Neonatal Calf Diarrhea

JONATHAN M. NAYLOR

Diarrhea and other digestive diseases are one of the big three causes of calf loss in beef calves and are the major cause of loss in unweaned dairy heifers born alive. Overall, beef calf mortality from diarrhea should be about 1%. In dairy calves diarrhea and other digestive diseases account for about 5% of total mortality from live birth to weaning.[1,2]

ETIOLOGY

The most commonly recognized causes of neonatal calf diarrhea are rotavirus, coronavirus, and cryptosporidia.[3-7] The major mechanism by which these and pathogens cause diarrhea is malabsorption. Enterotoxigenic *Escherichia coli* with the F5 (K99) antigen is less prevalent, probably because a highly effective vaccine has been developed.

Viral

Rotaviruses are the most commonly diagnosed cause of neonatal diarrhea. Typically they affect calves 4 to 14 days old, but infections can be seen either side of this age range. Rotaviruses invade and destroy the villus epithelial cells of the small intestine. This results in malabsorption of nutrients. Asymptomatic infections may occur in older calves and in adult cows. In cows, excretion of virus is particularly common around the time of calving. This is one method by which infection persists on a farm. Once an outbreak has started, diarrheic calves are the major source of contagion.

Coronaviruses are an important cause of diarrhea in 4- to 30-day-old calves. At least three strains of bovine coronavirus are responsible for respiratory infection, neonatal diarrhea, and winter dysentery. However, the winter dysentery and neonatal calf strains can infect both calves and adults. In calves, coronaviruses invade and destroy villous epithelial cells of the small intestine, causing villous atrophy. They also invade the epithelium of the large intestine. Because coronaviruses affect the large intestine, they may be associated with signs of colitis such as straining. Like rotavirus, excretion of coronavirus by asymptomatic adults may be an initial source of infection for calves. Clinically affected calves are the major source of virus once an outbreak is established.[3,8-14]

Bovine viral diarrhea (BVD) is an occasional cause of neonatal calf diarrhea. In outbreaks of BVD infection, diarrhea in calves has been documented as part of the clinical picture. Depending on the properties of the BVD virus and the time infection was acquired, oral lesions, thrombocytopenia and mucosal hemorrhages, blood in the feces, leukopenia, and signs of persistent infection and mucosal disease can occur.[15-19] BVD may also predispose to other enteric infections by reducing immunocompetence.

A variety of other viruses have been implicated as potential causes of calf diarrhea. These include Breda virus and Calicivirus. At present the importance of these agents is unknown.

Bacterial

A number of different groups of *E. coli* have been incriminated in outbreaks of calf diarrhea. Enterotoxigenic *E. coli* has a special fimbria, known as the K99 or F5 antigen, that allows it to attach to the surface of the small intestinal mucosa of neonatal calves. A second fimbrial attachment factor, the F41 antigen, has also been identified, but it is generally found together with F5 fimbria. Other attachment factors may exist. Enterotoxigenic *E. coli* produces enterotoxin (a heat stable form, ST) that stimulates secretion of sodium together with water and chloride ions by the mucosal cells. Enterotoxigenic *E. coli* also causes some villous atrophy.[20-25] In general, enterotoxigenic *E. coli* causes diarrhea in calves 1 to 4 days of age; in some cases this is profuse and watery and can rapidly result in hypovolemic shock and death. Enterotoxigenic *E. coli* can also secondarily infect older calves in which the mucosal cell type has been altered by prior infection with another pathogen.

Attaching and effacing *E. coli* (AAEC) is characterized by the possession of the eae gene, which produces the attachment protein intimin. This allows these bacteria to adhere to the mucosal surfaces of the colon and small intestine. Some strains carry Shiga's toxin (verotoxin) genes, which confer cytotoxicity in the vero cell or HeLa cell assays. *E. coli,* Shiga's toxin, and eae genes combined are called *enterohemorrhagic.* Other eae-carrying *E. coli* can be pathogenic as the result of the presence of other cytotoxic genes. In general, AAEC produce diarrhea in calves from 2 days to about 6 weeks of age. The bacteria adhere to the surface of the colon and sometimes the small intestine. Some are also internalized. The bacteria efface the surface microvilli and cause patchy mucosal stunting, erosion, and sloughing. At gross postmortem examination, changes vary from minimal to ileitis with mucohemorrhagic colitis. They produce diarrhea of variable severity that may be bloody.[26-35]

Necrotoxigenic *E. coli* produce a toxin that interferes with cell division and kills mucosal cells. Many strains also carry the F17 fimbrial attachment factor. Necrotoxigenic *E. coli* have been detected in the feces of 14% of healthy

calves. However, in neonatal colostrum-restricted calves some strains are capable of causing long-lasting diarrhea and septicemia. At necropsy there may be vascular congestion of the intestinal mucosa, hypertrophy of the mesenteric lymph nodes, and congestion of the lungs. Histologically, there may be enterocolitis and lymphadenitis.[36,37]

Salmonella typhimurium, dublin, newport, and other species are important causes of calf diarrhea in operations in which there is movement and mixing of calves at an early age (see Chapter 25). These risk factors are most common in dairy and veal operations. *Salmonella* sp. penetrate the mucosa and cause intense submucosal inflammation. This inflammation stimulates a secretory diarrhea. Because the organisms penetrate the mucosa, septicemia and bacteremia are common, particularly in calves younger than 1 month of age. These organisms are potentially zoonotic.

Clostridium perfringens type C may produce a terminal diarrhea. More commonly affected calves are presented in a collapsed state and rapidly die. Signs of colic and nervous signs may also be seen. *C. perfringens* type A may produce mucoid diarrhea in calves.

Protozoal

Cryptosporidia are an important cause of diarrhea in 1- to 4-week-old calves. *Cryptosporidium parvum* and the slightly larger *Cryptosporidium muris* have both been identified in calf feces. *C. muris* is primarily an abomasal parasite and is not associated with diarrhea. *C. parvum* causes diarrhea in calves and people, although different strains may be more pathogenic in a particular species. Asymptomatic infection occurs in adult cows where fecal excretion is increased around the time of calving. The oocysts are resistant and are found in the environment associated with manure and manure contamination.

C. parvum invades the epithelium of the distal small intestine and the large intestine. It resides just beneath the cell membrane and causes loss of microvilli, villous atrophy, and villous fusion. Later in the disease process inflammatory changes develop. Oocyst secretion starts at the same time diarrhea commences and generally persists for a few days after the end of clinical signs. Because the oocysts are infectious within the intestine, autoinfection can lead to chronic disease. Clinical signs vary from mild to severe with feces of variable consistency. Tenesmus and occasionally the presence of blood in the feces may be seen.[6,38-44]

Giardia duodenalis infection is common in calves. However, its role in diarrhea is unclear. Some studies suggest that temporarily reducing the load of *Giardia* by treating with metronidazole or fenbendazole can give transient improvements in calf health, but reinfection soon occurs.[45-48]

PATHOGENESIS

Intestinal pathogens produce diarrhea via three major mechanisms. Although a certain mechanism may predominate, pathogens often cause diarrhea by a variety of mechanisms. Furthermore, it is common for more than one etiologic agent to be present in an outbreak of calf diarrhea, particularly in severe cases.

Secretory diarrhea is characterized by excess net secretion from the mucosal cells, mainly those of the small intestine. Enterotoxigenic *E. coli* is the classic example of this type of diarrhea. It produces an enterotoxin that alters the concentrations of intracellular messengers; this in turn alters the activity of the cell membrane pumps with increased net secretion of sodium, potassium, and chloride ions. The cell structure is mostly left intact. Diarrhea is typically profuse with no blood or straining. Affected calves develop signs of depression, weakness, and sometimes shock and death secondary to hypovolemia; acidemia is often mild.

Villous atrophy, malabsorption, and *osmotic diarrhea* go hand in hand. Destruction of the absorptive surface results in malabsorption of water and electrolytes. In addition, malabsorbed nutrients may have an osmotic effect that helps retain water within the gastrointestinal tract. The presence of unabsorbed nutrients in the gastrointestinal tract leads to bacterial overgrowth, particularly in the distal small intestine and large intestine. Some of these bacteria may be pathogenic, and others may cross the damaged mucosal surfaces to produce endotoxemia, bacteremia, or septicemia. Bacterial fermentation of undigested nutrients can lead to the production of D-lactic acid,[49] which is a potent neurotoxin responsible for many of the clinical signs of depressed central nervous system (CNS) function in severely affected calves.[50] Affected calves have signs of diarrhea, hypovolemia, acidemia, weakness, CNS depression, endotoxemia, and bacteremia of variable severity. Because it is difficult for a calf to tolerate both severe acidemia and hypovolemia, there is no relationship between the severity of dehydration and acidemia.[51] The profuseness of diarrhea and dehydration is poorly related to the severity of weakness and CNS depression. The three most commonly recognized enteric pathogens of calves, rotaviruses, coronaviruses, and cryptosporidia all produce villous atrophy, intestinal bacterial overgrowth, malabsorption, and osmotic diarrhea.

Inflammatory diarrhea is typical of *Salmonella* sp. These invade through the mucosa and stimulate an intense inflammation. Some of the inflammatory mediators stimulate the mucosal cells to secrete electrolytes and fluid. In addition, there is some villous atrophy. In calves, bacteremia and septicemia from the invading microorganisms are common. Systemic effects are due to some mixture of endotoxemia, hypovolemia, and acidemia.

Origin of Clinical Signs

Irrespective of the inciting infectious agent, diarrheic calves suffer from common sequelae.

Diarrhea. All agents increase the loss of water and electrolytes into the intestine, in those cases in which the compensatory ability of lower parts of the intestine to resorb water and electrolytes is exceeded, diarrhea results. *Dehydration* develops if the calf cannot compensate for this increased fluid loss by drinking and absorbing more water and electrolytes. *Hyponatremia* and whole-body potassium depletion are the result of loss of electrolytes with the diarrhea.[52-55] However, calves presented to veterinarians for treatment may be either hyponatremic or hypernatremic, presumably because oral electrolyte use by farmers is now widespread. Diarrheic calves may be

hyperkalemic, normokalemic, or hypokalemic despite whole-body potassium depletion secondary to increased fecal loss. Hyperkalemia is the result of several factors; acidemia and hypoglycemia favor movement of potassium from the intracellular to the extracellular space, as does hypothermia, which slows cellular metabolism. Poor renal perfusion limits the ability of the kidneys to correct hyperkalemia.

In those calves with malabsorption and continued nutrient intake, some degree of intestinal bacterial overgrowth in response to increased nutrient availability is inevitable. This, together with damage to the mucosa, predisposes to secondary bacteremia or septicemia. Bacterial overgrowth and excess luminal nutrient availability leads to fermentation and production of organic acids including D- and L-lactic acid. Luminally produced L-lactic acid is not a major cause of systemic acidosis, probably because it can be readily removed by mammalian tissues. D-lactate, however, is poorly metabolized by mammals, and plasma concentrations correlate with ruminal and fecal D-lactate.[49] Chronic malabsorption leads to weight loss, particularly if malaise or therapeutic feed restriction limit caloric intake.

Acidemia is common in the more severely sick diarrheic calves. Of the documented causes, D-lactic acid is the major component. L-lactic acid can be important, particularly in severely hypovolemic calves in which tissue anoxia increases production of L-lactic acid from glucose and hepatic removal is reduced.[49,56,57] Fecal bicarbonate loss is another cause of acidemia, but its importance and whether this is due to decreased absorption of bicarbonate or to the trapping or bicarbonate by luminal acids has not been quantified.

Causes of Weakness and Central Nervous System Depression

Signs of weakness are usually the result of some mixture of hypovolemia, D-lactatemia, hypothermia, and endotoxemia.

The most important factors affecting CNS function are hypovolemia, D-lactatemia, hypothermia, profound hypoglycemia (rare), and to some extent endotoxemia. D-lactate is a potent neurotoxin that penetrates the blood-brain barrier and produces signs of ataxia, decreased mentation, recumbency, and coma.[49,50,58,59] In calves with acidosis without dehydration syndrome, D-lactate concentrations correlate highly with weakness and loss of CNS function, suggesting it is the major neurotoxic agent.[60-62] D-lactate concentrations also correlate with the degree of weakness and CNS in diarrheic calves.[63] Acidemia alone has small effects on mentation or ambulation but may be responsible for loss of the suck reflex.[50]

Origin of Cardiac Arrhythmia

Bradycardia with a regular rhythm can be the result of hypothermia or profound hypoglycemia. Bradycardia complicated by an irregular rhythm (e.g., because of premature ventricular contractions) is caused by hyperkalemia. Cardiac arrhythmia is one cause of death.[64,65]

APPROACH TO THERAPY

The initial assessment of a diarrheic calf involves a general physical examination; assessment should include whether an arrhythmia is present, dehydration status, amount of weakness and CNS depression, severity of diarrhea, condition of the navel, presence of pneumonia, and hypothermia or fever. Following this, the veterinarian may advise monitoring and oral or intravenous (IV) therapy.

Transient diarrhea is common in calves, and many self-cure. The provision of free-choice water and a salt block will make it easier for the calf to maintain homeostasis. In some cases, this is sufficient if the calves are carefully monitored.

Fluid Therapy

Correction of fluid and electrolyte abnormalities is the foundation for treatment of diarrheic calves. For a complete discussion, see Chapter 104.

Calves that are not depressed but have profuse diarrhea or are depressed and still have a good suck reflex should be treated with oral electrolyte solutions. Depending on the severity, this may take the form of an additional feeding of 2 L of oral electrolyte solution a day to the complete removal of all milk or milk replacer feeding and the substitution of three feeds of 2 L each of oral electrolyte a day. When choosing an appropriate oral electrolyte solution for more severely affected calves, look for one that, when reconstituted, contains sodium at 100 to 120 mmoles/L and 50 to 80 mmoles of acetate or propionate as the major alkalinizing agents.[66] Avoid products containing a lot of bicarbonate because these raise abomasal pH, which may make it easier for ingested pathogens to gain entry to the intestines. Bicarbonate and high levels of citrate also interfere with milk clotting in the abomasum.[67] Clotting is part of the normal digestive process for calves fed whole cow's milk.

Intravenous Fluid Therapy

Calves that have lost their suck reflex should be treated with IV fluids to correct dehydration, correct acidemia, and reduce serum D-lactate concentrations below 1 mmol/L.

Fluid Requirements

When calculating fluid requirements, it is customary to calculate the amount of fluid to correct dehydration and add amounts for ongoing losses and maintenance requirements. In diarrheic calves fed milk and oral electrolyte solutions, ongoing fecal water losses are generally between 1 and 4 L a day.[68] Maintenance water requirements for calves are not fully documented, but 70 mL/kg body weight prevented the development of dehydration and hypovolemia in one experiment.[69] Table 21-1 shows the application of these principles. The IV route allows for the administration of relatively large volumes of fluid without inefficiencies because of incomplete absorption. It also avoids problems with poor suck reflex and ileus. Ileus delays or prevents the absorption of oral fluids.

Table **21-1**	
Examples of 24-Hour Fluid Requirements for a 50-kg Diarrheic Calf	
Item	**Dehydration 10%, Severe Diarrhea**
Replacement, L	5
Ongoing losses, L	3
Maintenance (70 mL/kg), L	3.5
Total 24-hour requirement	11.5

Table **21-2**

Predicted Base Deficit, mmol/L, of Diarrheic Calves Based on Their Age and Clinical Signs

Rights were not granted to include this table in electronic media.
Please refer to the printed publication.

(From Naylor JM: *Can Vet J,* 30:577-580, 1989.)

Diarrheic calves fed either no or small amounts of fluid orally often rapidly develop formed feces. Usually a mixture of isotonic sodium bicarbonate and isotonic saline, lactated Ringer's, or acetated Ringer's solution are used as the IV fluid.

Correction of Acidosis

Base deficit[70] is best measured using a blood gas machine or total CO_2 apparatus.[71] It can also be empirically assessed from clinical signs when this option is not available (Table 21-2). In calves with mild acidemia and base deficits less than 10 mmol/L, rehydrating the calf with lactated or acetated Ringer's solution is often sufficient to correct acidosis. More severe acidemia responds best to sodium bicarbonate solution, a fact that has been empirically proven in randomized, controlled, blinded trials in diarrheic calves.[61,72,73] Typically, correction of acidosis requires 1 to 4 L (25 to 100 mL/kg) of isotonic 1.3% sodium bicarbonate administered over about 4 to 8 hours. The remaining fluid deficits are met with isotonic saline solution.

Correction of D-Lactic Acidosis

Several important questions still need to be answered about the correction of D-lactic acidosis. One of the more important questions is whether correction of acidemia speeds the clearance of D-lactate. Conventional IV fluid therapy with saline and sodium bicarbonate given in accordance with the preceding principles has been shown to rapidly correct hyper D-lactatemia in diarrheic calves.[49] This is also associated with the excretion of D-lactate in urine.[74] In a controlled trial in calves with acidosis without dehydration syndrome, sodium bicarbonate was more effective than an equal volume of saline in correcting CNS depression,[61] suggesting that sodium bicarbonate therapy helps speed removal of D-lactate.

Antibiotics

The common indications for administering antibiotics to some diarrheic calves are for treatment of bacterial causes of diarrhea; reduction of intestinal bacterial overgrowth; and treatment of secondary bacteremia, septicemia, or intercurrent infections.[75]

The majority of cases of enteritis are the result of nonbacterial causes. Bacterial overgrowth can be managed by antibiotic administration or nutritional management.

In one study, septicemia and bacteremia were present in about 30% of diarrheic calves. Calves with low serum immunoglobulin status, recumbent calves, calves with no suck reflex, and those younger than 1 week of age are more likely to be bacteremic or septicemic, and these calves have a higher mortality rate.[76,77] In general this means that calves sick enough to require IV fluid therapy should be placed on systemic antibiotics. A wide variety of organisms can be cultured from the blood of diarrheic calves, but *E. coli* predominates. In my opinion, ceftiofur, trimethoprim sulphonamide combinations, or amoxicillin-clavulanate combinations are good choices. Pathogenic *E. coli* can be resistant to antimicrobials; therefore culture and sensitivity can be helpful in guiding therapy.

Halofuginone (Coccidiostat)

Halofuginone lactate (60-100 µg/kg body weight or 5 mg/calf in 10-ml carrier SID) fed orally by syringe into the back of the pharynx following the morning milk feed from birth for 7 days reduces the fecal shedding of cryptosporidium oocysts and the incidence of diarrhea.[78,79] This is the only known pharmacologic method of reducing the incidence of infection with cryptosporidium in calves.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs only appear to be beneficial in calves that have blood in their feces.[80]

Probiotics

Depending on the study, probiotics either show no or some benefit in either the prevention or treatment of diarrheic calves.[7,81-86]

PREVENTION

The main cornerstones of prevention are to boost immunity and reduce the load of infectious agents in the environment.

About 25% of dairy calves are partially or completely deficient in colostrally derived antibody. Many, but not all, studies indicate that this is a risk factor for neonatal disease including calf diarrhea.[87-93] Therefore it is

important to make sure that dairy calves receive adequate colostrum. Colostrum deprivation is less of a problem in beef calves. However, farmers should monitor newborn calves carefully and assist those that have not sucked to nurse colostrum. If this is not feasible, calves suspected to be colostrum deprived can be tube fed with a commercial colostral antibody source containing at least 80 g of immunoglobulin.

Vaccinating the cows before parturition with a product against the K99 antigen of *E. coli* is a highly effective way of reducing this type of diarrhea disease. However, *E. coli* K99 is unique in that it mainly attacks calves in the first few days of life. In North America, vaccination against other diarrheal diseases does not appear to be beneficial or has only minor benefit.

In beef operations the major risk factors for outbreaks of calf diarrhea are large herd size, high stocking density, lack of a large sheltered area, poor drainage with standing water in the nursing area, failing to separate cows and heifers, poor nutrition, and a large number of heifers in the herd.[94-96] Avoid running cows or heifers through a small calving area (e.g., one particular corral or a barn). These rapidly become contaminated and a source of neonatal infection. Small herds, fewer than 40 cows, have a lower incidence of scour problems. Large herds may be best split into groups of 50 to 75 head and managed separately. Stocking density is important; cattle managed at pasture with large amounts of space have less diarrhea than those managed more intensively in corrals at calving time. However, if the weather is adverse, cattle managed at pasture will crowd together into a small space if adequate shelter is not available. There should be a minimum of 100 m² and ideally 200 m² (1000 to 2000 ft²) of area per cow. This area must be clean and sheltered from adverse weather. Damp conditions and standing water are a major risk factor for scours, particularly if more than 5% of the nursing area is affected. Contaminated water can be ingested and directly infect calves. Damp or muddy conditions favor the accumulation of dirt on the flanks, udder, and teats of the cow, where it will be ingested during nursing or grooming. The calving and nursing areas should be well drained, and any standing water should be fenced off. Drinking water should be provided from a clean source. Separating cows and heifers before calving is critically important. This allows the heifers to receive better nutrition. Calves born to heifers are much more likely to develop diarrhea; by separating these high-risk calves, spread to the rest of the herd is reduced. The diet fed to the cows should be complete and balanced. A high percentage of heifers, more than 20%, indicates herd expansion. However, it is also a risk factor for scours. When herds are being expanded it is particularly important to ensure that all other aspects of management are optimized. Another practice that may be beneficial is having an isolation area to treat diarrheic calves. This is likely to be of particular benefit for early cases, before contagion spreads throughout the facilities. Producers should be discouraged from buying in calves to replace a calf lost to dystocia or disease—this is an easy way to import disease.

In operations in which calves are hand reared, it is important to ensure that calves get adequate colostral antibody intake at an early age. This may help protect against enteric disease and definitely helps protect against secondary septicemia.[76,88,90,97,98] The next most important factor is cleanliness; at calving both cows and calving area should be clean. The calf-rearing facility must be clean, the feeding utensils must be clean at every feeding, and the feed must be clean. Cleanliness requires constant attention. A variety of factors have been implicated in increasing the risk of calf diarrhea or fecal excretion of cryptosporidia (Table 21-3). In general, calves have least

Table 21-3

Factors Associated with Risk of Diarrhea or Cryptosporidial Infection in Hand-Reared Calves

Risk Factor	Increased Risk	Decreased Risk
Calving Area	Being born in loose housing	
Many cows in maternity pen	Yes	
Floor of maternity pen	Soil	Concrete
Daily removal of soiled bedding from maternity pen and calf-raising areas	No	Yes
Ease of calving	Assistance	No assistance
Cleanliness of cows	Dirty	Clean
Feeding Method	Use of a nipple	Feeding from bucket
Number of milk feeds a day	One	Two
Feeding Concentrate	None	Yes
Solid food	High-moisture ear corn	
Building	Damp	Dry
Bedding	Damp	Dry
Ammonia smell in building	Present	None
Restraint method for calves	Tying by a collar	Loose
Quarantine Facilities for Sick Calves or Cows	Yes	No
Stocking Density	Tie stall: Less than 1.6 m² per calf	Tie stall: More than 1.6 m²
	Free stall: Less than 1 m² per calf	Free stall: More than 1 m²
Placing calf pens against a wall	Yes	No
Vaccination Against Enteric Pathogens	Yes	Vaccination against enteric disease caused by *Escherichia coli*
Calf rearer	Adult male	Women or children
Herd Size	Large	

(From data in references 98-103.)

problems if they are fed whole cow's milk or milk replacers made only from dairy products. If waste milk is fed to calves, it is best to pasteurize the milk before it is fed.

References

1. UDSA: Dairy 2002. Part I: Reference of Dairy Health and Management in the United States USDA:APHIS:VS:CEAH. NRRC Building B., M.S. 2E7, 2150 Centre Avenue, Fort Collins, CO 80526–8117, 2002.
2. USDA: Part II: Reference of 1997 Beef Cow-Calf Health & Health Management Practices. Centers for Epidemiology and Animal Health, USDA:APHIS:VS, attn. NAHMS, 555 South Howes, Fort Collins, CO 80521, 1997.
3. Bouda J, Doubek J, Medina-Cruz M et al: Pathophysiology of severe diarrhoea and suggested intravenous fluid therapy in calves of different ages under field conditions, *Acta Veterinaria Brno* 66:87, 1997.
4. McLaren IM, Wray C: Epidemiology of *Salmonella typhimurium* infection in calves: persistence of salmonellae on calf units, *Vet Rec* 129:461, 1991.
5. Radke BR, McFall M, Radostits SM: Salmonella Muenster infection in a dairy herd, *Can Vet J* 43:443, 2002.
6. Snodgrass DR, Terzolo HR, Sherwood D et al: Aetiology of diarrhoea in young calves, *Vet Rec* 119:31, 1986.
7. Waltner-Toews D, Martin SW, Meek AH: An epidemiological study of selected calf pathogens in dairy farms in southwestern Ontario, *Can J Vet Res* 50:307, 1986.
8. Athanassious R, Marsolais M, Assaff R et al: Detection of bovine coronavirus and type A rotavirus in neonatal calf diarrhea and winter dysentery of cattle in Quebec: evaluation of three diagnostic methods, *Can Vet J* 35:163, 1994.
9. Bulgin MS, Ward ACS, Barrett DP et al: Detection of rotavirus and coronavirus shedding in two beef cow herds in Idaho, *Can Vet J* 30:235, 1989.
10. Gelinas AM, Boutin M, Sasseville AMJ et al: Bovine coronaviruses associated with enteric and respiratory diseases in Canadian dairy cattle display different reactivities to anti-HE monoclonal antibodies and distinct amino acid changes in their HE, S and ns4.9 protein, *Virus Res* 76:43, 2001.
11. Hasoksuz M, Sreevatsan S, Cho-Kyoung Oh et al: Molecular analysis of the S1 subunit of the spike glycoprotein of respiratory and enteric bovine coronavirus isolates, *Virus Res* 84:101, 2002.
12. Mebus CA, Stair EL, Rhodes MB et al: Pathology of neonatal calf diarrhea induced by a coronavirus-like agent, *Vet Pathol* 10:45, 1973.
13. Traven M, Naslund K, Linde N et al: Experimental reproduction of winter dysentery in lactating cows using BCV: comparison with BCV infection in milk-fed calves, *Vet Microbiol* 81:127, 2001.
14. Tsunemitsu H, Smith DR, Saif LJ: Experimental inoculation of adult dairy cows with bovine coronavirus and detection of coronavirus in feces by RT-PCR, *Arch Virol* 144:167, 1999.
15. Bolin SR, Ridpath JF: Differences in virulence between two noncytopathic bovine viral diarrhea viruses in calves, *Am J Vet Res* 53:2157, 1992.
16. Castrucci G, Frigeri F, Osburn BI et al: A study of pathogenetic aspects of bovine viral diarrhea virus infection, *Arch Virol* 3(suppl):101, 1991.
17. Corapi WV, French TW, Dubovi EJ: Severe thrombocytopenia in young calves experimentally infected with noncytopathic bovine viral diarrhea virus, *J Virol* 63:3934, 1989.
18. Hall GA, Bridger JC, Brooker BE et al: Lesions of gnotobiotic calves experimentally infected with a calicivirus-like (Newbury) agent, *Vet Pathol* 21:208, 1984.
19. Torgerson PR, Dalgleish R, Gibbs HA: Mucosal disease in a cow and her suckled calf, *Vet Rec* 125:530-531, 1989.
20. Acres SD, Laing CJ, Saunders JR et al: Acute undifferentiated neonatal diarrhea in beef calves. I. Occurrence and distribution of infectious agents, *Can J Comp Med* 39:116, 1975.
21. Acres SD: Enterotoxigenic *Escherichia coli* infection in newborn calves, *J Dairy Sci* 68:229-256, 1985.
22. Bywater RJ: Some effects of *Escherichia coli* enterotoxin on unidirectional fluxes of water and sodium in calf Thiry-Vella loops, *Res Vet Sci* 14:35, 1973.
23. Gulati BR, Sharma VK, Taku AK: Occurrence and enterotoxigenicity of F17 fimbriae bearing *Escherichia coli* from calf diarrhoea, *Vet Rec* 131:348, 1992.
24. Mahdi-Saeed A, Bowersock T, Runnels L et al: The role of pathogenic *Escherichia coli* in the etiology of veal calf hemorrhagic enteritis, *Prevent Vet Med* 17:65-75, 1993.
25. Moon HW, Whipp SC, Skartvedt SM: Etiologic diagnosis of diarrheal disease of calves: frequency and methods for detecting enterotoxin and K99 antigen production by *Escherichia coli*, *Am J Vet Res* 37:1025, 1976.
26. Aidar L, Penteado AS, Trabulsi LR et al: Subtypes of intimin among non-toxigenic *Escherichia coli* from diarrheic calves in Brazil, *Can J Vet Res* 64:15, 2000.
27. Fischer J, Maddox C, Moxley R et al: Pathogenicity of a bovine attaching effacing *Escherichia coli* isolate lacking Shiga-like toxins, *Am J Vet Res* 55:991, 1994.
28. Janke BH, Francis DH, Collins JE et al: Attaching and effacing *Escherichia coli* infection as a cause of diarrhea in young calves, *J Am Vet Med Assoc* 196:897, 1990.
29. Levine MM: *Escherichia coli* that cause diarrhea: enterotoxigenic, enteropathogenic, enteroinvasive, enterohemorrhagic and enteroadherent, *J Infect Dis* 155:377-389, 1987.
30. Mainil JG, Duchesnes CJ, Whipp SC et al: Shiga-like toxin production and attaching effacing activity of *Escherichia coli* associated with calf diarrhea, *Am J Vet Res* 48:743, 1987.
31. Mercado EC, Gioffre A, Rodriguez SM et al: Non-O157 Shiga toxin-producing *Escherichia coli* isolated from diarrhoeic calves in Argentina, *J Vet Med B* 51:82, 2004.
32. Pearson GR, Watson CA, Hall GA et al: Natural infection with an attaching and effacing *Escherichia coli* in the small and large intestines of a calf with diarrhoea, *Vet Rec* 124:297-299, 1989.
33. Schoonderwoerd M, Clarke RC, van Dreumel AA et al: Colitis in calves: natural and experimental infection with a verotoxin-producing strain of *Escherichia coli* O111:NM, *Can J Vet Res* 52:484, 1988.
34. Stordeur P, China B, Charlier G et al: Clinical signs, reproduction of attaching/effacing lesions, and enterocyte invasion after oral inoculation of an O118 enterohaemorrhagic *Escherichia coli* in neonatal calves, *Microbes Infect* 2:17, 2000.
35. Wray C, McLaren I, Pearson GR: Occurrence of "attaching and effacing" lesions in the small intestine of calves experimentally infected with bovine isolates of verocytotoxic *E coli*, *Vet Rec* 125:365, 1989.
36. Bost S, Roels S, Mainil J: Necrotoxigenic *Escherichia coli* type-2 invade and cause diarrhoea during experimental infection in colostrum-restricted newborn calves, *Vet Microbiol* 81:315, 2001.
37. Osek J: Characterization of necrotoxigenic *Escherichia coli* (NTEC) strains isolated from healthy calves in Poland, *J Vet Med B* 48:641, 2001.
38. Anderson BC: *Cryptosporidium muris* in cattle, *Vet Rec* 129:20, 1991.
39. Anderson BC, Bulgin MS: Enteritis caused by *Cryptosporidium* in calves, *Vet Med Small Animal Clin* 76:865-868, 1981.

40. Casemore DP, Sands RL, Curry A: *Cryptosporidium* species: a "new" human pathogen, *J Clin Pathol* 38:1321, 1985.

41. Morin M, Lariviere S, Lallier R: Pathological and microbiological observations made on spontaneous cases of acute neonatal calf diarrhea, *Can J Comp Med* 40:228, 1976.

42. Peeters JE, Villacorta I, Vanopdenbosch E et al: *Cryptosporidium parvum* in calves: kinetics and immunoblot analysis of specific serum and local antibody responses (immunoglobulin A [IgA], IgG, and IgM) after natural and experimental infections, *Infect Immun* 60:2309-2316, 1992.

43. Reif JS, Wimmer L, Smith JA et al: Human cryptosporidiosis associated with an epizootic in calves, *Am J Public Health* 79:1528, 1989.

44. Tzipori S, Angus K, Campbell I et al: *Cryptosporidium:* evidence for a single-species genus, *Infect Immun* 30:884, 1980.

45. Huetink RE, van der Giessen JW, Noordhuizen JP, Ploegar HW: Epidemiology of *Cryptosporidium* spp. and *Giardia duodenalis* on a dairy farm, *Vet Parasitol* 102:53, 2001.

46. O'Handley RM, Cockwill C, Jelinski M et al: Effects of repeat fenbendazole treatment in dairy calves with giardiosis on cyst excretion, clinical signs and production, *Vet Parasitol* 89:209, 2000.

47. Olson ME, Guselle NJ, O'Handley RM et al: Giardia and cryptosporidium in dairy calves in British Columbia, *Can Vet J* 38:703, 1997.

48. Xiao LH, Herd RP, Rings DM: Concurrent infections of *Giardia* and *Cryptosporidium* on two Ohio farms with calf diarrhea, *Vet Parasitol* 51:41, 1993.

49. Ewaschuk JB, Zello GA, Naylor JM, Brocks DR: Metabolic acidosis: separation methods and biological relevance of organic acids and lactic acid enantiomers, *J Chromatogr B Analyt Technol Biomed Life Sci* 781:39, 2002.

50. Zello GA, Abeysekara AWAS, Wassef AWA et al: Evidence for D-lactic acid as a neurotoxic agent in acidotic diseases, *S African J Clin Nutr* 49:291, 2005.

51. Naylor JM, A retrospective study of the relationship between clinical signs and severity of acidosis in diarrheic calves, *Can Vet J* 30:577-580, 1989.

52. Fisher EW, de la Fuente GH: Water and electrolyte studies in newborn calves with particular reference to the effects of diarrhoea, *Res Vet Sci* 13:315, 1972.

53. Lewis LD, Phillips RW: Water and electrolyte losses in neonatal calves with acute diarrhea: a complete balance study, *Cornell Vet* 62:596, 1972.

54. Lorenz I, Rademacher G: Bedeutung und Therapie der Hyponatriamie bei alteren Kalbern mit Durchfall. (Incidence and therapy of hyponatraemia in older calves with diarrhea), *Tierarztliche Praxis Ausgabe G, Grosstiere/Nutztiere* 27:268, 1999.

55. Whitten EH, Phillips RW: In vitro intestinal exchange of Na+, K+, Cl-,3H2O in experimental bovine neonatal enteritis, *Am J Dig Dis* 16:891, 1971.

56. Ewaschuk JB, Naylor JM, Zello GA: Anion gap correlates with serum D- and DL-Lactate concentrations in diarrheic calves, *J Vet Int Med* 17:940, 2003.

57. Naylor JM: Severity and nature of acidosis in diarrheic calves over and under one week of age, *Can Vet J* 28:168, 1987.

58. Petersen C: D-lactic acidosis, *Nutr Clin Pract* 20:634, 2005.

59. Lorenz I, Gentile A, Klee W: Investigations of D-lactate metabolism and the clinical signs of D-lactataemia in calves, *Vet Rec* 156:412, 2005.

60. Abeysekara S, Naylor JM, Wassef AW et al: D-lactic acid–induced neurotoxicity in a calf model. *Am J Physiol Endocrinol Metab* 293:E558-E565, 2007.

61. Kasari TR, Naylor JM: Further studies on the clinical features and clinicopathological findings of a syndrome of metabolic acidosis with minimal dehydration in neonatal calves, *Can J Vet Res* 50:502, 1986.

62. Schelcher F, Marcillaud S, Braun JP et al: Metabolic acidosis without dehydration and no or minimal diarrhoea in suckler calves is caused by hyper D-lactatemia, *Proc of XX World Buiatrics Congress* 371, 1998.

63. Lorenz I: Investigations on the influence of serum D-lactate levels on clinical signs in calves with metabolic acidosis, *Vet J* 168:323, 2004.

64. Fisher EW: Death in neonatal calf diarrhoea, *Br Vet J* 121:132, 1965.

65. Fisher EW, McEwan AD: Death in neonatal calf diarrhoea. Part II: The role of oxygen and potassium, *Br Vet J* 123:4, 1967.

66. Naylor JM: Alkalizing abilities of calf oral electrolyte solutions, *Proc World Congress Dis Cattle* 14:326, 1986.

67. Naylor JM: Effects of oral electrolyte solutions on clotting of milk, *J Am Vet Med Assoc* 201:1026, 1992.

68. Heath SE, Naylor JM, Guedo BL et al: The effects of feeding milk to diarrheic calves supplemented with oral electrolytes, *Can J Vet Res* 53:477, 1989.

69. Gottardo FS, Mattiello S, Cozzi G et al: The provision of drinking water to veal calves for welfare purposes, *J Anim Sci* 80:2362, 2002.

70. Ganong WF: Regulation of extracellular fluid composition & volume. In *Review of medical physiology*, ed 13, Norwalk, Conn, 1987, Appleton & Lange, pp 607-614.

71. Naylor JM: Evaluation of the total carbon dioxide apparatus and pH meter for the determination of acid-base status in diarrheic and healthy calves, *Can Vet J* 28:45, 1987.

72. Booth AJ, Naylor JM: Correction of metabolic acidosis in diarrheal calves by oral administration of electrolyte solutions with or without bicarbonate, *J Am Vet Med Assoc* 191:62, 1987.

73. Kasari TR, Naylor JM: Clinical evaluation of sodium bicarbonate, sodium L-lactate and sodium acetate for the treatment of acidosis in diarrheic calves, *J Am Vet Med Assoc* 187:392, 1986.

74. Ewaschuk JB, Naylor JM, Zello GA: D-lactate production and excretion in diarrheic calves, *J Vet Int Med* 18:744, 2004.

75. Constable PD: Antimicrobial use in the treatment of calf diarrhea, *J Vet Int Med* 18:8, 2004.

76. Fecteau G, Van Metre DC, Pare J et al: Bacteriological culture of blood from critically ill neonatal calves, *Can Vet J* 38:95, 1997.

77. Lofstedt J, Dohoo JR: A model for the prediction of sepsis in diarrheic neonatal calves, *Proc Am Coll Vet Int Med* 14, pp 473-474, 1996.

78. Jarvie BD, Trotz-Williams LA, McKnight DR et al: Effect of halofuginone lactate on the occurrence of *Cryptosporidium parvum* and growth of neonatal dairy calves, *J Dairy Sci* 88:1801, 2005.

79. Villacorta I, Peeters JE, Vanopdenbosch E et al: Efficacy of halofuginone lactate against *Cryptosporidium parvum* in calves, *Antimicrob Agents Chemother* 35:283, 1991.

80. Barnett SC, Sischo WM, Moore DA et al: Evaluation of flunixin meglumine as an adjunct treatment for diarrhea in dairy calves, *J Am Vet Med Assoc* 223:1329, 2003.

81. Abdala AA, Zimmerman G, Calvinho LF et al: Evaluacion de la eficacia de un probiotico incorporado a un sustituto lacteo y a la leche entera, en la crianza de terneros (Efficacy of a probiotic added to whole milk and to a milk substitute), *Revista de Medicina Veterinaria Buenos Aires* 83:196, 2002.

82. Ewaschuk JB, Zello GA, Naylor JM: *Lactobacillus GG* does not affect D-lactic acidosis in diarrheic calves, in a clinical setting, *J Vet Int Med* 20:614, 2006.

83. Ewaschuk JB, Naylor JM, Chirino-Trejo M et al: *Lactobacillus GG* is a potential probiotic for calves, *Can J Vet Res* 68:249, 2004.

84. Goncalves GD, Santos GT, Rigolon LP et al: Influencia da adicao de probioticos na dieta sobre o estado sanitario e

desempenho de bezerros da raca Holandesa. (The influence of probiotics addition in the diet on the sanitary state and the performance of calves Holstein), *Brazil J Vet Res Animal Sci* 37:74, 2000.

85. Muscato TV, Tedeschi LO, Russell JB: The effect of ruminal fluid preparations on the growth and health of newborn, milk-fed dairy calves, *J Dairy Sci* 85:648, 2002.

86. Timmerman HM, Mulder L, Everts H et al: Health and growth of veal calves fed milk replacers with or without probiotics, *J Dairy Sci* 88:2154, 2005.

87. Dardillat J, Trillat G, Larvor P: Colostrum immunoglobulin concentration in cows: relationship with their calf mortality and with the colostrum quality of their female offspring, *Ann Recherches Vet* 9:375, 1978.

88. Naylor JM, Kronfeld DS, Bech-Nielsen S et al: Plasma total protein measurement for prediction of disease and mortality in calves, *J Am Vet Med Assoc* 171:635, 1977.

89. Parreno V, Bejar C, Vagnozzi A et al: Modulation by colostrum-acquired maternal antibodies of systemic and mucosal antibody responses to rotavirus in calves experimentally challenged with bovine rotavirus, *Vet Immunol Immunopathol* 100:7, 2004.

90. Postema HJ, Mol J: Risk of disease in veal calves: relationships between colostrum-management, serum immunoglobulin levels and risk of disease, *Zentralblatt fur Veterinarmedizin A* 31:751, 1984.

91. Smith HW: Observations on the aetiology of neonatal diarrhoea (scours) in calves, *J Path Bact* 84:147, 1962.

92. Snodgrass DR, Stewart J, Taylor J et al: Diarrhoea in dairy calves reduced by feeding colostrum from cows vaccinated with rotavirus, *Res Vet Sci* 32:70, 1982.

93. Woode GN, Jones J, Bridger J: Levels of colostral antibodies against neonatal calf diarrhoea virus, *Vet Rec* 97:148, 1975.

94. Clement JC, King ME, Salman MD et al: Use of epidemiologic principles to identify risk factors associated with the development of diarrhea in calves in five beef herds, *J Am Vet Med Assoc* 207:1334, 1995.

95. Dutil L, Fecteau G, Bouchard E et al: A questionnaire on the health, management, and performance of cow-calf herds in Quebec, *Can Vet J* 40:649, 1999.

96. Schumann FJ, Townsend HG, Naylor JM: Risk factors for mortality from diarrhea in beef calves in Alberta, *Can J Vet Res* 54:366, 1990.

97. Curtis CR, Scarlett JM, Erb HN et al: Path model of individual-calf risk factors for calfhood morbidity and mortality in New York Holstein herds, *Prev Vet Med* 6:43, 1988.

98. Harp JA, Woodmansee DB, Moon HW: Effects of colostral antibody on susceptibility of calves to *Cryptosporidium parvum* infection, *Am J Vet Res* 50:2117, 1989.

99. Frank NA, Kaneene JB: Management risk factors associated with calf diarrhea in Michigan dairy herds, *J Dairy Sci* 76:1313, 1993.

100. Greene HJ, Bakheit HA: A study of the aetiology, epidemiology and control of calf diarrhoea in Ireland, *Irish Vet J* 38:63, 1984.

101. James RE, McGilliard ML, Hartman DA: Calf mortality in Virginia Dairy Herd Improvement herds, *J Dairy Sci* 67:908, 1984.

102. Kertz AF, Reutzel LF, Mahoney JH: Ad libitum water intake by neonatal calves and its relationship to calf starter intake, weight gain, feces score, and season, *J Dairy Sci* 67:2964, 1984.

103. Lorino T, Daudin JJ, Robin S et al: Factors associated with time to neonatal diarrhoea in French beef calves, *Prevent Vet Med* 68:91, 2005.

104. Matoock MY, El-Bably MA, El-Bahy MM: Management practices for minimizing environmental risk factors associated with *Cryptosporidium* in dairy calves, *Vet Med J Giza* 53:565, 2005.

Recommended Readings

Abeysekara S, Naylor JM, Wassef AW et al: D-lactic acid–induced neurotoxicity in a calf model. *Am J Physiol Endocrinol Metab* 293:E558-E565, 2007.

Constable PD, Walker PG, Morin DE et al: Clinical and laboratory assessment of hydration status of neonatal calves with diarrhea, *J Am Vet Med Assoc* 212:991, 1998.

Sigaard-Andersen O: Titratable acid or base of body fluids, *Ann New York Acad Sci* 133:41, 1966.