Medicine of the Calf – Including Advanced Fluid Therapy

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Temporal clustering of disease is a common feature of health problems in calves. A simple awareness of these temporal associations is helpful for prioritizing diagnostics during disease investigations and for making therapeutic decisions when managing sick calves. Common disease clusters include perinatal mortality (birth through 2 days), diarrhoea (4 – 28 days of age), and pneumonia and diarrhoea around weaning (7 – 16 wks). While the problems may manifest independently neonatal compromise at or shortly after parturition increases the risk of disease during the first 6 months of life and may compromise lifetime productivity.

Perinatal Mortality

Between 50 - 70% of neonatal mortality occurs in the first three days of life with dystocia, starvation, and hypothermia responsible for 50 - 60% of these losses. Reduced foetal viability often reflects mismanagement of maternal nutrition and or the maternal environment during the last trimester of pregnancy and or the pre and peripartum period.

Dystocia may reflect maternal and or foetal compromise**.** Maternal variables associated with dystocia include parity, conformation, and nutrition. The incidence of dystocia and stillbirths in heifers is usually double that of cows and feto-pelvic disproportion is the most common cause of dystocia in heifers. Age at first calving is not correlated with risk of dystocia as long as heifers are fed and managed to achieve appropriate growth and stature prior to calving. Use of calving ease bulls over primiparous cows helps to reduce the incidence of dystocia. The heritability of calving ease is relatively low, estimates of maternal calving ease range from 0.03 to 0.24 and paternal heritability around 0.147. Despite the relatively low heritability of calving ease, selection for calving ease should not adversely affect other production parameters in dairy cattle as the genetic correlation between calving ease and other dairy production traits are generally close to zero. Obesity, hypocalcemia, and negative energy balance are common maternal risk factors for dystocia that may be prevented through appropriate nutritional management prior to calving.

Foetal variables associated with dystocia include sex, birth weight, number, environmental stress, infectious agents, toxins, and genetics. The frequency of dystocia for male calves is approximately double that of females. High and low birth weight calves are at greater risk of mortality. Small calves experience greatest mortality in multiparous cows and large calves at first parity. Environmental stress prior to or around the time of parturition may compromise the fetus or neonate. Maternal heat stress impedes calf growth in the last trimester of pregnancy and depresses colostral quality and immunoglobulin transfer. Twins are more likely to die than single calves. Infectious agents capable of compromising foetal viability include numerous viruses (IBR, BVD, Bluetongue, Akabane virus), bacteria (*Hemophilus somnus*, *Leptospirosis* spp., *Campylobacter* spp., *Listeria monocytogenes*), Protozoa (*Neospora*, *Toxoplasma gondii*, *Tritrichomonas fetus*), Fungi (*Aspergillus* spp., *Morterella*), and Rickettsia (*Chlamydia* spp. *Coxiella burnetti*). The manifestations of disease associated with infectious and toxic agents in the newborn are dependent on the agent or compound and the timing of exposure. Abnormal neonatal behavior in the immediate postnatal period is most often secondary to perinatal hypoxia. In-utero infections and congenital neurologic abnormalities should also be considered. Collection of sera prior to feeding colostrum is useful for diagnosing *in utero* infections.

Failure of Passive Transfer - No intrauterine transfer of immunoglobulin occurs in ruminants; hence, at birth, neonatal ruminants are agammaglobulinaemic and immunologically naive. Colostrum provides a concentrate source of energy, immunoglobulins, and maternal leukocytes. Immunoglobulins are concentrated in colostrum by an active, receptor mediated transfer of IgG_1 from the blood of the dam across the mammary gland secretory epithelium beginning several weeks prior to parturition. Bovine colostrum contains approximately 45 mg/ml of immunoglobulin and 10^6 leukocytes/ml. At birth calves should be fed 120 g of IgG. Passively derived immunoglobulins enhance neonatal immunity via functioning as neutralizers and opsonins. Colostral leukocytes participate in regulation of the neonatal immune response enhancing humoral immunity and phagocyte function.

Infectious disease is the leading cause of morbidity and mortality in calves greater than three days of age. Failure of passive transfer increases the risk of neonatal mortality. Tube feeding dairy calves 3-4 litres of colostrum at birth is recommended as failure of passive transfer is high (61%) in dairy calves left to nurse their dams. Respiratory acidosis secondary to a difficult delivery and hypothermia reduce the efficiency of passive transfer. Bacterial contamination of colostrum also interferes with efficient colostral transfer.

Management variables that contribute to failure of passive transfer include

1. Delayed harvesting of colostrum (a linear reduction in colostral IgG concentration is observed following calving)
2. Delayed administration of colostrum (the calf's capacity to absorb IgG is best during the first 12 hours of life).
3. Harvesting colostrum into dirty containers and pooling colostrum. Both practices are associated with microbial contamination of colostrum.
4. Inappropriate storage of colostrum (large volumes at room temperature or in the refrigerator).
5. Poor management of calving pens, resulting in compromised calves (respiratory distress, pathogen exposure and hypothermia)
6. Administering an insufficient volume of poor quality colostrum.

Historically it has been recommended to check colostral quality with a colostrometer and to give calves 2 litres of colostrum with a specific gravity > 1.050. A drawback of this approach is the associated wastage of colostrum. An alternative approach is to force feed a larger volume of colostrum (4 litres for Holsteins, and 3 litres for Jerseys). The increase in volume of colostrum compensates for the reduced concentration of IgG in lower quality colostrum. Excess colostrum may be frozen in 1 litre Ziploc bags. Freezing and pasteurizing colostrum destroys colostral leukocytes. It is important to ensure that equipment used to medicate sick calves is not used to administer colostrum, the use of common equipment for both purposes is an effective method of spreading disease to newborn calves.

Hypothermia - The range in ambient temperatures over which newborn animals are able to maintain homeothermy is narrower than adult animals. Neonates are more susceptible to fluctuations in environmental temperature due to their large surface area to mass, evaporation of amniotic fluid, and limited caloric reserves. Thermoregulation is important as recovery from acidosis is delayed by hypothermia. Cold stress leads to increased metabolic needs and produces hypoxia, hypercarbia, metabolic acidosis and potentially hypoglycemia. Thermo neutrality is maintained by shivering and metabolism of brown adipose tissue. Starvation exacerbates the effects of environmental stress by reducing the available substrates for heat production, and energy depletion leads to hypoglycemia. Administration of glucose to hypothermic neonates prior to and during warming is important to avoid deaths from cerebral hypoglycemia induced by increased utilization of glucose by peripheral tissues.

Neonatal Infection - Sepsis, both generalized and localized, is an important cause of morbidity and mortality in neonates; bacteria cause most infections. The prognosis for septicaemic neonates is poor because by the time of presentation infections are usually well established in many organs, particularly the bones and joints. Most neonatal infections are caused by opportunistic bacteria that normally live in the genital tract, on the skin, or in the environment. Infection may be acquired pre-natally, through the placenta, from the birth canal, or from the environment following birth. Portals of entry include the

respiratory and gastrointestinal tracts, the placenta, and the umbilicus. Infections contracted *in utero* are uncommon compared to postnatally acquired infections. Perinatal stress, including chronic *in utero* hypoxia, prematurity, dystocia, and birth asphyxia, renders the neonate more susceptible to infection. Unsanitary environmental conditions, overcrowding, poor ventilation, and contamination of the environment with pathogenic bacteria also predispose to infection. The time of onset of clinical signs of infection in the neonate depends on whether the infection was acquired *in utero* or postnatally. Animals infected *in utero* generally begin to show signs sometime during the first 24 hours of life, whereas postnatally infected animals often appear relatively normal for the first 2 days of life or longer. Bone and joint infections in neonates may not be obvious for several days to weeks.

The propensity for contagious and opportunistic infections in neonates reflects the immature status of their immune system. Septicaemia in ruminant neonates commonly involves multiple organs with the respiratory and gastrointestinal systems most commonly affected. Clinical signs are often non-specific and may include lethargy, poor suckle reflex, weakness, dehydration, tachycardia, tachypnoea, and recumbency. Findings suggestive of involvement of a particular organ system include diarrhoea, lameness, omphalophlebitis, neurologic and ocular signs, and cardiac murmurs. Depressed mentation, diarrhoea and dehydration are the most common clinical signs of sepsis in neonatal ruminants, but clinical presentation is variable. Rectal temperature, heart rate, and respiratory rate are poor predictors of sepsis in calves. Fever is inconsistent and the possibility of infection should never be ruled out because of the absence of fever.

Umbilical infections – A high incidence of umbilical infections reflects problems with sanitation and passive transfer. Most infections are acquired during the first two weeks of life. Manifestations of umbilical infections include; umbilical abscess, umbilical hernias, acquired patent urachus, omphalitis, omphalophlebitis and omphaloarteritis. Associated bacteremia may result in septic arthritis and osteomyelitis. The umbilicus should be examined closely for patency, increased size, moistness or discharge, and tenderness. Abdominal palpation, using both hands pressing together, is useful for evaluating the internal umbilical remnants. Enlargement of the umbilical arteries can be palpated coursing caudally toward the bladder and enlargement of the umbilical vein coursing cranially to the liver. Application of pressure caudal to the xiphoid often elicits a soft grunt from calves with a septic umbilicus and associated peritonitis. Extensive adhesion of bowel to inflamed umbilical structures produces a large easily palpable intra-abdominal mass. Treatment includes systemic antimicrobial therapy and surgical resection of infected structures.

Septic arthritis in neonatal calves is usually derived from hematogenous spread. Common primary sites of infection include enteritis, pneumonia and inflamed umbilical structures. Failure of passive transfer increases the risk of sepsis. The most common pathogens isolated from septic joints of neonatal calves are enteric organisms including *E. coli* and *Salmonella spp.* *Streptococcus spp.* , *Staphylococcus spp.*, and *Arcanobacterium pyogenes* are less common isolates. In older calves, *Arcanobacterium pyogenes* is isolated more frequently. Treatment options include joint lavage or arthrotomy to remove destructive inflammatory products and long term antimicrobial therapy. It is often difficult to effectively lavage septic joints in cattle using needles due to accumulation of fibrin in the joint space. Details of antimicrobial therapy are provided in the accompanying notes on antimicrobial therapy.

Bacterial meningitis is common in neonates following bacteremia; diarrhoea, septic arthritis, omphalophlebitis, and uveitis are frequent concurrent clinical problems. The clinical signs of meningitis in neonates, lethargy, anorexia, and recumbency are non-specific. Affected animals typically have depressed mentation and a poor suck reflex. Owners will often refer to them as "stupid". The prognosis for survival is poor. In a review of 32 cases, mortality was reported to be 100%. Therapy is generally attempted for commercial calves. If aggressive treatment is instigated early in the course of disease success is possible. Prolonged antimicrobial therapy should be anticipated. Empirical antimicrobial therapy for meningitis in neonatal calves should include a gram negative and positive spectrum. Further discussion of antimicrobial therapy of meningitis is provided in the lecture on rational antimicrobial therapy.

Neonatal Diarrhoea

Diarrhoea may result from either increased secretion or decreased absorption. Bacteria such as enterotoxigenic *E. coli*, and, to some extent, *Salmonella* cause neonatal diarrhoea by secreting enterotoxins which stimulate increased intestinal secretions. Sodium absorption linked to glucose and amino acid transport across the mucosal epithelium is not affected. Protozoa and enteric viruses cause neonatal diarrhoea as a result of the destruction of the absorptive villous epithelial cells. In rota and coronavirus infections there is compensatory hyperplasia of the crypt cells. Diarrhoea results because intestinal digestive secretions continue whilst absorption is impaired. The crypt cells have secretory functions and their multiplication adds to the secretory load. The osmotic effect of the unabsorbed nutrients drags water into the gut and contributes to the diarrhoea. Marked inflammation is a feature of salmonellosis and clostridiosis. This contributes to diarrhoea by destroying absorptive cells and by increasing prostaglandin production which in turn stimulates secretory mechanisms within the enterocytes.

Aetiology - The incidence of the various aetiologic agents varies with the age of the calf and age should be considered in the signalment when investigating calf mortality problems. It is usually impossible to make a definitive aetiologic diagnosis on clinical grounds alone.

Bacteria

Eschericia coli - Cause diarrhoea in calves as a result of septicemia or enteric infection. Enteric infections are divided into enterotoxigenic, enteropathogenic, enterohaemorrhagic, enteroadherent and enteroinvasive forms.

Enterotoxigenic E. coli is mainly a problem in calves up to 4 days of age. Enterotoxigenic *E. coli* produce fimbria or pili that they use to bind to enterocytes. Fimbrial antigens were originally given K designates but are more correctly named using the F designation, important antigens include F5 (K99) and F41. The affinity of F5 antigen for enterocytes declines rapidly with age. Viral enteritis can modify the type of enterocytes present and increase susceptibility to *E coli* binding, thus enterotoxigenic *E coli* infections may complicate enteropathies produced by other infectious agents in older calves. Enterotoxigenic *E coli* also secrete an enterotoxin that stimulates secretion of water, sodium and chloride. Heat labile (LT) and heat stable (ST) varieties of toxin exist. Enterotoxigenic *E coli* can produce a discrete clinical syndrome characterized by diarrhoea, dehydration and weakness in calves 1 to 4 days of age. The course is rapid and the calf may progress from health to recumbency and death within 6 to 12 hours. Weakness may be noted before diarrhoea is observed. When the diarrhoea breaks it is profuse and watery and is passed without straining. The progression of the disease can be halted by oral antimicrobials and electrolytes to maintain hydration and correct electrolyte and acidbase derangements.

Attaching and effacing E. coli attach to and destroy the microvilli of the brush border. Enterohaemorrhagic shiga-like toxin (Vero and HeLa cytotoxic factors) producing *E. coli* produce a mucohemorrhagic colitis, with petechial or ecchymotic haemorrhages in the wall of the colon and rectum. *E. coli* that carry this toxin are F5 (K99) negative, and may belong to O serogroups 5, 26 and 111. The most common clinical sign is diarrhoea but dysentery and dehydration are seen in some cases.

Salmonella - are an important cause of diarrhoea and septicemia in calves, particularly in situations where calves are brought together from a variety of sources. Calves are often infected during the first 24 hours of life. Transmission is predominantly faecal oral with calves acquiring the infection from their dam, faecal contamination of the environment, equipment, colostrum, milk, or other infected calves. The incubation period before the onset of clinical signs ranges from 24 – 72 hours depending on the immunity of the host and the size of the challenge inoculum. *S. typhimurium* and *S. dublin* are commonly isolated serotypes. Signs of septicaemia may predominate. Affected calves have depressed mentation, fever, and a profuse diarrhoea; dysentery is an inconsistent feature. Bacteremia is common in calves under a month of age and may result in septic arthritis and meningitis. Pneumonia is a feature of *S. dublin* infections in calves.

Clostridium perfringens - Type C mainly causes disease in calves less than 10 days of age. Typical signs include sudden death or weakness and prostration. Signs of colic, nervous derangement and a terminal diarrhoea are less common. At necropsy there is haemorrhagic enteritis with necrosis of the small intestine. The mesenteric lymph nodes may be swollen and haemorrhagic and there may be petechial or ecchymotic hemorrhages - especially on the pericardium and thymus. *Cl perfringens* type A may be responsible for a mucoid diarrhoea in calves. Antemortem diagnosis of clostridial diseases is difficult as clostridia may be cultured from the faeces of normal calves. Diagnosis is based on the signalment, dietary history, and compatible necropsy findings.

Viruses

Rotaviruses – Rotaviruses are the most common cause of neonatal diarrhoea in calves. Typically they belong to serogroup A and cause diarrhoea in calves 4 to 14 days old, but they can also be a problem in younger and older calves. Colostral antibodies confer local protection against rotavirus attack until antibody levels in milk decline 48 to 72 hours postpartum. Rotaviruses invade small intestinal villus epithelial cells. Once susceptible epithelial cells have been destroyed there are no further target cells. Although infection is short lived, it takes time for the villi to repair. Adult cattle may maintain subclinical infections providing a potential source of infection for their calves.

Coronaviruses – Coronavirus predominantly causes problems in calves 4 to 30 days of age. Pathology involves both the small and large intestine. In the small intestine they destroy the absorptive epithelial cells of the intestinal villi where they can cause a more severe villous atrophy than that produced by rotavirus. In the spiral colon there is widespread destruction of the cells of the colonic ridges. Because coronaviruses produce more widespread pathology than rotaviruses they are more likely to be associated with signs of colitis such as straining and passage of mucus, or occasionally blood, in the faeces. Coronavirus can also invade the upper respiratory tract and lung and produce a mild interstitial pneumonia. Aerosol transmission is possible. Coronavirus particles are also excreted by adult cattle. Excretion tends to increase around the time of parturition and calves born to dams excreting virus are at higher risk of developing diarrhoea. Adults are usually asymptomatic shedders but coronavirus has been implicated as a cause of winter dysentery in adult cattle. Infection and viral shedding persists for weeks in apparently recovered calves.

Bovine Viral Diarrhoea Virus infrequently produces diarrhoea in neonatal calves. The virus has a trophism for bone marrow, lymphoid tissue (Peyer's patches), platelets, and the epithelium of the digestive system. Affected calves usually show oral ulcerations, particularly on the hard and soft palate. The buccal papillae are often blunted and the tips may be ulcerated. Some variants of the virus produce intestinal bleeding, petechiation, ecchymosis, or prolonged bleeding from venipuncture sites secondary to thrombocytopoenia. Hematological findings often include leucopoenia and thrombocytopoenia.

Protozoal

Cryptosporidia are a major cause of calf diarrhoea. *C. parvum* is the most important pathogenic species in calves, although the slightly larger *C. muris* has also been isolated from cattle. Cryptosporidia are capable of infecting most domestic mammals and man. Cross infection between mice, lambs, calves and pigs is possible. The parasite invades the enterocytes of the distal small intestine and large intestine. It lives in the space just under the cell membrane - not in the cytoplasm. Pathology is usually most severe in the distal small intestine and is characterized by villous atrophy and villous fusion. Diarrhoea is the result of villous atrophy leading to malabsorption and secondary milk fermentation. The disease is common in 1 to 4 week old calves. Although the disease is usually characterized by a high morbidity and low mortality, auto-infection (without the protozoa leaving the host) occurs, so relapses and protracted infections leading to chronic diarrhoea and cachexia may be seen. Oocyst secretion starts at the same time as diarrhoea and usually persists for a few days after the end of the diarrheic phase. Cryptosporidia are resistant to all commonly available antimicrobial / anticoccidial agents, most disinfectants, and can survive for long periods in the environment.

Eimeria sp produce clinical disease in calves over 3 to 4 weeks of age. Disease is usually observed when calves are co-mingled following weaning. Crowded conditions promote faecal-oral contamination and warm moist conditions favor survival of the organism in the environment. Calves debilitated by coccidiosis are susceptible to respiratory disease. Coccidiostats (lasalocid, monensin, decoquinate, or amprolium) may be included in the feed to prevent disease.

Nutritional

Healthy calves can handle large quantities (16 to 20% of body weight/day) of whole cows milk without getting diarrhoea. However, feeding normal amounts of whole cows milk (10% of body weight) exacerbates diarrhoea and depression during the initial stages of infectious diarrhoea. Although restricting intake of milk and milk replacers may be beneficial in calves with diarrhoea, deliberate underfeeding in healthy calves predisposes to diarrhoea.

The composition of milk replacers can also be a problem. Calves may perform well on soy protein containing milk replacers when healthy but, during diarrhoea outbreaks, weight gain is better and mortality lower in calves fed whole milk. As milk enters the abomasum, chymosin (rennin) and pepsin, in the presence of calcium and HCl, cleave the peptide bonds involving phenylalanine and methionine in kappa casein leading to clot formation. The clot is formed within 10 minutes and consists of casein with interspersed milk fat globules. Digestion of the clot takes 12-18 hours. In contrast, whey and lactose begin to reach the duodenum within 5 minutes of feeding. During the first three weeks of life, secretion of rennin predominates and the pH of the abomasum is around 4, which is optimal for the activity of rennin. During the first three weeks when rennin predominates, digestion of non-milk proteins is low. With advancing age secretion of pepsin and HCl increases, abomasal pH declines to 2, the optimal pH for the activity of pepsin, and the capacity of the calf to digest non-milk proteins improves. Small intestine protein digestion is also influenced by age as secretion of intestinal trypsin and chymotrypsin are lowest two days after birth and subsequently double by the end of the first month.

Historically, milk replacers utilized dried skim milk as a protein source. High temperature heat treatment reduces the digestibility of milk proteins, lowers growth rates, and increases the incidences of scouring. Dry skim milk that is to be used in milk replacers should be derived from liquid skim milk that is preheated prior to drying to a temperature not greater than 77°C for 15 seconds. The severity of heat treatment of milk replacers containing dry skim milk can be estimated by the rennet coagulability test. Whole milk clots in 22-37 seconds, low-heat, spray dried skim milk clots in 30-47 seconds and high-heat, spray dried skim milk does not clot.

As a result of increased costs, dry skim milk is no longer the major protein source for milk replacers. The primary milk based protein source currently utilized is whey. Whey is a by-product of cheese production and is roughly 40% the cost of dried skim milk. It has been argued that whey is an inferior protein source to skim milk because of problems in handling, variability in protein content and lower casein content relative to skim milk. However, the digestibility and biological value of milk replacers containing 100% whey protein concentrate are higher than milk replacers containing 100% dry skim milk during the first four weeks of life. Body weight change, average daily gain (ADG), feed efficiency and dry matter intake are similar in calves fed dry skim milk or whey based milk replacers. The lack of difference in calf performance suggests the clotting effect of DSM is not essential. Because whey does not clot within the abomasum, clotting tests are of no value in evaluating whey based milk replacers.

Source of the protein used in the milk replacer is an important determinant of its cost. As a result, there has been a significant effort to find a cheap, acceptable source of non-milk protein. In general, non-milk proteins have low digestibility and calves exhibit poor weight gains and increases in morbidity and mortality. The causes of reduced digestibility of non-milk proteins are varied. Lower secretions of pepsin, trypsin and chymotrypsin that occur during the first month of life most likely play an important role since digestion of non-milk proteins becomes more efficient after 3 weeks of age when the transition from rennin to pepsin occurs. Because non-milk proteins do not clot in the abomasum, transit time is increased and has been associated with a decrease in the apparent digestibilities of dry matter and nitrogen.

Additionally, soy protein, one of the most commonly used non-milk proteins, contains various anti-nutritional factors. These include trypsin inhibitors which decrease the activity of chymotrypsin and can cause hypertrophy of the pancreas, lactins which bind sugars or glycoproteins of the gut wall, tannins which complex with proteins and enzymes, and antigenic proteins. Soy proteins are usually processed to reduce anti-nutritional factors. However, there is no current practical method for determination and quality control of anti-nutritional factors.

Diagnostics

Enteric infections in calves often involve multiple pathogens. Pathogens may also be isolated from healthy calves therefore isolation of a pathogen does not conclusively indicate that it is causing the disease. Ideally multiple pieces of information are collected to establish a diagnosis.

Clinical diagnosis is based on the isolation of enteropathogens from diarrheic calves, excluding the presence of other known enteropathogens, by response to specific therapy, and by the finding of pathology and histopathology compatible with the suspected agent. Variations in virulence influence the likelihood of seeing clinical signs. *E. coli*, campylobacter and *Cl. perfringens* are normal inhabitants of the gastro-intestinal tract and isolation of these agents by themselves is not significant unless correlated with identification of virulence attributes (K99) and or compatible pathology and histopathology.

Protozoa – Faecal flotation. Eimeria oocysts are readily detectable. Cryptosporidia are small (3 to 5 microns) and easily missed. Diagnosis of cryptosporidiosis is usually based on faecal flotation with Schearer's solution (sucrose) followed by staining for the oocysts, which are acid fast, with modified Ziehl-Neelsen stains. The organisms are stable in faeces for many days at room temperature.
Salmonella – faecal culture
Enterotoxigenic E. coli – Elisa or agglutination for K99
Viruses – Fluorescent antibody of tissues, ELISA, or electron microscopy.

Necropsy - Demonstration of the agent associated with damaged intestinal tissue with pathology typical of that produced experimentally by the agent. It is important to examine several calves so that a representative sample is obtained. Best results are obtained when the calves are early in the course of disease and are examined fresh. Samples should be fixed by laying a square of gut on paper, serosal side down, and dropping into fixative, or by tying off sections of gut, injecting fixative into the segment, then dropping the segment into fixative. Tissues are examined for the presence of bacteria adhering to the mucosa and cryptosporidia associated with the brush border of epithelial cells. Fluorescent antibodies techniques can be used for F5 (K99) *E. coli* and virus identification.

Treatment

Fluid Therapy - The goal of fluid therapy is to restore and maintain cardiovascular function, improve perfusion pressure and correct dehydration, acid-base balance, osmolality, and electrolyte disturbances. In assessment of the need for fluid therapy, both the state of hydration (sunken eyeballs, decreased skin turgor, dry mucous membranes, generalized weakness, decreased urine output) and the state of circulating volume (heart rate, pulse quality, capillary refill time, temperature of limbs) should be assessed. When losses are very acute gross abnormalities in effective circulating volume may not yet be reflected in decreased skin turgor or sunken eyeballs, but heart rate or pulse quality may be abnormal. Calves with moderately to severely sunken eyes are estimated to have lost 8% to 10% of body weight. The estimated fluid deficit in a 40-kg animal that is 10% dehydrated would therefore be 4 L. Laboratory parameters are useful for formulating a fluid therapy plan. The fluid therapy plan is calculated to supply maintenance needs and to replace deficits and meet ongoing losses.

Saline based fluids are suitable for rehydration but most severely depressed calves are acidotic and more consistent recovery is obtained if an alkalizing agent is also used. Many diarrhoeic calves require large amounts of bicarbonate to correct their acidosis. This is best given in isotonic solutions to avoid problems

with hypertonicity and salt overload. An isotonic solution (156 mmol/L) of bicarbonate can be readily made by dissolving 13g of sodium bicarbonate (baking soda) in 1 L of water.

The rate of fluid administration is determined by the degree of dehydration, severity of cardiovascular compromise, and maintenance requirements. A general rule of thumb is to replace one half the calculated deficit in the first 6 hours of fluid therapy, the rest over 12-24 hrs. Neonates experiencing septic or hypovolaemic shock may require fluid administration rates of 40 - 80 mls/kg/hr initially until their blood pressure is stable. Maintenance fluid requirement for neonates are 4 - 6 ml/kg/hr. If severe diarrhoea is present, the daily fluid requirements can reach 500 ml/kg/day.

Under field conditions it is sometimes necessary to administer fluids more rapidly. It is unusual to see problems when the fluid and acid-base deficits are corrected over 4 hours although the calf may continue to improve after this period. After 24 hours of appropriate therapy one would expect the calf to be standing and show a good suck reflex. Persistent depression is usually a sign of uncorrected acidosis or toxaemia.

When ongoing intravenous fluid administration is anticipated delivery is best achieved using an indwelling intravenous catheter. Intra-osseous infusion technique is an alternative method for rapid delivery of fluids in the critically ill neonate when IV access is not possible. In calves intraosseous fluids may be administered via placement of a 16 or 14 gauge needle in the head of the femur or humerus. A 16 or 14 gauge needle is inserted in a longitudinal plane. Neonatal bones are soft so the needle can be drilled into the bone using finger pressure. Commonly a core of bone will plug the needle requiring the drilling needle to be discarded and replaced with a new needle placed in the same hole. After placement of the needle attach a 60 cc syringe and inject sterile saline under slight pressure to start the flow. As the fluid is administered check for subcutaneous leakage to ensure the needle is correctly placed within the bone marrow. One to 2 litres of saline or isotonic bicarbonate administered to the severely dehydrated calf is often sufficient to restore blood pressure sufficiently for placement of an intravenous catheter.

In any depressed, weak, or seizuring animal, blood glucose levels should be checked, since hypoglycemia is one of the most frequently observed metabolic derangements accompanying many neonatal diseases. For treatment of hypoglycemia, a continuous infusion of 5% to 10% dextrose is sufficient to reach and maintain adequate blood glucose levels in most neonates. Hypertonic glucose boluses (25% to 50%) may aggravate preexisting central nervous system insults and frequently result in rebound hypoglycemia 30 to 40 minutes after infusion. Therefore they should be avoided.

Another metabolic derangement commonly observed in the large animal neonate is *metabolic acidosis*. This disorder may be caused by accumulation of acid, by loss of buffers from the body, or by a combination of the two. Whenever possible, treatment should be directed at correcting the underlying cause of the acidosis. Acidosis caused by low cardiac output or decreased peripheral oxygen delivery should be treated by measures to increase tissue perfusion (e.g., plasma volume expansion, cardiac inotropes, nasal oxygen insufflation). In this type of acidosis there is no actual loss of bicarbonate from the body, and bicarbonate therapy often produces disappointing results and adverse reactions. If respiratory dysfunction is present, considerable caution should be exercised in the use of sodium bicarbonate. Bicarbonate functions as a buffer only in an "open" system in which carbon dioxide can be transported to the lungs and eliminated.

Mild acidosis (HCO_3 deficit 5 - 10 mEq/L) associated with dehydration, can be corrected by simple rehydration. Bicarbonate supplementation is recommended when HCO_3 deficits are $>$ 10 mEq/L (serum [HCO_3] $<$ 15 mEq/L) or whenever the pH is $<$ 7.2. Bicarbonate deficits can be calculated using the following equation:

Bicarbonate deficit (mEq) = 0.6 X Body weight (kg) X Base deficit (mEq)

An isotonic bicarbonate solution is preferred since excessive bicarbonate administration results in increased CO_2 production leading to respiratory embarrassment, and increased risk of CNS acidosis and

haemorrhage. Isotonic bicarbonate can be made by adding 150ml of 8.4% bicarbonate solution to 850-ml sterile water, or 200 ml 5% bicarbonate solution to 800 ml of sterile water.

Measurements of serum total carbon dioxide content or bicarbonate are also reliable estimates of bicarbonate requirements. Bicarbonate requirements are:

mmol bicarbonate = Body Weight, Kg x (30 - TCO_2) x 0.6

For example a 40 kg calf has a serum bicarbonate or TCO_2 of 10 mmol/L. The calf has a bicarbonate deficit of 30 mmol/L - 10 mmol/L = 20 mmol/L, so 40 kg x 20 mmol/L x 0.5 = 400 mmol bicarbonate is required to replace existing deficits. Ongoing diarrhoea may require additional bicarbonate.

Hyperkalaemia is often observed with metabolic acidosis due to the transcellular shift of potassium ions into the extracellular fluid in exchange for hydrogen ions. As the metabolic acidosis is corrected the hyperkalaemia resolves. Bicarbonate solution should not be combined with any calcium containing solution or precipitation will occur.

Hypokalaemia can occur with anorexia, diarrhoea, and diuretic therapy. Potassium supplementation can be estimated using the following equation:

Replacement K (mEq) = 0.4 X Body weight (kg) X K deficit (mEq)

Potassium can safely be added to fluids at a rate of 20 - 30 mEq /L. The rate of potassium administration should not exceed 1 mEq/kg/hr.

Hypernatraemia is observed sporadically in calves associated with errors in mixing milk replacer and oral electrolyte preparations. Hypernatraemia produces cerebral depression similar to metabolic acidosis and will not be appreciated if serum electrolyte concentrations are not measured. Correction of hypernatraemia with hypotonic solutions has been described but was associated with 100% mortality. Rapid restoration of plasma osmolality in chronically hypernatraemic animals leads to brain edema seizures and death. Correction of hypernatraemia via controlled, gradual reduction of serum sodium over 2 -3 days has been successful in calves. Strict regulation of sodium fluid load (intravenous and oral) and repetitive monitoring of serum electrolytes is required.

Oral electrolytes - Once a calf is able to nurse or drink, therapy is usually switched to oral electrolytes. This is also the route of choice for treatment of mildly affected calves on the farm. Calves with weak suck reflexes and calves which are unused to hand feeding can be tubed. There are a wide variety of oral electrolyte preparations on the market and different products are suited to different situations. Almost all the products contain water and electrolytes and are suitable for rehydration. Beware of products that are designed for medicating hundreds of litres of water, the final solution is often very dilute (<10 g electrolytes/L) and will not rehydrate sick calves. Glucose and glycine are added to oral electrolyte solutions to facilitate sodium absorption. This glucose/glycine - sodium co-transport mechanism remains intact in calves with enterotoxigenic *E. coli* diarrhoea, but is likely to be less functional in viral diarrhoea where there is destruction of the absorptive cells.

The ability to counteract acidosis varies greatly between oral electrolytes. Some have a net acidifying effect whereas others alkalinize blood. These differences are therapeutically important and are responsible for differences in survival rates between products. Highly alkalinizing solutions give the best results. Acetate, lactate, citrate, gluconate, and bicarbonate are all used as alkalizing agents in oral electrolyte solutions. Bicarbonate combines with hydrogen ions directly whereas the other agents remove hydrogen ions during their metabolism within the body. Acetate is the best choice for treating calves that are still receiving milk - it has excellent alkalinizing ability and does not interfere with milk clotting in the abomasum. Bicarbonate is also an excellent alkalinizing agent but it interferes with milk clotting. Breakdown of abomasal milk clots results in gradual release of some nutrients into the small intestine. Some studies with diarrhoeic calves show that bicarbonate can greatly reduce milk digestibility. Citrate is

an effective alkalinizing agent but it is a strong inhibitor of milk clotting. Thus any of the commonly used alkalinizing agents are acceptable if the calf is held off milk. Oral electrolyte solutions should contain 50 to 80 mmol/L of alkalinizing agent.

Chronically scouring calves require nutritional support. Maintenance metabolizable energy requirements for a 50 kg calf are about 2000 kcal, and 3500 kcal are required to support a weight gain of 0.5 kg/day. These requirements can be met by 3.3 and 5.7 L of whole cows milk respectively. Comparative studies indicate that weight loss in calves fed oral electrolytes are inversely proportional to the energy content of the solutions. Assuming a 4L daily intake and 100% digestibility of oral electrolyte nutrients, regular electrolyte solutions supply between approximately 15% and 25% of energy needs. As a result diarrhoeic calves that are held off milk for a prolonged period loose weight and become emaciated. High energy oral electrolyte solutions deliver 50 - 75 % of energy needs when fed 2 or 3 times a day respectively.

Withdrawing milk may reduce the severity of diarrhoea and depression in severe scours. This is because malabsorption exacerbates diarrhoea through the osmotic effect of unabsorbed milk nutrients and also promotes bacterial overgrowth and possibly malfermentation with production of organic acids. However, milk withdrawal reduces weight gain in diarrhoeic calves and can result in severe cachexia and other signs of malnutrition. In many calves, particularly the less severely affected, there is often a considerable degree of residual absorptive capacity - enough to support body weight gain if limited amounts of milk are fed. Milk should continue to be fed to calves that have an appetite. Conversely force feeding milk to calves that are depressed and not interested in sucking tends to exacerbate the disease. In most cases electrolyte therapy will restore a calf's vigor and sucking drive within 1 to 2 days. Milk can then be reintroduced in small amounts e.g. 1L given 2 to 4 times daily. If the calf is not interested in drinking or gets depressed when re-introduced to milk, a high energy oral electrolyte preparation can be tried instead.

Antimicrobial Therapy - Antibiotics are frequently used in the treatment of the diarrhoeic calf even though enterotoxigenic *E. coli* and *Salmonella* are the only common agents that respond to antimicrobials. Antibiotic resistance is common in *E. coli* and *Salmonella* species and, when faced with herd level decisions, performing a culture and sensitivity is useful for selecting an appropriate antibiotic. Indiscriminate use of antibiotics leads to selection for resistant strains and complicates future therapeutic efforts. Most other causes of diarrhoea in calves are viral or parasitic and are not directly sensitive to antibiotics. *Cryptosporidia* are refractory to treatment with all licensed veterinary pharmaceuticals including ionophores, the potentiated sulfonamides and a variety of anticoccidials. Despite this there may be benefit to systemic antimicrobial therapy in diarrheic calves, particularly those with severe systemic signs. Intercurrent disease is not uncommon, and there is evidence for leakage of microbes across damaged intestine, leading to bacteremia or septicaemia. This is particularly likely in diarrhoeic calves under a week of age that are recumbent or have a poor suck reflex. Survival is enhanced in calves treated with systemic antibiotics, partly because of the benefits in controlling inter-current infections.

Rapid recognition and treatment of sepsis improves the likelihood of a successful outcome. Gram negative bacteria account for approximately 80% of bacterial isolates, *E. coli* is the most common bacteria isolated. Empirical antimicrobial therapy should include a gram negative and positive spectrum. Other considerations pertinent to antimicrobial selection include the pharmacokinetics of the drug in neonates, likelihood of antimicrobial resistance, and potential for violative antimicrobial tissue residues. Determination of antimicrobial susceptibility (minimal inhibitory concentration, MIC) prior to therapy is desirable but often not possible. Alternatively, a drug may be selected and given at a dosage that has been shown to be effective for ≥ 90% of similar isolates tested (MIC 90%). The objective of measuring antimicrobial MIC's is to facilitate antimicrobial selection that is likely to achieve a therapeutic concentration of drug for the target pathogen. The MIC data is of limited value without information on serum/tissue concentrations attainable using the intended drug dose.

Antimicrobial drugs with a gram negative spectrum of activity include third generation cephalosporins (ceftiofur), trimethoprim sulfonamides (TMS), fluoroquinolones (enrofloxacin), aminoglycosides, sulfonamides, and tetracyclines. The bacteriostatic action and frequency of antimicrobial resistance to tetracyclines and non potentiated sulfonamides limits their effectiveness in septic neonates. TMS may be

used to treat sepsis in neonatal calves, but its half life rapidly declines as rumen function develops. In ruminating (6-8 wk old) calves, subcutaneous or oral administration of TMS leads to high serum levels of sulfadiazine but little or no serum trimethoprim. Bacterial resistance to trimethoprim sulfa is less common than resistance to sulfa drugs alone but still may be high. Ceftiofur has an appropriate antimicrobial spectrum, is bacteriocidal, and has been used to treat septic calves with good clinical results using a dose of 5 mg/kg twice a day. The label dose of 1 mg/kg once a day may not achieve minimal inhibitory tissue drug concentrations for some bacteria commonly isolated from neonates. Deviation from the labeled dose requires implementation of a meat withholding period.

Respiratory Disease

A number of *respiratory disease* syndromes may be observed in neonatal calves. Pneumonia in calves less than 3 days of age typically reflects aspiration of milk subsequent to inappropriate feeding practices or pharyngeal dysfunction (white muscle disease). A mixture of gram positive, gram negative, and anaerobic bacteria may be introduced into the lungs inciting a severe inflammatory response necessitating broad spectrum antimicrobial and anti-inflammatory therapy. *Pasteurella hemolytica* and *Pasteurella multocida* infrequently cause pneumonia in calves less than 2 weeks of age. However, outbreaks of respiratory disease may be associated with mixed infections with *Mycoplasma bovis* in this age group, or secondary to bovine virus diarrhoea infection. Mycoplasmas are not susceptible to agents that interfere with synthesis of folic acid or that act on the cell wall. Tylosine, tetracyclines, erythromycin, tilmicosin, florfenicol, and aminoglycosides have been shown to have activity against one or more mycoplasma species.

Outbreaks of respiratory disease in weaned calves usually reflect pathogen exposure in the face of compromised host immunity. Host immunity may be compromised by inclement weather, poor ventilation (ammonia), over crowding, weaning, dusty conditions, and transportation. Viral pathogens associated with respiratory disease in cattle include parainfluenza-3, adenovirus, bovine respiratory syncytial virus, and infectious bovine rhinotracheitis (bovine herpes 1). Bacterial pathogens include *Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, Haemophilus somnus, and Mycoplasma spp. Arcanobacterium pyogenes* is a common isolate from animals with chronic lung disease and lung anscess, it is generally considered a secondary invader.

Defenses of the respiratory tract include filtration by the nasal cavity, sneezing, coughing, laryngeal reflex, mucocilliary transport mechanisms, alveolar macrophages, and systemic and local immunoglobulin. The cilia beat most effectively in mucus at a certain elasticity, viscosity and chemical composition. Anything which interferes with the secretion and maintenance of normal mucus interferes with the clearance of particles from the upper respiratory tract. In viral pulmonary disease ciliary activity can be disrupted by temporary loss of cilia or lesions of the respiratory mucosa. Viral infections also depress alveolar macrophage function. Dehydration alters the viscosity of mucus and dusty environments increase the demand on mucocillary clearance mechanisms.

Clinical signs may include polypnoea, tachypnoea, dyspnoea, coughing, nasal discharge, depressed mentation, and abnormal breath sounds. Rapid shallow breathing is the cardinal sign of early pneumonia. Dyspnoea occurs in the late stages of the disease when a large portion of the lung is no longer functional. Coughing is frequently observed and should always be considered a potential indicator of respiratory disease. Consolidation of the cranial ventral lung lobes is often observed with infectious causes of pneumonia. Lung sounds are therefore loudest over this area and an elevated percussion line may be demonstrable. A foul odour is a common feature of necrotic laryngitis and lung abscess. Extension of the pneumonia to the visceral surface of the pleura results in pleuritis, pleural effusion and thoracic pain. When pleurisy is present a pleural friction rub may be heard on auscultation.

Antimicrobial therapy is the cornerstone of therapy for bacterial respiratory disease. The prognosis is largely dependent on the stage of the disease at the time therapy is initiated. A discussion of antimicrobial therapy is provided in the lecture on antimicrobial therapy.

The incidence of respiratory disease may be minimized by provision of a comfortable well ventilated environment, good nutrition, avoiding dusty feeds, and through immunization against specific diseases. Infected animals should be isolated if possible to reduce pathogen exposure in the remainder of the group.

Prevention of Disease in Neonates

The principles of disease prevention are to:

1. Ensure adequate colostral intake
2. Provide adequate nutrition
3. Provide a clean and comfortable environment
4. Boost specific immunity
5. Minimize pathogen exposure

Vaccination against enterotoxigenic *E. coli* is generally effective. The vaccine is given 6 and 3 weeks prior to calving. Vaccinating cows that are more than 10 days from parturition can give protection against death from enterotoxigenic *E. coli* infection. Vaccination against rota and coronavirus diarrhoea has had mixed success. Early work indicated that vaccinating calves orally with a tissue culture adapted rotavirus vaccine would protect against rotavirus diarrhoea. However, it appears that the vaccine is inactivated in many calves by anti rotaviral antibody from colostrum. Modified live *Salmonella* vaccines provide protective immunity to *Salmonella* infection in calves by induction of innate and acquired immune mechanisms. *Salmonella* bacterins are generally ineffective at protecting calves against *Salmonella* infections as the infections are often acquired prior to induction of acquired immune mechanisms. Limited protection of calves against *Salmonella* infection may be acquired passively through immunization of pregnant cows.

On a herd basis the diarrhoeic neonate is a major source of contamination of the environment. Once a herd begins to experience problems infected animals amplify environmental contamination producing an increase in morbidity. Most enteropathogens can survive for long periods of time in the environment. Cleanliness of the calving area is very important large numbers of cows should not be cycled through a few stalls. The use of calf hutches provides individual isolated housing for each calf. Cleaning is facilitated because the hutches can be moved to new sites between calves. Keeping pre-weaned calves in groups larger than 6 puts them at increased risk of diarrhoea. Cleaning and disinfection after each batch of calves is important for reducing transmission between successive groups. The key to decontamination is cleaning. All movable equipment should be removed and scrubbed down. Ninety percent of bacteria are removed by cleaning. High pressure hosing can remove 99.98% of contamination, even when no disinfectants are used. The most readily cleaned surfaces are made of smooth impervious materials such as plastic and varnished wood. In addition to cleaning between batches it is important to clean nipple buckets and other feeding utensils between each feeding.

Operations that buy in calves for rearing purposes should be encouraged to buy from as few sources as possible. Direct purchase from one farm is best; assembling collections of calves through auction markets should be avoided if possible.

Diet is an important factor in preventing diarrhoea. Calves that are fed milk from mastitic quarters or antibiotic containing milk are at increased risk of diarrhoea. Young calves have less problems with diarrhoea when fed whole cows milk rather than milk replacer.