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Diseases of the Hematologic, Immunologic, and Lymphatic Systems (Multisystem Diseases)

BENJAMIN W. NEWCOMER, CHRIS CEBRA, MANUEL F. CHAMORRO, EMILY REPPERT, MARGARET CEBRA, AND MISTY A. EDMONDSON

In this chapter, multisystemic diseases are discussed in small ruminants (sheep, goats, and cervids). These include diseases of the hematologic, immunologic, and lymphatic systems. In general, species will be discussed together, but when pertinent data are available, each species will be considered separately. The terms "cervid" and "deer" have been used interchangeably in parts of this chapter by the authors.

Basic Hematology

An adequate volume of blood for hematologic and biochemical analysis is best obtained from the jugular vein. A docile animal may be restrained in a standing position or tipped up (sheep only) with the head turned away from the jugular vein to be used. Wilder ones, such as some cervids, may require restraint devices or chemical sedation. Ideally, the animal should be restrained by someone other than the blood collector, although the same person may be able to both restrain a sheep and collect blood if the animal is tipped up or a halter is used (see Chapter 1). The animal should be at rest, with minimal excitement. The collector parts or clips the wool or hair to visualize the jugular vein and then uses the hand not holding the needle to apply digital pressure proximally just above the thoracic inlet to block blood movement through the vein. The vessel may take a second or more to distend after pressure is applied. The collector may then use the needle-bearing hand to "strum" the vessel and cause the blood to oscillate. If in doubt about whether the distended vessel is the jugular vein, the collector can release the hand placing pressure on the vessel and observe whether the distended vessel disappears; if it does, the distended vessel was probably the jugular vein. The collector should avoid vessels that pulsate because these are likely to be the carotid arteries. The area should be cleaned with alcohol or other disinfectant, water, or a clean, dry gauze sponge. An 18- or 20-gauge, 1- to 1.5-inch needle is usually adequate to collect blood from an adult, whereas a 22-gauge needle may be used in a neonate. The skin of adults or males may be thicker and more difficult to penetrate with the needle. A syringe or evacuated tube attached to a Vacutainer (Becton Dickinson Inc., Rutherford, NJ) can be used to collect blood. The needle should be plunged through the skin into the vein at an approximate 30-degree angle. The blood should not come out of the vessel in pulsatile waves; this is suggestive of an arterial stick. After aseptically obtaining an adequate volume of blood, the collector removes the needle and releases the pressure on the vessel near the thoracic inlet. Pressure should be applied to the site of puncture for a minute or more to prevent extravascular leakage of blood and hematoma formation. The blood should be carefully transferred to a vial containing the appropriate anticoagulant to prevent red blood cell (RBC) rupture. Goat erythrocytes are small and particularly prone to hemolysis. To minimize this problem, goat blood should be collected with a needle and syringe, not a Vacutainer. White blood cell (WBC) differential distribution, individual blood cell staining characteristics, and morphology may be assessed by microscopic examination of a stained blood film. The differential distribution provides more information than total WBC count because inflammatory conditions in artiodactyls often result in a shift in neutrophil populations toward more degenerate, toxic, or immature forms without changing the overall WBC count.[1] The preferred anticoagulant for a complete blood count (CBC) is ethylenediaminetetraacetate (EDTA), and tubes should be filled to ensure the proper blood-to-anticoagulant ratio. Blood samples should be processed as soon as possible after collection. If a delay is anticipated, the blood sample should be refrigerated (4° C) and an air-dried blood smear should be made because prolonged contact of blood with EDTA causes changes in WBC morphology and the separation of some RBC parasites. Blood can be refrigerated for 24 hours and still yield an accurate CBC.

A reference range for hematologic data for sheep and goats is provided in Table 16.1 (see Appendix 2, Tables 1 and 2). Goats tend to have a low mean corpuscular volume (MCV) because of their small erythrocytes. Sheep and goats younger than 6 months old tend to have lower hematocrit, RBC count, hemoglobin, and

TABLE 16.1 Normal Hematologic Parameters for Sheep and Goats.

Parameter (Units)	Adult Sheep	Adult Goat
Hematocrit (%)	27–45	22–36
Hemoglobin (g/dL)	9–15.8	8–12
Red blood cell count ($\times 10^6/\mu L$)	9–17.5	8–17
Mean corpuscular volume (fL)	28–40	15–26
Mean corpuscular hemoglobin concentration (g/dL)	31–34	29–35
Platelet count ($\times 10^5/\mu L$)	2.4–7.0	2.8–6.4
Total white blood cell count (/μL)	4000–12,000	4000–13,000
Segmented neutrophils (/μL)	1500–9000	1400–8000
Band neutrophils (/μL)	0	0
Lymphocytes (/μL)	2000–9000	2000–9000
Monocytes (/μL)	0–600	0–500
Eosinophils (/μL)	0–1000	0–900
Basophils (/μL)	0–300	0–100
Total plasma protein (g/dL)	6.2–7.5	6.0–7.5
Fibrinogen (mg/dL)	100–600	100–500

plasma protein concentrations, as well as a higher total WBC count. Neonates often have a high hematocrit at birth that decreases with colostral ingestion. Lactating animals may have decreased hematocrits, RBC counts, and hemoglobin concentrations. Animals grazing at high altitude (mountain goats and Bighorn sheep) tend to have increased RBC counts, hematocrits, and hemoglobin concentrations.

Interpreting hematologic changes in cervids is more complex. Restraint method affects a variety of parameters in non-acclimated individuals. Physical restraint yields red cell counts and hematocrit and hemoglobin concentrations that are 20 to 40% higher than animals immobilized chemically.[2,3] Neutrophil, lymphocyte, monocyte, and total white cell counts are also 70 to 100% higher in physically restrained cervids (see Appendix 2, Tables 1 and 2).

Adult deer also have seasonal variations in their hemogram. Red cell numbers and related values are highest during midsummer and late winter.[3] White cells, especially neutrophils, are also highest in midsummer, and platelet counts are highest in spring and fall. These changes may relate to diet or to seasonal activities, such as antler growth and rutting conflicts, which increase the chance of trauma.

Red cell stickling has also been reported in a variety of deer species. This appears to relate to a mutation in hemoglobin's β-globin component, similar to the disorder in people, but no pathologic role has been described.[4]

Additional Hematologic Assessments

Bone Marrow Aspiration

Bone marrow aspirates and core biopsy samples taken from sites of active erythropoiesis can be useful to evaluate erythrocyte production and determine the cause of anemia and other hemogram abnormalities. The sites of biopsy include the sternebrae, femur, and ileum. The procedure should be done under chemical sedation or anesthesia (see Chapter 18). The area over the biopsy site is clipped and surgically prepared; the sampler should wear sterile gloves to maintain asepsis. Aspirates can be obtained by inserting a sterile needle attached to a 3- or 6-cc syringe containing one or two drops of EDTA through the bone and into the bone marrow. Drawing back on the syringe plunger several times may aid in the procurement of an acceptable sample; such a sample may consist of as little as 0.5 mL of bone marrow. If the sample is going to be processed immediately, no anticoagulant is required. Core biopsies are obtained using a Jamshidi or Westerman-Jensen biopsy needle. The skin is incised with a scalpel and the biopsy needle is inserted into the bone and turned several times to obtain a core sample. More than one site may be used. The sampler then closes the skin with sutures or staples. Biopsy samples are preserved by placing them in 10% neutral buffered formalin solution. Impression smears can be made from these samples by gently rolling them on a clean glass slide before placing them in the formalin solution. Information obtained from bone marrow samples includes subjective data regarding cell density, megakaryocyte numbers, abnormal cells, maturation patterns of RBCs and WBCs, and the ratio of erythroid to myeloid cells. Prussian blue stain can be used on bone marrow to demonstrate iron stores. Bone marrow aspirates and biopsies are painful and invasive procedures. Therefore, animals should be placed on antibiotics and antiinflammatory drugs prophylactically.

Blood Cultures

Blood cultures can be useful in diagnosing bacteremia in an intermittently or persistently febrile animal or one with numerous sites of organ infection. Ideally, the clinician should obtain the sample before instituting antimicrobial therapy. However, if this is impossible, antimicrobial therapy should be discontinued 48 to 72 hours before sampling. Samples should be taken before and during febrile episodes. The jugular vein is most commonly used to attain a blood culture. As described previously, the skin over the jugular vein should be clipped and surgically prepared. The person collecting the blood sample should wear sterile gloves and use a sterile needle and syringe. Blood samples should be placed immediately in a blood culture flask. The chances of attaining a positive culture from bacteremic animals increase with the size of the sample up to about 30 mL, but adding more than the recommended amount to any single culture vial may overwhelm the capacity of the specialized antibiotic-absorbing resins within the flasks. The clinician should change the needle on the sample syringe after collecting the blood and before putting the sample in the culture medium. Samples should be refrigerated until they can be sent to a diagnostic laboratory, where aerobic and sometimes anaerobic cultures are made.

The FAMACHA System of Assessing Anemia

As an alternative to hematologic testing, comparing conjunctival color to swatches on a standardized FAMACHA chart has been used as a rapid and inexpensive assessment of anemia in whole flocks, primarily to assess the impact of *Haemonchus contortus* and other blood-sucking parasites.[5,6] Results from a number of trials have yielded fair to good sensitivity to packed cell volume and *H. contortus* load in both sheep and goats. Similar to body condition scoring systems, it is essential to calibrate assessors to ensure consistency when using this system.[7] Also, some breeds

read differently on the cards, and use of an electronic color analyzer, while more expensive and less field-friendly, may detect anemia earlier (see Chapter 6, Figure 6.4A, B, and Chapter 19).[8] Easy use of this technique in deer is limited by their intractability and has not been reported.

Changes in the Hemogram

The most common and significant abnormality of the hemogram is anemia. Anemia occurs most commonly after blood loss, hemolysis, or chronic disease. Blood loss is usually covert and commonly caused by gastrointestinal or external parasites. Overt blood loss is usually caused by major trauma such as that caused by dog bites, severe lacerations, male rivalry fighting, or complications of castration or dehorning. CBC values appear normal immediately after acute blood loss. However, after a few hours of fluid redistribution, anemia and hypoproteinemia are evident. Evidence of red cell regeneration (macrocytosis, reticulocytosis, and nucleated red cells) should appear within a day or two of the blood loss.

Hemolysis occurs most commonly after ingestion of toxic plants, RBC parasitism, intravenous (IV) injection of hypotonic or hypertonic agents, contact with bacterial toxins, water intoxication, or immune-mediated destruction of opsonized erythrocytes. Ingested toxins include sulfur compounds from onions and *Brassica* plants (kale and canola),[9–12] nitrates, nitrites, and copper.[13–16] Except for that caused by copper, hemolysis usually occurs within a day or two after ingestion. Copper toxicosis can occur after acute overingestion but more commonly is seen in animals that are chronically overfed copper and suffer some stressful event. Goats are more tolerant of excess copper than sheep are, and certain breeds of sheep, particularly the Suffolk, are highly sensitive to copper toxicosis (see Chapters 2 and 5).

Hemolytic bacterial toxins include those from *Clostridium perfringens* type A, *Clostridium haemolyticum*, and *Leptospira interrogans.*[17,18] Intraerythrocytic parasites include *Anaplasma* species, *Mycoplasma (Eperythrozoon)* species, and *Babesia* species.[19–23] Immune-mediated RBC destruction is very uncommon except with parasitemia, the administration of certain drugs (penicillin), or bovine colostrum to small ruminant neonates.[24] Rapid reduction of plasma osmolality can lead to osmotic lysis of erythrocytes. This can occur locally as a sequela to rapid IV injection of hypotonic substances or after ingestion of a large quantity of water following a period of water deprivation and dehydration (water intoxication). Selenium and copper deficiency have also been associated with Heinz body anemia.[25]

Parasite infestation, opsonization, and ingestion of toxic plants typically cause extravascular hemolysis. In these cases, damaged erythrocytes are removed by cells of the reticuloendothelial system, resulting in anemia, pallor, weakness, depression, icterus, and dark urine. Bacterial toxins, changes in plasma osmolality, and copper toxicosis cause intravascular hemolysis, resulting in the additional signs of hemoglobinemia and hemoglobinuria. Other signs such as fever, neurologic symptoms, and sudden death may be seen with specific diseases. Signs of regeneration should be seen on the hemogram 1 to 2 days after the onset of hemolysis.

Anemia that is not related to the loss or destruction of erythrocytes usually results from a lack of production and thus are nonregenerative. Although mild forms may exist in pregnant sheep and goats and those deficient in vital minerals (e.g., iron, selenium, copper, and zinc), the most common cause of nonregenerative anemia is chronic disease. Under these conditions, iron is sequestered in an unusable form in the bone marrow; staining a marrow sample with Prussian blue stain reveals large iron stores, differentiating this disease from iron-deficiency anemia. The causes of anemia of chronic disease are numerous and include infectious conditions (e.g., pneumonia, foot rot, and caseous lymphadenitis), malnutrition, and environmental stressors.[1]

Treatment of Anemia

Most anemia does not require treatment. Unless loss of RBC mass is rapid and severe, the animal is usually able to compensate to the decreased oxygen-carrying capacity by decreasing activity. It is important to remember in this regard that anemia often first becomes apparent to the manager of a flock or herd when animals appear overly stressed or die during movement or handling.

If possible, the cause of the anemia should be addressed. This can involve trying to control internal and external parasites, changing the diet, and treating infectious diseases. Maintaining adequate hydration is essential in animals with intravascular hemolysis to avoid hemoglobin-induced renal tubular damage. Specialty compounds such as molybdenum salts, such as ammonium molybdate, and sulfur or penicillamine for copper toxicosis[16] and methylene blue (15 mg/kg in a 4% solution in 5% dextrose or normal saline intravenously) for nitrate toxicity are usually too expensive or difficult to be used on a flock-wide basis but may be useful in valuable individual animals. Veterinarians should be aware that methylene blue is no longer approved for use in food-producing animals.

Animals with severe acute blood loss or hemolysis may benefit from a whole blood transfusion. Because transfusion reactions are rare and strong erythrocyte antigens have not been identified in small ruminants (including cervids), almost any donor of the same species is acceptable for a first transfusion. Cross-matching can be done to ensure compatibility, which becomes more important if the animal receives more than one transfusion. Blood should be withdrawn aseptically from the donor and collected by a bleeding trocar into an open flask or by a catheter into a special collection bag. Blood should be mixed at a 7.5:1 ratio with acid-citrate dextrose, or 9:1 with 2% sodium citrate, or another suitable anticoagulant and administered through a filtered blood administration set. If the jugular vein is not accessible, blood may be infused into the peritoneal cavity, but the slower absorption from that site makes it less effective for treating acute blood loss. The first 15 to 30 minutes of administration should be slow. If no reaction is seen (fever, tenesmus, tachypnea, tachycardia, and shaking), the rate may be increased. Transfused erythrocytes may only survive a few days, and therefore, the original cause of the anemia must be addressed.[1]

Changes in the Leukogram

Peripheral WBCs include granulocytes (neutrophils, eosinophils, and basophils) and mononuclear cells (lymphocytes and monocytes). Immature forms of neutrophils and lymphocytes may be seen during severe inflammatory diseases. Abnormalities of the neutrophil line are usually the best cellular evidence of inflammation in small ruminants, and inflammation is almost always a sequela of infection. An increase in neutrophil numbers and their proportional contribution to the total WBC count is usually seen in mild gram positive, subacute, or chronic bacterial infections. Animals with more severe disease may exhibit high or normal counts, but a greater proportion of the neutrophils will have toxic changes or be immature forms (band cells, metamyelocytes, or myelocytes). In severe, acute inflammation and many diseases caused by gram negative bacteria, a temporary reduction in neutrophil numbers is observed, often with a concurrent shift toward more toxic or immature forms.

If the animal survives the peracute disease, neutropenia should resolve over 3 to 4 days, first through an increase in immature cells, and later through a mature neutrophilic response. Another important cause of increased total and relative neutrophil counts is stress (or glucocorticoid administration), which inhibits neutrophil margination and extravasation and thereby increases the number of these cells in the midstream blood.

Increases in eosinophil counts are usually related to exposure to eukaryotic parasites. Decreases are rarely of clinical significance and may be part of the stress response. Idiopathic allergic-type reactions also are indicators of pathology but are very rare. Increases in basophils are rarely clinically significant.

Increases in lymphocyte counts often reflect chronic inflammatory disease such as that seen with internal abscesses. In rare cases, lymphocytosis may consist of abnormal, blast-type cells and indicate a lymphoproliferative neoplasm. Lymphopenia is an important part of the stress response; nevertheless, the clinician must keep in mind that many diseases stimulate a stress response. Therefore, lymphopenia and neutrophilia may represent either stress or inflammation, and an examination of neutrophil morphology and plasma fibrinogen concentrations may be useful in distinguishing the two situations. A high fibrinogen concentration, toxic changes, and high counts of immature neutrophils indicate inflammation under those circumstances. Blood monocyte counts also may indicate stress or chronic inflammation. The difficulties in interpreting individual cell count abnormalities highlight the importance of obtaining a differential WBC count and description of cellular morphology in assessing sick sheep and goats.

Leukogram abnormalities are rarely given specific treatment. It is far more common and useful to use the information from the leukogram to develop a plan to treat the disease responsible for the abnormality.

Assessment of the Lymphatic System

Palpation of external lymph nodes is part of the thorough physical examination. Lymph nodes that can be found in normal sheep and goats include the submandibular, prescapular, and prefemoral nodes. None of these should be prominent or painful on palpation. Additional nodes that may be palpated occasionally in normal animals include the parotid, retropharyngeal, supramammary, perirectal, and popliteal nodes. Internal lymph nodes that may be identified during specialized diagnostic procedures include the mediastinal, mesenteric, and other abdominal nodes.

Enlargement of lymph nodes may be focal, multifocal, or generalized. Identification of a single enlarged superficial node does not always rule out a multifocal or generalized disorder because the status of the internal nodes often cannot be determined. Enlargement generally indicates either inflammation or neoplasia. Inflammatory enlargement is generally related to an associated disease with an infectious component. Small ruminants are particularly sensitive to lymph node–based infections (e.g., caseous lymphadenitis), so the search often does not extend beyond aspirating or draining the lymph node itself. Neoplastic enlargement almost always results from lymphosarcoma.

Diseases of the Lymphatic System

Lymphosarcoma

Pathogenesis. Neoplastic transformation of a member of the lymphocyte cell line leads to unregulated clonal expansion of that cell. The cause of transformation is usually unknown; in rare cases, especially in flock outbreaks in sheep, it can be linked to exposure to the bovine leukemia virus, which has occurred experimentally and as a result of the administration of whole blood *Anaplasma* vaccines. Whether the bovine leukemia virus can induce lymphosarcoma in goats and cervids is still unclear. Multicentric lymphosarcoma has been reported sporadically in white-tailed deer *(Odocoileus virginiatus)* and other deer, but bovine leukemia virus infection has not been diagnosed in cervids.[26]

In one study of neoplastic diseases affecting goats from 1987 to 2011, lymphoma was identified as the most common neoplasm, accounting for 17.7% of the assessed tumors.[27] In contrast to other species such as cattle, sheep, and horses, lymphomas in goats are predominantly T-cell lymphomas affecting the mediastinum. A recent study attempted to classify the type of lymphoma affecting 15 goats. Using immunohistochemistry (IHC), it was determined that 73% (n = 11) of affected goats had T-cell lymphoma and only 27% (n = 4) had B-cell lymphoma.[28] Proliferation of T or B lymphocytes leads to mass lesions and infiltration of viscera. These changes cause physical obstruction (to breathing, blood flow, urination, defecation, etc.), ulceration of mucosal surfaces (blood loss, bacterial invasion), immune system dysfunction, organ failure, and generalized malaise and cachexia. Tissue masses may be internal or visible on external examination.

Clinical Signs. Clinical signs in affected animals vary according to the type of lymphoma (T- or B-cell) and the location of the masses. T-cell lymphomas in goats are usually localized in the thoracic cavity and/or neck, suggesting thymic origin or homing.[27] In contrast, B-cell lymphomas tend to have a multicentric distribution.[27] Lymphoma in small ruminants usually presents with non-specific signs that can mimic other respiratory or gastrointestinal conditions. Slowly progressive weight loss is the most common finding. In some cases, generalized peripheral lymphadenopathy and expansile masses are noted[29]; at first, they usually are presumed to be caseous lymphadenitis abscesses. Progressive chemosis and exophthalmos have been reported in a sheep and a goat with multicentric B-cell lymphoma.[29,30] Most masses form at the sites of internal or external lymph nodes. In sheep, masses in the brain, skin, joint, and lymphoid tissue have been reported.[30] Leukemia is rare. The most common abnormalities are those of chronic disease and cachexia and include nonregenerative anemia and hypoalbuminemia. Bone marrow examination may reveal clonal expansion of lymphoid precursor cells.

In cervids, lymphadenopathy and multifocal masses affecting the heart, blood vessels, kidney, urinary bladder, and peritoneum have been reported.[31] A more recent report described a subcutaneous maxillary mass in a 13-year-old captive-born, female white-tailed deer.[26] The mass was diagnosed as focal lymphosarcoma with local metastasis.

Diagnosis. History and clinical signs are important in the diagnosis of lymphoma in small ruminants. Age of affected animals ranges from 2 to 18 years and no gender or breed predisposition has been reported.[29] Final diagnosis of affected animals is achieved through necropsy, histopathology, and IHC. Lesions seen at necropsy include homogeneous white to tan masses that bulge on the cut surface. They may be small or large. Less commonly, diffuse paleness of the reticuloendothelial organs is noted. Microscopic examination of these tissues reveals infiltrates of abnormal cells of the lymphocyte line.

Prevention. Avoiding exposure to the bovine leukemia virus and restricting the use of instruments to one animal between cleaning procedures may help prevent the spread of lymphosarcoma. In most animals, however, this neoplasm appears to develop spontaneously.

Failure of Passive Transfer

Pathogenesis. Lambs, kids, and fawns are born with functional lymphocytes that can produce endogenous immunoglobulin. These cells develop the ability to respond to foreign antigens in the fetus during mid to late gestation. Because of a lack of in utero exposure, however, basal concentrations of immunoglobulin are very low at birth. These cells therefore are naïve to foreign antigens and unable to develop protective immunity through specific cell-mediated and immunoglobulin production. Additionally, as with other ruminants, no transplacental passage of maternal immunoglobulin to fetal sheep, goats, and fawns occurs. Lambs, kids, and fawns depend exclusively on intestinal absorption of maternally derived colostral antibodies, immune cells (T-lymphocytes), and other immune factors to provide a ready supply of specific immunity and allow opsonization of pathogens for the first months of life.

Adequate passive transfer requires delivery of a sufficient quantity of good-quality colostrum (immunoglobulin G [IgG] concentration in mg/mL) into the gastrointestinal tract, as well as adequate absorption of antibodies (timely) from the colostrum into the blood. However, the amount of maternal colostrum produced by the dam, and its composition, as well as the ability of the newborn to stand and nurse in a timely manner, can be affected by several factors. Colostrum IgG concentration and volume of production can be influenced by breed, age, nutrition, body condition score (BCS) at parturition, and vaccination status of the dam. The IgG concentration in colostrum samples from ewes of different breeds can vary between 60 and 125 mg/mL.[32] One study demonstrated that primiparous ewes with low BCS (< 2.75) at lambing produced less colostrum compared with multiparous ewes with similar BCS. Additionally, ewes with higher BCS (> 2.75) tended to produce higher volumes of colostrum compared with ewes with lower BCS.[32] Another study suggested that undernutrition of ewes during late gestation can affect colostrum quality and immune development and function in newborn lambs.[33] It has been suggested that at least 30 g of total IgG should be fed to newborn lambs and kids during the first 24 hours of life to reach adequate transfer of passive immunity. Adequate transfer of passive immunity in small ruminant neonates has been suggested as serum IgG levels at 24 hours of life of ≥ 15 mg/mL. One study indicated that lambs that nurse low-quality colostrum (IgG < 30 mg/mL) had lower serum IgG concentrations compared with lambs that that nurse colostrum of higher quality (IgG > 110 mg/mL), indicating that the concentration of IgG in colostrum is a determining factor for the presentation of failure in the transfer of passive immunity.[34] Other factors such as pregnancy toxemia, gastrointestinal parasitism, excess of iodine intake during pregnancy, and inadequate vaccination of the dam can result in poor colostrum synthesis and quality.[35]

Timely consumption of maternal colostrum during the first hours of life is essential to achieve adequate transfer of passive immunity. In small ruminants, cells of the small intestine are able to internalize and transfer IgG into the blood during the first 24 hours of life; however, the absorption efficiency of IgG is higher during the first 6 to 12 hours of life.[32,36] Factors associated with the neonate, such as weakness, inability to stand, and congenital abnormalities, will prevent timely nursing of maternal colostrum and lead to failure of passive transfer (FPT). Litter size and body weight (BW) of the kid(s) have also been correlated with inadequate absorption of IgG from colostrum. One study demonstrated that litter sizes of three light goat kids (< 2.8 kg BW) or more had significantly lower mean serum IgG levels at 24 hours of life when compared with litter sizes of one or two heavier kids (9.85 versus 18.30 mg/mL, respectively).[37] This suggests that special attention and monitoring should be paid to multiple fetus gestation as the risk of FPT under these circumstances at kidding is higher; however, the quality of colostrum, amount ingested, and adequacy of absorption are rarely monitored by small ruminant producers in natural or artificial rearing systems. The use of monitoring tools to evaluate colostrum quality and IgG absorption is common in modern dairy cattle operations, and these tools are readily available for small ruminant production systems. Recent reports have presented the use of %Brix in maternal colostrum and neonate serum and its positive correlation with serum total proteins (STPs) at 24 hours as effective monitoring tools of FPT in lambs and goat kids.[38–40] The use of STP has also been used to monitor colostrum deficiency intake in mule deer fawns[41]; however, adequate values of serum IgG for cervid neonates have not been established yet.

Inadequate colostrum intake and low serum IgG at 24 to 48 hours of life have been consistently associated with higher morbidity and mortality rates in lambs, goat kids, and fawns. One study reported that 46% of lamb mortality between 24 hours and 5 weeks of age can be attributed to FPT.[42] Another study suggested that colostrum deficiency and low serum IgG in goat kids resulted in higher mortality rates at weeks 10 and 12 of life due to chronic infections with *Pasteurella multocida* and *Escherichia coli*.[43] Other reports demonstrated that 45% of lambs with a serum IgG of < 6 mg/mL at 24 hours died before 3 weeks of age compared with only 5% of the lambs with a serum IgG of > 6 mg/mL at 24 hours.[34] In a previous report, mule deer *(Odocoileus hemionus)* fawns with a STP of ≤ 5 g/dL between days 1 and 7 of age developed diarrhea and died before 17 days of age compared with fawns with STP > 5 g/dL.[41] In a more recent report, a 7-day-old Formosan sambar deer *(Rusa unicolor swinhoei)* with a history of colostrum deprivation died due to severe suppurative meningitis caused by *E. coli* infection.[44]

In addition to immunoglobulins, colostrum also contains large quantities of fat-soluble vitamins that do not cross the placenta. The most important of these are vitamins A, D, and E, which are important in bone development and the immune or inflammatory response. Neonates that have not ingested enough colostrum are likely to be deficient in these vitamins.

Diagnosis. History of dam dystocia, inadequate colostrum nursing, complete colostrum deprivation, and signs of undernourishment or sepsis in the first few days after birth are usually a presumptive indication of failure in the transfer of passive immunity. A high prevalence of diarrhea and respiratory disease in neonates should prompt investigation and evaluation of passive transfer of immunity in affected herds or flocks. Owners occasionally evaluate lambs or kids for adequate intake by picking up the animal and holding it at ear level, while carefully cradling the head and neck, and then shaking the abdomen to hear milk in the abomasum; however, this is not a reliable indication of adequate transfer of passive immunity. A definitive diagnosis of FPT can be

made by direct laboratory measurement (single radial immunodiffusion [SRID]) of IgG in serum at 24 hours of life. Although some practitioners use the value of IgG used in dairy calves (10 mg/mL), others have suggested an IgG value < 15 mg/mL to establish the presence of FPT in small ruminants.[45]

Numerous semiquantitative methods of estimating IgG are available and are easy to use in sheep, goats, and cervids. The most common is the measurement of serum total solids or STP values at 24 hours of life through an optical refractometer. The STP at 24 hours of life in a well-hydrated animal has demonstrated correlation with serum IgG in calves, lambs, and goat kids. Studies in goat kids indicated that an STP between 5.3 and 5.4 g/dL was associated with adequate transfer of passive immunity.[39,40] Another study demonstrated FPT in lambs with STP values < 4.5 g/dL at 24 hours of life.[32] A study in mule deer suggested that fawns with an STP ≤ 5 g/dL had inadequate colostrum intake and FPT. Recently, the measurement of %Brix in maternal colostrum and serum with a digital Brix refractometer has become an alternative method to evaluate colostrum quality and FPT in dairy operations. Colostrum %Brix > 22% and serum %Brix > 8.4% have been associated with adequate transfer of IgG in calves and goat kids.[39] Other qualitative methods to assess the transfer of passive immunity in large animals include various agglutination (glutaraldehyde), precipitate assays (sodium sulfate), and measurement of γ-glutamyl transferase (GGT) in serum. These methods may be relied on to give an overall flock assessment of adequacy of passive transfer, but they are rarely accurate enough to provide definitive information on individual animals.

Treatment. FPT is not in itself pathologic, but it greatly increases the neonate's susceptibility to infectious diseases. The amount of colostrum absorbed across the gut decreases with time, especially in animals that have been ingesting other proteins (e.g., the casein in milk); it also decreases with illnesses that decrease gastrointestinal function. Neonatal small ruminants should receive at least 4 g of IgG/kg of BW or ideally 30 g of total mass of IgG from a good-quality colostrum source (> 50 mg/mL of IgG) during the first hours of life.[32] Other authors recommend an intake of 180 to 210 mL of colostrum/kg during the first 18 hours of life.[46] In artificial rearing systems or lamb feedlots, feeding of colostrum every 6 hours until 24 hours of life is recommended.[47] When same species' maternal colostrum is unavailable, goat colostrum or bovine colostrum/colostrum replacers or are a good alternative; however, hemolysis has been reported in lambs receiving cattle colostrum.[48] One study demonstrated that there was no difference in serum IgG levels of lambs that received the same volume of sheep or goat colostrum at birth.[47] Another study demonstrated that lambs that received 250 mL of a bovine colostrum replacer at birth in addition to 250 mL of stored sheep colostrum at 6 hours of life had higher serum %Brix values at 24 hours and had less incidence of disease during the preweaning period compared with lambs that received the same volume of stored sheep colostrum at birth and at 6 hours of life.[38] Since IgG absorption cannot be extended more than 24 hours after birth, administration of an oral colostrum source is the best treatment in the immediate postpartum period in still-healthy neonates. After the window for immunoglobulin absorption has closed, plasma, serum, or whole blood administered by the IV or intra-peritoneal route is the best way to raise the neonate's blood immunoglobulin concentrations. Adult donor plasma contains approximately 2.5 to 3.5 g of immunoglobulin/dL, so administration of a volume equivalent to 10% of BW or a dose of 20 to 40 mL/kg has been recommended for the treatment of large animal neonates. If plasma is used instead of colostrum, administration of vitamins A, D, and E also may be beneficial.

If colostrum and plasma are unavailable or cost-prohibitive, "closing" the gut as quickly as possible with milk, maintaining high standards of hygiene, and possibly administering prophylactic antibiotics offer the greatest prospects for preventing infectious disease. Vaccination of the neonate or the administration of antitoxin hyperimmune serum should not be considered protective but may be of value.

Prevention. Prevention of FPT should be based on the establishment of an adequate colostrum program managing the previously mentioned factors that affect production, quality, and absorption of maternal colostrum components in lambs, goat kids, and fawns. Ensuring colostral quality is best done through good nutrition, health care, and vaccination of dam (see Chapters 2 and 19). Administration of vaccines 6 weeks before parturition, followed in 2 weeks with a booster, provides the highest quantity of protective immunoglobulin in the colostrum. Antepartum leakage is rarely the problem in small ruminants that it is in horses and cattle. However, in a flock or herd environment, still-pregnant dams may steal babies from other sheep or goats. To prevent such theft and the resultant loss of colostrum by the "adopted" neonate, owners may choose to keep pregnant animals separate from those that have already delivered. If complete separation is not possible, the dam and her offspring should be allowed to bond with each other in a private pen ("jug" or "crate") for at least 24 hours before being placed back with the flock. Clipping excessive wool or mohair from around the perineal area and udder before lambing or kidding, expressing the teats to ensure they are not plugged, and having extra colostrum available when pregnant females are placed in jugs or crates are other good preventive measures.

Uncomplicated Neonatal Diarrhea

Etiology and Pathogenesis. Uncomplicated diarrhea in lambs, goat kids, and fawns may be caused by infectious agents such as viruses, bacteria, and protozoa. In goat kids and elk calves, metabolic causes of diarrhea have been described.[49,50] Group B and A rotavirus, enterotoxigenic *E. coli* K99, *Cryptosporidium parvum*, and other *Cryptosporidium* spp. have been commonly identified as causal agents of diarrhea in small ruminant neonates.[51–54] With recent advances in diagnostics and metagenomics of the enteric environment of large animals, novel viruses have been identified as potential causal agents of diarrhea in lambs and goat kids. Adenovirus, Astrovirus, Calicivirus, Coronavirus, and Picornavirus have been identified in feces of diarrheic lambs and goat kids[55]; however, their role in the pathogenesis of neonatal diarrhea is still uncertain. These organisms differ from the agents of complicated diarrhea in that they do not invade beyond the gut wall or result in systemic toxemia (see Chapter 5). Additional causes of diarrhea reported in goat kids and elk include lactose intolerance and hypernatremia, respectively.[49,50] Less frequently, bacteria such as *C. perfringens*, *Clostridium difficile*, and attaching and effacing *E. coli* have been associated with complicated diarrhea in small ruminant neonates.[54,56]

The net result of such an infection is that a large volume of water and electrolytes are lost into the bowel due to malabsorptive, hypersecretory, or hyperosmolar processes. If enough fluid and electrolytes are lost, dehydration and metabolic acidosis arise, inducing systemic clinical signs of depression and weakness in association with diarrhea. In goats, this clinical entity is one component of the floppy kid syndrome.

Clinical Signs. Profuse, watery, yellowish-green to brown diarrhea without fever is the hallmark clinical sign. With severe dehydration

and acidosis, affected lambs, kids, and fawns become weak and dull and lack appetite.[50–52] Excessive salivation and loss of suckle reflex have also been reported in affected lambs and kids.[51,52] Mucous membranes become tacky, and skin tenting times are prolonged. Shock signs may develop. Physical assessment often must take the place of clinicopathologic analysis in affected neonates.

Mild, nonclinically complicated diarrhea is characterized by profuse diarrhea with minimal systemic signs. The affected animal is bright and alert, with minimal skin tenting, and can stand and eat readily, with a strong suckle reflex. It is less than 5% dehydrated, with a blood pH of 7.35 to 7.50, and bicarbonate deficit is minimal.

Moderate uncomplicated diarrhea is characterized by profuse diarrhea in a dull but responsive animal. Skin tenting is prolonged, but eye luster is normal. The affected animal is able to stand and eat but eats slowly and has a weak suckle reflex. The head typically is held down. It is 5 to 7% dehydrated, with a blood pH of 7.10 to 7.25 and a bicarbonate deficit of 5 to 8 mEq/L. Severe uncomplicated diarrhea is characterized by profuse diarrhea. The affected animal is dull and minimally responsive, with a very long skin tent time and dull, sunken eyes. It can stand only with assistance and prefers to stay in sternal recumbency with its head up. The animal eats very slowly, if at all, and has a minimal suckle reflex. It is 8 to 10% dehydrated, with a blood pH of 6.90 to 7.10 and a bicarbonate deficit of 10 mEq/L.

Very severe uncomplicated diarrhea is characterized by profuse diarrhea and profound weakness. The animal's skin remains tented for more than 1 minute, and its eyes are very sunken and dull. It is nonresponsive with no suckle response. It is unable to maintain sternal recumbency, lying on its side instead. The animal is 10 to 12% dehydrated, with a blood pH of 6.8 to 7.0 and a bicarbonate deficiency of 15 to 20 mEq/L.

Epidemiology. Morbidity and mortality of uncomplicated diarrhea in small ruminants and fawns vary depending on the cause. Reports of rotaviral diarrhea in newborn lambs indicate morbidity rates between 50% and 100% and mortality rates between 0 and 10%[51,52]; however, one study reported a 50% case fatality rate in lambs affected with types B and A rotavirus diarrhea.[52] Another study reported mortality rates between 10% and 30% in lambs and kids affected with *C. parvum* diarrhea.[57] Most of infectious agents associated with uncomplicated neonatal diarrhea in small ruminants are shed by adult animals and older lambs/kids around stressful events such as lambing/kidding and extreme weather conditions. One study reported that pregnant does shed 7 to 10 times more oocysts during the 3 weeks around kidding compared with other time periods.[58] Additionally, poor husbandry/hygiene of lambing/kidding sheds, fecal soiling, flock size (> 200 animals), lambing/kidding season (winter/spring), and the presence of *C. perfringens* type A in feces have been suggested as potential risk factors for uncomplicated diarrhea in small ruminant neonates.[58–60]

Clinical Pathology. The leukogram should be normal or show abnormalities compatible with stress. Serum biochemical or blood gas analysis may reveal evidence of intestinal malabsorption, electrolyte loss, metabolic acidosis (hypoglycemia, hyponatremia, hypochloremia, hyperkalemia, low bicarbonate, and increased anion gap), and dehydration (hyperalbuminemia and increased blood urea nitrogen [BUN] and creatinine). In contrast with the common leukogram and biochemical abnormalities found in calves, lambs, and goat kids with uncomplicated diarrhea, elk calves with diarrhea develop leukocytosis, hyperchloremia, and hypernatremia (serum Na > 153 mEq/L).[50] Additionally, increased anion gap, BUN, creatinine, and albumin concentrations have been reported in affected elk calves.[50]

Diagnosis. A presumptive diagnosis may be based on the characteristic history and clinical signs. Response to conservative treatment also is supportive of this diagnosis. Identification of the specific causative agent is less important than proper treatment of affected animals; however, feces or intestinal contents from affected animals can be submitted for electron microscopy, reverse-transcription polymerase chain reaction (PCR), and cell culture immunofluorescent assays to identify viruses.[51–53] Additionally, intestinal tissue can be submitted for IHC for rotavirus and *C. parvum.*[53,57] Feces of affected animals can also be submitted for enzyme-linked immunosorbent assay (ELISA), Ziehl-Neelsen staining technique, light or fluorescence microscopy, sugar flotation, and auramine or fluorescent antibody staining for the diagnosis of *C. parvum* infection.[60] Fecal culture to determine a bacterial cause is recommended.

Treatment. The immediate goals of treatment are rehydration, replacement of lost electrolytes, and restoration of acid-base balance as these are usually the leading causes of death in affected neonates. Less immediate goals are provision of nutrition and replacement of ongoing losses. The aggressiveness of treatment is dictated by the severity of the condition, as well as economic considerations.[61]

1. *Rehydration*: Calculate the percent dehydration and use to calculate fluid requirements for a 24-hour period.
   Example: 10% dehydration in a 3-kg lamb:
   Dehydration: 0.1 × 3 kg × 1 kg/L = 0.3 L or 300 mL.
   Maintenance: 100 mL/kg/day = 0.3 L or 300 mL.
   Total fluids to replace in 24 hours = 0.6 L or 600 mL
   Fluid loss due to dehydration (300 mL in this case) should be replaced during the first 4 hours and the rest can be replaced in the next 20 hours.
2. *Replace lost electrolytes*: Sodium, chloride, and bicarbonate are lost roughly in proportion to extracellular fluid (ECF) in the acute phase of diarrhea (1–2 days) in untreated animals. Potassium tends to be increased in this phase due to the presence of metabolic acidosis and care should be taken when selecting fluids containing potassium to treat affected animals at this time. In chronic cases of diarrhea, and especially in cases where the owner/producer has given oral milk replacer or electrolyte supplements/replacements to affected animals before veterinary evaluation, the serum concentration of sodium, potassium, and bicarbonate might be variable or increased. Special care should be taken in these cases when selecting fluids to treat affected animals as the risk of causing hypernatremia is higher.[61] In cases of diarrhea in elk calves, hypernatremia is common, and fluids should be selected accordingly.[50] In the majority of cases, initial replacement of sodium, chloride, and bicarbonate with fluids containing proper composition is recommended.[61]
3. *Restore the acid-base balance*: Estimate bicarbonate deficit by blood gas analysis (24 mEq, as measured), serum bicarbonate concentration, or physical assessment. In calves, clinical signs of posture, demeanor, and presence of absence of suckle reflex can be used to estimate base deficit, and this might be applied for small ruminant neonates. Briefly, diarrheic neonates that are alert, are standing, and have a suckle have a bicarbonate deficit < 8 mEq; those that are depressed, are sternal recumbent, and have no suckle have a bicarbonate deficit between 8 and 10 mEq; and those that are severely depressed, laterally recumbent, no suckle animals have a bicarbonate deficit > 15 mEq.[61] After calculating the bicarbonate deficit, calculate the whole body need of bicarbonate using the following formula:

$$\text{Bicarbonate needs} = 0.6 \times \text{bicarbonate deficit (mEq)} \times \text{BW (kg)}$$

Example: Assessment suggests a bicarbonate deficit of 16 mEq bicarbonate in a 3-kg, comatose lamb with prolonged skin tenting (0.6 is the multiplier for ECF in a neonate): 0.6 × (16 mEq) × 3 kg = 29 mEq bicarbonate. Commercial IV 8.4% sodium bicarbonate solutions contain 1 mEq of bicarbonate per milliliter and could be added directly to IV fluids in severely dehydrated and acidotic animals.[61]

Therefore, the immediate goal is to provide 300 mL of fluid and 29 mEq of bicarbonate to this lamb in a formulation that resembles normal ECF. Fluids can be given by various routes. Selection of route of administration of fluids depends on degree of dehydration, presence or not of a strong suckle reflex, and degree of depression. Neonates with advanced degrees of dehydration, depression, and absence of suckle reflex will benefit from IV fluid therapy. In contrast, neonates with mild dehydration and active suckle reflex can be effectively treated with oral electrolytes[61]; however, if oral fluids have not produced an improvement within 2 to 4 hours, IV treatment should be strongly considered. Other routes such as subcutaneous, intra-peritoneal, and intra-osseous can also be used for fluid administration to neonates.

Routes

Oral

- *Advantages*: Oral fluids are inexpensive (nonsterile) and easy to give. They are less likely to cause fatal arrhythmias or neurologic disease than IV fluids.
- *Disadvantages*: An animal receives a maximum of its gastric volume (5% of BW), and good gastric motility is required. Oral fluids may not be well absorbed by a damaged gut. Absorption also is slow.

Intravenous

- *Advantage*: This method allows rapid correction of all deficits, even in moribund animals.
- *Disadvantages*: It is expensive (sterile), requires venous access, and can rapidly lead to overcorrection.

Subcutaneous

- *Advantages*: This method does not require venous access or good gut motility.
- *Disadvantages*: It is expensive (sterile), and the fluids may not be well absorbed in very dehydrated animals. Absorption is not as quick as by IV administration. Animals should be given only hypotonic or isotonic fluids.

Intra-peritoneal

- *Advantages*: This method does not require venous access or gut motility. Fluids are absorbed quickly by this route.
- *Disadvantages*: It is expensive (sterile) and can cause peritonitis. Isotonic fluids are best used in this route. Only a limited volume can be given.

Many commercial oral electrolyte solutions for neonatal ruminants are available; however, not all of them fulfill the requirements to adequately replace fluids and electrolytes in neonatal ruminants with diarrhea. Oral electrolyte solutions must contain enough sodium (90–110 mEq), provide agents that increase absorption of water (glycine, glucose, and acetate), provide an alkalinizing agent (bicarbonate, propionate, acetate, and citrate; acetate has demonstrated best results), and an energy source (glucose).[61] The amount of carbohydrates might vary and is usually higher in "high-energy" solutions specifically used for severely affected neonates that are not eating and develop negative energy balance. Less carbohydrate is needed in less severely affected animals because they are usually eating some and are less likely to have severe negative energy balance. Fluids to be avoided include medicated milk replacers and unbuffered saline solutions.

IV treatment should be provided with a sterile commercial product. Such preparations typically contain 25 to 30 mEq/L of base. Additional sodium bicarbonate solution or sterile powder can be added to fluid therapy based on the bicarbonate deficit (1 mEq/mL of 8.4% solution and 12 mEq of bicarbonate/g of powder, respectively). The bicarbonate deficit should be over the first 4 hours.

After deficits are replaced, the following continued treatments and adjuncts may be considered:

1. Continued administration of fluids (oral rather than IV, if possible) to replace ongoing losses:
   - Oral electrolytes at a volume equal to 5% of the BW per feeding can be given; the number of feedings can be increased from two (normal) to three to six per day.
   - IV fluids can be continued at twice the maintenance fluid rate until appetite is restored.
   - More bicarbonate may be necessary.
2. Consideration of addition of milk to the treatment regimen:
   - Milk or milk replacers should be added to the therapy of neonates with diarrhea. They provide nutrition to the affected neonate, preventing negative energy balance and promoting intestinal healing.
   - Care should be taken to NOT mix oral electrolyte solutions with milk or milk replacers in the same container as the concentration of sodium and overall osmolarity of the solution can dramatically increase, leading to hypernatremia or other metabolic abnormalities.
   - Milk or milk replacers should be given in small volumes (~20% of total requirements) but at a higher frequency (every 3–6 hours) to avoid overloading the abomasum and intestine of affected animals. Lambs fed milk lose less weight with scours.
   - Free water helps prevent hypernatremia.
   - Milk is a good potassium source (see Chapter 3).

Elk Deer Calves. Elk deer calves commonly develop diarrhea with hypernatremia (serum Na > 153 mEq/L) compared with other large animal neonates, where hyponatremia is more common.[50] Therefore, administration of oral electrolyte solutions designed for other ruminants (calves, lambs, and kids) should be avoided in these animals. A dilution (1:2 or 1:4) of commercially available bovine calf electrolyte solutions to reduce sodium content is recommended for the treatment of elk calf diarrhea.[50] The use of lactated Ringer's solution, which has a low sodium concentration in addition to a very low reduction rate of serum sodium (< 1.7 mEq/L/hour) has been advocated in the fluid therapy of hypernatremic elk calves with diarrhea.[50]

Additional Therapy. Dextrose (2.5–5%) solutions can be added to the fluid therapy of hypoglycemic animals. The use of nonsteroidal antiinflammatory drugs (NSAIDs) in neonatal ruminants with diarrhea is controversial due to the risk of renal damage and abomasal ulceration; however, in cases of diarrhea complicated by septicemia or endotoxemia, NSAIDs should be used to reduce the effects of systemic inflammation. Flunixin meglumine at a dose of 1.1 to 2.2 mg/kg is the only NSAID approved for food animal use. Similarly, the use of oral or systemic antibiotics in cases of uncomplicated diarrhea is controversial due to its potential effect on the intestinal microbiota and development of bacterial resistance; however, their use is warranted in the presence of septicemia or endotoxemia in addition to diarrhea. In these cases, β-lactams such as oral amoxicillin or systemic ceftiofur are usually good choices. The effect of mucosal protectants and probiotics in cases

of diarrhea is unknown in small ruminant neonates, and their use is left to practitioners based on their own experiences (see Appendix 1).

Prevention. Prevention of uncomplicated diarrhea in small ruminant neonates is based primarily on the timely feeding of adequate amounts of good quality maternal colostrum or colostrum replacer (see "Failure of Passive Transfer" section). Vaccination of dams with antigens of common infectious agents associated with uncomplicated neonatal diarrhea before parturition has demonstrated to be effective increasing colostrum immunity and prevention of diarrhea in lambs.[62] Maintenance of adequate husbandry and hygiene conditions in lambing/kidding sheds or barns is necessary to reduce neonatal exposure to infectious agents normally shed in feces of dams during parturition such as rotavirus and *C. parvum*.

Other Causes of Weakness and Depression in Neonates

Ruling out infectious causes of depression and weakness is difficult, and clinicians often do well to assume that an infectious disease is contributing to clinical signs when making treatment decisions. However, several noninfectious systemic disturbances also can depress neurologic and muscular function. Successful treatment often requires identification and correction of each of these disturbances. Among the more common abnormalities leading to depression in neonates are hypoxemia, metabolic or respiratory acidosis, hypothermia, hyperthermia, hypoglycemia, dehydration, azotemia, and some electrolyte imbalances.

Hypothermia and hyperthermia can easily be diagnosed by measuring body temperature with a rectal thermometer. Hypothermia is far more common and can result from weakness, shock, and environmental stress. Cold, windy weather or tube feeding with cold milk replacer or fluids can lead to a rapid drop in core body temperature, especially in neonates that are small or weak or have been inadequately licked off or were rejected by their dams. Strong, vigorous neonates usually are protected by heat produced during muscular activity and are able to seek food and shelter. Clinical signs appear when the rectal temperature drops to 98° F (36.7° C) or below. Protection from wind and cold such as with an individual ewe jug or pen, heat lamps (positioned far enough away so as not to burn the neonate), hot water bottles, blankets, and administration of warm fluids is helpful in treating and preventing hypothermia. Shearing the ewe before lambing is of value because it forces the ewe to seek shelter. If this management technique is used, care should be taken to avoid inducing severe hypothermia in the dam.

Environmental hyperthermia is much less common than fever in neonates. Therefore, treatment for infectious diseases in young animals with high temperatures usually is warranted. Providing cool shelter with good ventilation, minimizing stressful events, ensuring adequate fluid intake, and shearing the adults are the best defenses against environmental heat stress.

Hypoglycemia also is easy to diagnose with the aid of an inexpensive, portable glucose meter. Lambs and kids typically develop hypoglycemia under the same circumstances as those leading to hypothermia. Administering 50 mL/kg of dextrose (approximately 3.5 fl oz/lb, or 5% of BW) in warm milk replacer or 1 mL/kg of 50% dextrose, by either the IV or oral route (diluted to 5% dextrose), should provide ample energy to correct hypoglycemia. IV administration may be necessary if gut motility is absent. Follow-up treatment may be necessary if the neonate does not regain its appetite.

Except during severe conditions, normal lambs and kids should be able to maintain normal body core temperature. They should therefore be examined for an underlying disorder if they exhibit signs of hypothermia or hyperthermia. Clinicians and owners should not assume that warming and feeding a cold, weak neonate will always correct the problem.

Hypoxemia is much more difficult to diagnose. Portable blood gas meters for arterial analysis and radiography units for thoracic imaging are available but are still not in common use in small ruminant practice. For those reasons, hypoxemia usually is underdiagnosed. Hypoxemia can result from prematurity or dysmaturity, infection, depression or weakness (decreased ventilation), meconium aspiration, bullous emphysema, hernias, and other thoracic fluid or tissue masses. It is likely to be a contributing factor in illness and death in most weak neonates younger than 3 days of age. Such animals benefit from the provision of supplemental oxygen, either through a nasal insufflation tube or by oxygen tent. In addition to its direct effect on general wellbeing and behavior/attitude, hypoxemia at birth leads to poor gut function and subsequent poor colostral absorption. Many animals that exhibit FPT and subsequent sepsis had a previous bout of hypoxemia.

Azotemia, metabolic acidosis, and electrolyte imbalances are difficult to diagnose without clinicopathologic analysis. Therefore, these problems are best treated in animals showing signs of dehydration with the administration of a balanced, physiologic electrolyte solution. Metabolic acidosis usually is accompanied by either obvious evidence of bicarbonate loss (diarrhea) or severe dehydration. However, neither of these conditions is present with floppy kid syndrome. This descriptive title is applied to muscle weakness, anorexia, and depression in kids observed in the first 2 weeks of life. By its strictest definition, *floppy kid syndrome* refers to metabolic acidosis with a high anion gap without dehydration or any known cause in young kids that were normal at birth. A variety of disorders and conditions have been proposed as the cause of metabolic acidosis without dehydration, including intestinal fermentation of milk in well-fed kids with subsequent absorption of volatile fatty acids, transient neonatal renal tubular acidosis, and lactic acidosis secondary to toxic impairment of cardiovascular function. Overgrowth of *C. perfringens* type A often is suggested as a source of the toxin. With a high anion gap, a pathologic condition that leads to overproduction of an organic acid is more likely than one that leads to bicarbonate loss. The disease can occur in individual animals or in outbreaks; although parity of the dam and number of offspring have not been associated with this metabolic disturbance, aggressively feeding kids are more likely to suffer from milk fermentation or clostridial overgrowth. An infectious etiology appears to be more likely in herds displaying an increased incidence of this metabolic disturbances as the kidding season progresses. The disease also is reported to be more common in meat goats than in dairy goats. The prevalence can vary tremendously from year to year in a single flock or region. A similar disease has been reported in calves and llama crias, and lambs are likely to be susceptible under the right conditions.

Because blood gas analysis and exclusion of other diseases often are impractical, the term *floppy kid syndrome* frequently is used by owners to refer to any kid that is weak and does not have an overt, organ-specific sign (e.g., diarrhea). Different pathologic processes are grouped together by their common clinical endpoint (as with "thin ewe syndrome"), and the veterinarian is charged with determining the etiology in a specific flock. Most possible causes are found in the previous list of conditions that cause weakness and

depression in neonates. Among these entities, sepsis and hypoxemia are the most important items and therefore must also be considered possible causes of floppy kid syndrome. Treatment and prevention of floppy kid syndrome currently follow the same lines as for treatment and prevention of neonatal sepsis or enteritis. Spontaneous recovery of animals with floppy kid syndrome may occur. However, in valuable kids, quick assessment of blood chemistry and base deficits will allow requisite correction of electrolyte and blood pH abnormalities with 1.3% sodium bicarbonate.[63]

Diseases Caused by Tissue-Invading Clostridia

Tissue-invading clostridia are large, straight, gram positive rods that are 3 to 10 μm in length. *C. perfringens* and *C. haemolyticum* are smaller bacteria, and *Clostridium novyi*, *Clostridium chauvoei*, and *Clostridium septicum* are larger. The bacteria grow best under anaerobic conditions and produce waste gases. Clostridia bear spores, which may be the only viable form in the environment (soil and decomposed organic matter). Identification of these spores within bacteria on microscopic examination is useful to identify clostridia, but it is not diagnostic of disease. Spores in *C. perfringens* are central and do not affect the shape, whereas most other species have the spore toward one end and appear slightly club shaped.

Clostridia cause infectious, noncontagious disease. The bacteria inhabit the intestinal tract and are present in the feces of ruminants. Small numbers of organisms in their dormant spore form also may reside in tissues such as liver and skeletal muscle. They can be isolated from soil, where most are thought to have short life spans. Soil concentrations are highest in locations recently contaminated with ruminant feces, especially crowded, overused facilities such as feedlots and lambing sheds. Environmental contaminations are associated with cool, damp times of the year such as late winter and spring.

The concentration of organisms and their toxins found in the feces, gut contents, and internal organs of most adult ruminants usually is small. Competition and peristalsis prevent overgrowth in the gut, and aerobic conditions prevent overgrowth in other tissues in live animals. However, rapid overgrowth and tissue invasion ensue after death, making rapid postmortem examination essential to ascertain whether clostridial organisms are responsible for the death. Pathogenic clostridial organisms all produce heat-labile protein exotoxins. Most make a variety of toxins, and the relative contribution of each toxin to the disease state is not known.

Enteric Infections

C. perfringens is a normal commensal of the intestinal tract of clinically healthy large animals, including cervids; however, the number of bacteria and their toxin production within the intestine usually remain low due to peristalsis and normal homeostasis.[64] *C. perfringens* is classified into five biotypes (A, B, C, D, and E) based on the production of four major exotoxins, namely alpha (CPA), beta (CPB), epsilon (ETX), and iota (ITX); however, the production of more than 16 different exotoxins in various combinations has been associated with these bacteria, including perfringolysin O (PFO), enterotoxin (CPE), and beta2 toxin (CPB2).[64] The different biotypes of *C. perfringens* cause different diseases in relation with the exotoxins they produce. The major effect of the phospholipase/sphingomyelinase CPA, produced by all *C. perfringens* biotypes, is cell lysis and hemolysis, and its role on intestinal disease of large animals is not well understood. However, this toxin has been associated with hemolytic disease and hemorrhagic enteritis in large animals; CPB, produced by *C. perfringens* types B and C, is a trypsin-labile toxin associated with necrotizing enteritis and enterotoxemia in large animal neonates; ETX, produced by *C. perfringens* types D and B, is a trypsin-activated necrotizing toxin associated to vasculitis, edema, and necrosis of the CNS and enterotoxemia; and ITX, another trypsin-activated necrotizing toxin produced by *C. perfringens* type E, has also been associated to intestinal disease in small ruminants.[64,65] *C. perfringens* types C and D are considered the most important types in veterinary medicine as they can cause disease in most farm animals.[66] Severe clinical disease due to bacteria sporulation and massive toxin production only occurs when the normal intestinal environment and microbial balance are disrupted in affected individuals. Decreased peristalsis and poor ruminal and abomasal function have also been proposed as factors that contribute to disease presentation. Weather and handling stresses, feed changes, and an overabundance of high-energy feeds such as milk, bakery products, and cereal grains might promote bacteria overgrowth and exotoxin synthesis and release. Additionally, other enteric infections that disrupt the mucosal border may increase systemic absorption of toxins and promote severe disease.

C. perfringens type A Disease

C. perfringens type A is a normal inhabitant of the intestinal tract of large animals and is ubiquitous in the environment (soil). One study reported *C. perfringens* type A as the most common isolate among other clostridia from healthy young lambs.[67] *C. perfringens* type A has been associated with a fatal hemolytic syndrome in younger lambs and cattle but not goats ("yellow lamb disease"),[66,68] acute hemorrhagic enteritis and hemolytic enterotoxemia in cattle (hemorrhagic bowel/jejunal syndrome) and goats,[66,69,70] and intestinal hemorrhage and splenomegaly in farmed deer.[71,72] Risk factors for infection have not been established; however, high soluble carbohydrate diets and high BCSs have been associated with clinical disease.[69,70,72] This disease occurs most commonly in lambs 2 to 6 months old. Under favorable conditions, the organisms proliferate and cause a corresponding increase in alpha toxin production. The alpha toxin (CPA), in synergy with the beta2 toxin (CPB2), is responsible for hemolytic crisis, vasculitis, and gastrointestinal lesions. The clinical course usually is less than 24 hours.

Clinical Signs. In most cases, sudden death or history of found dead is common. Clinical signs observed usually include weakness, depression, fever or hypothermia, icterus, anemia, hemoglobinuria, tachypnea, colic, hemorrhagic diarrhea or absence of feces, and terminal recumbency.[66,69,70–72] Adult animals also are susceptible to hemolytic disease and vasculitis caused by *C. perfringens* type A infection.[66] Fatal abomasitis and rumenitis in neonates and juveniles also have been blamed on *C. perfringens* type A, but the rapid postmortem proliferation of the organism makes substantiation of this claim difficult.[73] Morbidity in a flock is lower than for many of the other enteric clostridial diseases, but the mortality rate is very high.

Diagnosis. The most characteristic clinicopathologic change is neutrophilic leukocytosis with a left shift. Other evidence of systemic toxemia (metabolic acidosis, azotemia, and increases in liver and muscle enzymes) also may be seen. Laboratory evaluation reveals evidence of intravascular hemolysis. Necropsy in sheep, goats, and cervids usually reveals evidence of hemolysis, pallor, jaundice, hemoglobinuria, hyperemic and edematous intestines,

splenomegaly, gastrointestinal serosal and mucosal hemorrhage, and multifocal internal petechial hemorrhages.[66,69,70–72] The isolation of *C. perfringens* type A from necropsied animals is not itself diagnostic. Definitive diagnosis can be made based on identification of the alpha toxin and the absence of other toxins by ELISAs or older, live animal assays. More recently, multiplex PCR techniques are replacing immunodiffusion assays for the identification of a specific toxin-producing gene isolate, typing of bacteria, and demonstration of toxins or toxin genes.[74] Gut content and intestinal samples collected from freshly dead animals make the most meaningful samples for diagnosis.[74]

Treatment. Administration of high doses (> 30,000 IU/kg BID) of penicillin and *Clostridium* antitoxin (10–20 mL subcutaneously [SC] or orally [PO]) is the mainstay of treatment, although animals may die acutely before therapies can be instituted.

Prevention. A conditionally licensed toxoid against the clostridial alpha toxin is available for cattle in the United States. A recent report demonstrated that a new vaccine including recombinant CPA, CPB, and ETX was effective at inducing protective antibodies to *C. perfringens* biotypes in cattle, sheep, and goats. This could be an alternative for the prevention of morbidity and mortality caused by *C. perfringens* type A. Prevention efforts should focus on environmental hygiene and avoiding gut conditions favorable for proliferation of the organism (high content of soluble carbohydrates in the diet). Because this type appears to survive better in soil than other types, preventing ingestion of soil may be important in preventing disease.

C. perfringens Type B and C Disease

C. perfringens types B and C occur in the soil and the animals' housing environment and can be shed by asymptomatic individuals. The reported geographic range of both diseases is limited (type B to the United Kingdom and South Africa and type C to the United Kingdom, Australia, and North America), even though infection with *C. perfringens* type C appears to occur worldwide. These organisms cause very similar diseases called *lamb dysentery* and *hemorrhagic enterotoxemia*, respectively. Very young lambs and kids (1–4 days to 2–3 weeks of age) are usually affected due to the presence of trypsin inhibitors in colostrum.[75] Older animals may become susceptible as a result of overwhelming infection or trypsin inhibition by some soy and sweet potato products or temporary suppression of pancreatic trypsin production (Struck in adult sheep). With both diseases, the beta toxin (CPB) is a required pathophysiologic factor, and inactivation of this toxin after maturation of pancreatic trypsinogen secretion is what commonly limits the susceptible population to neonatal animals. The cytolytic and necrotizing effects of the beta toxin (CPB), in synergy with the beta2 toxin (CPB2), cause necrosis and ulceration of the intestinal mucosa and are translocated into circulation, causing severe toxemia and death.[75] The diseases initially affect lambs and kids younger than 3 days of age, with illness occasionally occurring in older lambs. The incidence of disease in lambs and kids can be around 15 to 30%, with a case fatality rate of 100%. High stocking density in lambing areas, cold weather, single-born lambs, and high milk production of dams have been suggested as potential risk factors for type B and C enterotoxemia.[76] Because of management practices in young animals and age-related vulnerability, fecal contamination of teats, hands, and equipment that enter the mouths of the neonates (orogastric tubes and nipples) is a major cause of infection.

Clinical Signs. Severely affected animals or those at the beginning of an outbreak usually are found dead. Less acutely affected animals expel initially yellow, fluid feces that progressively become brownish and/or hemorrhagic. Feces may also contain flecks of blood and show splinting of the abdomen, especially when handled, along with signs of colic and feed refusal. The clinical course usually is short, and the disease is almost always fatal. One study reported acute abdominal pain, hemorrhagic diarrhea, and death within 24 hours of experimental oral inoculation of three goat kids with a field strain of *C. perfringens* type C.[75] Dehydration, anemia, and severe weakness are also common clinical signs in affected animals. Terminal convulsions and coma occasionally are noted, especially in outbreaks in the United States. *C. perfringens* type C in older sheep causes the disease known as "struck." Affected animals usually are found dead or with signs of toxemia. Specific antemortem signs of gastrointestinal disease are rare. Specific antemortem signs of gastrointestinal disease are rare. Clinical pathology changes observed in these animals include neutrophilic leukocytosis with a left shift. Additional evidence of systemic toxemia (metabolic acidosis, azotemia, and increases in liver and muscle enzymes) also may be seen.

Necropsy Findings. Postmortem examination reveals focal hemorrhagic ulcers (up to 2.5 cm in diameter) in the small intestine (mostly in the ileum) with type B infection and diffuse reddening with hemorrhage and necrosis of the abomasum and the entire segments of the intestine with type C infection. Type C infections in ruminants can also present with generalized peritonitis, subendocardial and subepicardial hemorrhages, and hemorrhagic lymph nodes. Animals that die very rapidly may exhibit minimal or no gross abnormalities of the intestine. A similar syndrome of type C enterotoxemia has been previously reported in a sika deer *(Cervus nippon)*.[72] Sudden death, severe hemorrhagic gastritis including forestomach and abomasum, and catarrhal enteritis was observed in the affected animal.

Diagnosis. Diagnosis of these diseases is made by identification of characteristic history, clinical signs, postmortem lesions, and positive toxin assays. Because the beta toxin is very labile, negative toxin assays are less significant than negative assays for presence of other tissue-invading clostridia. The isolation of *C. perfringens* type B or C from necropsied animals is not itself diagnostic. Immunodiffusion assays or multiplex PCR of intestinal contents for specific isolate and beta toxin (CPB) identification are recommended to obtain final diagnosis (see "Diagnosis" in "*C. perfringens* type A" section).

Treatment. If the infection is identified early in the disease course, high doses of oral and parenteral penicillin and *C. perfringens* C and D antitoxin may be of benefit. IV fluids and antiinflammatory agents may be indicated as well. Usually, the condition is not recognized early enough, and animals are found dead or dying.

Prevention. A beta toxoid is available in the United States and other countries. It usually is packaged with an epsilon toxoid. The best protection is achieved by vaccinating pregnant dams twice, with the second dose administered approximately 3 to 4 weeks before lambing or kidding and annual booster. Deer does should receive double the dose of sheep as low antibody responses to clostridia have been reported in these animals.[77,78] Vaccination of pregnant dams is directed to increase specific colostrum antibodies to protect neonates. Juveniles also should be vaccinated twice or three times at 2 months, 3 months, and 4 months. Adults, including males, should receive an annual booster. In the face of an outbreak, the lambing area should be moved to a different place. Additionally, vaccination of dams and newborns with a

beta toxoid and administration of *C. perfringens* C and D antitoxin can be carried out in the face of an outbreak to reduce morbidity and mortality.

C. perfringens Type D Disease

C. perfringens type D produces epsilon toxin (ETX), which is responsible for causing type D enterotoxemia in sheep, goats, calves, and deer.[79,80] Other common names for the disease include "overeating disease" or "pulpy kidney disease." The disease has a worldwide distribution and occurs primarily in suckling lambs of 1 to 10 weeks of age, although it has also been reported in weaned lambs up to 10 months of age and adult sheep. The disease is also common in grazing goats and deer. The prevalence of disease has been reported from 1.49 to 3.14%, with a 100% case fatality rate in feedlot lambs.[81] One study on proportional distribution of goat-herd mortality in the province of Quebec, Canada, reported a 17.1% mortality of goats to *C. perfringens* type D enterotoxemia.[82] The disease is more common in feedlot lambs after they enter the lot. Tail docking, castration, and other management interventions are thought to decrease the incidence of this disease by temporarily decreasing appetite. The disease also affects unvaccinated adult sheep, even without any history of stressors or feed changes. Sudden changes in the diet are the main predisposing factor in goats. The disease can occur in vaccinated goats, as vaccination has not demonstrated to be completely protective in this species.[83,84]

C. perfringens type D is normally found in the gastrointestinal tract of healthy ruminants, but the acid environment of the abomasum and continuous peristalsis help to keep numbers of bacteria and levels of toxin production low. However, under specific conditions such as overingestion of high-energy feeds (milk, grain, and lush pasture), excess of fermentable starches in the intestine, and intestinal stasis, the organism proliferates rapidly, producing lethal quantities of epsilon toxin. These conditions are usually triggered in well-conditioned, fast-growing animals that are on a highly nutritious diet. The epsilon toxin, once produced, acts locally, causing increasing gut permeability and widespread tissue damage. Epsilon toxin and other exotoxins are then absorbed through the intestinal tract into systemic circulation and transported to the brain, lungs, and kidneys, causing increased endothelial permeability, perivascular edema, and generalized necrosis.[79,83] The characteristic increased vascular permeability and perivascular edema in the kidney and brain are responsible for the name of "pulpy kidney disease" and "focal symmetric encephalomalacia."

Clinical Signs. The course of the disease is usually very short (0.5–12 hours), so sudden or spontaneous death is a common clinical sign across affected small ruminant species.[80,84–86] Natural disease caused by *C. perfringens* type D differs between sheep and goats, possibly because of a difference in relative local and systemic actions of the epsilon toxin, although experimental models have demonstrated that both species develop similar lesions.[84,87,88] In sheep, systemic actions of the toxin leads to mostly neurological signs such as dullness, depression, ataxia, trembling, stiff limbs, opisthotonus, convulsions, frothy mouth, and rapid death. In goats, actions of the toxin appear to be more localized to the intestinal tract, causing enterocolitis, colic, diarrhea, dehydration, and occasional neurological signs.[85,86]

Necropsy Findings. Postmortem findings in sheep are characterized by edema of the brain, lungs, and heart in addition to hydropericardium.[89] Edema of the kidneys (pulpy kidney lesion) is inconsistent. Sheep usually demonstrated minor and inconsistent intestinal changes.[89] Other lesions reported in cattle and deer include hemorrhages on the epicardium, thymus, and diaphragm and petechial hemorrhages in the jejunal mucosa.[80,90] Necropsy lesions reported in goats include pseudomembranous enterocolitis with mucosal ulceration, as well as fibrin, blood clots, and watery contents in the bowel lumen. Evidence of systemic toxemia, including multifocal petechial and ecchymotic hemorrhage, proteinaceous exudates in body cavities, pulmonary edema, hydropericardium, and cerebral malacia with perivascular cuffing, have also been reported in goats and affected deer.[80,84,87,88,91]

Clinical Pathology. Characteristic clinicopathological changes include pronounced hyperglycemia and glucosuria, which are considered a hallmark of *C. perfringens* D enterotoxemia.[86] Additionally, neutrophilic leukocytosis with a left shift and evidence of systemic toxemia (metabolic acidosis, azotemia, and increases in liver and muscle enzymes) also may be seen.

Treatment. In general, the course of disease is too acute for the establishment of any treatment. However, as with infections with types B and C, if the disease is identified early in the disease course, high doses of oral and parenteral penicillin in addition to *Clostridium* C and D antitoxin may be of benefit. IV fluids and antiinflammatory agents may be indicated as well.

Prevention. Vaccination of pregnant ewes with two doses of toxoid, with the second dose given 3 to 4 weeks before lambing, and adequate ingestion of colostrum are the best methods of protecting newborn lambs. Vaccination of older lambs should occur before exposure to diets rich in carbohydrates (grain—feedlot settings) or lush pastures. In these cases, lambs should be vaccinated twice or three times around 2, 3, and 4 months of age. Males and adult females that are not part of the breeding program may be vaccinated annually. Vaccination has been shown to protect goats from experimental disease, but clinical evidence suggests that well-vaccinated goats are still susceptible to developing clostridial enteritis. The toxoids may not protect against local action of the toxins in the goat, which appears to play a greater role in their disease than it does in the sheep.[84,87,88] More frequent vaccination (every 6 months) in goats is suggested to increase protection. The adjuvant present in some multivalent clostridial vaccines may cause subcutaneous reactions that may lead to abscess formation. In the face of an outbreak, immediate mass administration of C and D antitoxin (200 IU/kg) in addition to vaccination is recommended.[92]

Nonenteric Clostridial Infections

C. novyi, *C. septicum*, *C. chauvoei*, and *C. sordelli* have been identified as causal agents of severe muscle, liver, and abomasal necrosis in small ruminants and cervid species.[66,93–95] These organisms are usually present in the soil and environment and in the gastrointestinal tract and liver of healthy ruminants.[66] Pathogenesis is usually facilitated by trauma of affected tissues, local multiplication of the organism, local and systemic damage by exotoxin production, and ultimately death.[66,96] Four types of *C. novyi* have been described, A, B, C, and D. *C. novyi* type C is considered nontoxigenic and therefore is not associated with disease. *C. novyi* type A produces alpha toxin and is associated with wound infections and myonecrosis in cases of "bighead" and "malignant edema." *C. novyi* type B produces alpha and beta toxins and is associated with infectious necrotic hepatitis or "black disease."[97,98] The temporal and geographic distributions of black disease resemble those of fascioliasis, with the highest incidence of disease in milder, moister months in many countries. Black disease is less common in sheep than in cattle and is rare in goats.[66,96] *C. novyi* type D *(C. haemolyticum)* produces beta toxin and is associated

with bacillary hemoglobinuria (red water disease). *C. septicum* produces alpha toxin and is associated with malignant edema and necrotic abomasitis (Braxy). *C. chauvoei* produces alpha and beta toxins and is associated with severe myonecrosis observed in blackleg and *C. sordelli* produces a hemolytic toxin associated with myonecrosis in cases of malignant edema and blackleg.[96,97]

Black Disease

Pathogenesis. Spores of the organism shed in feces of carrier animals contaminate the environment and are ingested with feed/grass and stored within Kupffer cells.[97,98] Liver damage caused by migrating liver fluke larvae (*Fasciola hepatica*, *Fasciola gigantica*, and *Cysticercus tenuicollis*) create perfect ischemic conditions that induce germination of *C. novyi* type B spores and toxin synthesis and production.[97,98,99] The alpha toxin is necrotoxic and causes liver necrosis and diffuse damage of the vascular system.[98] The beta toxin is produced in smaller amounts and contributes to vascular damage and systemic toxemia. Infective organisms also may be brought into the liver by the flukes.

Clinical Signs. The course of disease from first illness to death is short and never lasts more than a few hours in sheep. Therefore, peracute or sudden death is not uncommon in this species. Well-nourished adult sheep between 2 and 4 years are more commonly affected. The disease course is a little longer (1–2 days) in cattle and deer.[66,95] Affected sheep are debilitated, fail to keep up with the flock, and exhibit generalized weakness, sternal recumbency, separation, and anorexia. Tachypnea and tachycardia may be seen; high fever (105–107° F) occurs early in the disease. Clinical signs observed in cattle, goats, and deer are similar and may include severe depression, anorexia, abdominal distention, colic, ruminal stasis, and lateral recumbency.[66,94,95,99,100,101] A report of black disease in a forest reindeer *(Rangifer tarandus fennicus)* described serosanguinous discharge from mucocutaneous orifices (nostrils and anus), periorbital edema, and nystagmus in addition to other clinical signs.[95]

Necropsy Findings. Necropsy might be difficult due to rapid autolysis of tissues in affected animals. Severe venous congestion usually darkens the underside of the skin of affected animals, giving this disease its common name of "black disease." Fluid in the pericardial sac, pleural space, and peritoneal cavity is usually present.[66] Endocardial and epicardial hemorrhages are a common finding. The liver is swollen and congested and on its diaphragmatic surface presents pale foci of coagulation necrosis; however, solid organs such as liver and kidneys could be in an advanced state of autolysis. Characteristic lesions of black disease in the liver are single or multiple yellow to white areas (1–2 cm in diameter) of necrosis surrounded by a bright hyperemic zone.[102] A recent report of black disease in a reindeer described moderate amounts of dark red thoracic and pericardial fluid, edema of the lungs and upper respiratory tract, swollen spleen, and several well-circumscribed areas of black discoloration in the liver.[95]

Diagnosis. The most characteristic clinicopathological change is neutrophilic leukocytosis with a left shift. Additional evidence of systemic toxemia (metabolic acidosis, azotemia, and increases in liver and muscle enzymes) also may be seen; however, diagnosis of black disease is based on characteristic history (endemic liver fluke areas), clinical signs, and postmortem findings and testing. An impression smear of the margins of the liver might reveal large numbers of gram positive rods, but this is not definitively diagnostic. Anaerobic culture of *C. novyi* from typical liver lesions, in addition to demonstration of the alpha/beta toxins from peritoneal fluid or liver (fresh—refrigerated), through ELISA or PCR is required to establish final diagnosis.[98,100] The use of fluorescent antibody and IHC for the identification of *C. novyi* on liver impression smear samples or other liver (formalin-fixed) samples have also been described.[95,100]

Treatment and Prevention. Treatment is rarely possible because of the fulminant clinical course of the disease; however, if treatment is attempted, high doses of penicillin G sodium (20,000–40,000 IU/kg) IV every 6 hours or oxytetracycline 10 mg/kg IV every 12 hours should be initiated. Supportive care, including IV fluids, nutritional support, and stress reduction, may be beneficial. In the face of an outbreak, vaccination of the whole herd/flock should be initiated immediately.

Efforts to control fluke infestation constitute the most effective approach to prevention of this disease. Administration of multivalent clostridial vaccines containing *C. novyi* is highly effective. Animals should be vaccinated every 6 months starting around 2 to 3 months of age and before parturition as protective immunity is short lived. In flocks at high risk for developing this disorder, a booster vaccine given 1 month before expected fluke exposure may provide additional protection.[99,100] Deer should be vaccinated in the same fashion as sheep but double the vaccine dose for sheep should be used for these animals as they do not develop a strong antibody response to commercially available multivalent vaccines.[77,78] Efforts to eliminate the organism from soil and environment are usually unrewarding but carcasses of animals dying from the disease should be burned, deeply buried, or removed from the premises.

Bacillary Hemoglobinuria (Red Water Disease)

Pathogenesis. *C. novyi* type D *(C. haemolyticum)* is the etiologic agent associated with red water disease. *C. haemolyticum* is similar to other clostridial species in its life cycle and appears to thrive on alkaline soils and pastures with standing water. The disease tends to be seasonal occurring at times of high larval fluke migration. Similar to *C. novyi* B, *C. haemolyticum* colonizes the livers of healthy animals and proliferates after liver damage, including damage caused by migrating flukes (*F. hepatica*, *Fascioloides magna*, *Dicrocoelium dendriticum*, and *C. tenuicollis*), liver abscessation (*Fusobacterium necrophorum* or *Trueperella pyogenes*), or damage incurred during liver biopsy.[100,103] Under ischemic conditions of the liver, spores of *C. haemolyticum* germinate and produce high amounts of beta toxin. The beta toxin causes localized hepatic necrosis and after reaching circulation induces severe intravascular hemolysis and damage of the capillary endothelium.[103] Intravascular hemolysis leads to rapid anemia and death due to anoxia. The disease is seen worldwide and is more commonly reported in sheep than in goats. Bacillary hemoglobinuria has been reported in a free-ranging elk calf *(Cervus elaphus roosevelti)* found dead in the southwest of the state of Washington, United States.[104]

Clinical Signs. Bacillary hemoglobinuria usually affects well-nourished animals older than 1 year of age.[105,106] In most cases, the disease is per-acute and sudden dead or found dead is the only sign.[103] In cases where signs are recognized antemortem, affected animals appear weak, depressed, and febrile (104–106° F); blood or blood-tinged froth may be present in the nostrils; rectal bleeding and bloody feces may be present; and severe hemoglobinuria (dark red, port wine-colored urine) is usually observed.[105,106] Blood appears thin and watery and mucous membranes are pale and icteric. Heart and respiratory rates are high and become much higher with any sort of effort or stress. Other terminal signs

include bloat and the presence of blood in the nostrils, mouth, vagina, and rectum. Death occurs within hours to a few days after onset of clinical signs.[100]

Necropsy Findings. Gross lesions include jaundice of mucous membranes and tissues and subcutaneous petechial/ecchymotic hemorrhages, edema, and emphysema. Marked autolysis of internal organs might prevent identification of typical lesions. Dark red urine is present in the bladder.[102] Lymph nodes and spleen are congested and hemorrhagic. Hemorrhagic abomasitis and enteritis might occur, as well as the presence of hemoglobin-stained transudate in pleural and peritoneal cavities and pericardial sac. Pulmonary edema is common. The pathognomonic lesion is the ischemic hepatic infarcts ranging from 5 to 30 cm in diameter with a hyperemic interface with healthy liver tissue.[100,102]

Diagnosis. Clinicopathological abnormalities usually include anemia, leukocytosis with mature neutrophilia, and degenerative left shift (immature forms of neutrophils and toxic changes) often is present.[106,107] Serum biochemical evaluation may reveal increased levels of liver enzymes such as sorbitol dehydrogenase, GGT, aspartate aminotransferase, and increased indirect total serum bilirubin.[105–107] Presumptive diagnosis can be made on history, clinical sigs, clinicopathological abnormalities, and postmortem findings; however, similar to black disease, final diagnosis should be based on anaerobic culture of *C. novyi* from typical liver lesions in addition to demonstration of the beta toxins from peritoneal fluid or liver (fresh—refrigerated) through ELISA or PCR techniques.[98,100,104,106] The use of fluorescent antibody and IHC for the identification of *C. novyi* on liver impression smears or other liver (formalin-fixed) samples has also been described.[95,100] More recently, a PCR assay for the detection of *C. novyi* type D in cattle has been reported.[107]

Treatment and Prevention. Treatment is rarely possible because of the fulminant clinical course of the disease; however, if treatment is attempted, high doses of penicillin G sodium (20,000–40,000 IU/kg) IV every 6 hours or oxytetracycline 10 mg/kg IV every 12 hours should be initiated. Supportive therapy should include the administration of IV fluids, blood transfusions, and antiinflammatory agents. Efforts to control liver flukes and prevent other causes of liver damage are most important. Administration of multivalent clostridial vaccines containing *C. novyi* is highly effective. Animals should be vaccinated every 6 months starting around 2 to 3 months of age and before parturition as protective immunity is short lived. In flocks at high risk for developing this disorder, a booster vaccine given 1 month before expected fluke exposure may provide additional protection.[100] Deer should be vaccinated in the same fashion as sheep, but double the vaccine dose for sheep should be used as these animals as they do not develop a strong antibody response to commercially available multivalent vaccines.[77,78] Efforts to eliminate the organism from soil and environment are usually unrewarding but carcasses of animals dying from the disease should be burned, deeply buried, or removed from the premises.

Bighead

Pathogenesis and Clinical Signs. Fecal and soil contamination of wounds received during fighting (head-butting) or dehorning (disbudding) leads to proliferation of *C. novyi* type A in damaged head and neck tissues.[100] Accumulation of secreted toxins leads to swelling, edema, serohemorrhagic exudates, and local tissue necrosis. Wounds appear and smell gangrenous. Systemic toxemia may affect internal organs, leading to the death of the animal. *C. sordelli* causes identical disease.

Diagnosis. Laboratory analysis may reveal an increase in enzymes of muscle or liver origin as well as neutrophilic leukocytosis with many immature and toxic neutrophils. Postmortem findings include local necrosis around the injury site. Diagnosis usually is made by characteristic clinical signs and lesions.

Treatment. Wound management (disinfection, debridement) and administration of high doses of penicillin G sodium (20,000–40,000 IU/kg) IV every 6 hours are important treatment considerations.

Prevention. Ram management may aid in the prevention of head-butting wounds. Vaccination with multivalent clostridial toxoids starting around weaning time (3–6 months of age) and with annual boosters also may be helpful. In flocks with a high prevalence of this disorder, a booster vaccine given to rams 1 month before the breeding season and to ewes/does before parturition may provide additional protection.[100]

Malignant Edema and Braxy

Pathogenesis. *C. septicum* is the most important agent in the pathogenesis of malignant edema and braxy. In the case of malignant edema, other tissue-invasive clostridia (*C. chauvoei*, *C. sordelli*, and *C. perfringens* A) have also been associated with this disease, and mixed infections are common. The pathogenesis of infection is often similar to that seen with bighead and blackleg: soil or fecal clostridial invasion of a contaminated wound. In sheep and goats, this disease has been reported following lambing/kidding, after shearing of tail docking.[100] *C. septicum* can also invade the abomasal lining of lambs, causing severe hemorrhagic, necrotic abomasitis known as braxy.[108] Activation of dormant bacteria in previously damaged tissue (myositis/abomasitis) similar to that seen in clostridial necrotic hepatitis also occurs.[108] In both cases (malignant edema and braxy), bacterial toxins precipitate local tissue necrosis and systemic toxemia. The alpha, beta, gamma, and delta toxins produced by *C. septicum* are lecithinase, deoxyribonuclease, hyaluronidase, and hemolysin, respectively. Commonly affected sites of malignant edema include castration, dehorning, and injection sites; the umbilicus; and the postpartum uterus.[100] Factors that promote braxy have not been identified, although it usually affects weaned and yearling lambs in the winter after ingestion of frozen feedstuffs implicated as initial causes of abomasitis.[100,108] Both forms of the disease have worldwide distribution and are described more in sheep than in goats.[100,108]

Clinical Signs. Malignant edema is characterized by local lesion (wound) or regional pain characterized by swelling and edema that progressively becomes tense and dark (skin). High fever, signs of shock/toxemia, and frothy exudation of the wound are usually present. Evidence of subcutaneous gas production is less common in this infection than in blackleg. Uterine infection may cause a fetid vaginal discharge. Death occurs within hours to a few days after onset of clinical signs.[100] Braxy usually causes death before any abnormalities are noted. On rare occasions, signs of sudden onset of illness with high fever, abdominal distention, depression, colic, and recumbency may be seen before death.[100]

Diagnosis. Characteristic clinicopathologic changes include neutrophilic leukocytosis with a left shift. A decrease in WBC and RBC counts also is possible because of the leukocidal and hemolytic effects of the toxins. Additional evidence of systemic toxemia (metabolic acidosis, azotemia, and increases in liver and muscle enzymes) also may be seen. Examination of a Gram-stained smear from the edematous swelling(s) or wound swabs could give an early diagnosis. One study reported the successful use of a PCR assay for the identification of bacteria associated with malignant

edema in cattle, sheep, and other ruminants.[109] Postmortem changes with malignant edema include dark red, swollen muscle filled with hemorrhagic, proteinaceous exudate and little or no gas. With braxy, the abomasal wall is hemorrhagic and necrotic. Both diseases are associated with rapid postmortem decomposition of the carcass.

Treatment and Prevention. Wound management and the rapid administration of high doses of penicillin (penicillin G sodium at 20,000–40,000 IU/kg IV every 6 hours) are important in treating malignant edema. Local treatment consists of surgical incision of the affected area to provide drainage and irrigation with peroxide. Injection of penicillin directly into or in the periphery of the lesions may help. Ancillary treatments such as IV fluids, antiinflammatory agents (e.g., flunixin meglumine, 2 mg/kg IV), and nutritional support may be necessary. Maintenance of good hygiene during procedures such as lambing, tail docking, shearing, castration, obstetric manipulation, and administering injections is helpful in preventing malignant edema. Multivalent clostridial toxoids may provide some protection and should be given annually to animals at risk for the disorder.[110]

Blackleg

Pathogenesis. Several species of clostridial organisms can cause myonecrosis in small ruminants.[93,111,112] The disease is acute to per-acute, has a short course of duration, and is usually fatal. *C. chauvoei*, *C. septicum*, and *C. sordelli* are commonly involved with clostridial myonecrosis in ruminants.[111–113] Blackleg can be enzootic in some areas or farms because of increased bacterial contamination and occurs more commonly in the warm months of the year.[113–115] Animals between 4 months and 3 years of age can be affected.[111,112] *C. chauvoei* is the most important cause of blackleg. *C. sordelli* tends to be involved in the myonecrosis of older feedlot animals.[112] These organisms are found in the soil and can gain access to muscles after translocation from the gastrointestinal tract and liver into systemic circulation. Additionally, direct inoculation of the organisms by penetrating wounds or intramuscular injections has been suggested. Local tissue trauma, wounds, unsanitary procedures (i.e., shearing, tail docking, and castration), umbilical infection (neonates), or vaginal trauma from lambing can create perfect conditions for the germination of clostridial spores inducing rapid toxin synthesis and production.[113] In some cases, bacterial proliferation appears to occur in a site distant from the original wound (i.e., fetal infections after shearing of a ewe and myocardial necrosis in cattle and sheep).[113] Bacterial toxins cause severe local tissue necrosis, systemic toxemia, and ultimately death. As with braxy, several other strains of tissue-invasive clostridia can cause this disease and mixed infections are common.

Clinical Signs. Clostridial myonecrosis usually progresses rapidly and sudden death or history of found dead is not uncommon.[111–113] Clinical signs in animals who are still alive include local to regional painful, edematous swelling most commonly in the limbs or trunk muscles. Skin of the affected area can become discolored and crepitus; however, in affected sheep, subcutaneous edema and gaseous crepitation are uncommon and cannot be felt before death.[111] Other signs might include stiff gait, lameness, fever, and signs of shock. In cases where the infection occurred through a wound, there is extensive local damage and malodorous serosanguinous fluid discharge. *C. chauvoei* also causes uterine infection and severe gangrenous mastitis in postparturient ewes.[111,113] In these cases, uterine and mammary infections may cause fetid vaginal and mammary discharge, respectively. Death often occurs within 12 to 36 hours after onset of clinical signs.

Necropsy Findings. Rapid tissue autolysis is not uncommon in animals that succumb to clostridial myonecrosis. Blood-stained fluid and froth can be observed discharging from nostrils and anus. In small ruminants and especially sheep, affected muscle areas are more localized and deeper, brown to black discoloration is present, the subcutaneous edema is not as severe, and, although there is gas present, is not in such large amounts as in cattle. In cases of infection from skin wounds, the area demonstrates subcutaneous edema, swelling, and underlying muscle discoloration. In cases of infection through the urogenital tract, typical lesions are found in the perineal area, vagina, uterus, and fetus. Lung congestion, fibrinohemorrhagic pleuritis, pericarditis, myocardial damage, and bloat are also common findings.[111,112]

Diagnosis. It is rarely possible to obtain samples for clinicopathological analysis due to the per-acute course of the disease. If samples can be obtained, common findings include neutrophilic leukocytosis with a left shift. A decrease in WBC and RBC counts also is possible because of the leukocidal and hemolytic effects of the toxins. Additional evidence of systemic toxemia—metabolic acidosis, azotemia, and increases in liver and muscle enzymes—also may be seen. Presumptive diagnosis can be made from history, characteristic clinical signs, and gross pathology findings; however, aspirates or tissue specimens from affected muscles for direct smear examination, fluorescent antibody testing, or anaerobic culture are required for definitive diagnosis.[111,112] A multiplex PCR is available for identification of pathogenic clostridia on fluid and tissue samples.[109]

Treatment and Prevention. Aggressive antibiotic therapy (e.g., penicillin G sodium or potassium penicillin at 20,000–40,000 IU/kg IV every 6 hours), in combination with surgical debridement of affected tissues (fasciotomy), and supportive care (nutritional support, IV fluids, and antiinflammatory agents) are important within the treatment plan for clostridial myositis. Prognosis for treatment of all types of clostridial myositis cases is usually guarded to poor and depends on the duration and extension of the lesions. Maintaining excellent hygiene during invasive procedures such as castration, obstetric manipulation, shearing, tail docking, and administering injections is helpful in preventing blackleg. Multivalent clostridial toxoids may provide some protection and should be given to all animals starting at weaning time, before parturition, and annually.[114,115]

Diseases Caused by Noninvasive Clostridia

Both tetanus and botulism are important diseases in small ruminant medicine. These two diseases are covered elsewhere in this book (see Chapters 5, 11, 13, 19, and 20).

Juvenile and Adult Sepsis

Pathophysiology

Older animals are generally more resistant to sepsis than neonates because they have larger amounts of circulating antibodies. However, this resistance can be overwhelmed by aggressive bacteria, or loss of immune function can allow invasion by opportunistic bacteria. Malnutrition, parasitism, transport, overcrowding, other diseases, extreme weather conditions, and other stressors are the major causes of immune suppression.

Clinical Signs

Sepsis may produce peracute, acute, or chronic disease signs. Peracute signs include fever, injected mucous membranes (including the sclera), tachycardia, tachypnea, dyspnea, swollen joints, lameness, splinting of the abdomen, weakness, depression, anorexia, recumbency, seizures, coma, and sudden death. Acute signs are similar, except that they persist for a longer period and therefore are more likely to be noticed. Chronic signs usually result from the partial clearance of infection after an acute episode, which may be clinical or inapparent.

Gram Negative Sepsis

Pathogenesis. Gram negative bacteria and their toxins gain access to the blood from a site of proliferation or destruction. The most important toxin is endotoxin, a group of lipopolysaccharide molecules that reside within the wall of the bacteria. Bacteria or endotoxins incite a systemic inflammatory response, chiefly through activation of host macrophages and stimulation of host cytokine release. These cytokines cause inflammation, produce leukocyte recruitment, increase capillary permeability, induce fever through stimulation of the hypothalamus, and have regional or diffuse vasomotor effects.

Because the ruminant gut has a plentiful population of gram negative bacteria, it is implicated as the source of most cases of gram negative sepsis. Grain overload causes a die-off of the normal gram negative ruminal flora, ulcerative enteric disease allows invasion of bacteria or absorption of their toxins, and ingestion of pathogens provides a suitable place for proliferation and route for invasion of the body. Gram negative sepsis caused by opportunistic organisms is best recognized in immunocompromised neonates but also can be seen in stressed or immunocompromised animals of all ages. *E. coli* is commonly found in fecal material, *Klebsiella pneumoniae* is found in feces and wood products, *F. necrophorum* lives in the gastrointestinal tract and in soil and invades through compromised gastric mucosa or foot-rot lesions, and *Pseudomonas aeruginosa* is commonly found in water and wash solutions.

Primary pathogens are most common in adults. Although some coliform bacteria may fit into this category, by far, the most important genus is *Salmonella.* Sources of *Salmonella* infection are numerous and include carrier animals of the same species, cattle, rodents, birds, other animals, environmental contamination, and possibly feedstuffs. Only one serotype of *Salmonella* is specifically adapted to sheep *(Salmonella abortus ovis)*, and it is not found in North America. No strain is known to be host-adapted to goats or cervids. Therefore, all infections in sheep, goats, and cervids have the potential to spread to and from other species, including humans. Serotypes of *Salmonella* that have caused important infections in sheep or goats include *Salmonella typhimurium*, *Salmonella dublin*, and *Salmonella montevideo.* Most of these infections lead to bacteremia with mild systemic signs, followed by abortion. *S. dublin* and *S. typhimurium* tend to cause more illness in adults because of fibrinonecrotic enteritis.

Clinical Signs. Affected animals can exhibit anything, from mild depression with a low-grade fever to shock. Common signs include fever, tachycardia, tachypnea, depression with slow or absent eating and drinking, weakness or recumbency, and injection or cyanosis of mucous membranes. Organ-specific signs may betray the source or at least the primary location of the infection. Fetid discharge may be seen with metritis or abortion; dyspnea and abnormal lung sounds may be seen with pulmonary infection; and bloat, ruminal atony, abdominal distention, and diarrhea may be seen with gastrointestinal infections.

Diagnosis. The most common abnormality identified on a CBC with peracute gram negative sepsis is panleukopenia. Over the course of several days, this condition may resolve, first through an increase in immature neutrophils and later through an increase in mature neutrophils and restoration of lymphocyte counts. Very immature cells, severe toxic changes, and persistence of neutropenia suggest a poor prognosis. Serum biochemical changes often reflect the severity of the condition. The greater the evidence of shock or tissue damage, the worse the prognosis. Metabolic acidosis with a large anion gap and azotemia suggest advanced disease. Necropsy findings include diffuse evidence of inflammation, including pulmonary congestion, and polyserositis with body cavity exudates. Hemorrhagic pneumonia or fibrinonecrotic enteritis may be seen and reflect the source of bacterial invasion. In all cases, diagnosis is best confirmed by bacteriologic culture of body tissues or fluids. In the live animal, culture of blood, feces, or tracheal fluid yields the best results. When several animals are infected, environmental samples (including feed, water, and bedding) should be tested for the presence of the bacteria. Bacteriologic culture of aborted fetuses or placentas frequently yields heavy growth of the organism.

Prevention. Maintaining overall good health and hygiene is the best means of preventing gram negative sepsis. Anti-endotoxin bacterins are available for cattle in the United States, but their use in small ruminants has been too limited to assess their efficacy. During a flock outbreak, the use of autogenous bacterin may help prevent the spread of disease on a farm.

Important Bacterial Causes of Sepsis

Actinobacillus seminis is a gram negative bacillus or coccobacillus that affects primarily the male and female reproductive tracts. Infection causes posthitis, epididymitis, and orchitis in rams and metritis and abortion in ewes. Other sites of infection, including rare occurrences of chronic sepsis, also are possible. Serologic tests are much more useful for identifying infected flocks than infected individuals within flocks. Definitive diagnosis depends on bacteriologic culture of the organism and differentiation of it from *Brucella ovis.* The bacillus is common in sheep in some parts of the world but is uncommon in North American sheep and goats.

T. pyogenes is best known as an abscess-forming bacterium because of the thick pus formed in response to infection by it and the fibrinous response it elicits. It occasionally also causes sepsis. Its association with chronic sepsis lends credence to the belief that *Trueperella* is often a secondary invader that colonizes tissues damaged by another bacterium (see Chapter 10).

Bacillus anthracis is a large, gram positive, anaerobic bacillus that causes anthrax. It forms spores under aerobic conditions (such as on culture plates) but rarely does so when oxygen tensions are low, as in carcasses. The organism affects most mammals, with herbivores being most susceptible. It is usually carried from one area to another by shedding or dying animals and also can multiply in alkaline, nitrogenous soils. Periods of heat and intermittent flooding promote overgrowth of the organism. *B. anthracis* spores may be inhaled or ingested; in rare cases, the bacillus itself may be spread by biting flies. After local replication, the organism gains access to the blood, where it multiples readily. Large numbers of the organisms colonize the spleen. *B. anthracis* secretes a holotoxin made of edema factor), protective antigen, and lethal factor. This toxin impairs phagocytosis, increases capillary permeability, and

inhibits clotting. Splenic engorgement, generalized edema, circulatory shock, and bleeding diathesis are the most common lesions and signs of anthrax. Generalized infection should be considered uniformly fatal. Death may occur before or within hours of initial recognition that the animal is sick. Prophylactic antibiotic treatment of healthy animals (oxytetracycline 10 mg/kg IV SID) may decrease spread and mortality during outbreaks. The disease is reportable in many areas. Local forms of anthrax also occur, most commonly after transmission through a skin wound or fly bite. Local heat, pain, swelling, and necrosis are seen first, and the generalized syndrome often follows.

Treatment for Sepsis (Adult and Juvenile)

Bacterial organisms are rarely identified before important treatment decisions must be made. Therefore, treatment should follow general principles and have a wide spectrum of efficacy. Antimicrobial drugs are the cornerstone of treatment. In meat- or milk-producing animals, the veterinarian must be careful to use drugs within label directions or have a rational plan for extra-label drug use. The issue of extra-label drug use is especially important in small ruminants and cervids because very few pharmaceutical products have been licensed for them in North America.

Unless a specific organism is suspected (clostridiosis or anaplasmosis), a single antibiotic or combination of antimicrobial drugs to provide a broad spectrum of coverage should be selected. Penicillins, macrolides, tetracyclines, and cephalosporins all provide effective coverage against gram positive pathogens. The newer third-generation cephalosporins are effective against many systemic and enteric gram negative pathogens. The gram negative pathogens of the respiratory tract are often sensitive to other classes of antibiotics. Macrolides and tetracyclines also are effective against *Mycoplasma* species and rickettsial organisms.

NSAIDs are almost always beneficial in severe infectious conditions because of their antiinflammatory, antipyretic, and antiendotoxic effects. They are likely to be more effective than corticosteroids because they provide benefits without suppressing the immune response. All such drug use should be considered extra-label and administered accordingly with appropriate withdrawal times established. Specific antisera are available for some of the clostridial diseases and may be beneficial if given before widespread tissue necrosis has occurred. Severely compromised animals should be treated with fluids for shock (see Chapter 3).

Zoonotic Infections

Contagious Ecthyma

The most common zoonotic disease risk posed by exposure to small ruminants is orf, also known as contagious ecthyma in animals (see Chapter 10). The disease is caused by an epitheliotropic poxvirus and is transmitted to humans by direct contact with infected animals. Skin trauma is a significant risk factor for transmission in both humans and animals. In humans, erythematous macules or papules appear at the site of infection 2 to 3 days following exposure. The infection is generally self-limiting in immunocompetent individuals with complete healing occurring within 8 weeks.

Reproductive Pathogens

Brucella Melitensis. Apart from contagious ecthyma, the greatest risk of zoonotic disease from small ruminants is due to pathogens typically found in the reproductive tract that are transmitted to humans through contact with aborted fetuses, the placenta, or birthing fluids or through the consumption of raw or improperly pasteurized dairy products. *B. melitensis* is more common in goats than sheep (see Chapter 8). Swine, cattle, and other ruminants are common hosts. Infection in animals usually causes inapparent mammary infection and abortions; infection in humans is characterized by undulant fever, myalgia, and fatigue.

Coxiella Burnetii. C. burnetii is a rickettsial organism that is an important cause of abortion in sheep and goats (see Chapter 8). Wildlife and farm-raised deer may serve as reservoir hosts for infection in other ruminants and humans.[116] Infection is a documented cause of reproductive failure in farmed deer and prolonged shedding of the organism is an important source of environmental contamination.[117] In addition to abortion, newly infected sheep and goats occasionally have mild, transient fevers. *C. burnetii* is far more important as the cause of Q fever in humans, who become infected after inhaling particles, handling contaminated animals, or coming into contact with contaminated body fluids (uterine fluid, milk) from infected animals. Infection in humans may be asymptomatic, present with flu-like symptoms, or, in the chronic form, present as granulomatous hepatitis, osteomyelitis, or bacterial endocarditis.

***Chlamydophila* spp.** *Chlamydophila abortus* (previously *Chlamydia psittaci*) is an obligate intracellular parasite and the cause of enzootic abortion of small ruminants (see Chapter 8). *Chlamydophila pecorum* may cause polyarthritis and keratoconjunctivitis (see Chapter 14) in sheep and goats. Transmission between animals and to humans most commonly occurs through direct contact with infected tissues or materials. Infection in humans results in an acute febrile syndrome or respiratory symptoms. Chlamydial diseases are more commonly reported in sheep than in goats. Chlamydial diseases are suspected to cause disease in other species, including deer. Recent serologic evaluation of wild ungulates identified multiple species of deer with antibodies against several Chlamydial species.[118] The clinical significance of serological infection in these species remains undetermined.

Francisella Tularensis. *F. tularensis* is more common in sheep than goats. The organism has many hosts, of which the most important are wild rabbits and rodents. It can contaminate water sources. Transmission to sheep is usually through biting arthropods that have previously fed on an infected wild mammal. Acute or chronic sepsis may be seen, with more widespread and severe disease occurring in sheep with poor immune function. At necropsy, the disease is characterized by military foci of necrosis in the liver, and less commonly in the lymph nodes, spleen, and lungs. Most cases in humans result in acute onset of flu-like symptoms a few days after exposure.

L. interrogans. Pathogenesis. *Leptospira* spp. are spirochete bacteria that live in moist environments. Their survival time outside of hosts is usually short, so their most important reservoirs are the kidneys of infected animals, especially rodents. Infected animals shed the organisms through urine and most other body fluids. Organisms enter new hosts through mucous membranes and skin breaks and cause bacteremia. Signs of sepsis range from inapparent to severe, with more severe signs predominating in neonates. Intravascular hemolysis may result. In animals that survive the acute stage, infection may localize in sites such as the kidneys, eyes, and fetoplacental unit. Abortion may occur a month or more after acute signs first become evident while renal shedding may occur for several months. Leptospirosis is zoonotic. In most cases, infections in humans are asymptomatic and self-limiting. However, in approximately 10% of cases, severe, and

potentially fatal, systemic disease may develop, including jaundice, renal failure, and pulmonary hemorrhage.

Clinical Signs Acute leptospirosis causes signs of sepsis, including fever, depression, dyspnea, exercise intolerance, weakness, and death (see Chapter 12). Additionally, many affected animals show signs of intravascular hemolysis such as anemia, icterus, and hemoglobinuria.

Diagnosis Evidence of intravascular hemolysis such as anemia, hyperbilirubinemia, hemoglobinuria, and hemoglobinemia is suggestive of this disease. In chronic infection, non-specific inflammatory changes and azotemia may be seen. Animals dying in the acute hemolytic stage are likely to have dark, discolored urine, bladder, and kidneys. Spirochetes can be identified on dark-field microscopy of fresh urine or plasma from infected animals and may be cultured with special techniques. In animals with less severe infection, a rise in antibody titers can be used to support a diagnosis of leptospirosis.

Prevention Numerous vaccines are available for sheep. Because protection is serotype specific, it is important to vaccinate against common serotypes in the area. *Leptospira pomona* is the most consistent isolate from sheep and goats; *Leptospira hardjobovis* is the predominate serovar in deer.[119] Vaccination immunity is thought to be short lived; boosters should be given at least twice a year in endemic areas. Vaccination of deer against serovars *Hardjobovis* and *Pomona* has been associated with decreased urine shedding and increased growth rate in young animals.[120]

Listeria Monocytogenes

Pathogenesis. *L. monocytogenes* causes disease with similar frequency in sheep and goats (see Chapter 13). The organism is a common soil and fecal contaminant. It also proliferates in silage that is not properly acidified and in rotting, woody debris. Risk of exposure depends on the feed and environment of the animals. Environmental and fecal contamination is a more common source than silage in small ruminants overall because most sheep and goats throughout the world are not fed silage. Infection in humans almost always results from ingestion of contaminated food products or unpasteurized milk.

Clinical Signs. Nervous system dysfunction and abortion are the most common manifestations of the disease. Animals with the brainstem form of the disease display signs reflective of cranial nerve dysfunction, including drooped ears or eyelids, decreased facial sensation, and deviated nasal septum. A head tilt and circling may be present; in advanced cases of the disease, the animal is recumbent. Clinical signs are mainly unilateral, occasionally bilateral, according to the nerve nuclei affected.

Diagnosis. Antemortem diagnosis of listeriosis is difficult. A presumptive diagnosis is made based on history, clinical signs, and potential response to treatment. Histopathologic identification of microabscesses in the brainstem and culture of the organism from affected tissues can be used to confirm the diagnosis.

Pasteurella and Pasteurella-Like Infections

P. multocida

Pathogenesis. *P. multocida* is a small, gram negative, bipolar, ovoid rod that inhabits the pharynx of healthy ruminants. It can survive in soil and water for varying amounts of time after contamination with ruminant nasal secretions. Healthy ruminants shed *P. multocida* much more frequently than *Mannheimia haemolytica.* Disease occurs when bacteria colonize the lower respiratory tract or enter the blood. Risk factors for pulmonary and systemic infection include viral or mycoplasmal respiratory diseases, temperature extremes, respiratory tract irritants, transport, overcrowding, changes to higher-energy feeds, and handling stress. These factors are thought to both increase bacterial replication in the airway and suppress mechanisms to clear the infection. Pasteurellosis is a major problem in feedlot sheep but less common in small breeding or hobby flocks. Pasteurellosis also is a significant disease in certain wild small ruminants such as bighorn sheep.

Direct spread of the organism between animals occurs with nasal contact, and indirect spread occurs after contact with infected nasal secretions. The organism persists in the environment for longer periods during warm, moist weather. *P. multocida* produces a polysaccharide capsule that inhibits phagocytosis and an endotoxin that contributes to clinical signs. The major disease caused by *P. multocida* is pneumonia (see Chapter 7). However, *Pasteurella* spp. also are capable of entering the blood to cause septicemia in young lambs and hemorrhagic septicemia in adults. Occasionally, focal infections such as septic arthritis and mastitis are found.

Clinical Signs. Clinical signs of pneumonic and septicemic pasteurellosis include severe depression, bilateral purulent nasal discharge, coughing, diarrhea, anorexia, high fever, and edema of the head, neck, and brisket. The disease course can be short with septicemic pasteurellosis and is usually more insidious with *P. multocida* pneumonia. *Pasteurella* mastitis is characterized by the bluebag condition or gangrene of the udder.

Diagnosis. Inflammatory changes in the leukogram and hyperfibrinogenemia are the most frequent abnormalities. With severe disease and in the septicemic form, immature neutrophils may predominate over mature cells. Inflammation of the intestine and abomasum also may be seen. Hemorrhage and fibrin are usually absent or less prominent than in pneumonia caused by *M. haemolytica.* Samples for bacteriologic culture are usually obtained postmortem. Blood or tracheal fluid may be obtained before death if the value of the animal warrants it.

M. haemolytica

M. haemolytica is a gram negative rod that is a common commensal inhabitant of the tonsils of young animals. Disease is much more frequently described in sheep than in goats and occurs when the organism gains access to the lower respiratory tract.

Clinical Signs and Diagnosis. The most common syndrome is enzootic pneumonia, which is seen in young lambs and their dams (see Chapter 7). Hemorrhagic bronchopneumonia is the major lesion and respiratory signs predominate. Gangrenous mastitis (bluebag) is seen in some of the dams, presumably after they have been nursed by infected offspring. Factors that promote respiratory disease, including viral infections, airborne irritants, high stocking density, and stress, are thought to promote invasion of the lower airway by these bacteria.

Bibersteinia trehalosi

B. trehalosi is a gram negative rod that is a commensal inhabitant of the upper respiratory tract (see Chapter 7). Disease is much more frequently described in sheep than in goats and occurs when the organism gains access to the lung or blood. Replication occurs in the lung and systemic toxemia or bacteremia resulting in septicemic pasteurellosis. Septicemic pasteurellosis is a significant cause of mortality in young lambs and in some farms is the leading cause of death in the age group.

Clinical Signs. Septicemic pasteurellosis occurs most commonly in weaned lambs, often following some form of stress such as transport, marketing, or weaning itself. The course of the disease is relatively rapid, and animals may be found dead within 6 hours without showing premonitory clinical signs. When observed, clinical signs include depression, recumbency, and signs of toxemia.

Diagnosis. Septicemic pasteurellosis should be suspected when presented with a dead, recently weaned, sheep with a recent history of stress. Diagnosis is best confirmed by typical lesions at necropsy and culture of the organism from bodily tissues. Demonstration of *B. trehalosi* in nasal swabs is of limited value due to the high prevalence of upper respiratory tract colonization in healthy lambs. At necropsy, there may be no evidence of pneumonia, but blood-stained foam can be found in the upper respiratory tract. Ulceration of the pharynx and esophagus is commonly present as is subcutaneous hemorrhage of the neck and thorax.

Prevention. Treatment is difficult due to the rapid course of disease. Efforts should be made to minimize stressors, particularly during and following weaning, and to manage management factors that may contribute to the disease. Vaccination with *Pasteurella* bacterins is rarely effective at controlling natural outbreaks of disease.

Other Bacterial Causes of Disease

Common Abscess-Forming Bacteria

Pathophysiology. Abscess-forming bacteria are usually able to survive phagocytosis and thereby avoid destruction by cells of the immune system. Alternatively, they invoke such an inflammatory response that the host body "walls off" the entire region with fibrous tissue. Abscesses may occur locally, frequently after a wound infection, or at numerous or distant sites from the point of infection. For abscesses to occur at the latter sites, the organism must travel either by way of the blood or within leukocytes. Disease characterized by multifocal or internal abscesses usually results from a low-grade, transient event of bacteremia.

The best known and most important abscess-forming bacterium in small ruminants is *Corynebacterium pseudotuberculosis*, the gram positive, facultative anaerobic coccobacillus that causes caseous lymphadenitis. Infection is usually maintained in a flock by infected animals that spread the organism to others through purulent material draining from open abscesses. The organism is very hardy, so infection can occur through direct contact or indirect contact with contaminated common instruments and facilities. Infection is usually introduced into a flock through acquisition of an infected animal, although it also can occur when a naive flock is moved into a contaminated area. Horses, cattle, and humans also are minor hosts. Infection is thought to occur after ingestion, inhalation, or wound contamination. Except for lower respiratory tract invasion, a surface break is thought to be necessary. Contaminated shears, tail-docking knives, and emasculators readily spread the organisms through a flock. Abscesses can form at the site of invasion or more commonly at the site of the local lymph node.

Clinical Signs. Clinical signs of external abscesses include surface swellings and draining lesions. Drainage may be intermittent and usually consists of thick, yellow-white purulent material. Internal abscesses are more difficult to diagnose. Thoracic masses may cause inspiratory dyspnea or occlude venous return to the heart. Abdominal lesions may cause tenesmus, stranguria, and occasionally colic. The most common sign of internal abscesses is weight loss with or without intermittent fever. Common external sites include the submandibular or retromandibular space and the preinguinal, prefemoral, and supramammary lymph nodes. Head and neck lesions are more common in goats, whereas sheep have a more even distribution of cranial and caudal lesions, presumably as a result of shearing wounds. External infections rarely cause clinical illness beyond the draining abscess, although some degree of cachexia may be present.

Diagnosis. Diagnosis is often made by the characteristic lesions with their thick, nonmalodorous pus. Bacteriologic culture provides a definitive diagnosis, which may be important for flock management. Serologic tests have been developed to identify carrier animals and may be useful if the manager wishes to eliminate infection from the flock.

Treatment. Treatment is often unrewarding: antibiotic sensitivity profiles do not reflect the degree of protection afforded the organisms within the abscesses. Long-term treatment with antibiotics and drainage of any compromising masses may lead to some degree of resolution, but internal abscesses are likely to persist.

Prevention. Prevention through the use of vaccines has been attempted. Vaccines appear to reduce the severity of the disease but do not completely prevent infection. Moreover, live attenuated bacterins lead to de facto infection of all vaccinated animals and therefore should not be used in naïve flocks.[121]

Other abscess-forming bacteria are most important as differential diagnoses for caseous lymphadenitis. *T. pyogenes* is another wound contaminant that affects focal areas or regional external lymph nodes. It also commonly colonizes damaged internal tissues such as postpneumonic lungs, postacidotic livers, and damaged feet and heart valves. It is thought to be ubiquitous and poorly invasive in ruminants and therefore does not have the same flock significance as *C. pseudotuberculosis.* Flocks with outbreaks of this infection often have suboptimal management. *F. necrophorum* causes similar disease and often coinfects with *T. pyogenes.* It is generally more necrotizing and leads to greater systemic signs of acute illness, including death. *F. necrophorum* also produces fetid pus, whereas *T. pyogenes* usually does not. *Rhodococcus equi* is a rare cause of pulmonary abscesses in sheep.

Numerous small, coalescent, nodular skin abscesses may result from *Pseudomonas pseudomallei* infection (melioidosis). Infection usually occurs after the sheep or goat is bitten by an insect that previously fed on an infected rodent. This organism is found in many subtropical regions, including the Caribbean, but is not reported in North America.

Fusobacterium Infections

F. necrophorum causes or is associated with a variety of diseases in sheep and is likely to cause many similar diseases in goats. It is best known as a cause of foot rot and hepatic abscesses and appears to be important in lip-leg ulceration. It is an enteric gram negative anaerobe and as such can cause gram negative sepsis after entrance of the bacteria or its toxins into the circulation. *F. necrophorum* has a poor ability to invade healthy tissue. However, it readily colonizes regions damaged by trauma, persistent moisture, and infection. In addition to endotoxin, the bacterium produces leukocidal and cytolytic toxins that form zones of necrosis around bacterial colonies. This tissue necrosis and the foul-smelling waste gases produced by the bacteria are characteristic of necrobacillosis, or *F. necrophorum* infection. Clinical signs include necrotic, fetid lesions, usually of the mouth or feet, that can cause ingestion

or lameness problems. Efforts to maintain good hygiene are helpful in preventing fecal contamination. Additionally, preventing trauma to foot and mouth tissues through good surface choices and proper pasture drainage is important.

Yersiniosis

Pathogenesis. *Yersinia* spp. are gram negative bacteria. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* both have many mammalian and avian hosts, including humans, and cause clostridial enteritis–like disease in goats. Rodent and bird hosts may be important reservoir populations for infections in domestic animals. Kids younger than 6 months develop enteritis, bacteremia, and diarrhea that is watery but not bloody. Severe toxemia and sudden death can occur. Older kids and flocks with chronic exposure tend to have less severe acute disease. Instead, chronic diarrhea and weight loss are seen, usually in association with gut wall and abdominal abscesses. Sheep, deer, and wild ungulates are rarely affected.

Clinical Signs. Signs of enteritis or sepsis predominate in acute disease, whereas signs of wasting are more common in chronic disease.

Diagnosis. Evidence of acute or chronic inflammation is provided by blood work. Characteristic necropsy lesions include numerous microabscesses in the gut wall and mesenteric lymph nodes, as well as other evidence of enteritis or sepsis. Culture of lesions and demonstration of a rising antibody titer are diagnostic.

Prevention. Avoiding exposure to sources and maintaining overall flock health are helpful in preventing losses due to yersiniosis.

Mycobacterial Disease

Pathogenesis. *Mycobacteria* are small, aerobic, straight or curved pleomorphic rods with thick lipid cell walls. They can be stained with acid-fast stains and are usually gram positive. The bacteria live within infected animals of many mammalian species and survive for several years in warm, moist environments. Infection occurs after ingestion or inhalation. An identifying characteristic of the mechanism of infection by *Mycobacteria* is the bacteria's ability to survive within macrophages by preventing fusion of phagosomes and lysosomes. The organisms are carried to local lymphatic vessels or lymph nodes, where they form granulomas. As they enlarge, granulomas may develop necrotic or mineralized centers surrounded by macrophages and giant cells. Disease can be local, regional, or generalized, depending on the distance the organism is carried from the original site of infection. Granulomatous pneumonia, enterocolitis, and lymphadenitis are the most common local and regional forms of the disease.

Organisms from ruptured granulomas may be spread in contaminated respiratory secretions and feces. Mycobacterial infections of all types are uncommon in North American sheep, goats, and cervids, and these species are considered to be relatively resistant to infection. *Mycobacterium bovis* is the most common organism associated with ovine tuberculosis in other countries (see Chapter 7), but *Mycobacterium avium* is more common in the United States. The most common mycobacterial infection is Johne's disease (paratuberculosis) caused by the etiologic agent *M. avium* subsp. *paratuberculosis* (see Chapter 5). *Mycobacterium tuberculosis* is rare in the United States. Mycobacterial infections are reportable in most parts of the United States. Some debate is ongoing about human susceptibility to *M. avium* subsp. *paratuberculosis*; the other organisms are known to be pathogenic in people.

Clinical Signs. The most common clinical sign is emaciation. Diarrhea may be seen terminally in both tuberculosis and paratuberculosis. The disease is insidious, with signs becoming more apparent over several weeks to months. Respiratory signs may be seen, especially with infection by *M. bovis* or *M. avium* subsp. *paratuberculosis.*

Diagnosis. Reports of clinicopathologic abnormalities are rare. Hypoalbuminemia and hypoproteinemia are likely to be common with chronic enterocolitis caused by either tuberculosis or paratuberculosis. The most common necropsy lesions seen in tuberculosis are nodular lesions of the lung, liver, lymph nodes, spleen, and intestines. Histologic evaluation reveals the nodules to be granulomas with giant cells and acid-fast organisms. Frequently, the center of the lesion is necrotic and mineralized. Intestinal lesions appear to be more common than pulmonary lesions in goats. The lesions of paratuberculosis are centered around the ileocecocolic junction and the adjacent mesentery. The regions may appear normal or be notably thickened. Thickening of bowel or nodular infiltrates of lung or liver may be detected antemortem using imaging modalities, such as ultrasonography or computed tomography. Postmortem diagnosis is made by identifying characteristic lesions and culturing the organisms. Antemortem diagnosis of tuberculosis is best achieved by observing the reaction to intradermal injection of tuberculin with or without comparative injection of purified protein derivatives of *M. bovis* and *M. avium* subsp. *paratuberculosis.* All tuberculosis testing should be done in accordance with local regulations. Antemortem diagnosis of Johne's disease can be achieved by fecal culture of the organism, but this test takes several weeks to months to complete and is far less reliable in sheep or goats than cattle, with a sensitivity as low as 0.08. Serologic tests (e.g., ELISA) appear to be sensitive and specific for Johne's disease in animals demonstrating clinical disease rather than preclinical infection. Serologic detection of clinical Johne's disease in cervids has been shown to be highly sensitive and specific while the sensitivity of fecal culture is low in both sheep and goats. The recommended organism detection method in both species is fecal PCR.[122] Fecal or milk PCR can be used on pooled samples for flock identification and to type the organism.

Prevention. Tuberculosis should not be endemic in flocks in the United States because positive animals are quarantined or destroyed. Preventing exposure to wild ruminants and other possible sources is crucial. Except in goat flocks raised for the production of milk that is to be sold unpasteurized, testing is uncommon, so animals are usually not identified until they develop overt disease. Paratuberculosis is much more common and may be maintained in flocks by carrier animals. No effective treatment is available for either disease, nor should any be encouraged because efforts should be concentrated on eliminating infection from the flock or herd. Vaccination of sheep is used extensively in Australia to control paratuberculosis. Prolonged vaccination has been shown to decrease fecal shedding in infected animals over time.[123]

Nonhemotropic Mycoplasmal Diseases

Pathogenesis. *Mycoplasma* spp. are very small, simple bacteria that parasitize cells of higher species. They are common inhabitants of mucous membranes and can have either a commensal or pathogenic relationship with the host. Transmission between animals is most likely through direct or indirect contact with body fluids from infected animals, inhalation of respiratory droplets,

and arthropod vectors. Common sites for superficial infection include the ocular membranes, lung, mammary gland, and female reproductive tract. The organisms can also enter the blood and cause septicemia, abortion, pleuritis, and polyarthritis. Flare-ups often occur during times of crowding and during parturition, when neonates can spread the organisms from the mother's mouth to her udder and in turn become infected by ingesting contaminated milk.

The most important mycoplasma species in the United States are *Mycoplasma conjunctivae*, *Mycoplasma capricolum*, and the less pathogenic *Mycoplasma ovipneumoniae.* They are most commonly associated with keratoconjunctivitis, acute or chronic sepsis, and pneumonia, respectively. *M. conjunctivae* and *C. abortus* are the most common causes of pinkeye in North American small ruminants. *Mycoplasma* spp. are thought to inhibit tracheal ciliary function and thus may have a role similar to viruses in "shipping fever pneumonia" in facilitating lower respiratory tract invasion by primary bacterial pathogens. Many of the major pathogenic serotypes found in other countries (some of which cause severe pleuropneumonia without the participation of another bacteria), including *Mycoplasma mycoides* subsp. *mycoides*, *Mycoplasma mycoides* subsp. *capri*, *Mycoplasma agalactiae*, and strain F38, are not found in or have been eradicated from North America

Clinical Signs. Keratoconjunctivitis, mastitis, exudative vulvovaginitis, fever, cough, dyspnea, exercise intolerance, abortion, lameness, swollen joints, neonatal death, and depression may all be seen with mycoplasma infections.

Diagnosis. No specific clinical pathologic findings occur with these diseases. Mycoplasma infection should be suspected in sheep and goats with severe exudative pleuropneumonia in some parts of the world. Mycoplasma can be identified by bacteriologic culture or staining of exudates. Examiners must take care in interpreting positive cultures from body surfaces because nonpathogenic mycoplasma are common.

Prevention. Vaccines against mycoplasmal infections are available in some parts of the world, but not in the United States. Providing fly control, preventing stress and overcrowding, and isolating sick animals from healthy ones may help prevent the spread of disease.

Blood and Tissue Parasites

Anaplasma ovis, *Mycoplasma ovis*, and *Babesia* spp.

Pathogenesis. *A. ovis* and *M. ovis* are small bacteria that lack cells walls and parasitize erythrocytes. These and similar organisms have undergone recent reclassification following molecular analysis. Other species of hemotropic mycoplasmas may affect sheep and cervids.[116] The organisms are spread from animal to animal by insect or mechanical vectors. Known arthropod vectors for *A. ovis* include ticks and horseflies; other biting flies may be more important with *M. ovis* infection. Hypodermic needles and equipment used for tail-docking, castrating, or disbudding animals may be important in iatrogenic transmission. After being introduced into a naive host, the organisms proliferate, and the number of red cells infected increases rapidly until an effective immune response begins 1 to 2 weeks later. A similar proliferation of organisms may occur in chronically infected animals after temporary immune suppression. The humoral and cellular immune responses against *A. ovis* lead to opsonization of parasitized erythrocytes and their removal by cells of the reticuloendothelial system; *M. ovis* infection is thought to cause more intravascular hemolysis. The result in both cases is hemolytic anemia.[117] The protozoon parasites *Babesia ovis* and *Babesia motasi* have similar life cycles and cause similar diseases, but they have been eradicated and are reportable in the United States. *Babesia* spp. affecting small ruminants are generally less pathogenic than are their bovine counterparts.

Animals surviving acute hemolytic crisis reduce the parasites to low numbers but rarely clear the infection completely; they serve as sources of infection for other animals. Sheep and goats are susceptible to infection by either organism; goats generally appear to be more resistant to the development of severe parasitemia and clinical signs.

Clinical Signs. Signs present during hemolytic crises include fever, weakness, pale mucous membranes, and pigmenturia. Urine discoloration results from increased amounts of bilirubin in most cases, although hemoglobinuria may be seen in some sheep with *M. ovis* infection. Icterus is usually present only after the acute hemolytic crisis. Clinical signs are exacerbated during times of stress, and infection is often first noted when the animals are moved or handled. Chronically infected animals may appear clinically normal, may have recrudescence of infection after stress, or may display signs of ill-thrift such as poor body condition and fleece. Babesiosis occasionally causes concurrent central neurologic signs.

Diagnosis. The major clinical laboratory finding is regenerative anemia with detection of the intraerythrocytic bodies. Chronically infected sheep often have high counts of nucleated erythrocytes. Because *M. ovis* consumes glucose, hypoglycemia and metabolic acidosis may be detected, especially in blood samples that are not processed immediately. Diagnosis is by identification of the organisms on blood smears. Special stains are available to make the organisms more visible. Postmortem lesions include pallor or icterus of membranes and splenomegaly. Some evidence of vasculitis, including edema or exudates in body tissues or cavities, may be seen with *M. ovis* infection.

Treatment. *Mycoplasma* spp. and *Anaplasma* spp. are sensitive to tetracycline antibiotics. Babesiosis is more difficult to treat. Effective drugs include diminazene, pentamidine, and imidocarb dipropionate. Supportive care for all blood parasite infections includes whole blood transfusions, nutritional support, and administration of fluids.

Prevention. Prevention in most cases involves maintaining low levels of parasites rather than eliminating them entirely. This method ensures continual stimulation of the immune response, whereas eradication often leaves the animal susceptible to another bout of acute infection. Vector control can also be important in management of the disease.

Anaplasmataceae of WBCs

Pathogenesis. Two organisms belonging to the *Anaplasmataceae* family, *Ehrlichia ovis* and *Anaplasma phagocytophilum*, infect ovine WBCs, causing fever, immune suppression, and some organ damage. *A. phagocytophilum* is the causative agent of tick borne fever in sheep and granulocytic anaplasmosis in horses, dogs, and humans. The organism is transmitted by ticks (*Ixodes* spp.) and maintained in the environment by asymptomatic carrier animals. The distribution and incidence of disease is seasonal with the life cycle of the tick. The organism infects cells of the granulocytic lineage, leading to severe persistent neutropenia and acute

lymphopenia. Fever occurs 1 to 2 weeks after infection, lasts as long as 2 weeks, and occasionally relapses. Chronic infection is common. Spleen, lung, liver, and kidney tissue may show some damage because of immune destruction of infected cells, but organ-specific signs are usually the result of secondary infection. Secondary bacterial joint infections in lambs infected with *A. phagocytophilum* develop debilitating lameness known as tick pyemia.

E. ovis causes fever (benign ehrlichiosis) 1 to 2 weeks after infection. Because of this organism's predilection for mononuclear cells, the degree of immunosuppression and subsequent importance of this disease are much less than for *A. phagocytophilum* infection.

Diagnosis. Specific diagnosis is best made by identifying darkly stained bodies at the periphery of granulocytic cells, as well as occasional large bodies deep within the cytoplasm of some cells. Stained bodies also can be seen on the periphery of mononuclear cells from a blood smear during the acute febrile stage or in tissues during chronic infection. Serologic tests are available for detection of *Anaplasmosis*. The available cELISA is incapable of distinguishing species of anaplasma and serologic results must be interpreted appropriately, and the species confirmed by PCR.

Both infections affect sheep and goats (*A. phagocytophilum* also affects many other ruminants, including white-tailed deer), but neither has been reported in North America. A recent study demonstrated that sheep are capable of being experimentally infected with a human isolate *A. phagocytophilum.* Interestingly, the sheep did not develop clinical disease.[118] Such findings suggest that sheep could serve as asymptomatic carriers and potential reservoirs for humans. *A. phagocytophilum* is widespread in northwestern Europe, including the United Kingdom, Scandinavia, and India, and *E. ovis* is found mainly in countries bordering the Indian Ocean. In spite of documented seropositive status of animals, there have been no reports of sheep or goats naturally infected with *A. phagocytophilum* in the United States developing clinical disease.

Treatment and Prevention. Treatment and prevention efforts should focus on reducing vectors and bacterial counts during vector season. Both organisms are susceptible to treatment with tetracycline.

Trypanosomiasis

People and animals can become infected with trypanosome protozoa. The trypanosomes can complete their developmental cycle only in tsetse flies (*Glossina* species). Trypanosomes multiply in blood, tissues, and body fluids of their vertebrate hosts and are transmitted between vertebrate hosts in the saliva of blood-sucking flies as they feed. The trypanosome species that are known to infect goats and sheep include *Trypanosoma congolense*, *Trypanosoma vivax*, *Trypanosoma brucei* subsp. *brucei*, *Trypanosoma evansi*, and *Trypanosoma simiae*.

Pathogenesis. After entering through the skin, trypanosomes reach the bloodstream by way of the lymphatic system. The parasites multiply, and the prepatent period lasts for 10 to 14 days after infection. The infection is characterized by periods of parasitemia, followed by the absence of parasites. This pattern of infection occurs because of antigenic variation: Trypanosomes vary the antigenic nature of their glycoprotein surface coat to evade the host's immune system. This immune system–evasive maneuver prolongs infection and is responsible for chronic disease. Some trypanosomes tend to invade extravascular spaces, such as the ocular aqueous humor and cerebrospinal fluid. The pathogenicity of trypanosomes varies with the different host species. Trypanosomes may produce a hemolysin early in the course of the disease that causes anemia in the host. Later, increased phagocytic activity results in massive erythrocyte destruction.

Clinical Signs. The clinical signs are variable and non-specific and depend on the speed of onset of anemia and the degree of organ impairment. Entire herds may be affected. All aspects of production are impaired—fertility, birth weight, lactation, weaning weight, growth, and survival. Trypanosomiasis may predispose the animal to the development of other diseases that mask the underlying trypanosome infection.

Trypanosomiasis may be acute, subacute, or chronic, with chronic infection occurring most commonly. Acute disease often causes abortion. Dairy goats may show a sudden drop in milk production. Depression, anorexia, and a stiff gait may be present. Physical examination reveals tachycardia, tachypnea, and a slight fever. Hyperemic mucous membranes and excessive lacrimation may be noted. Affected animals often become recumbent and anorexic and die within 1 to 3 weeks of onset of clinical signs. If the animal survives, progression to the subacute phase, characterized by listlessness, weight loss, enlargement of superficial lymph nodes, and a dull, dry hair coat, may occur. In such cases, auscultation findings are similar to those in other forms of acute cardiac disease, as well as pale mucous membranes and a pronounced jugular pulse. The animal may linger for several weeks or months, or the chronic form of the disease may develop. Affected animals show ill-thrift: dull and dry hair coat, inelastic skin, lethargy, emaciation, peripheral lymphadenopathy, pale mucous membranes, and exercise and stress intolerance. Death may occur many months or even years after infection and usually results from congestive heart failure. Subclinical trypanosomiasis causes acute episodes when animals are stressed by inadequate nutrition, increased production demands, or concurrent disease.

Diagnosis. Diagnosis is difficult because the parasitemia is intermittent, clinical signs are non-specific, and infection is not always synonymous with disease. A PCR assay is gaining acceptance as the most sensitive diagnostic modality, but not all infected animals exhibit clinical disease. Although a tentative diagnosis of pathologic trypanosomiasis can be made on the basis of history, clinical signs, and the presence of appropriate vectors, a definitive diagnosis requires identification of trypanosomes on a fresh blood smear, a Giemsa-stained blood smear, or less commonly, a lymph smear. Examination of the buffy coat of centrifuged blood with darkfield phase-contrast spore illumination is the most sensitive direct microscopic method and is useful when parasite numbers are low. Pathogenic trypanosomes must be distinguished from more ubiquitous, nonpathogenic species particularly common in cattle, such as *Trypanosoma theileri*. Repeated blood sampling in individual animals often is necessary, because as noted, parasitemia is intermittent. The diagnosis is supported by evidence of anemia on a CBC. Indirect diagnostic methods include an indirect fluorescent antibody test and the ELISA. These tests are less helpful for diagnosis of a single clinical case but are useful in assessment for herd infection. Both *T. congolense* and *T. brucei* readily infect rats and mice, and detection of these pathogens can be used to diagnose the infection indirectly.

Treatment. Treatment consists of the use of trypanocidal agents and supportive care. Animals with acute, subacute, and subclinical disease respond better to treatment than those with chronic disease because of the irreversible damage to hematopoiesis associated with chronic infection. With most trypanocides, the therapeutic index is low and varies with the host species.

Trypanocide efficacy also varies with the species of trypanosome present; resistance to agents is common. Some trypanocides are irritating to the skin and may cause severe inflammation at the injection site.

In sheep and goats with *T. brucei* infection, the trypanocide of choice is diminazene aceturate, which should be used at a higher dosage rate (7 mg/kg given intramuscularly [IM] or SC) than that recommended for cattle. Protection after trypanocide use usually lasts 2 to 4 months, depending on the season. Animals must be rested before and after treatment. Supportive care consists of providing fluids, an environment conducive to rest, good nutrition, and possibly blood transfusions.

Prevention. Vector control, stress and nutrition management, and selection of trypanosome-tolerant breeds of sheep and goats all help control or prevent trypanosomiasis. No vaccine is available. Animals can be treated with insecticides (pyrethroids) to prevent bites by tsetse flies and other flies. Control is accomplished by strategic use of trypanocides during the peak season. Continued parasitologic and clinical surveillance is essential to determine the efficacy of control measures.

Sarcocystis spp. and *Neospora caninum*

Pathogenesis. *Sarcocystis* spp. are protozoon parasites that have a two-host life cycle. Sexual reproduction occurs in the bowel of a carnivore (mainly dogs and wild canids) after the carnivore ingests cysts in the muscles of sheep, goats, and cervids. Sporocysts are passed in the carnivore's feces and later ingested by a sheep, goat or cervid. The sporocysts hatch in the ruminant gut and invade the vascular endothelium during three phases of asexual reproduction. After the third phase (approximately 8 to 10 weeks after ingestion), merozoites enter the ruminant's muscle tissue and encyst. Clinical signs are uncommon but can occur during the stages of reproduction and muscle invasion of the host. *N. caninum* has a similar life cycle and causes similar disease, except that it appears more likely to cause abortion and affect the central nervous system.

Clinical Signs. Most infections are asymptomatic. However, if a large number of sporocysts are ingested, tissue damage may occur during the intestinal, vascular, and muscle stages of the *Sarcocystis* life cycle. Fever, lameness or a stiff gait, reluctance to move, and diarrhea may be seen. Central neurologic signs (blindness, changes in mentation, and seizures) may occur if the organisms invade the brain or interrupt blood flow to it. Abortion can occur as early as 4 weeks after ingestion. With severe chronic infections, emaciation and anorexia are seen.

Diagnosis. The most characteristic abnormality is an increase in muscle enzyme activity in the blood. Anemia is common and may result from extravascular hemolysis. Cerebrospinal fluid may show mild mononuclear pleocytosis or may appear normal. On necropsy, muscles may display pale streaks or macroscopic cysts throughout. Other evidence of vasculitis includes hemorrhagic serosal surfaces, body cavity fluids, and lymphadenopathy. Microscopic or ultrastructural examination of affected tissues should reveal the presence of organisms. Specific antibody tests are available and do not cross-react with *T. gondii* antibodies. Blood antibody titers often peak around the onset of clinical signs and should be markedly higher than baseline values. Antibody preparations also are available for identification of organisms in tissue preparations.

Treatment. Sheep infected with *Sarcocystis* species can be treated with salinomycin (200 ppm in complete feed), monensin (0.5–1 mg/kg PO), or amprolium (25–40 mg/kg PO). Drugs such as sulfadiazine or trimethoprim (25–44 mg/kg IM SID), pyrimethamine (0.5–1 mg/kg PO SID), and clindamycin have shown some success in treating *Neospora* infections. These treatments are off-label and thus are governed by regulations regarding extra-label drug use.

Prevention. Preventing contamination of feedstuffs with the feces of infected carnivores and preventing ingestion of raw meat by carnivores are most important, but these measures may not be possible in flocks handled with dogs or those living on range land. Anticoccidial drugs appear to decrease the chance of clinical disease.[119]

T. gondii

Pathogenesis. *T. gondii* is a protozoon parasite with a life cycle very similar to *Sarcocystis*, except that the definitive host is the cat and that a wider range of mammalian and avian species, including humans, appear to be capable of acting as intermediate hosts. Sporocysts are infective a few days after passage in cat feces, and most ruminants are infected by eating feed contaminated with cat feces. People can become infected by ingesting raw meat or milk from infected animals.

Abortion, stillbirth, and neonatal death are the most common forms of clinical disease in sheep and goats, and *Toxoplasma* should be considered one of the most common causes of perinatal losses in small ruminants (see Chapter 8). Abortion usually occurs during the final month of pregnancy. Fever, vasculitis-induced disease, and neurologic disease are less common manifestations.

Clinical Signs. Beyond abortion, clinical disease is rare in adults and resembles systemic sarcocystosis. Clinical signs include fever, dyspnea, depression, and anorexia. Neurologic signs are more common than with *Sarcocystis* infection, especially in lambs and kids infected in utero.

Diagnosis. No specific laboratory abnormalities are associated with toxoplasmosis. Nodular lesions similar to sarcocysts may be seen in various tissues, including the brain. Aborted or stillborn fetuses may appear normal except for histologic lesions in the brain, liver, or lung, but more commonly fetuses are macerated. The placenta is usually abnormal, with gross and microscopic evidence of necrosis of the cotyledons. Microscopic identification of the organism in body tissues is the most common means of diagnosis. Serologic tests also are available.

Treatment and Prevention. Drugs similar to those used to treat *Neospora* may be effective against *Toxoplasma.* Preventing contamination of feeds with cat feces and preventing ingestion of dead animals by cats are the most important ways of stemming the spread of this organism. Both methods are likely to be difficult in most flocks. Direct spread from one animal to another is rare.

Acute Viral Diseases

Bluetongue

Etiology. Bluetongue is an acute viral disease of domestic and wild ruminants caused by an RNA virus in the genus *Orbivirus* and family *Reovirus*; it is transmitted by the insect vector *Culicoides varipenniis* in North America and other *Culicoides* species in other countries. Six of the 24 serotypes of the virus are found in the United States. Of the domestic ruminants, sheep are most severely affected. Goats and cattle rarely develop acute disease.

Clinical Signs. Bluetongue disease has two different manifestations—reproductive problems (see Chapter 8) and acute

vasculitis of several organ systems. With vasculitis, a spiked fever often precedes depression, anorexia, and rapid weight loss. Leukopenia is present. Affected animals may develop edema of the lips, tongue, throat, ears, and brisket. Other signs include excessive salivation and hyperemia or cyanosis of the oral mucosa, including the tongue (hence the name *bluetongue*). Affected sheep often produce profuse serous nasal discharge that soon becomes mucopurulent and produces crusts and excoriations around the nose and muzzle. Oral lesions progress to petechial hemorrhages, erosions, and ulcers. Pulmonary edema is often severe, and pneumonia may develop. Skin lesions can progress to localized dermatitis. Affected sheep may exhibit stiffness or lameness because of muscular changes and laminitis. Cyanosis or hemorrhagic changes of the skin of the coronet can extend into the horny tissue. After recovery, a definite ridge in the horn of the hoof may be present for many months. In severe cases, the hoof sloughs. Mortality varies widely. In Africa, the virus is much more virulent than in the United States, and mortality ranges from 2 to 30%. The reproductive or teratogenic form of the disease varies greatly with strain, host, and environmental factors. Teratogenic effects include abortions, stillbirths, and weak, live "dummy lambs." Congenital defects may include hydranencephaly.

Diagnosis. In parts of the world where the disease is common, the diagnosis is usually based on clinical signs alone. The virus can be isolated from blood, semen, or tissues (spleen and brain from aborted fetuses). Viral isolation from blood obtained during the viremic state is the most definitive means of diagnosis. Serologic evaluation involves two types of viral antigen groups called *P7* and *P2.* The former is found in all bluetongue viruses, and the latter determines the serotype. Sera are commonly tested with complement fixation, agar gel immunodiffusion (AGID), or one of several ELISA tests. A competitive ELISA is considered the best serologic test for detecting group antibodies to bluetongue virus. A direct fluorescent antibody test is available. Molecular tests (e.g., PCR) for bluetongue have recently become available and are extremely sensitive and specific. They can be useful for distinguishing serotypes. Other clinicopathologic signs that aid in diagnosis include leukopenia during the early febrile stage of the disease and an increase in serum CK corresponding to the latter phase of muscle stiffness and lameness.

Treatment. Treatment is non-specific and consists of nursing care. Because of the reluctance of animals to eat, they should be fed a gruel of alfalfa pellets by stomach tube or encouraged to eat soft feeds and green grass. Broad-spectrum antimicrobials are often used to treat secondary pneumonia and dermatitis. Animals should be kept on soft bedding with good footing. Water and shade should be readily available. NSAIDs are commonly used.

Prevention. The *Culicoides* vector is difficult to eliminate, so animals should be kept indoors during periods of peak gnat activity (dusk and early evening). Owners should attempt to eliminate gnat breeding grounds such as overflowing watering troughs and shallow septic systems and should limit exposure of sheep to gnats with the use of repellent sprays.

Modified live vaccines based on local strains and serotypes are available in some parts of the world. Some cross-protection among serotypes does occur. The vaccine should be administered at least 2 weeks before breeding season to prevent teratogenic effects. Vaccinated breeding rams may have a slight risk of decreased fertility. Lambs can be vaccinated in the face of an outbreak. Pregnant animals cannot be vaccinated with modified live vaccines. Sheep that have recovered from an attack of bluetongue are solidly resistant for months to infection by the same viral strain and to some other viral types. Active immunity in sheep requires both humoral and cellular immunity.

Epizootic Hemorrhagic Disease

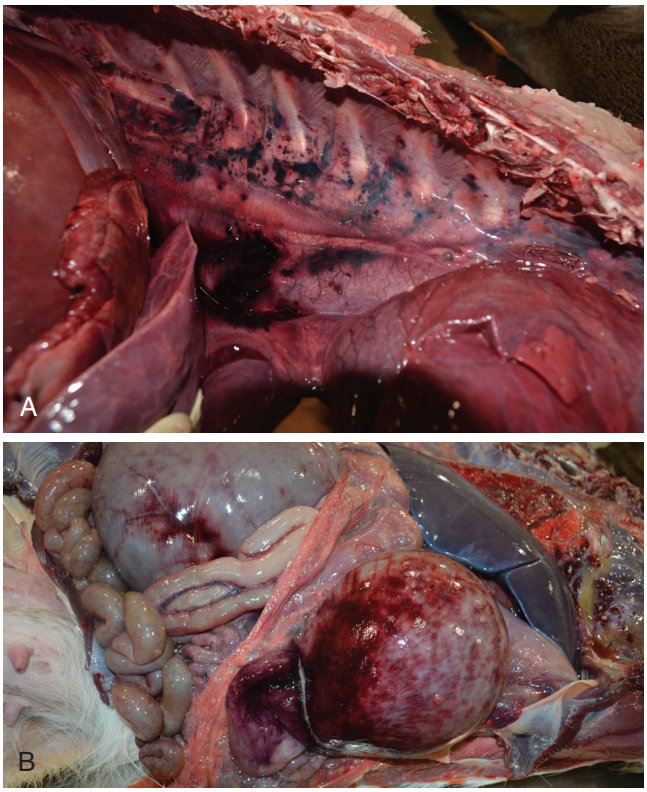
Etiology. Epizootic hemorrhagic disease virus (EHDV) is an orbivirus belonging to the family *Reoviridae*. The virus is structurally related to bluetongue virus, and the pathogenesis and clinical signs of disease resulting from these two viral infections are very similar. At least seven distinct serotypes of EHDV are recognized, although formal classification of serotypes has yet to be finalized. Only two serotypes (EHDV1 and EHDV2) have historically circulated throughout North America, and those serotypes are largely considered to be endemic in almost all areas of the United States, with the exception of the northeast and arid areas of the southwest. However, in 2006, EHDV6 was isolated from surveillance efforts in dead white-tailed deer.[124] Since then, EHDV6 has been increasingly identified from both surveillance samples and clinical cases and is also believed to be endemic in several regions.[125]

Pathogenesis. Epizootic hemorrhagic disease (EHD) is a noncontagious disease that is transmitted by the *Culicoides* biting midges. *Culicoides sonorensis* is the primary vector of EHDV in the United States, although other species are also suspected to transmit the disease based on the geographic distribution of clinical cases, although this has yet to be formally shown. Due to the vector-borne route of transmission, peak incidence of the disease is closely associated with peak vector population, namely, in the late summer and fall of the year.

Although capable of infecting a wide range of wild and domestic ruminants, EHDV is largely a pathogen of wild cervids, particularly white-tailed deer. Episodes of clinical disease are less common in mule deer, pronghorn antelope, and bighorn sheep and have lower morbidity and mortality. Sheep are only rarely infected with the virus and goats appear to be resistant to the virus. Cattle are commonly infected based on seroprevalence surveys, but overt clinical disease is uncommon. As a rule, infection in livestock is usually asymptomatic except for periodic epidemics. The last major EHD epidemic in the United States occurred in 2012 and affected a variety of captive and wild ruminant species.[126] In endemic areas, seroprevalence in cervids and other ruminants is high, but clinical disease is not commonly seen. Conversely, where seroprevalence is low, introduction of the virus results in widespread infection, where morbidity and mortality can reach 90% and 60%, respectively.

Following transmission of the virus by biting midges, EHDV replicates in the endothelial cells of the lymphatics surrounding the site of the bite. A primary viremia allows for systemic spread of the virus and secondary replication in lymph nodes throughout the body and the spleen. Viremia is important for disease propagation and generally lasts no more than 3 weeks following infection, although the virus can occasionally be isolated from deer infected 50 days previously. Antibodies to EHDV are first detected 10 to 14 days following infection but are not always capable of completely neutralizing the infection. Thus, it is possible to find both neutralizing antibodies and live virus in the same animal. Passive antibodies in fawns can be found up to approximately 4 months of age. As in adults, antibodies in fawns may not protect from infection but generally protect from severe clinical signs.

Clinical Signs. Clinical disease in white-tailed deer can be peracute, acute, or chronic. The course of the peracute syndrome of diseaseis relatively short, with death often occurring within 36 hours of infection, with or without the presence of clinical



• **Fig. 16.1 A.** The lungs of the adult pen-raised, white-tailed deer, have been retracted to reveal to ecchymoses on the ventral surface of the "ribcage." Petechiae and ecchymoses can occur anywhere within the carcass in cases of epizootic hemorrhagic disease (EHD), but common locations are on the epicardium, on the pleural surface the ribs, subcutaneously, and on the surface of the spleen. **B.** Ecchymoses over the surface of the reticulum (bottom right of photo) and the surface of the rumen (left side of photo). In addition to EHD, this deer also had bronchopneumonia (fibrin overlying consolidated lung can be seen in the far right of photo). (Courtesy Dr. Kelley Steury, Auburn, AL.)

signs. When present, clinical signs include severe edema of the head and neck, swelling of the tongue and conjunctiva, anorexia, fever, weakness, and respiratory distress. Hemorrhagic diatheses are not present antemortem but may occur after death. In contrast, in the acute form of the disease, the clinical signs of the peracute form are accompanied with bleeding throughout body tissues (Figure 16.1A, B). Ulcers may be evident in the oral cavity and throughout the upper gastrointestinal tract, forestomachs, and abomasum. Case fatality rates are high for both the peracute and acute forms. Deer that recover after several weeks of illness are said to suffer from the chronic form of the disease. Signs of previous illness may include breaks or rings in the hoof horn due to interrupted growth and synthesis leading to lameness, sometimes severe. Ulceration and scarring of the rumen and gastrointestinal tract may result in loss of body condition despite a seemingly normal appetite and ample nutrition. Widespread evidence of vasculitis may be observed histopathologically.

Diagnosis. The gold standard for EHDV diagnosis is virus isolation. Demonstration of neutralizing antibodies to EHDV reference strains is evidence of previous infection but may be of limited value in endemic areas where seroprevalence levels are expected to be high. Also, all potentially suspected serotypes must be used when testing the sample, thereby increasing the time and cost involved with the test. Continued research and refinement of molecular techniques, including PCR, are ongoing and are attractive due to the short turnaround times and the potential for high throughput of samples. However, it is important to remember that a positive result using molecular techniques does not equate to the presence of infectious virus, and thus, interpretation of results must be done with caution.

Control. Control of EHD is difficult and relies on a combination of disease surveillance, vector control, and potentially, vaccination. Eradication of vector-borne diseases from endemic areas is difficult and time-consuming, and thus, disease control is likely more attainable than strict eradication. Vector control is more important in the late fall and summer, when populations are at peak levels and viral transmission is more likely. Midge-proofed housing and the treatment of animals with pyrethroid insecticides have been attempted but may be logistically challenging and have yet to have been demonstrated efficacious. Vaccine availability in North America is limited, but inactivated autogenous vaccines have been developed from isolates obtained from ill or recently diseased animals. Autogenous vaccines are tested for purity but not necessarily for efficacy. Vaccine usage must be approved by the U.S. Department of Agriculture prior to administration.

Peste des Petits Ruminants (Pseudorinderpest)

Etiology. Peste des petits ruminants (PPR) is an acute or peracute, febrile, often fatal disease of ruminants caused by a virus in the family *Paramyxoviridae* and genus *Morbillivirus.* Sheep are less susceptible than goats and white-tailed deer. Cattle are only subclinically infected, and some wild ungulates, as well as camels, appear to suffer the occasional epizootic. The virus (PPRV) is serologically related to the virus that causes rinderpest. Geographically, the virus is found throughout Northern Africa, the Middle East, and adjacent regions of Asia, with possible movement into southern Africa and Europe noted.

Pathogenesis. The main route of infection is respiratory, and PPR is spread by airborne droplets. All secretions and excretions of infected animals are contagious throughout the course of the disease, but no carrier state exists. The virus targets lymphoid tissue. Lymphocytes are destroyed in germinal centers in lymph nodes, Peyer's patches, tonsils, splenic corpuscles, and cecal lymphoid tissue. Immunosuppression results from lymphoid destruction. Lymphocytes are partially replaced by plasma cells, macrophages, an eosinophilic acellular matrix, and occasionally neutrophils. The epithelial lining of the mouth and digestive tract is highly vulnerable to the PPRV. With the loss of the alimentary tract mucosa, weight loss and diarrhea become severe. The incubation period is usually 2 to 6 days, with up to 10 days possible.

Clinical Signs. The clinical disease produced by PPRV in sheep and goats closely resembles that of rinderpest, but the course is much more rapid. With the acute form, sheep and goats typically display an abrupt rise in temperature to 104° to 106° F (40°–41° C). Within a few days, infected animals develop nasal and lacrimal discharge, depression, thirst, anorexia, and leukopenia. Congestion of the conjunctival and other mucous membranes occurs, followed by serous and mucopurulent exudates. Sheep and goats develop oral erosions with necrotic foci, which results in excessive salivation. Diarrhea that may be profuse but rarely hemorrhagic develops within 2 to 3 days and is accompanied by abdominal pain, tachypnea, emaciation, and severe dehydration. Bronchopneumonia, particularly that caused by *Pasteurella* spp., may be a terminal

sequela. Death usually occurs 5 to 10 days after the onset of fever. Pregnant sheep or goats with PPR may abort.

Diagnosis. A presumptive diagnosis of PPR can be made on the basis of clinical, pathologic, and epizootiologic findings. The diagnosis can be confirmed by isolating the virus from blood or tissues, including lymph nodes, tonsils, spleen, and lung. Immunocapture ELISA or PCR may be used to detect infection several days before the development of clinical disease. Most serologic tests (complement fixation or AGID) cannot differentiate between PPR and rinderpest. Characteristic postmortem findings include necrotic stomatitis that is generally confined to the inside of the lower lip and adjacent gum, the cheeks near the commissures, and the ventral surface of the free portion of the tongue. Abomasal erosions are often present. In the small intestine, Peyer's patches are markedly affected, particularly in the first portion of the duodenum and terminal ileum. The large intestine may be severely affected. Lesions occurring near the ileocecal valve, at the cecocolic junction, and in the rectum are often described as *zebra stripes* that indicate areas of congestion along the folds of the mucosa.

Treatment and Prevention. Infection with PPRV has no specific treatment. Mortality can be reduced by supportive care, including the administration of antimicrobial and antiinflammatory agents, as well as nutritional support. In the United States, state and federal veterinarians should be notified if PPRV is suspected. Methods used to eradicate rinderpest are useful in the eradication and control of PPR. All sick sheep and goats and those exposed should be slaughtered and disposed of by burning, burying, or rendering. The premises should be decontaminated, and the area quarantined. Sheep and goats can be protected against PPR by immunization with rinderpest vaccines or by the simultaneous administration of PPR hyperimmune bovine serum and virulent PPRV.[127]

Louping Ill

Pathogenesis. Louping ill is a tickborne disease caused by a flavivirus. It affects mainly lambs but occasionally also affects other livestock species and infrequently affects deer, camelids, and humans. Transmission is most common during tick season, and *Ixodes ricinus* is thought to be the most important infective host.

Many sheep clear the infection after a few days of fever and viremia, but others develop severe, fatal viral encephalitis. The virus is shed in many secretions, including milk, which is an important source of infection for other animals (and humans). The severity of the disease depends on herd immunity because previous exposure gives long-lasting immunity. Colostrum from immune females is protective for the neonate. High antibody titers also appear to shorten the duration and level of viremia and thereby prevent invasion of the central nervous system. Naïve flocks may have fatality rates as high as 60%.

Clinical Signs. High biphasic fever, anorexia, and depression are seen in most infected sheep. Lambs may die quickly before illness is noted. Some sheep also develop central neurologic signs, including hyperexcitability, muscle tremors, and rigidity. Abnormal coordination and muscle activity may cause sheep to move with a bounding gait (hence the name *louping ill*).

Diagnosis. The condition has no characteristic gross lesions. Microscopic examination of animals with neurologic signs reveals evidence of viral meningoencephalitis. Diagnosis is made by history (based on location, signs, and time of year), the identification of characteristic lesions, virus isolation, or fluorescent antibody staining of fresh brain tissue. A demonstrated increase in specific antibody titers in survivors strongly suggests the presence of this infection.

Prevention. Vaccines are available in endemic areas to control infection. Vector control during tick season also is important. Lambing season should also be timed so that lambs have high colostral antibody protection at the time of exposure to ticks.

Foot-and-Mouth Disease and Vesicular Stomatitis

Pathogenesis. Foot-and-mouth disease is caused by a highly contagious picornavirus and has been eradicated from the United States. Vesicular stomatitis is caused by a rhabdovirus and is intermittently eradicated from the United States. Both diseases are highly contagious, nearly indistinguishable from each other clinically, and reportable. Foot-and-mouth disease has a broad host range that includes most hoof stock (including pigs but not horses) and several other mammalian species. Vesicular stomatitis also affects many species of hoof stock, including both pigs and horses. Sheep and goats are relatively less susceptible than cattle, particularly to vesicular stomatitis.

The viruses are spread by aerosol and mechanical vectors and primarily colonize skin or mucous membranes. Milking machines, flies, birds, and humans all may be important mechanical vectors. Vesicular stomatitis tends to remain at the site of infection, and colonization is facilitated by damage to the skin. Oral mucous membranes, coronary bands and interdigital skin, and teat-end skin are common sites of lesions. Vesicular stomatitis outbreaks in the United States tend to occur in the summer or fall and end with the first killing frost.

Viremia plays more of a role with foot-and-mouth disease. The virus is present in most body tissues and fluids in infected animals and can be transmitted through milk, meat, bone, and hide products; semen; equipment that pierces the skin; and biting arthropods. It also tends to spread through the circulation from the site of infection to other susceptible tissues, including the sites of vesicular stomatitis, as well as to the nasal cavity, mammary glandular epithelium, and ruminal pillars.

The basic lesion for both diseases are the vesicles that form in the oral cavity and on the teats and coronary band. The vesicles quickly rupture and may not be visualized before forming erosions. Ruptured vesicles leave deep erosions on the skin or mucous membranes and appear to cause pain. Tissue damage and inflammation are often compounded by secondary bacterial infection, which can cause greater morbidity and mortality than the original viral infection. Morbidity is related to feed refusal, increased recumbency, and secondary infections of the mouth, udder, and feet.

Clinical Signs. Sheep and goats usually develop minor lesions, if any, and are more important in many outbreaks as transport or multiplying hosts than as primary clinical cases. However, identification of lesions should raise suspicion of this disorder. In the worst cases, vesicles, erosions, and ulcers are seen at target sites. They may appear mildly inflamed and erythematous; if they are infected, they may appear severely inflamed with hemorrhage and necrosis. Other signs vary according to the location and severity of the lesions. Lingual and buccal lesions cause salivation, dysphagia, and feed refusal. Foot lesions, which are the most common clinical manifestation in small ruminants, cause lameness and recumbency. Teat lesions cause reluctance to be milked or nursed and a decrease in production. Fever also may be seen early in the disease, when vesicles are most apparent. The fever then usually abates, and vesicles are replaced by erosions or ulcers. Abortion may occur, especially with foot-and-mouth disease, and is

probably related to the fever rather than to fetal infection. The disease is usually self-limiting; most animals recover within 2 to 3 weeks. Shedding of the virus causing vesicular stomatitis is thought to subside soon after healing of lesions. Foot-and-mouth disease virus may be shed for as long as 6 months, and all body secretions and tissues should be considered contagious, including milk, semen, meat, and offal. Both viruses have zoonotic potential and cause a disease in humans that resembles mild influenza. The diseases are self-limiting, but people can shed the viruses in sufficient quantities to infect other animals.

Diagnosis. No characteristic clinicopathologic changes are reported for either virus. Gross lesions resemble those seen before death and include vesicular, erosive, and ulcerative lesions of the mouth, feet, and teat ends; foot-and-mouth disease also causes lesions of the mammary gland and ruminal epithelium. Microscopic findings include hydropic degeneration of cells of the stratum spinosum of the epidermis without inclusion bodies. Secondary bacterial infection may lead to deeper ulcers and complicate identification of the viral etiology of these lesions. Myocarditis lesions may be seen with some forms of foot-and-mouth disease.

A presumptive diagnosis may be made by identifying characteristic lesions during a season and in an area at risk for one of these infections. In North America, bluetongue should be considered as an important differential diagnosis for ulcerative oral lesions in sheep. A confirmed diagnosis of foot-and-mouth disease is achieved by a combination of virus isolation (from vesicles), IHC, and serology by regulatory officials. Identifying the source of infection also is very important. Diagnosis of vesicular stomatitis is achieved by complement fixation or fluorescent antibody staining of virus in vesicular fluid or detection of a rise in antibody titers. Flocks with either of these diseases in the United States are subject to quarantine and possible destruction (especially for foot-and-mouth disease).

Prevention. Meticulous personal hygiene and avoidance of contact with new animals are important during outbreaks to prevent spread between flocks. Vaccines against foot-and-mouth disease are available in many parts of the world, but not in the United States. Most nations slaughter or quarantine affected animals. Vaccines against vesicular stomatitis are available and are most commonly used if the risk of outbreak is high, but vaccination does not prevent infection or shedding. Good hoof and teat care and soft feeds may help prevent spread of the virus by providing a healthy, intact barrier against invasion.

Sheep and Goat Pox

Pathogenesis. Sheep and goat pox are caused by two closely related poxviruses. Some strains are infective to both sheep and goats; most are species specific. They are maintained in populations by infected animals, and transmission occurs by aerosol or direct or indirect contact. Flies may play an important role as mechanical vectors in some flocks. Viruses remain infective in the environment for as long as 6 months.

After infection, viremia and inflammation of the oral, nasal, and ocular mucous membranes occur. Erythematous papular pox lesions appear a few days later. Severity varies according to strain pathogenicity, breed susceptibility, and immune status. Mild infections are characterized by lesions concentrated in the non-wooled or hairless regions of the skin. Severe infections produce lesions throughout the oral cavity, respiratory tract, and peritoneal cavity. Secondary infection is common with the severe form and mortality is high. If the animal survives, lesions heal in 3 to 4 weeks. Both diseases have been eradicated from the United States and are reportable. People can develop mild disease on exposure to these viruses.

Clinical Signs. Fever, inappetence, conjunctivitis, and upper respiratory signs are seen in the initial stages. Pox lesions are visible shortly thereafter. Secondary infection can lead to a variety of more serious signs indicative of respiratory disease, sepsis, and shock.

Diagnosis. Characteristic pox lesions are highly suggestive of this disease. Microscopic analysis reveals eosinophilic intracytoplasmic inclusion bodies, acantholysis, and pustule formation within the epidermis and occasionally the dermis. Viral particles may be seen on ultrastructural examination. Gross and microscopic lesions are characteristic with the severe form, but mild disease may produce mild lesions that are difficult to differentiate from other viral diseases that cause oral proliferative or ulcerative lesions. Virus can be isolated from blood or tissues (mainly skin) during the acute viremic stage and identified by antibody staining of more chronic lesions. Serologic tests are available to detect rising titers in convalescent animals.

Treatment and Prevention. No specific treatment is available for sheep or goat pox. Antibacterial drugs may be useful to treat secondary infection. Judicious use of insecticides and confinement of affected animals may prevent spread. Vaccines are available in some countries, but not in the United States. Infected flocks are placed under quarantine or destroyed in regions where the diseases are not endemic. These viruses are difficult to eradicate from flocks because of their environmental persistence and the constant supply of susceptible hosts.

Chronic Viral Diseases

Caprine Arthritis-Encephalitis Virus Infection

Caprine arthritis-encephalitis virus (CAEV) is an enveloped, single-stranded retrovirus in the *Lentivirus* genus. Like other retroviruses, CAEV integrates into the host chromosomal DNA before replicating. The virus is able to remain latent or undergo sporadic bouts of productive viral replication. CAEV is closely related to ovine lentiviruses.

Clinical Signs. Clinical disease may be evident in only 10% of goats from a CAEV-infected herd at any given time. As many as 85% of seropositive goats may be clinically normal. CAEV produces four clinical syndromes: encephalomyelitis, arthritis, interstitial pneumonia, and indurative mastitis. The pattern of disease usually varies with age. Arthritis is generally seen in sexually mature goats, whereas encephalomyelitis is generally seen in kids 2 to 4 months old. Interstitial pneumonia and indurative mastitis are more common in adult goats. Some goats suffer from a wasting disorder characterized by poor body condition and rough hair coat.

Diagnosis. A presumptive diagnosis of CAEV can be made on the basis of history and clinical signs suggestive of one or more of the syndromes. In general, ELISA tests are better for detecting disease in an individual animal because the sensitivity of the test is higher than that of the AGID, whereas the AGID is better for herd screening that requires high specificity. With the AGID test, false negatives may occur in goats that have not yet seroconverted to recent infection. Individual goats may take months or years to seroconvert or may never do so. Parturition or advanced stages of disease also may contribute to a false-negative result. False positives may occur in goats younger than 90 days old that have colostral antibodies. For this reason, it is often suggested that kids be at least 6 months old before they are tested. PCR testing has high specificity and sensitivity and can detect infection within a

day of exposure. Other less commonly used tests include a Western blot to detect antibodies and a Northern blot to look for mitochondrial RNA. Because of the limitations in interpreting serologic results, CAEV-induced disease can only be definitively diagnosed by identification of characteristic lesions from examination of biopsy specimens or postmortem viral isolation.

Treatment. No specific treatments are available for any of the syndromes associated with CAEV. Young goats suffering from encephalomyelitis may benefit from physical therapy if they are recumbent, and bottle feeding may help maintain hydration and caloric intake. Antibiotics may be beneficial to goats affected with interstitial pneumonia or mastitis if secondary bacterial infection is present. Generally, the prognosis is poor for the encephalitic form and guarded for the other forms.

Prevention. Prevention of CAEV is crucial because infection is lifelong. Infected colostrum and milk are the most important sources of infection. Newborn kids should be prevented from ingesting colostrum from infected does and should instead be fed pasteurized goat's milk or milk from CAEV-negative goats. All goats in a herd should undergo serologic testing twice yearly; seropositive goats should be segregated or culled to prevent direct contact between infected and uninfected animals.

Ovine Progressive Pneumonia Virus Infection

Ovine progressive pneumonia (OPP) is an ultimately fatal retroviral disease that causes chronic, progressive, debilitating inflammatory conditions of the lungs (United States) and central nervous system (other parts of the world). It also is called *maedi-* (mæði is Icelandic for "shortness of breath") *visna* (meaning "wasting"). The virus is a member of the *Lentivirus* genus of retroviruses and is closely related to CAEV. Recombination between OPP and CAE viruses has been observed.[128]

The virus primarily affects sheep and rarely goats and has been identified worldwide, except in Australia and New Zealand. The disease has a long incubation period and protracted clinical course.

Pathogenesis. Only sheep older than 2 years of age are affected by OPP virus (OPPV). The virus is spread by direct contact, probably in respiratory and salivary secretions, and by excretion in the milk and colostrum. Transplacental transfer is of minor importance. Virus is excreted by animals that exhibit clinical signs and asymptomatic animals. Infection is established in the monocyte and macrophage cell line and spread by these cells to the lungs, lymph nodes, choroid plexus, spleen, bone marrow, mammary gland, and kidneys. Like CAEV, OPPV evades the cellular and humoral immune system of the host by incorporation of its provirus in host DNA, low-grade replication of virus only when monocytes differentiate into macrophages (restricted replication), and production of antigenic variants that are not neutralized by existing antibodies. Continual antigenic stimulation of the host by low-grade replication of OPPV results in chronic inflammation and resultant lymphoid proliferation in various target tissues. The virus may prevent B lymphocytes from differentiating into plasma cells in lymph nodes and may thereby impair immunoregulation. Seroconversion occurs within 2 to 3 weeks after infection.

Clinical Signs. In the United States, serologic surveys reveal infection rates of between 30 and 67% but rarely is more than 5% of a flock lost to OPPV. Icelandic, Texel, Border Leicester, and Finnish Landrace appear to be susceptible sheep breeds. More resistant sheep breeds include Rambouillet, Suffolk, and Columbia.

Various clinical syndromes are associated with OPPV and include wasting (thin ewe syndrome), dyspnea occasionally with a dry cough, pneumonia, mastitis ("hard bag"), posterior paresis, arthritis, and vasculitis. In North America, pneumonia and indurative aseptic mastitis are common sequelae of infection. Coinfection with the Jaagsiekte virus (the cause of pulmonary adenomatosis) worsens respiratory signs. Visna, the neurologic form, is more common in goats. Over the course of up to a year, subtle signs such as a head tilt or hindlimb weakness progress to gross incoordination, whole body tremors, and rarely more profound cranial nerve signs.

Diagnosis. A presumptive diagnosis can be made on the basis of clinical signs, poor response to treatment, characteristic postmortem findings, and serologic testing. Definitive diagnosis requires PCR or isolation of the virus from WBCs (buffy coat of whole blood sample) or tissues. Less expensive and faster serologic tests include AGID, ELISA, and an indirect immunofluorescence test. The AGID test is frequently used as a flock screening test, but the ELISA is more sensitive on an individual basis and can detect antibodies earlier in the course of the disease. As with CAEV, false negatives and false positives are possible.

Characteristic postmortem lesions include generalized wasting and firm, noncollapsing lung or firm, mottled mammary glands, both with regional lymphadenopathy. Microscopic evaluation of those tissues reveals interstitial non-septic, mononuclear cell infiltrates, although these may be complicated by secondary infections. Histopathology of nervous tissue reveals meningoleukoencephalitis.

Treatment. No effective treatment is available for OPPV. Supportive therapy that includes appropriate husbandry and control of secondary infection with antibiotics may prolong life for a few weeks or months but, ultimately, the disease is fatal. Because of the poor prognosis and risk of exposure of naive animals to clinical disease, long-term treatment is not recommended.

Prevention. The only known method of preventing OPPV infection in a flock is to prevent exposure to the virus. Management practices that help decrease the incidence of horizontal transmission include disinfection of milking equipment, dehorning instruments, and tail docking and castration tools before use and between animals. Contaminated feed and water also are potential routes of infection and should not be shared among infected and uninfected animals. Serologic testing and separation or culling of seropositive animals may help reduce infection. Although OPPV can readily be isolated from ewe colostrum, colostral transmission of OPPV has not been definitively established. However, many prevention guidelines recommend that offspring from infected dams be separated from the dam before they nurse and then be fed cow colostrum and artificially reared. Quarantine and serologic testing of flock additions before placing them with the current flock and purchase of sheep only from OPPV-free flocks are important to prevent the introduction of new infections. Because of the potential cross-species spread, all precautions taken for sheep also apply to contact goats. Serologic testing should be performed at least annually in a flock until two consecutive negative test results are obtained.

Border Disease Virus

Border disease virus (BDV) is in the genus *Pestivirus* and family *Flaviviridae*, which also includes the two genotypes of bovine viral diarrhea virus (BVDV) and classical swine fever virus. It rarely causes disease in adults and is most important as a cause of in utero infection of lambs and kids. The condition gets its name from the fact that it was first reported in sheep along the Welsh border of the United Kingdom. Other names such as "hairy shakers" and

"fuzzy lamb disease" refer to some of the clinical signs seen in affected newborns. It is important to recognize that although BDV is genetically distinct from the two types of BVDV, sheep and goats also are susceptible to some strains of BVD.

Pathogenesis. Horizontal transmission of BDV occurs through contact with secretions and excretions of body fluids and tissues from infected animals. The virus crosses intact mucous membranes and can spread rapidly through a flock. The major reservoir is the persistently infected sheep or goat. These reservoirs are usually asymptomatic, congenitally infected, and often seronegative animals that shed large quantities of virus. These may be residents of a flock with an ongoing problem or bought in as replacement animals to a naïve flock. Some cross-infection from other species is possible, particularly from cattle.

Adult, immunocompetent sheep rarely show any signs of acute infection. However, if a pregnant ewe or doe is infected, the virus may be transmitted vertically to the embryo or fetus. Depending on the stage of gestation, embryonic or fetal infection may have different outcomes ranging from embryonic reabsorption to normal birth. These infections are the most important aspect of border disease.

The major organ system targeted by BDV is the fetal central nervous system. The hallmark lesion is hypomyelination, or degeneration of oligodendroglial cells. Three factors contribute to this lesion. The first is direct viral damage. The second is viral-induced inhibition of the thyroid gland that causes decreased secretion of thyroid hormones. In the absence of these hormones, a resultant lowered concentration of a specific nucleotide in the central nervous system also contributes to the hypomyelination. The third factor is altered immune function. The virus causes the host to produce a virus-specific delayed hypersensitivity reaction that causes inflammation in the central nervous system. It also causes immunosuppression. Death often results from opportunistic conditions such as parasitism, diarrhea, and bronchopneumonia.

Clinical Signs. Clinical signs depend on the time during gestation when the fetus or embryo is exposed to the virus. Clinical signs also may vary in severity from animal to animal because different fetuses develop competent immune systems at different times. If the fetus or embryo is exposed to the virus within 45 days of conception, it dies and is resorbed or aborted. These losses are not usually noticed by the flock manager. The principal manifestation in the flock is a large number of open ewes and a small lamb crop. Infection of the fetus between days 45 and 80 of gestation causes damage to rapidly growing systems such as the skin and nervous, lymphoid, thyroid, and skeletal systems. Congenital malformations are seen at birth. Lambs have abnormal fleece characteristics (hairy rather than woolly in consistency), small stature, domed heads, shortened legs, and dark pigmentation of the skin, particularly on the dorsal aspect of the neck. The lamb may exhibit tonic-clonic tremors ("hairy shakers") when awake, which may prevent standing or suckling. Most of these lambs die within a few days of birth. If they survive, the hair changes disappear in 9 to 12 weeks and the central nervous system signs resolve by 20 weeks. Goats infected at this time have similar symptoms except that they rarely exhibit hair coat changes. If kids are infected before day 80 of gestation and are still viable, they may become persistently infected and immunologically compromised. They are small at birth and generally weak.

Typical outbreaks of border disease cause abortions and birth of weak lambs in the first year as the virus rapidly spreads throughout a susceptible flock and then insignificant losses in the succeeding years as adult sheep develop immunity. However, if new naïve ewes are introduced in the flock, substantial losses may occur in perpetuity.

Diagnosis. Border disease viral antigens can be demonstrated in abomasum, pancreas, kidney, thyroid, skin, and testicle tissues from aborted fetuses and persistently infected animals using fluorescent antibody tests. However, IHC on ear notch samples is not considered as reliable for detecting persistently infected small ruminants as it is for cattle. The virus can be isolated, or viral antigen detected by ELISA, from serum, heparinized whole blood, and tissue taken from brain, spinal cord, spleen, and bone marrow from affected lambs. Whole blood is better than serum if colostral antibodies are likely to be high; serum is an adequate sample in neonates and juveniles that have not suckled.

Antibodies to the virus may be quantified by serum neutralization, AGID, and complement fixation with hyperimmune BVD antiserum. Serologic tests are useful to detect exposure in late-gestation (after day 80) neonates and unvaccinated animals but may be confounded by colostral antibodies in suckling neonates, previous exposure, and vaccination in older animals. Any titer in a presuckling neonate indicates in utero exposure, whereas a serum neutralization titer of 1:20 to 1:320 suggests infection in adults. The presence of specific antibodies in the cerebral spinal fluid suggests BDV infection. Negative presuckling serologic tests do not rule out exposure because persistently infected lambs tend to be immunotolerant to the BDV and therefore are born without an antibody titer. These animals may subsequently develop a titer that is indistinguishable from that of a normal animal. Although persistently infected animals do not respond immunologically to the strain of the virus they carry, they may respond to other strains of the virus, including vaccine strains.

As with BVD, PCR assays are gaining popularity for the detection of BDV in fluids and tissue samples. These assays appear to be superior to other techniques, except in autolyzed tissues. Real-time PCR may also be used to differentiate BDV from BVD and to type isolates.

Gross postmortem findings include hydranencephaly, porencephaly, microcephaly, cerebellar hypoplasia, abnormal rib curvature, brachygnathia, doming of the frontal bones of the skull, narrowing of the distance between the orbits, shortening the crown-to-rump length, shortening of the diaphyseal length, retention of secondary hair fibers, and abnormal skin pigmentation. The major histopathologic changes include hypomyelination and hypercellularity of the white matter. Glial cells appear normal.

Treatment. No treatment is available for border disease infection. Supportive care may include assistance in nursing and standing for affected lambs, provision of good bedding and solid footing, and treatment of secondary opportunistic infection.

Prevention. Control is primarily achieved by eliminating persistently infected carrier animals from the flock and preventing the addition of new carrier animals. This is easiest in a closed flock but especially difficult in small ruminant flocks because of the frequent desire to import new genetics. To identify carriers, virus isolation must be performed on every animal in the flock; carrier animals must be culled. Additionally, all unborn animals must be considered potential carriers and should be tested at birth. An alternative solution in hobby flocks is to arrest breeding activity until all animals have been shown to be free of infection. New animals should be quarantined and tested before admission to the flock. Herd screening with the ear skin biopsy test using fluorescent antibody staining to detect virus is less expensive and more convenient than the whole blood virus isolation test.

The role of vaccination in preventing infection is still unclear. No vaccine against BDV is available, but some reports suggest that BVDV vaccines for cattle may be helpful for sheep at risk. However, these vaccines have proven to be more effective at preventing clinical disease in vaccinated animals than in preventing in utero infection because they do not prevent transient viremia. Vaccination decreases viremia and fetal infection but does not eliminate them. Therefore, vaccines play a role in decreasing economic loss but do not replace culling of carrier animals as the major method of control.

Scrapie

Another member of the slow infection group of diseases of small ruminants is scrapie. It is an afebrile, chronic, progressive degenerative disorder of the central nervous system of sheep and occasionally of goats (see Chapter 13). Scrapie is caused by a prion and, as such, is one of the transmissible spongiform encephalopathies.

Sheep (and goats and mouflon to a lesser degree) are the natural hosts for scrapie. Clinical signs often do not usually appear until animals are 2 years old, and animals as old as 5 years may exhibit clinical disease. Both vertical and horizontal transmission have been demonstrated experimentally in sheep and goats. Abnormal scrapie protein has been identified in milk, urine, and seminal plasma of sheep up to 20 months prior to the development of clinical signs. Also, new evidence from deer with chronic wasting disease, a similar disorder, suggests that infective prions are excreted in the saliva and feces well before the development of clinical signs. These new revelations may help explain horizontal transmission of infection.

Clinical Signs. The onset of scrapie is insidious. Initially, sheep show subtle changes in behavior such as mild apprehension, staring or fixed gaze, failure to respond to herding dogs, and boldness around humans. Several months later, the animals become intolerant of exercise and develop a clumsy, unsteady gait and floppy ears. Later, the sheep develop itchy skin that causes them to rub themselves excessively against firm, immobile objects (origin of the name *scrapie*). This leads to excoriations and wool damage. There is a general decline in body condition and coordination.

Diagnosis. Histologically, the only consistent lesions are degenerative changes in the central nervous system consisting of bilaterally symmetric vacuolation of the neurons in the brainstem and spinal cord with accompanying spongy degeneration. As a preclinical test, IHC may be performed in lymphoid tissue from the tonsils, third eyelid, or rectoanal mucosa, but none of these methods is foolproof. CWD is discussed in Chapters 13, 19, and 20.

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