils in these fluids and surrounding tissues. Hemorrhage may also be observed in the periarticular tissues, and there may be foci of necrosis in the musculature of the limbs and back. All lymph nodes are usually enlarged and edematous. Pulmonary emphysema and fibrinous bronchiolitis are standard findings, and subcutaneous emphysema along the dorsum may be observed. Characteristic microscopic findings consist of a mild vasculitis of small vessels, with perivascular neutrophils and edema fluid plus intravascular fibrin thrombi. Necropsy examinations of animals that develop persistent recumbency have shown severe degenerative changes in the spinal cord similar to those produced by physical compression, but the pathogenesis of these lesions remains uncertain. Although nucleic acid sequences of the agent are known, PCR tests are not yet widely utilized. Antigen in reticuloendothelial cells can be detected by immunoperoxidase and immunofluorescent techniques. Samples for Confirmation of Diagnosis

• Virology—chilled lung, spleen, synovial membrane, pericardium (virus isolation)

• Serology—pericardial fluid (ELISA)

• Histology—formalin-fixed samples of previously mentioned tissues.

DIFFERENTIAL DIAGNOSIS

The diagnosis of ephemeral fever in a cattle population is not difficult on the basis of its epidemiology and clinical presentation. It can produce difficulties in individual animals where differentials include the following:

• Botulism • Parturient paresis • Pneumonia • Traumatic reticulitis

TREATMENT

Palliative treatment with nonsteroidal antiinflammatory drugs such as IV or IM flunixin meglumine (2.2 mg/kg/d), or IM ketoprofen (3 mg/kg/d) results in remission of signs without in any way influencing the development of the disease. There is little effect on the respiratory manifestations of the disease but a major effect on stiffness, lameness, and anorexia. All treatments are continued for 3 days. Phenylbutazone may be most effective, but the injection frequency is not practical and creates slaughter residue concerns. Moreover, phenylbutazone use in cattle is not permitted in some countries. Parenteral treatment with calcium borogluconate should be given to cows that show signs of hypocalcemia, and field observations are that parenteral treatment with calcium solutions often helps to get a recumbent cow to her feet. Proper nursing of the recumbent animal is required.

CONTROL

Restriction of movement from infected areas is practiced, but vaccination is the only effective method of control. Vaccines prepared from attenuated tissue culture virus or in mouse brain and adjuvanted in Freund's incomplete or Quil A adjuvants are commercially available in Australia, Japan, Taiwan, and South Africa. Two vaccinations are required and are effective in preventing disease in natural outbreaks for periods up to 12 months. The use of vaccination in Japan is credited with preventing further major outbreaks. Attenuated vaccines are expensive to

produce and have a short shelflife, and breakdowns are recorded after their use. There is also concern about backmutation of the attenuated strain to a virulent form, particularly given the high mutation rate of RNA viruses, and contamination with other viruses during preparation of the vaccine. The use of inactivated vaccines therefore offers an attractive alternative, such as formalin killed vaccines with and without adjuvants. Unfortunately, inactivated vaccines appear to need at least three vaccinations to provide longer-term immunity, requiring frequent boosting for effect. Immunity is positively correlated with the level of specific antibody measured with a blocking ELISA or as virus-neutralizing antibody.