**ENTEROTOXEMIA ASSOCIATED WITH *CLOSTRIDIUM PERFRINGENS* TYPE D (PULPY KIDNEY, OVEREATING DISEASE)**

**ETIOLOGY**

* Enterotoxemia results from the proliferation of *C. perfringens* type D in the small intestine. This organism produces a number of toxins, of which the epsilon toxin is the most important and results in vascular damage and the damage to the nervous system typical of this disease.
* The presence of *C. perfringens* type D in the intestine does not in itself result in disease unless other factors intercede that promote proliferation and the production of toxin.
* The natural habitat of the organism is in the intestine and in soil contaminated by feces, although it does not persist in soil for long periods of time.

**EPIDEMIOLOGY**

**Occurrence**

* Enterotoxemia associated with *C. perfringens* type D is a disease of ruminant animals, primarily of lambs, and is worldwide in its distribution. The common practice of vaccination against this disease has reduced its prevalence, but it is still a common disease .
* The highest incidence of the disease is in suckling lambs between 3 and 10 weeks of age, although lambs as young as 1 to 5 days old can be affected. The risk for disease in this age group is highest when ewes are grazed on lush pastures that result in profuse lactation.
* The disease can occur following rain in set stocked flocks, and in flocks newly introduced to lush pastures it is often manifested 5 to 14 days after introduction.
* Larger and more rapidly growing single lambs are more susceptible than twins.
* Weaned lambs up to 10 months of age are the second most susceptible age group, and again the occurrence of disease is associated with highly nutritious diets.
* Feeder lambs are most commonly affected soon after they are introduced into feedlots.

**PATHOGENESIS**

* In the normal course of events, ingested *C. perfringens* type D are destroyed in large numbers in the rumen and abomasum, although some survive to reach the duodenum, in which multiplication occurs and toxin is produced.
* Toxemia does not occur because the movement of ingesta keeps the bacterial population and toxin content down to a low level. In certain circumstances, this does not hold and multiplication of the organisms and the production of toxin proceeds to the point in which toxemia occurs.
* One of the circumstances has been shown to be the passage of large quantities of starch granules into the duodenum when sheep overeat on grain diets or are changed suddenly from a ration consisting largely of roughage to one consisting mainly of grain. Other factors such as heavy milk feeding may have the same effect.
* A slowing of alimentary tract movement has also been thought to permit excess toxin accumulation and it may be that any factor that causes intestinal stasis will predispose to the disease.
* The epsilon toxin of *C. perfringens* type D is a pore-forming protein that increases the permeability of the intestinal mucosa to this and other toxins, facilitating its own absorption.
* A receptor for epsilon toxin has been identified on vascular endothelial cells, and the clinical signs and pathologic findings can be explained by the widespread vascular damage and increase in vascular permeability.
* Acute cases are characterized by the development in the brain of degeneration of vascular endothelium; perivascular and intercellular edema; and microscopic foci of necrosis in the basal ganglia, thalamus, internal capsule, substantia nigra, subcortical white matter, and cerebellum.
* The damage to the vascular endothelium leads to the accumulation of protein-rich fluid effusions observable in heart, brain, and lung.
* The postmortem autolysis of kidney tissue that occurs so rapidly and is the characteristic of “pulpy kidney” has the same basis.
* There is a pronounced hyperglycemia caused by the mobilization of hepatic glycogen; severe hemoconcentration; and elevation of blood concentrations of pyruvate, lactate, and α-ketoglutarate.
* In contrast to sheep, goats with enterotoxemia produced by *C. perfringens* type D also have a hemorrhagic enterocolitis that is present in both the natural and the experimental disease. The genesis of this lesion is uncertain, but it is responsible for the major clinical signs that present in goats with this disease.
* A degree of natural immunity may be attained by nonlethal exposure to the toxin. Because a proportion of lambs, calves, and kids appear to be exposed to subclinical but antigenic levels of *C. perfringens* toxin, they become immune without having shown signs of illness or without having been vaccinated.

**CLINICAL FINDINGS**

**Lambs**

* The course of the illness is very short, often less than 2 hours and never more than 12 hours.
* Many lambs are found dead without previously manifesting signs.
* In closely observed flocks the first signs may be dullness, depression, yawning, facial movements and loss of interest in feed.
* Acute cases may show little more than severe clonic convulsions with frothing at the mouth and rapid death.
* Cases that survive for a few hours show a green, pasty diarrhea, staggering, recumbency, opisthotonus, and severe clonic convulsions.
* The temperature is usually normal but may be elevated if convulsions are severe.
* Death occurs during a convulsion or after a short period of coma.

**Adult Sheep**

* These usually survive for longer periods of up to 24 hours.
* They lag behind the flock and show staggering and knuckling; champing of the jaws; salivation; and rapid, shallow, irregular respiration.
* There may be bloat in the terminal stages. Irritation signs, including convulsions, muscle tremor, grinding of the teeth, and salivation, may occur but are less common than in lambs.,

**NECROPSY FINDINGS**

* The body condition of the animal is usually good, but there is often fecal staining of the perineum and rapid decomposition of the carcass.
* In peracute cases there may be no gross lesions. More frequently, there is an excess of clear, straw-colored pericardial and thoracic fluid that clots on exposure to air.
* Many petechiae are present in the epicardium and endocardium, and there is pulmonary edema.
* Patchy congestion of the abomasal and intestinal mucosae is usual, and the small intestine often contains a moderate amount of thin, creamy ingesta. The content of the large intestine may be watery and dark green.
* The characteristic finding of soft, pulpy kidneys is only useful in animals necropsied within a few hours after death because it is nonspecific and merely correlates to a more rapid rate of autolysis.
* Microscopy of experimentally induced ovine type D enterotoxemia cases confirms that the renal changes represent autolysis and not a true nephrosis.
* The liver is dark and congested.
* The rumen and abomasum of feedlot lambs may be overloaded with concentrates.
* In goats there is acute fibrinonecrotic and hemorrhagic enterocolitis, although microscopic examination may be needed to detect this change.
* In sheep that have not died acutely there may be symmetric areas of hemorrhage, edema, and liquefaction in the brain, especially in the area of the basal nuclei. Again, microscopic evaluation of the tissue is critical.
* Gram-stained smears of ingesta from several levels in the small intestine should be examined. In affected animals the short, fat, gram-positive rods dominate the slide to the almost complete exclusion of other bacteria.
* Bowel filtrates can be tested for toxicity by injection into mice. If the filtrate is toxic, the type of toxin can be determined by protection of the mice with specific antisera. This does not determine the type of clostridia, but detection of β-toxin indicates the presence of types B or C, and ε-toxin indicates the presence of B or D.
* The time taken for diagnosis by mouse neutralization tests, as well as humanitarian considerations, has promoted the development of alternative tests.
* Commercial enzyme-linked immunosorbent assay (ELISA) kits and multiplex PCR assays have become available for toxin detection and require minimal amounts of intestinal content.
* Nevertheless, it is important to base a diagnosis on epidemiologic, clinical, and pathologic information, not just the detection of toxin at postmortem.
* ε-Toxin is stable if frozen, but at average temperatures it is possible to identify the toxin from the intestine of a sheep dead for up to 12 hours. The addition of one drop of chloroform to each 10 mL of ingesta will stabilize the toxin for up to 1 month.
* Alternatively, intestinal contents can be absorbed on filter paper and shipped at environmental temperatures, with little loss of activity for as long as 74 days as detected by immunoassay.
* Hyperglycemia and glucosuria may also be detected in necropsy material.

**Samples for Confirmation of Diagnosis**

* Bacteriology: 20 to 30 mL of intestinal content, frozen in a leak-proof glass or plastic container (ELISA, latex agglutination, bioassay, anaerobic culture, PCR); air-dried smears of ingesta from several levels of gut (cyto-Gram stain)
* Clinical pathology: urine (assay– glucose) (best performed at time of necropsy)
* Histology: fixed colon, ileum, jejunum, entire brain

**DIFFERENTIAL DIAGNOSIS**

**Lambs**

• Acute pasteurellosis

• Septicemia associated with *Histophilus*  *somni* (formerly *Haemophilus agni*)

• *Clostridium sordellii*

• Polioencephalomalacia

• Rumen overload

**Sheep**

• Hypocalcemia

• Hypomagnesemia

• Focal symmetric encephalomalacia (chronic enterotoxemia)

• Rabies

• Pregnancy toxemia

• Louping-ill

**TREATMENT**

* In general, the clinical course of the disease is too acute for effective treatment.
* Hyperimmune serum, an efficient short-term prophylactic, is unlikely to be of much value in sick animals because of the acute nature of the disease.
* In goats the course is longer, and antitoxin in combination with orally administered sulfadimidine may be effective in treatment.

**CONTROL**

* There are three major control measures available: reduction of the food intake, administration of antitoxin, and vaccination.
* These may be used individually or in combination.

**Reduction in Food Intake**

* Reduction in food intake is the cheapest but least effective in control and is used as a short-term control while waiting for immunity to develop after vaccination.
* Reduction in food intake will cause a setback in the growth of the lambs and for this reason farmers tend to rely more on vaccination as a control measure. However, exercise of lambs, by mustering or herding around the paddock, may help slow the course of an outbreak.

**Antitoxin**

* Antitoxin can be administered to all sheep as soon as an outbreak commences.
* The administration of ε-antitoxin 200 IU/kg BW will provide for protective circulating antitoxin levels for 21 to 29 days.
* Immediate losses are prevented, and in most instances the disease does not recur.
* Toxoid is cheaper, but to administer it alone at such times may result in further serious losses before active immunity develops.

**Vaccination**

* Immunity in sheep is readily produced by suitable vaccination.
* A blood level of 0.15 Wellcome unit of ε-antitoxin per milliliter of serum is sufficient to protect sheep.
* Vaccines available are toxoids, and adjuvants generally improve the antigenicity. Activated alum-precipitated toxoid is the common vaccine in use.
* A recombinant *C. perfringens* type D toxoid has been shown to induce antibody titers comparable to a traditional toxoid and may offer a more consistent or cost-effective method of vaccine production.
* Vaccination of maiden **ewes** twice at an interval of at least 1 month and with the last vaccination approximately 4 weeks before lambing will result in good passive immunity in young lambs, with 97% of lambs having protective antibody levels at 8 weeks of age and a significant proportion at 12 to 16 weeks of age.
* This is sufficient to protect lambs during their highest risk period.
* Older ewes that have been vaccinated the previous year receive a single booster vaccination 4 weeks before lambing. Sheep vaccinated for 3 consecutive years can be considered to be permanently immune and to require no further vaccination.
* When faced with an outbreak in lambs ,the recommended procedure is to administer antiserum and toxoid immediately and repeat the toxoid in a month’s time.
* The simultaneous administration of hyperimmune serum with this vaccine does not interfere with the stimulation of antibody production, nor does the presence of passively derived colostral immunity.
* Lambs can be vaccinated with toxoid when 4 to 10 weeks of age and again a month later