INTRODUCTION

Bluetongue (BT) is an arthropod-borne viral disease of domestic and wild ruminants, particularly sheep. It is characterized by inflammation, haemorrhage, ulceration and cyanosis of the mucous membranes of the oronasal cavity, coronitis, laminitis, oedema of the head and neck and torticollis. The name of the disease derives from cyanosis of the tongue, which may occasionally be severe.

Bluetongue was first described in South Africa where infection with BT virus has probably been endemic in wild ruminants from antiquity. The disease has been recognized since Merino sheep were introduced into the Cape Colony in the late eighteenth century. From the outset, bluetongue was known to be most prevalent during the summer months, especially in wet seasons.

Bluetongue was initially thought to be confined to the African continent. In 1943 the first confirmed outbreak outside Africa was reported in Cyprus, but the disease may have occurred there as early as 1924. Outbreaks have subsequently been reported in Israel, the USA, Portugal, Spain, Pakistan and India. BT virus infection of ruminants has now been identified throughout temperate and tropical regions of the world, involving all continents except Antarctica. The global range of BT virus has been considered traditionally to be between latitudes of 350 South and 40 – 500 North. Only transient incursions of single BT virus serotypes occurred in Europe during much of the 20th century but, since 1999, multiple BT virus serotypes became established throughout extensive portions of Mediterranean Europe. Furthermore, in 2006 a highly virulent strain of BT virus serotype 8 appeared in northern Europe and quickly spread to the British Isles, Scandinavia and much of continental Europe. Coincident with this spread of BT virus throughout Europe, novel BT virus serotypes were detected for the first time in previously endemic regions such as the southeastern United States, the Middle East, and Australia. Climate change may have contributed to this dramatic recent expansion in the global distribution of BT virus.
The first experimental proof that BT virus is transmitted by *Culicoides imicola* (= *C. pallidipennis*) was obtained by Du Toit in 1943. Subsequently *Culicoides variipennis* (now *C. Sonorensis*) and other *Culicoides* spp. were proved to be vectors of BT virus in the USA and Australia. Indeed, it is now clear that different species of *Culicoides* midges serve as vectors of distinct constellations of BTV serotypes in relatively discrete and stable global ecosystems.

Bluetongue virus is the type-species of the genus *Orbivirus* in the family *Reoviridae*. It was the first virus of domestic animals to be shown to possess a double-stranded RNA genome, initially thought to be unique to reoviruses. The genome consists of ten segments which can be separated electrophoretically after disruption of the virion. These segments vary in size and function as genes (i.e. they are translated individually into functional viral proteins). Genome segments are labelled 1 to 10 in descending order of size, whereas viral polypeptides are divided into structural proteins (VP1-VP7) and non-structural proteins (NS1-NS3).

The existence of multiple BT virus serotypes was first discovered in a series of tests in sheep when Neitz found that each of ten viral isolates from field cases produced solid immunity against itself but only partial or no protection against heterologous strains. Additional BTV serotypes recently have been identified through intensive molecular investigations, notably Toggenburg orbivirus in Swiss goats and a putative BT virus serotype 26 amongst livestock in Kuwait.
Livestock Health, Management and Production › High Impact Diseases › Vector-borne Diseases › Bluetongue ›

Bluetongue

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EPIEEMIOLOGY

The endemic areas for BT are largely defined by suitable climatological factors which are mainly confined to the tropics and subtropics. The distribution of the disease in these areas is dependent on the presence of reservoir and amplifying hosts such as wildlife and cattle, and on suitable species of Culicoides being present in large enough numbers to effect transmission to sheep. Apart from certain high altitude regions, such as parts of the north-eastern Cape Province and Lesotho, the entire southern African region should be regarded as endemic.

Even in the very early descriptions of BT it was clearly recognized that the disease is geographically limited, seasonal in its occurrence, most common in areas with high rainfall and after good rains, and that sheep can be protected by being housed at night and dipped in an insecticide. These observations, as well as the disappearance of the disease after the first frosts, were convincing evidence for the role of an insect vector in the occurrence of the disease. More recently, BT virus has been isolated in various parts of the world from a variety of Culicoides spp., the most important being C. imicola in Africa and the Middle East, C. Sonorensis (varipennis) and C. insignis in North America, and the Caribbean, C. brevitarsis and C. wadai in Australia. Novel vector species have been incriminated in the transmission of BT virus in Europe, notably members of the Culicoides obsoletus group as well as C. dewulfi, C. chiopterus, C. scotius and others.

Bluetongue is not contagious and very little virus is found in the secretions and excretions of infected animals. Oral transmission of BTV via infective colostrum has clearly been shown in dairy calves but animal tissues and products, even from infected animals, can be disregarded as a source of infection except to carnivores. One exception is semen from viraemic bulls, which can infect cows after either natural service or artificial insemination.
The role that embryo transfer might play in the transmission of BT seems to be negligible with the possible exception of European BT virus serotype 8.

Although traditionally regarded as a sheep disease because of its economic importance in this species and the occurrence of major epidemics that cause heavy economic losses in sheep-rearing countries, BT affects a wide range of species. The outcome of infection, however, varies between different species and breeds as well as among individuals of the same species. Indigenous breeds of sheep are less severely affected by BT than are exotic breeds.

Indigenous sheep, such as these Damaras are less severely affected than exotic breeds

In sheep the viraemia reaches a relatively high level (about 105 sheep ID50/ml) and is usually associated with severe clinical disease in fully susceptible animals. In cattle and goats clinical disease is rare, and, when present, is much milder than in sheep. Evidence of inapparent infections has subsequently been found in many other species and it is now accepted that all ruminants are probably susceptible to infection. African antelopes do not develop clinical disease, whereas white-tailed deer (*Odocoileus virginianus*), pronghorn (*Antilocapra americana*) and desert bighorn sheep (*Ovis canadensis*) of the North American continent may develop severe clinical disease.

Canine fatalities and abortion have recently been found to be associated with a vaccine contaminated with BT virus. Subsequently evidence of natural BT infection in a number of African carnivores has been obtained. It is surmised that such infection follows the ingestion of carcasses of infected ruminants.

Bluetongue virus may be transmitted throughout the year in areas where the winter is mild. However, overwintering of the virus in areas with long, cold winters is more difficult to explain, as transovarial transmission of BT virus in *Culicoides* spp. apparently does not occur. It is possible that cattle are able to act as reservoirs, although recent investigations only partially support this contention as viraemia in cattle
is not considered to persist longer than 60 days. Furthermore, replication of BT virus in tissues of experimentally infected calves was transient and truly persistent infection could not be demonstrated. It has also been postulated that the primary replicative cycle involves one or more species of African antelope and Culicoides midges, and that the role of antelopes has been largely supplanted by cattle in areas where agricultural development has displaced wild animals. Outbreaks of the disease in sheep usually occur simultaneously in widely separated localities in late summer or autumn, suggesting that populations of BT virus-infected midges build up in the primary cycle involving cattle or wild animals during spring and early summer, and that sheep become infected in a secondary cycle as a result of ‘spill-over’.
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## PATHOGENESIS

BT virus first multiplies in the regional lymph nodes after virus inoculation by the bite of a midge before spreading to the rest of the body. Viral replication occurs primarily in endothelial cells and pericytes of capillaries and small blood vessels. Cytopathic changes in these cells include degenerative and necrotic lesions such as cytoplasmic vesicles, nuclear and cytoplasmic hypertrophy, pyknosis and karyorrhexis. These changes, often accompanied by hyperplasia of the endothelium, lead to vascular occlusion, stasis and exudation, which eventually give rise to hypoxia, oedema and haemorrhage as well as to secondary lesions in the overlying epithelium. However, sheep with severe BT do not necessarily undergo disseminated intravascular coagulation, and it is proposed that pro-inflammatory and vasoactive cytokine mediators produced in infected sheep likely contribute to the severe vascular leakage and hypovolemic shock that are characteristic of fatal BT.

The severity of the secondary lesions is influenced by mechanical stress and abrasion, and severe lesions develop mainly in tissues exposed to the environment, such as the oral mucosa and skin of the coronary border of the hooves. Exposure of affected animals to sunlight exacerbates the severity of the disease. The mortality rate can escalate dramatically when infected sheep are exposed to cold, wet conditions as often happens in late autumn.

Following initial replication of the virus in mononuclear phagocytic cells (macrophages, dendritic cells) in lymphoid tissues and in endothelial cells, BT virus appears in the circulation three to six days after infection. The viraemia reaches a peak about seven to eight days after infection and accompanies or precedes a febrile reaction which normally lasts about four to eight days. In sheep the viraemia rarely persists for longer than 14 days and is usually present for six to eight days.
The viraemia in cattle is typically prolonged to about 50 days. It was found that \textit{in vitro} infection of bovine erythrocytes and non-replicating lymphocytes did not progress beyond adsorption after which virus particles persisted in invaginations of the cell membrane. This could explain both the prolonged viraemia and the absence of clinical disease.

Bluetongue virus in the blood is primarily associated with erythrocytes and, to a lesser extent, with the buffy-coat fraction, while only a small fraction is found free in the plasma. Panleukopaenia preceding the viraemia and febrile reaction is consistently found in BT, possibly as a result of viral replication in leukocytes or in the stem cells of the haemopoietic system.

Abortion or malformation, particularly of the central nervous system (CNS), of lambs may follow vaccination of ewes with attenuated live vaccines during the first half of pregnancy. Similarly, infection of bovine foetuses during the first trimester of pregnancy with laboratory-modified strains of BT virus results in severe CNS abnormalities. These teratogenic features were notable during the BT virus serotype 8 epidemic in Europe.
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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical signs and pathology

The extreme variability in the clinical manifestation of BT, not only between different ruminant species but also between different breeds of sheep, is a feature of the disease. Many infections in sheep are clinically inapparent and, even in fully susceptible animals it is difficult to reproduce severe clinical signs under laboratory conditions where there is limited exposure to sunlight or ultraviolet light.

The course of the disease in sheep can vary from peracute to chronic, with a mortality rate of between two and 30 per cent. Peracute cases usually die within seven to nine days of infection, mainly as a result of lung oedema and eventual asphyxia. They may show very few signs of illness prior to death. In chronic cases death can result from secondary bacterial pneumonia and exhaustion, or recovery can be very protracted. Mild cases usually recover rapidly and completely.

The incubation period, following natural infection, is about seven days (judging by the length of the period during which clinical cases continue to appear after frost). Following experimental infection the incubation period is usually four to six days but may vary between two and 15 days. The first clinical sign is a rise in temperature over a period of 48 hours, reaching a peak of 41 to 42 °C. The febrile reaction usually lasts about six to eight days and its termination is determined by the course of the disease and the extent of secondary infection.

Other clinical signs may appear within one or two days of the onset of fever. Hyperaemia of the buccal and nasal mucosae usually occurs first and may also develop on more exposed parts of the skin around the muzzle and eyes and on the ears.
Acute BT. Swelling of the lips, hyperaemia of the skin and erosion of the nostrils

Increased salivation and lachrymation as well as a serous nasal discharge may soon follow. Licking movements of the tongue and smacking movements of the lips may result in froth formation at the corners of the lips.

Oedema of the tongue, lips, face, eyelids and ears develop about 48 hours after the onset of fever. Submandibular oedema may be marked and occasionally extends down the neck to the axillae.

Acute BT. Subcutaneous oedema of the face and lips
Acute BT. Severe subcutaneous oedema of the face and submandibular region

Acute BT. Severe swelling of tongue, and submandibular oedema

Petechiae may be observed on the muzzle, papillae of the lips and mucous membranes of the mouth and conjunctivae. At this stage mild cases may recover uneventfully.

In severe cases the lesions progress and result in erosions on the muzzle and nostrils and in the mouth, particularly at sites subject to friction, such as parts of the cheeks and tongue adjacent to the molar teeth and the lower lip opposite the corner incisors.

Acute BT. Hyperaemia and erosive glossitis adjacent to the molar teeth

Subacute/chronic BT. Ulceration of mucosal lesions may occur following secondary bacterial infection of erosions.

Necrotizing mouth lesions result in foetid breath, which is sometimes the first clinical sign observed. They also induce pain which may cause the animal to submerge its mouth and lips in drinking water for
prolonged periods. Anorexia is common and may be exacerbated in some cases by severe swelling of the tongue, which may become cyanotic (‘blue tongue’) and even protrude from the mouth.

Acute BT. The tongue may be swollen and cyanotic (hence the name bluetongue)

Progressive weakness and emaciation follows, accompanied by rumen stasis and occasionally haemorrhagic diarrhoea before death.

The watery nasal discharge frequently becomes mucopurulent and eventually forms crusts which interfere with breathing and cause panting. In peracute cases, severe oedema of the lungs leads to dyspnoea, frothing from the nostrils and death by asphyxiation.

Foot lesions usually develop towards the end of the febrile reaction. Hyperaemia of the coronary bands and petechiae under the periople, which later become streaky in appearance as a result of haemorrhage into the fine medullary canals of the growing horn, give rise to a red zone or band in the horn of the hoof.

Acute BT. Coronitis manifested by hyperaemia and petechiation
As this lesion persists for some weeks after others have disappeared, it may constitute valuable evidence of BT during the recovery period. The lesion is most pronounced on the bulbs of the feet, and particularly of the lateral digits. The hind feet are most frequently affected. The feet are warm and painful, and affected animals are reluctant to move and often stand with arched backs or are recumbent. In affected sheep the gait is often stiff with varying degrees of lameness. Sometimes severely affected animals try to walk on their knees. In animals that recover, the bands of discolouration in the hooves grow out and a ‘break’ in the hoof may develop (‘slipper formation’), with the old horn eventually sloughing off after three to four months. Inability to move and recumbency may also be exacerbated by emaciation and muscle lesions.

Severe muscle degeneration and cachexia are sometimes seen in cases where buccal lesions are mild and the appetite undiminished. Degeneration and necrosis of skeletal muscles in the neck may lead to torticollis.

Hyperaemia of the skin is usually most severe in those areas that are exposed to sunlight (such as, in Merino sheep, the face, ears and legs which are not covered by wool), but may involve the whole body. In severely affected sheep, exanthema develops on the legs and other parts of the body subject to trauma. In such instances the slightest abrasion or handling may immediately result in extensive cutaneous haemorrhage, particularly in the groin and axilla. In most affected animals the wool fibres ‘break’ within the wool follicle and the fleece may be shed three to six weeks later. Normal new wool soon appears in recovered animals.
A “break” in the wool resulting in shedding of the fleece occurs in some recovering cases

A sheep shedding its fleece after recovery from BT

Clinical signs in cattle are rare, except following infection with highly virulent strains such as the European strain of BT virus serotype 8, and are usually limited to a transient febrile response, increased respiratory rate, increased lachrymation and salivation, stiffness and inflammatory and ulcerative changes in the skin.

Erosions in the buccal cavity may lead to drooling of saliva

Hyperaemia, erosions and crust formation encrusting of the muzzle occurs in some cases

Oral lesions initially consist of hyperaemia, oedema, cyanosis and haemorrhage of the mucous membrane. Destruction of epithelial cells gives rise to excoriations and ulcerations on the inside of the lips, dental pad, cheeks and tongue. These lesions are transient and usually disappear within days. Secondary bacterial infection is often responsible for the diphtheric necrosis of the ulcers. Microscopically, there is mononuclear cell infiltration and degeneration and necrosis of epithelial cells in which large acidophilic intracytoplasmic masses accumulate.
Hyperaemia, petechiation, erosions and ulcerations of the mucosa of the forestomachs, particularly of the papillae, rumenal pillars, reticular folds and oesophageal groove are common. Oedema and haemorrhages are often present in the submucosa, especially in the vicinity of the pylorus and the anterior third of the omasum.

Acute BT. Hyperaemia, haemorrhages and erosions of omasal mucosa. The oesophageal groove may show similar lesions

Acute BT. Necrosis of ruminal pillars

Lesions in the small intestines vary from mild localized areas of hyperaemia to severe catarrhal or haemorrhagic lesions extending into the large intestine.

Hyperaemia, oedema and petechiae occur in the mucosae of the nasal cavity, pharynx, and trachea, as well as in the lungs. Severe hyperaemia and oedema of the lungs accompanied by copious amounts of froth in the trachea and hydrothorax occur especially in acute fatal cases.

The widespread, but often localized occurrence of hyperaemia, oedema and haemorrhages is evidence of damage to the vascular system, although the precise roles of direct virus-mediated injury and that caused by the activity of vasoactive mediators remains to be determined.
Petechiae, ecchymoses and gelatinous oedema of the intermuscular connective tissue

Acute BT. Subcutaneous and intermuscular oedema

Acute BT. Hydropericardium and epi-and endocardial petechiae and ecchymoses are common

Petechiae, ecchymoses or even larger haemorrhages in the tunica media of the pulmonary artery near its base are characteristic of BT. These lesions are sometimes described as being pathognomonic for BT but they have also been seen on rare occasions in other infections such as Rift Valley fever, heartwater and pulpy kidney in sheep.
Pharyngeal, cervical and thoracic lymph nodes are commonly swollen and oedematous and the spleen may be slightly enlarged with subcapsular haemorrhages.

**Laboratory confirmation**

Blood (10 to 20 ml), collected as early as possible during the febrile reaction in anticoagulants, is the most suitable specimen for virus isolation. In fatal cases, specimens of spleen, lymph node or red bone marrow should be collected as soon as possible after death, kept at 4 °C and sent to the laboratory for virus isolation. Alternatively they may be frozen at -70 °C for storage prior to testing.

Initial efforts to develop molecular diagnostics to identify BT virus directly in blood samples or cultured cells, and also to identify BT virus serotypes lead to development of genomic probes. In this technique a DNA copy of one of the RNA segments is used as a probe to detect the viral genome in a northern blot hybridization assay. Both group-specific and serotype-specific probes have been developed. The sensitivity of probe assays is lower than serological assays unless radio-active labelling is used, which limits the use of probes to well-equipped laboratories. However, these assays were largely abandoned with the advent of the polymerase chain reaction (PCR) and its application to transcription-based in vitro gene amplification has led to the development of highly sensitive assays using non-radioactive probes. The use of quantitative reverse-transcriptase PCR (RT-qPCR) is now routine and the accepted global standard for detection of BT virus. A wide variety of such assays now have been developed and evaluated, including group specific RT-qPCR methods to detect all BTV serotypes as well as assays that identify individual virus serotypes.
Differential diagnosis

In southern Africa, the clinical signs of acute BT in sheep should be differentiated from early signs of hepatogenous photosensitivity caused by a variety of plant and mycotoxin poisonings. In areas where the disease does not normally occur, it should be differentiated from vesicular diseases such as foot-and-mouth disease. The clinical signs could also be confused with those seen in polyarthritis, foot rot and white muscle disease. In sheep that die after the typical lesions of BT (oedema of the lips and tongue, mouth and tongue erosions) have regressed, it may be difficult to differentiate BT from diseases such as heartwater and pulpy kidney disease.

In cattle clinical BT can easily be confused with clinical signs and lesions of epizootic haemorrhagic disease, malignant catarrhal fever, mucosal disease, foot-and-mouth disease and bovine herpesvirus type 1 infection.

The teratological effects of the central nervous system of the foetus in sheep and cattle caused by modified BT virus strains can be difficult to differentiate from other infectious causes.
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CONTROL / PREVENTION

Strategies for the control of BT differ according to whether outbreaks of the disease occur in endemic regions or in areas where the disease is not usually present. In the latter case the usual goal is eradication, whereas in endemic areas attempts can only be made to limit the occurrence of the disease and its economic impact.

In endemic areas, such as most of the African continent, a wide variety of domestic and wild ruminants (including cattle, goats and various species of antelope) can act as sources of BT virus. Immunization of cattle should therefore theoretically help to limit the incidence of BT, but the presence and ubiquitous distribution of other reservoirs, both known and unknown, makes eradication of the disease impossible.

To date, BT virus has been isolated from seven species of Culicoides, of which at least four play an important role in the transmission of BT in Africa and North America. Worldwide, a considerably greater number of species have been implicated in transmission of BTV and it is likely that more species of Culicoides, and even other insects, may be identified as biological vectors in future. Air-borne transport of infected Culicoides midges over long distances cannot be prevented, but unless the insects can establish themselves in the new environment epidemics which arise in this way are self-limiting unless the midges resident in the new region can themselves then transmit the virus (as apparently occurred recently in Europe).

Methods used to control Culicoides include the use of insecticides, larvicides and sterilization of males by irradiation, as well as the subcutaneous administration of ivermectin to cattle in an attempt to break the primary cycle before the infection spills over into sheep. Protecting sheep from exposure to Culicoides is a more practical approach and can be achieved by avoiding low-lying wet pastures, stabling animals from
late afternoon till morning, shearing in early summer to allow some wool growth before the onset of the BT season in late summer, and even the use of insect repellants.

Prophylactic immunization of sheep remains the most effective and practical control measure against BT in endemic regions. Vaccines comprised of attenuated virus strains are highly effective, especially in epidemic situations where only one serotype of BT virus is involved. In endemic areas such as South Africa, the situation is complicated by the existence of multiple serotypes. This necessitates the use of polyvalent vaccines with attendant problems resulting from interference between virus strains, differences in immunogenicity and growth rates between various strains, as well as differences in the response of individual animals to the components of such vaccines. To overcome these problems, three pentavalent vaccines have been developed in South Africa. They are administered to sheep at three-week intervals and repeated annually. After two or three annual immunizations, most sheep are immune to all the serotypes in the vaccine.

In addition to the inconvenience of repetitive inoculations of a multivalent vaccine there are some risks involved in the use of live attenuated vaccines and some important precautions must be observed when using them. Pregnant ewes should not be immunized during the first half of pregnancy, as brain defects may result in the foetus.

There are also indications of temporary infertility in both ewes and rams vaccinated for the first time, necessitating immunization well before or after the mating season. However, this should not pose a problem if sheep are vaccinated before they reach breeding age. More theoretical objections sometimes raised against the use of live attenuated vaccines include the possibility of reassortment and recombination between attenuated and virulent strains, resulting in reversion to virulence or even the production of new serotypes, and the possibility that insects may spread the vaccine virus. Circulation of
live attenuated vaccine virus in animals and insects has been unambiguously proven in Europe recently, as has reassortment of vaccine viruses with field virus.

Much progress has been made towards the development of safe, efficient, multivalent recombinant vaccines which should contribute significantly to the control of bluetongue, hopefully in the near future. However, until that time, it is likely that live-attenuated and inactivated BT virus vaccines will be used in areas where the virus is endemic and causes disease.
MARKETING AND TRADE / SOCIO-ECONOMICS

From an economic point of view, in addition to loss of wool, the pathological changes in the skeletal musculature are probably the most important lesion in BT, as they are usually associated with gross loss of condition, weakness, and a slow, protracted recovery period.

It is also clear that different strains of BTV have different virulence for livestock, so particularly virulent viruses such as the strain of BTV serotype 8 that recently emerged in Europe have a profound impact on livestock production.

Animal movement and trade restrictions are widely used by BTV-free countries/regions to prevent the introduction of BTV.
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REFERENCES


