BOVINE EPHEMERAL FEVER

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INTRODUCTION

Bovine ephemeral fever (BEF), also commonly known as three-day stiff-sickness, is an infectious disease caused by an arthropod-borne rhabdovirus (Bovine ephemeral fever virus (BEFV)) affecting cattle and water buffalo (Bubalus bubalis). Infection results in fever, stiffness and a temporary reluctance to move, followed, usually, by complete recovery. Economic losses are attributed to mortality of stock and draught animals, abortion, decreased milk production, reduced weight gain and lowered fertility of bulls and the costs of supportive care and treatment. It is possible that this disease has a wider distribution than may be recorded due to the relatively mild symptoms and good recovery rate in many cases. BEF, for the same reasons may also be misdiagnosed or diagnosis may not be confirmed by practitioners. Occasional outbreaks have been described clinically but not necessarily confirmed in feedlots within Southern Africa.

EPIDEMIOLOGY

Mosquitoes are the most important vectors, and BEFV has been isolated from culicine and anopheline mosquitoes. The European and American continents are free of infection whilst disease has been reported in Africa, Asia and Australasia. The latter includes the entire African continent, the Asian regions south of the former USSR, and Australasia but excluding Papua New Guinea and New Zealand.

In the subtropical and temperate areas of Africa, Asia and Australia, BEF occurs mostly during summer and autumn, disappearing after the first frost. In the literature, Finlaison et.al. (2010) found that a major factor contributing to halting of Israeli epidemics was the onset of cold weather, when the average ambient temperature decreases below 16°C at night. In tropical areas, outbreaks of clinical disease may be linked to the rainy seasons as the climatic conditions may become very favourable to the existence of a critical mass of vectors. An association between epidemics of BEF and prolonged rainfalls that resulted in a large population of mosquitoes have been reported.
BEF occurs regularly in South Africa, from the Limpopo River to the southern Cape coast and the severity and extent of outbreaks may vary between subsequent years. Certain districts on the Highveld, the Karoo and along the southern Cape coast may experience clinical disease less frequently. Clinical disease is typically seen in the second half of summer, but tends to occur a few months earlier in the winter rainfall region of the Western Cape Province.

The mechanisms by which the virus over-winters are largely unknown but it does not seem to take place in the cattle population. The virus does not survive long outside its vertebrate or invertebrate host as it is very susceptible to both high and low pH. The high levels of intramuscular lactic acid, formed during post mortem autolysis, rapidly inactivates the virus. Direct animal to animal transmission, fomites, bodily discharges or tissues therefore play no role in the transmission of BEFV.

During the past few years a number of articles have been published which investigated how the virus is spread over continents and vast distances. In general, epidemics have followed a pattern of spreading from northern to southern parts in Africa and Australia, whilst in the northern hemisphere it may spread in the opposite direction. Prevailing winds, their speed and direction, temperature (mild) and humidity (high) all play an important role in vector dispersal. The density and population sizes of both susceptible cattle and vectors, the availability of breeding places for vectors, in both primary and distant foci, also have a major impact on spread of infection. It has been reported that the development of new irrigation systems and dams, which provides more breeding sites to the mosquito vectors, may be favourable to maintaining epidemics. Viral incursions into surrounding countries and the introduction of new viral strains may further contribute to the spread of infection. Long intervals between epidemics may contribute to the existence of cattle populations that are highly susceptible to BEF.

Finlaison et al (2010) observed that heavy rainfall provided a suitable environment for vector breeding, resulting in the initiation and support of continuing BEF virus transmission. The development of a low-pressure system afterwards provided the means for rapid movement of infected vectors over vast distances on the Australian continent. In the same article, it was stated that mosquitoes can be dispersed overnight up to distances of 650 km compared to only 50 km during the day.

A number of wild African ruminants including the cape buffalo, waterbuck, wildebeest and hartebeest, have been shown to have neutralizing antibodies. In Australia marsupials seem to remain unaffected by BEFV although introduced deer species and water buffalo have been shown to develop antibodies. Sheep and goats seem to remain unaffected by BEFV.

Immunogenic diversity within the BEFV population does not seem to exist. BEFV strains isolated from mainland China, Taiwan, Japan, Turkey, Israel and Australia were grouped into three clusters and results showed that the phylogenetic relationships of the isolates were closely related to their geographical and chronological sources (Zeng et al 2012).

**PATHOGENESIS**
The site of initial replication of BEFV following infection is largely unknown, but, as the virus has been observed at high titres circulating in the blood approximately one day prior to
the onset of fever and associated neutrophilia, it seems that the virus is specifically present in the neutrophils.

Primary endothelial cell damage and development of a hypocalcaemia seems to be the typical pathogenesis of the infection. The virus primarily targets the endothelium of arterioles, venules and capillaries of the synovial membranes, tendon sheaths, muscles, fasciae and skin resulting in effusion of fibrin-rich fluid into joints, peritoneal, pleural and pericardial cavities, and discharges from nasal and ocular mucosal surfaces. In a small percentage of affected animals severe pulmonary emphysema may be seen and this is commonly referred to as atypical three-day stiff-sickness.

Decreased total calcium (ionized and bound), iron and zinc and an increase in copper blood levels have been reported. Paresis is usually evident in the acute phases of disease. Depression, muscular fibrillation, rumen stasis, inability to swallow, constipation and recumbency may also be seen associated with the hypocalcaemia.

Primary neural lesions do not usually seem to be responsible for the temporary paralysis as animals may respond to calcium infusion. There seems to be many similarities between the biochemical and haematological changes which occur in BEF and those of periparturient hypocalcaemia. Wallerian degeneration may be observed in the cervical spinal cord in a few cases which remain permanently paralysed but the pathogenesis thereof remains obscure. In the Guillain-Barré syndrome of humans interferon produced by various viruses has been implicated with acute temporary demyelinization of nerves and ascending paralysis. BEF infection is associated with high titres of circulating interferon and it has been proposed that the BEF virus causes the massive interferon production with consequential tissue damage.

Partial blockage of the air passages by exudate, as well as necrosis of the bronchiolar walls causing rupture of bronchioles and alveoli are all proposed mechanisms resulting in emphysema. Air may then disperse into the connective tissue septa and lymphatics of the lungs extending subpleurally to reach the mediastinum, spreading through the thoracic inlet to the subcutaneous tissue.

**CLINICAL SIGNS**

The incubation period in natural outbreaks is unknown but suspected to be as short as 36–48 hours. In experimental infections it was recorded to vary from 29 hours to 10 days and mostly averaging between 3 - 5 days. Disease is characterized by a sudden onset which can rapidly progress to severe illness with apparent recovery within a period of 3 days – which gave rise to its common name of “three-day sickness”. Mortality is generally low and seldom exceeds 2 to 3 %. In a study by Yeruham *et al* (2007) morbidity and mortality rates of 2.6% and 0.1% respectively, has been reported in a large outbreak on the Israeli coastal plain. The lowest morbidity rate was reported as 5.5% in young heifers and as 75% in adult cows. Only heifers over the age of three months were clinically affected.

Typical clinical signs would be a sudden onset of fever, with temperatures as high as 41°C, a sudden and severe drop in milk production, inappetence, lethargy, salivation, nasal discharge,
stiffness with a shifting lameness, reluctance to move and recumbency. Clinical symptoms may be subtle and difficult to differentiate from other viral diseases.

The fever is typically biphasic, with two or more peaks 12 to 24 hours apart. Clinical signs in the first febrile phase, are mild or may even go unnoticed. Cattle more severely affected may become anorexic and stiff. Other clinical signs may include swelling of the joints, accelerated pulse rate, cyclical increased respiratory rate, fasciculation or muscle tremors of the subcutaneous muscles and periorbital and subcutaneous oedema of the head. Recumbency may be seen progressing from sternal to lateral. Animals may still be able to rise in the early sternal stages, retaining some reflex responses, but they may become completely unable to do so as the disease progresses. Loss of the swallowing reflex, bloat, rumen stasis, constipation, and excessive salivation may all be evident. Total reflex loss, coma and death may be the ultimate consequence in lateral recumbency. Resolution of clinical signs may still occur spontaneously up to and including the early paralytic stage.

Rales can be heard in the lungs in the second febrile stage. Pneumonia may be a secondary complication, and the clinical signs associated with severe pulmonary emphysema, which may eventually result in subcutaneous emphysema of the backline rarely extending over most of the body, have been observed in a small proportion of cases.

Clinical signs are usually more severe in lactating than non-lactating cows, characterized by a sudden decrease in milk production, a severe decline in milk quality and high somatic cell counts. Milk yield does not usually regain pre-illness levels upon recovery except for some cows which were at a very early stage in lactation at onset of disease.

Complications, particularly in bulls and cows that are obese or in good body condition, may include an inability to rise due to nerve and large muscle damage. Bulls may frequently suffer from infertility afterwards, which is sometimes permanent. The cause of the temporary infertility as well as abnormal spermatozoa in bulls is unknown and early treatment of bulls with anti-inflammatory drugs may prevent this from occurring. Five percent of pregnant cows, especially those in late pregnancy, may abort with loss of an entire lactation period although the fertility subsequent to abortion does not seem to be affected.

During May 2009 three feedlot calves were initially diagnosed and treated for respiratory disease on the basis of high fever and non-specific symptoms. Both cases subsequently became downers and showed signs of severe pain with swollen joints particularly the carpal joints and were euthanased after supportive treatment failed.

Post mortem examination of these animals showed consistent very severe carpal tendonitis and relatively non-specific histopathological changes including fibrinopurulent bronchopneumonia. All three were negative for BVD PI. Joint fluid tested positive for *Mycoplasma* spp. and in one case yielded a pure culture of highly resistant *Klebsiella* spp. bacteria. Unfortunately no tests were done for BEF but in retrospect many of the typical epidemiological conditions for BEF were met.
Figure 1 – joint of calf with severe yellowish periarticular gelatinous fluid.

**PATHOLOGY**
Macroscopic lesions are characterized by serofibrinous polyserositis which may affect the synovial, pericardial, thoracic, and peritoneal cavities to varying degrees. The serosal surfaces may show variable degrees of oedema and haemorrhages. The oedema fluid accumulating in the body cavities often contains fibrin clots. Joints may show brown or yellow gelatinous periarticular fluid especially if severely affected, which may extend along tendon sheaths and facial planes. Patchy pulmonary oedema, visceral and parietal pleuritis, epicarditis (mostly at the base of the heart) and oedema of lymph nodes (in the febrile stage) may be observed. Necrosis may be seen in some skeletal muscles, usually in the quadriceps and larger muscle groups of the shoulder and back. In the atypical cases severe pulmonary emphysema with formation of small to larger bullae in the lungs may be seen. Emphysema may also be seen in the mediastinum, subperitoneal and the subcutis.

**DIAGNOSIS**
A diagnosis may be supported by the presence of a typical clinical history, typical clinical signs and typical post mortem and histological findings. Viral culture (from the leukocyte fraction of the blood) is time consuming as well as expensive and therefore not routinely employed. Serological diagnosis can be attempted via neutralizing antibody tests however,
false positives do occur and the diagnosis depends on the demonstration of rising antibody titres on paired serum samples collected 2-3 weeks apart. The blocking ELISA test is more specific and can differentiate BEF from other antigenically related viruses.

A high percentage of neutrophils with many immature forms is not pathognomonic for ephemeral fever, but if not present, the field diagnosis is likely to be wrong and a differential leukocyte count thus provides the most rapid supporting evidence for the field diagnosis. Eosinopaenia also occurs. It has been reported (T. D. St. George, D.V.Sc) that if blood that is taken during illness is allowed to clot, it usually fails to contract on standing, even over several days, and it may be streaked with fibrin.

Zheng et al (2011) describes a loop-mediated isothermal amplification (RT-LAMP) assay for the detection of bovine ephemeral fever virus (BEFV) which in their study exhibited higher sensitivity when compared with conventional reverse-transcription polymerase chain reaction (RT-PCR) and virus isolation methods. Thirty six blood samples were tested and the results indicated that RT-LAMP could detect early infection with BEFV and that this method is useful for the diagnosis of BEFV infection in blood samples.

The most important differentials, especially in the South African context, would be osteomalacia including aphasisis, laminitis associated with Crotalaria burkeana (and other Crotalaria species) and Diplodia maydis poisoning. Clinically, individual cases should be differentiated from early Rift Valley fever, heartwater, botulism, babesiosis or black quarter. Mycoplasma spp infections should also be considered since this organism has been reported to cause not only severe pneumonia but also swollen, painful joints in calves. Atypical BEF should be differentiated from the fog fever syndrome. When studying the epidemiology and investigating outbreaks care must be taken that other diseases such as Ibaraki disease and epizootic haemorrhagic disease of deer should not be confused with BEF.

TREATMENT AND CONTROL
Treatment can be rationally implemented based on
1. Symptomatic treatment
   a. Anti-inflammatory products of which there are a number currently available. The choice of a steroidal or non-steroidal product will depend on the preference of the clinician involved and the constraints of these products with regard to use in food producing animals. Such treatment is generally expected to restore treated animals to apparent normality in terms of fever and clinical appearance provided they are treated early in the course of the disease.
   b. Signs of hypocalcaemia such as rumen stasis, muscle tremors or paresis should be treated with intravenous calcium products with careful monitoring for clinical response and avoidance of overdosing. Oral administrations should not be administered in the absence of a good swallowing reflex.
2. Supportive treatment
   a. Protection from environmental conditions is recommended particularly in areas where heat and humidity are high and the ability of an affected animal to reach water or food may be compromised.
   b. Convalescent animals should not be stressed for a number of days to allow full tissue and electrolyte recovery to occur.

Control is based on immunisation of the host population and environmental control of insect vectors. Several forms of live-attenuated, inactivated and recombinant vaccines have been
reported but with variable efficacy and durability of protection. The BEFV G protein is a highly effective vaccine antigen, either as a purified subunit or expressed from recombinant viral vectors. Currently only one vaccine is advertised in South Africa and it is described as a freeze-dried live attenuated ephemeral fever virus.

Environmental control of the insect vectors presents a significant challenge considering the distances and speed with which the vectors may be moved by prevailing weather conditions. However control of mosquito egg-laying sites, control of mosquito larvae and adults may be considered in that order of importance, as well as using registered insecticides and control measures.

REFERENCES


CPD QUESTIONAIRE

Which one of the following statements are true:

1. Bovine ephemeral fever is:
   a) caused by an arthropod borne rhabdovirus.
   b) different to three-day stiff-sickness
   c) does not affect water buffaloes
   d) does not affect bovines
   e) affects mainly sheep

2. The distribution of disease is
   a) limited to the Sahara desert
   b) limited to Papua New Guinea
c) widespread including Asia, Africa, Australasia
d) most prevalent to Europe
e) characterized by very isolated occurrences in the Americas

3. The virus is known to overwinter in
   a) the joint fluid of adult cows
   b) the salivary glands of ticks
   c) a wildlife reservoir
   d) in mosquitoes
   e) a manner still largely unknown

4. The pathogenesis seems to be mostly related to
   a) hypercalcaemia and interleukin production
   b) hypocalcaemia and endothelial cell damage
   c) wallerian degeneration and interferon production
   d) increased ionized calcium and Zn levels
   e) none of the above

5. Atypical disease clinical signs are
   a) permanent paralysis
   b) high mortality rates exceeding 50%
   c) a biphasic fever at two weeks intervals
   d) pulmonary emphysema in a small percentage of affected animals
   e) permanent stiffness and shifting lameness

6. Once an animal is infected the virus seems to
   a) primarily penetrate neutrophils
   b) become confined to endothelial cells
   c) be found at very high levels in lymphocytes
   d) actively destroy neutrophils
   e) prevent leukocyte marginalization

7. High levels of neutralizing antibodies have not been found in
   a) Wildebeest
   b) Hartebeest
   c) African buffaló
   d) Waterbuck
   e) Sheep

8. Treatment of BEF should be primarily based on
   a) Nutritional supplementation
   b) Immediate oral rehydration
   c) Sulphonamide based antibiotics
   d) Anti-inflammatory and supportive treatment
   e) There is no effective treatment

9. Control of BEF relies upon
   a) Fly control
   b) Tick control
   c) Vaccination
d) Culicoides control

e) Prevention of contact with wildebeest

10. Early individual cases of BEF may be confused with
   a) Laminitis Arthritis/arthrosis
   b) Black quarter
   c) Rift valley Fever
   d) Enzootic haemorrhagic disease
   e) All of the above