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Treatment of Calf Diarrhea: Antimicrobial and Ancillary Treatments

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KEYWORDS

• Fluoroquinolones • Cephalosporins • Halofuginone
• Azithromycin • Acetate • Propionate

There are six major causes of diarrhea in calves less than 21 days of age: enterotoxigenic *Escherichia coli* (ETEC), rotavirus, coronavirus, *Cryptosporidium parvum (C parvum)* type II, *Salmonella enterica* (*S enterica*) subsp. *enterica* serovars, and nutritional. Regardless of the etiology, calves with diarrhea often have increased coliform bacterial numbers in the small intestine; small intestinal bacterial overgrowth is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia and endotoxemia.[1–3] The importance of bacterial overgrowth in calf diarrhea has garnered renewed attention with the realization that D-lactic acid plays an important role in the development of acidemia in calves with diarrhea. Production of D-lactic acid results from bacterial fermentation in the gastrointestinal tract and is a common finding in neonatal calves with and without diarrhea.[4–8] D-lactic acid is a major component of acidemia in diarrheic calves[6,8,9] and is accompanied by systemic signs of weakness and ataxia.[10]

This review focuses on adjunct therapy of diarrhea in the first 3 weeks of life and therefore does not address the efficacy of adjunct treatment for calf diarrhea due to *Eimeria bovis*, *Eimeria zurneii*, or *Giardia duodenalis*. The main principles of ancillary treatment in neonatal calves with diarrhea and systemic illness are: (1) treat or prevent Gram-negative septicemia and bacteremia; (2) decrease the numbers of coliform bacteria in the proximal small intestine and abomasum; (3) increase nonspecific resistance; (4) provide nutrients that facilitate repair of damaged intestine and prevent negative energy balance; and (5) provide analgesia and reduce stress to the calf. Treatment goals for all calves with diarrhea are accomplished by the parenteral

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administration of antimicrobials with a predominantly Gram-negative spectrum of activity, short-term administration of nonsteroidal anti-inflammatory agents such as flunixin meglumine or meloxicam, and continued milk feeding. For calves with diarrhea caused by *C parvum*, the oral administration of halofuginone or azithromycin appears to be effective in decreasing the duration and severity of diarrhea, as well as in decreasing fecal oocyst concentration and environmental contamination. Theoretically efficacious treatments include the administration of oral rehydration therapy solutions that contain acetate and propionate, and the administration of parenteral B vitamins and fat-soluble vitamins in calves that have chronic diarrhea. There is no evidence to support the efficacy of corticosteroids, motility modifiers, immunostimulants, intestinal ''protectants'' or ''absorbants,'' or probiotic substances in the treatment of calf diarrhea, and the administration of any of these items is not currently recommended.

RECOMMENDED TREATMENTS

Antimicrobials

Although some consider the use of antimicrobials to treat calf diarrhea to be controversial and not indicated,[11,12] a systematic review of the literature provided strong and unequivocal evidence that specific antimicrobials are efficacious in the treatment of calf diarrhea.[1] The initial concern about antimicrobial use in calf diarrhea was derived from the results of studies that indicated oral administration of penicillin, chloramphenicol, and neomycin increased the incidence of diarrhea in healthy calves, produced malabsorption, or reduced growth rate.[1] More recent concerns about antimicrobial use in calf diarrhea have focused on whether antimicrobial administration promotes antimicrobial resistance of enteric pathogens and facilitates the emergence of multiple resistant strains of *Salmonella enterica* subsp. *enterica serovars* typhimurium and newport. Important considerations when administering antimicrobials as part of the treatment of calves with diarrhea are: (1) administering as directed on the label or by a veterinarian whenever possible; (2) selecting an antimicrobial agent with an appropriate spectrum of activity; (3) using a dosage protocol that attains and maintains an effective therapeutic concentration at the site of infection; (4) treating for an appropriate duration; (5) avoiding adverse local or systemic effects and violative residues; and (6) minimizing the potential for transfer of antimicrobial resistance genes.[13] The overarching philosophy is that veterinarians should use and prescribe antimicrobials conservatively to minimize potential adverse effects on animal or human health.[14]

Calves with diarrhea have small intestinal overgrowth with *E coli* bacteria, regardless of the inciting cause for the diarrhea (**Fig. 1**),[1] and 20%–30% of systemically ill calves with diarrhea have bacteremia, predominantly due to *E coli*.[15–17] The frequency of bacteremia is high enough that treatment of calves with diarrhea that are systemically ill (as indicated by decreased appetite and activity or the presence of fever) should include routine treatment against potential bacteremia, with emphasis on treating potential *E coli* bacteremia. Bacteremia should also be suspected to be present in 100% of calves with clinical signs of *Salmonella* diarrhea, although the prevalence of bacteremia in calves with salmonellosis does not appear to have been determined.[18] A clinical sepsis score to predict bacteremia[19] does not appear to be sufficiently accurate to guide antimicrobial treatment decisions.

Antimicrobial treatment of diarrheic calves with systemic illness should be focused against *E coli* in the blood (due to bacteremia) and small intestine (due to bacterial overgrowth), as these constitute the two sites of bacterial infection. Fecal bacterial culture and antimicrobial susceptibility testing is not recommended in calves with

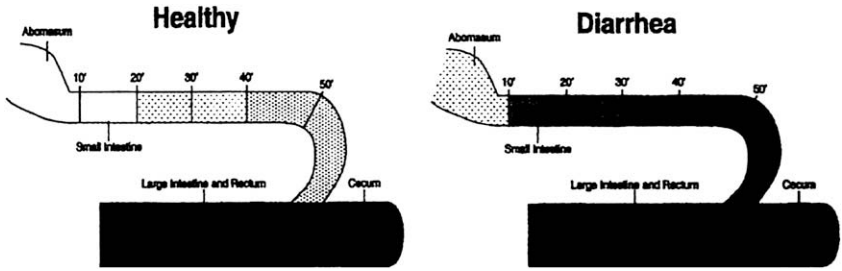

Fig. 1. Schematic of the distribution and concentration of *Escherichia coli* bacteria in the intestinal tract of a calf with undifferentiated diarrhea and a similarly aged calf without diarrhea. (*Adapated from* Reisinger RC. Pathogenesis and prevention of infectious diarrhea (scours) of newborn calves. J Am Vet Med Assoc 1965;147:1377–86.) The figure indicates that the number of *E coli* in the large intestine of diarrheic and healthy calves is similar but that diarrheic calves have increased *E coli* numbers in their small intestine, particularly in the distal jejunum and ileum. (*Reprinted from* Constable PD. Antimicrobial use in the treatment of calf diarrhea. J Vet Intern Med 2004a;18:8–17; with permission.)

diarrhea because fecal bacterial populations do not accurately reflect small intestinal or blood bacterial populations, and because the breakpoints for susceptibility test results have not been validated for calves with diarrhea.[1] Antimicrobial efficacy is therefore best evaluated by the clinical response to treatment. Antimicrobial treatment may also be effective in eliminating D-lactate–producing bacteria from the gastrointestinal tract of calves with diarrhea[3,7] and thereby hasten the time course of clinical improvement, although this supposition needs to be verified.

Oxytetracycline and sulfachloropyridiazine administered parenterally and amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, sulfamethazine, and tetracycline administered orally have been labeled by the US Food and Drug Administration (FDA) for the treatment of bacterial enteritis (scours, colibacillosis) caused by *E coli* bacteria susceptible to the antimicrobial.[1] Studies supporting the efficacy of parenteral oxytetracycline and sulfachloropyridiazine, and of oral amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridiazine, sulfamethazine, and tetracycline at labeled doses in treating calves with naturally acquired diarrhea do not appear to have been published in peer-reviewed journals.[1] Oral amoxicillin was effective in the treatment of experimentally induced diarrhea[20,21] but was not efficacious in the treatment of naturally acquired diarrhea in beef calves.[22] In view of the apparent lack of published studies documenting clinical efficacy of antimicrobials with a label claim for the treatment of naturally occurring calf diarrhea, and because the health of the animal is threatened (suffering or death may result from failure to treat systemically ill calves), extralabel antimicrobial use (excluding prohibited antimicrobials) is justified for the treatment of calf diarrhea.[1]

Antimicrobials should be administered to all calves with diarrhea that exhibit systemic signs of illness (as indicated by inappetance, dehydration, lethargy, or pyrexia) (**Fig. 2**); or have blood or mucosal shreds in their stool (**Fig. 3**); the latter indicates breakdown of the blood-gut barrier and a presumed increased risk of bacteremia. Parenteral administration of antimicrobials is preferred to oral administration, with the ideal parenteral antimicrobial being bactericidal and predominantly Gram-negative in spectrum.[1] The ideal parenteral antimicrobial should also be excreted in an active form in bile that results in a local antimicrobial effect in the small intestine.[1] Current evidence suggests that antimicrobials should not be administered

Fig. 2. A Jersey calf with diarrhea and systemic signs of illness. The calf is reluctant to stand and has a weak suckle reflex. Current knowledge indicates that this calf will benefit from parenteral antimicrobial administration, such as amoxicillin, ampicillin, or a third or fourth generation cephalosporin in countries where there use is permitted. Parenteral fluoroquinolone administration is not indicated because the calf does not need intravenous fluid therapy.

to diarrheic calves that have a normal appetite, activity level, rectal temperature, and hydration status and the absence of concurrent infections such as pneumonia or omphalophlebitis (**Fig. 4**).[23] Instead, these calves should be separated from other calves and their health status monitored frequently.

The success of antimicrobial therapy varies with the route of administration and whether the antimicrobial is dissolved in milk, oral electrolyte solutions, or water. Oral antimicrobials administered as bolus, tablet, or in a gelatin capsule maybe swallowed into the rumen and exhibit a different serum concentration-time profile to antimicrobials dissolved in milk replacer that are suckled by the calf.[13] Antimicrobials that bypass the rumen are not thought to alter rumen microflora, potentially permitting bacterial recolonization of the small intestine from the rumen. Individual antimicrobial treatment of sick calves increases the level of resistance in fecal *E coli* isolates, but the change in antimicrobial susceptibility is only transient.[24]

First choice antimicrobials for the treatment of diarrhea in systemically ill calves include parenteral amoxicillin or ampicillin (10 mg/kg, intramuscularly [IM] every 12 hours), parenteral potentiated sulfonamides (25 mg/kg, IV or IM every 24 hours), and oral amoxicillin trihydrate (10 mg/kg every 12 hours) alone or combined with the inhibitor clavulanate potassium (12.5 mg combined drug/kg every 12 hours).[1,13,25] Second choice antimicrobials in those countries where cephalosporin administration is permitted are third and fourth generation cephalosporins, such as ceftiofur and cefquinome.[1,13] Parenteral ceftiofur has evidence of efficacy in experimentally-induced *S*

Fig. 3. A Holstein-Friesian calf with profuse watery diarrhea that contains blood. The calf was admitted in lateral recumbency, and was pyrexic, markedly depressed, and inappetant. The calf was treated intravenously with 2 L of 1.4% sodium bicarbonate solution containing glucose and was able to stand within 2 hours of treatment. Current knowledge indicates that this calf should be treated with parenteral antimicrobials and a nonsteroidal anti-inflammatory agent such as meloxicam or flunixin meglumine. Parenteral fluoroquinolone or third or fourth generation cephalosporin administration may be indicated in countries where such administration is permitted because the calf needed intravenous fluid therapy. The extralabel administration of fluoroquinolones in food producing animals in the United States is prohibited by law because of concerns regarding facilitating the emergence of bacteria with multiple antimicrobial resistance, particularly pathogenic enteric bacteria in humans.

enterica subsp *enterica* serovar dublin infection.[18] Last choice antimicrobials are fluoroquinolones in those countries where fluoroquinolone administration is permitted to treat calves with *E coli* diarrhea and salmonellosis. However, parenteral fluoroquinolones should be administered only to critically ill calves, such as those calves requiring intravenous fluid administration.[13] Aminoglycosides should also not be administered orally because they are very poorly absorbed from the gastrointestinal tract. Aminoglycosides should not be administered parenterally because of prolonged withdrawal times for slaughter, potential for nephrotoxicity in dehydrated calves, and minimal excretion in bile.[1] The results of a 2002 survey of Italian cattle veterinarians indicated that fluoroquinolones and aminoglycosides were the first choice antimicrobials for treating calf diarrhea by 54% and 14% of respondents, respectively.[26]

Even though oral and parenteral fluoroquinolones have documented efficacy in treating calves with diarrhea and systemic illness,[1] the extralabel administration of fluoroquinolones in food-producing animals in the United States is prohibited by law because of concerns regarding facilitating the emergence of bacteria with multiple

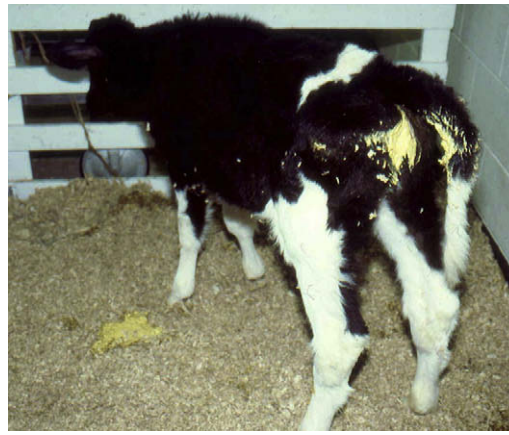

Fig. 4. A Holstein-Friesian calf with diarrhea but no systemic signs of illness. The calf is eager to stand and has a good suckle reflex. Current knowledge indicates that this calf does not need parenteral or oral antimicrobial administration.

antimicrobial resistance, particularly pathogenic enteric bacteria in humans. Another important issue is the potential ban on extralabel use of cephalosporins in the United States. At the time this article was written, the US FDA had proposed a final rule prohibiting any use of extralabel cephalosporins in food producing animals. Because there are no third or fourth generation cephalosporins specifically approved for the treatment of diarrhea in calves, their use would not be permitted if this rule is not amended.

Analgesic and Anti-Inflammatory Agents

Diarrhea can be accompanied by intestinal cramping and abdominal pain. The administration of an effective analgesic may therefore be beneficial as part of the treatment of calf diarrhea, provided that the side effects of such treatment are not deleterious. Meloxicam is an analgesic and anti-inflammatory agent that is labeled in Europe for the treatment of calf diarrhea when used in conjunction with oral rehydration therapy. In a randomized multilocation trial of 191 calves in Europe, a single IV injection of meloxicam (0.5 mg/kg bodyweight) in conjunction with a standard treatment (oral electrolyte rehydration solution therapy and parenteral gentamicin) increased feed intake, hydration score, and fecal consistency, and decreased the signs of visceral pain, relative to standard treatment alone.[27] In a recent randomized study of 56 calves in Ontario Canada, the subcutaneous administration of meloxicam (0.5 mg/kg, once) resulted in treated calves consuming starter rations earlier than placebo-treated calves. Treated calves also had improved starter ration intakes, a higher body weight gain, and increased activity level than placebo-treated calves.[28] Taken together, these results suggest that meloxicam should be considered as part of the initial treatment of calves with diarrhea and systemic illness in those countries where meloxicam is labeled for use in calves.

Two broad categories of anti-inflammatory agents could potentially be used as part of the treatment for calf diarrhea: corticosteroids and nonsteroidal anti-inflammatory agents (NSAIDs). The major therapeutic goals of anti-inflammatory administration are to decrease inflammation in the gastrointestinal tract and to ameliorate the effects of endotoxemia and septicemia secondary to translocation of enteric bacteria across

damaged intestinal epithelium. Although studies evaluating the prevalence of endotoxemia in calves with diarrhea do not appear to have been done, the results of a recent study in neonatal lambs with diarrhea indicated that affected lambs were frequently endotoxemic, as assessed by the Limulus amoebocyte lysate assay.[2]

The routine administration of corticosteroids to diarrheic calves is not recommended. This is because calves with diarrhea have higher plasma corticosteroid concentrations, relative to healthy calves,[29,30] and because corticosteroids suppress the immune system.

The routine administration of NSAIDs, such as meloxicam or flunixin meglumine, is recommended as part of the initial treatment in calves with diarrhea that are systemically ill. An empiric guideline for the treatment of diarrhea is to administer meloxicam once at a dose of 0.5 mg/kg bodyweight (0.22 mg/lb) or flunixin meglumine once at a dose 2.2 mg/kg (1.0 mg/lb), and not to exceed 3 doses of either meloxicam or flunixin meglumine. This recommendation is based on the need to avoid damaging the abomasal mucosa, particularly in intensive calf-rearing facilities with a history of calf deaths due to perforated abomasal ulcers.[3] The beneficial effects of meloxicam and flunixin meglumine could be caused by their analgesic, anti-inflammatory, antipyretic, or antisecretory properties, or due to underdetermined effects on intestinal motility. It is currently not clear which of these potential effects is the most important.

The administration of one dose of flunixin meglumine (2.2 mg/kg [1.0 mg/lb] intramuscularly) as an adjunct treatment for naturally occurring diarrhea resulted in fewer morbid-days and antimicrobial treatments, but only when calves had fresh blood visible in their feces.[31] In calves administered STa toxin as a model for experimentally induced ETEC infection, intramuscular administration of flunixin meglumine (2.2 mg/kg [1.0 mg/lb] every 8 hours) reduced fecal output, possibly by acting as an antisecretory agent.[32] Blockade of both cyclo-oxygenase isoforms (COX-1 and COX-2) is required to facilitate the uptake of sodium from the intestinal ileum of calves with diarrhea due to *C parvum*.[33] The clinical relevance of this finding remains unclear because the ileum is not a quantitatively important site of fluid flux in calves with diarrhea[34,35] and because doses needed for effective in vitro COX-1 and COX-2 blockade[33] have not been related to those obtained in vivo using standard dosage protocols for meloxicam or flunixin meglumine. An important effect of flunixin meglumine administration is the clinical impression that calves show improved suckle behavior and general well being after treatment.[3,36]

Calves administered a high dose of ketoprofen (6 mg/kg bodyweight, IV, twice 4 hours apart) tended ($P = .059$) to have reduced fecal output, relative to untreated controls,[37] whereas a lower dose of ketoprofen (3 mg/kg bodyweight, IV, twice 4 hours apart) had no effect. Orally administered aspirin (acetylsalicylic acid, 100 mg/kg bodyweight, once) was not effective in decreasing STa-induced intestinal secretion in calves, whereas intravenously administered sodium salicylate was effective when administered at a dose calculated to maintain a therapeutic serum salicylate concentration of 30 μg/mL.[38] Subsalicylate, a component in bismuth subsalicylate (“Peptobismol” in the United States) is believed to exert a similar effect to aspirin. Bismuth subsalicylate may therefore decrease intestinal epithelial secretion mediated by cAMP or cGMP in calves with diarrhea, although this has not been verified. There does not appear to be a persuasive reason to prefer bismuth subsalicylate, aspirin, or ketoprofen over meloxicam or flunixin meglumine as an ancillary treatment for calf diarrhea. Until such data is available, bismuth subsalicylate, aspirin, and ketoprofen are not recommended as ancillary treatments for calf diarrhea.

Halofuginone and Azithromycin for Cryptosporidiosis

Specific therapy of presumed Cryptosporidial infection in calves remains an active area of research. The results of studies indicate that halofuginone, azithromycin, and possibly lasalocid can be effective in the treatment of cryptosporidial diarrhea in calves. It is currently believed that fresh cow's milk should be fed in small quantities several times daily to optimize digestion and to minimize loss of body weight. Feeding of cow's milk may also be beneficial as a source of dietary lipid, which has been shown to be a potent inhibitor of cryptosporidium-host cell adhesion in vitro.[39]

Halofuginone, a quinazoline of unknown mode of action, is licensed in a number of countries in Europe for the prevention and treatment of cryptosporidiosis in newborn calves. Halofuginone (0.06 to 0.12 mg/kg bodyweight by mouth daily) improved the clinical status and decreased fecal oocyst excretion and mortality in a dose-dependent manner in calves with experimentally induced cryptosporidial infection.[40] A toxicity study indicated that 0.5 mg/kg daily by mouth was close to the toxic dose.[41] Halofuginone (5 mg orally daily from approximately day 7 to day 14 of life, equivalent to 0.1 mg/kg bodyweight daily), was efficacious in decreasing oocyst excretion, but had no effect on the prevalence of diarrhea, fecal water percentage, or the severity of dehydration in naturally infected calves in Quebec, compared with untreated controls.[42] In contrast, the results of a large 2007 study in the Czech Republic indicated that halofuginone (0.1 mg/kg bodyweight daily for 7 days, orally) decreased the intensity of diarrhea and the fecal oocyst count, when started on day 1 or day 8 of life.[43] The preponderance of evidence indicates that halofuginone (0.1 mg/kg bodyweight daily orally) is an effective treatment for cryptosporidial diarrhea in calves.

Azithromycin (1–2 g/calf orally once daily for 7 days, equivalent to 30–40 mg/kg daily) decreased the mortality rate and fecal oocyst shedding, and increased the clinical health and weight gain, of 10-day-old calves with naturally acquired *C parvum* infection in Turkey.[44] Azithromycin is a macrolide antibiotic that is well absorbed from the small intestine and is likely to have some prokinetic and antimicrobial effects, based on its structural similarity to erythromycin.[45–47] The results of the above study suggest that azithromycin is an effective treatment for cryptosporidial diarrhea in calves. However, because this macrolide is widely used in the treatment of respiratory disease in humans and is expensive, the administration of azithromycin should be restricted to sick calves with documented Cryptosporidial diarrhea that have not responded to treatment with oral halofuginone.

Decoquinate, a hydroxyquinolone that inhibits cytochrome-mediated electron transport in mitochondria, has been used to prevent and treat cryptosporidia in calves. However, decoquinate (125 mg orally daily from approximately day 7 to day 14 of life in a solid premix, equivalent to 2.5 mg/kg bodyweight daily) had no effect on oocyst excretion, the prevalence of diarrhea, fecal water percentage, or the severity of dehydration in calves, compared with untreated controls.[42] Decoquinate (2 mg/kg bodyweight orally daily from approximately day 1 onwards of life in a soluble formulation in milk replacer) had no effect on oocyst excretion, the total number of days of diarrhea, or mortality rate in calves, compared with untreated controls.[48] These studies suggest that decoquinate is not an effective treatment for cryptosporidial diarrhea in calves.

Paromomycin sulfate solution (100–200 mg paromomycin/kg bodyweight by mouth daily for 2 to 3 days) was effective in decreasing oocyst excretion and the prevalence of diarrhea in lambs with naturally acquired *C parvum* diarrhea.[49] Paromomycin is an aminoglycoside antibiotic that is poorly absorbed from the gastrointestinal tract but is efficacious in treating immunocompromized humans with cryptosporidosis. The mechanism of paromomycin's effect remains unknown.

Lasalocid, an ionophore, is an effective treatment for naturally acquired and experimentally-induced cryptosporidial diarrhea in calves,[50] with a daily oral dose rate of 15 mg/kg bodyweight. In an uncontrolled trial of calves in Turkey with naturally acquired *C parvum* diarrhea, the oral administration of Lasolocid (8 mg/kg bodyweight, daily) in milk was associated with a decrease in fecal oocyst count,[51] although such a decrease was likely to occur in untreated calves because of age-related changes in fecal oocyst shedding.

Continued Feeding of Cow's Milk

It has become increasingly evident over the past 20 years that a damaged intestine needs metabolic fuel to optimize repair, and that fresh cow's milk provides an excellent, inexpensive, and readily available source of nutrition and growth factors to facilitate repair. Milk is also more energy dense than oral rehydration therapy (ORT) solutions and continued milk feeding minimizes the weight loss associated with chronic diarrhea in calves.[52] Concurrent feeding of milk and ORT solutions results in improved intestinal morphology, compared with that from ORT solutions alone.

Glutamine supplementation has been investigated as an ancillary treatment of calf diarrhea, but the results of two studies indicate the addition of glutamine had deleterious effects on small intestinal villus height and villus surface area, and glutamine-treated calves had a lower mitotic rate in the small intestine than control calves.[53,54] It is currently believed that glutamine offers no advantage in improving gut morphology in diarrheic calves.[55]

TREATMENTS THAT MAY BE EFFECTIVE

B Vitamins and Fat Soluble Vitamins

Parenteral administration of B-vitamins and fat-soluble vitamins may have beneficial effects in calves with chronic diarrhea.[3] However, there is a lack of data supporting the beneficial effects of vitamins in the treatment of calf diarrhea.

Oligosaccharides

Oligosaccharides are sugar polymers present in cow milk that contain a small number of (usually up to ten) component sugars that are either *O*- or *N*-linked to compatible amino acids in proteins (called glycoproteins) or lipids. Because many Gram-negative bacteria attach to the intestinal epithelium via receptors that have a similar structure to oligosaccharides, milk oligosaccharides may provide competitive binding sites for the K99 (F5) fimbrae from enterotoxigenic *E coli*.[56] Bacteria bound to oligosaccharides move along the intestine with intestinal peristalsis and are eliminated in the feces because oligosaccharides are not enzymatically digested in the small intestine.[57]

The administration of exogenous oligosaccharides in water to neonatal calves decreased intestinal *E coli* counts in the small intestine of calves inoculated with ETEC.[56] Prophylactic addition of exogenous oligosaccharides to milk replacer resulted in fecal scores (scours) in calves which were similar to those observed when calves were fed milk replacer containing antibiotics.[57–59] It must be noted that data on morbidity and mortality were either low or remained undetermined in these studies,[58] and that scours may well have had nutritional rather than an infectious origin.[57]

Oligosaccharides show promise as a non–antimicrobial method for preventing ETEC or treating ETEC diarrhea in calves. However, the experimental studies performed to date do not support the routine administration of oligosaccharides to sick calves with diarrhea.

Increasing Nonspecific Resistance

Nonspecific resistance is conferred by factors such as low abomasal pH, short chain fatty acids (acetate, propionate), lactoferrin and leukocytes in colostrum, oligosaccharides in colostrum and fresh milk,[60] and the lactoperoxidase system, lysozyme, and medium chain fatty acids (particularly n-decanoic and n-octanic acid) in fresh milk.[61,62]

Abomasal pH of the calf is 4.4 at birth[63] and after colostrum ingestion ranges from 5.9 to 7.2 over the first 20 hours of life.[64] The mean preprandial pH is constant between 1.4 and 1.7 after day 5 of life.[65,66] The relatively high pH during the first day of life ensures ingested colostral immunoglobulins are minimally degraded before arriving in the small intestine, which is the site of immunoglobulin absorption. Unfortunately, the high abomasal pH also allows ingested *E coli* and *Salmonella* spp. to escape the ''abomasal sterilizer'' and large numbers of viable pathogenic bacteria can therefore arrive in the small intestine if colostrum is heavily contaminated.

As outlined in the following section, the administration of acidified ORT solutions, or the availability of acidified water or milk replacer that acidify the small intestinal lumen, is likely to be beneficial in the treatment of diarrhea due to *E coli* and *Salmonella*. Indeed, acidified water has gained widespread acceptance as a simple and effective method for decreasing the incidence and severity of diarrhea in weaned pigs.

Acidifying the small intestinal lumen

E coli cause two common diseases of neonatal calves: ETEC, in which the bacteria are localized to the lumen and mucosal surface of the small intestine, and colisepticemia, in which the bacteria invade the systemic circulation.[67] The main features of the pathogenesis of ETEC diarrhea are: (1) ingestion of ETEC; (2) passage through the low pH environment of the abomasum; (3) attachment by K99 (F5) fimbrae to epithelial cells in the ileum with colonization; (4) progressive anterior movement of colonization to involve the entire small intestine; (5) production of a heat stable enterotoxin (STa); and (6) binding of STa to intestinal epithelial cells and stimulation of secretion. This chain of events leads to acute profuse watery diarrhea and death in severe cases.[67] The main features of the pathogenesis of colisepticemia are: (1) ingestion of serum resistant strains of *E coli*; (2) passage through the low pH environment of the abomasum; (3) multiplication in the small intestinal lumen; and (4) translocation across intestinal epithelium to produce bacteremia and septicemia.

Mixed enteric infections are commonly diagnosed in diarrheic calves.[68,69] Primary viral damage facilitates small intestinal overgrowth with *E coli* that, in turn, exacerbates the morphologic damage and predisposes the calf to colisepticemia[70] and *E coli* bacteremia.[15–17] *E coli* bacterial numbers are increased 5 to 10,000 fold in the lumen of the duodenum, jejunum, and ileum of calves with naturally acquired diarrhea,[68,69,71–74] even when the diarrhea is not due to ETEC (**Fig. 1**). In calves with naturally acquired diarrhea, increased small intestinal colonization with *E coli* has been associated with impaired glucose, xylose, and fat absorption.[74] Calves with ETEC and non-ETEC diarrhea therefore have increased numbers of *E coli* bacteria in the small intestine, and this increase is deleterious to the calf's health.

The growth rate and viability of *E coli* varies markedly with pH. In gastric juice aspirated from human infants, a pH < 2.5 for 60 minutes was bactericidal for Gram-negative bacteria; an increase in pH from 2.5 to 5.0 was associated with an increased growth rate of Gram-negative bacteria; and the fastest growth rate occurred when pH > 5.0.[75] In an unpublished study using a small number of bovine ETEC and colisepticemic strains cultured in abomasal contents and other fluids, *E coli* was killed when pH $\leq$ 3.0 but multiplied when pH $\geq$ 5.0.[76] In a related unpublished in vivo study,

abomasal luminal pH influenced the numbers of *E coli* recovered from the abomasum and small intestine of calves infected with a mixture of ETEC and colisepticemic strains. At abomasal pH of 3.0 to 3.7, < 10% of the inoculum dose was recovered, with ETEC strains being more resistant to pH-mediated killing than colisepticemic strains. At abomasal luminal pH of 5.0, both ETEC and colisepticemic strains proliferated.[76] Taken together, these studies suggest that *E coli* is killed when pH $\leq$ 3.0 and multiplies when pH $\geq$ 5.0.

The abomasum and anterior small intestine of the suckling calf are much more acidic than caudal aspects of the intestinal tract (**Fig. 5**).[77,78] Preliminary data of the magnitude of the relative acidity of the proximal small intestine has been obtained from 13 healthy calves aged 2–14 days[73] and four calves aged <30 days.[78,79] Alimentary tract pH was measured 2 hours after ingestion of milk, with the following median values: abomasum, 4.9; small intestine (divided into 7 equal parts, from orad to aborad), 5.9, 6.1, 6.3, 6.5, 6.8, 7.2, 8.1; large intestine, 6.6; rectum, 6.0.[73] In another study, the median small intestinal pH in fasted suckling calves was 6.0 at 30% of the distance from the abomasum, 6.5 (at 50%), 8.1 (at 70%), and 8.0 (ileum).[79] Mean duodenal pH for 12 hours after feeding also decreases with age, being: 3.7 at 7 days, 3.5 at 24 days, and 3.0 at 63 days.[80] Because bovine ETEC strains do not express K99 pili when pH < 6.5,[81] the relative acidity of the proximal small intestine explains why ETEC bacteria first colonize the distal small intestine, followed by anterior progression of bacterial adhesion.[82] Maintaining a luminal pH < 6.5 should therefore increase nonspecific resistance to ETEC diarrhea.

Decreasing proximal intestinal pH also decreases STa production by attached ETEC, because production of STa enterotoxin is greatly decreased when pH < 7.2[83]

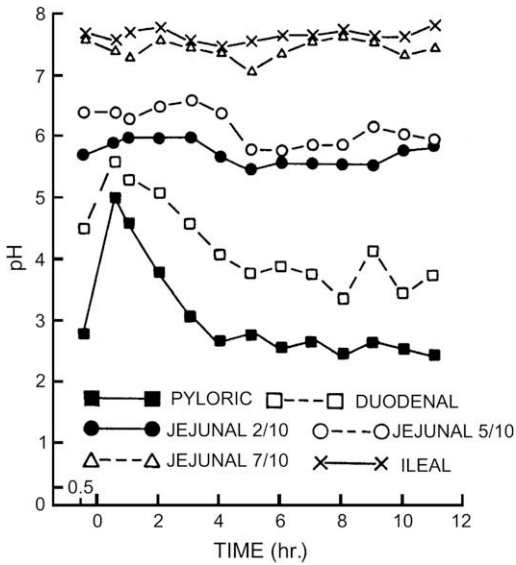

Fig. 5. The pH of intestinal contents from milk fed calves suckling cow's milk at time = 0 hours. Note that the pH fluctuates with milk feeding in the abomasum and anterior small intestine but is more stable in the distal half of the small intestine. Note also that luminal pH becomes increasingly alkaline moving aborad from duodenum toward the ileum. (*Reprinted from* Mylrea PJ. Gastro-intestinal disorders and the functioning of the digestive tract of young calves. Res Vet Sci 1968;9:14–28; with permission.)

and because STa toxin is a much more potent secretagogue in the proximal small intestine. Although STa receptor affinity and density are greatest in the ileum and distal jejunum of the neonatal calf,[84] in studies using ligated intestinal segments of Jersey calves aged 3 to 7 days and Holstein calves aged 1 day inoculated with ETEC, a much larger secretory volume was obtained from segments in the proximal small intestine, with the terminal jejunum and ileum producing very little volume following inoculation.[34,35] The mean volumes secreted in the small intestine following ETEC inoculation were as follows (with the intestine divided into six equal parts, from orad to aborad): 36, 24, 30, 13, 10, 0 mL.[34] Colonization of the proximal intestine is therefore the critical determinant of the severity of dehydration following infection with ETEC because colonization of the ileum and distal jejunum with ETEC has minimal effect on hydration status as STa is an ineffective secretagogue in this section of the intestinal tract. In summary, decreasing luminal pH in the proximal small intestine will increase nonspecific resistance to ETEC by preventing adherence to epithelial cells by K99 pili and preventing secretion of STa enterotoxin. This observation suggests that feeding ORT solution or water of acidic pH will be beneficial in treating and preventing calf diarrhea. Moreover, alkalinization induced by bicarbonate-containing ORT solutions potentially facilitates growth of ETEC bacteria, expression of K99 pili, and production of STa enterotoxin in the small intestine.

Neonatal calves are particularly susceptible to infection by *Salmonella enterica* subsp. *enterica* because of their immature immune system and suspected high abomasal pH during the first 24 hours of life.[85–87] Calves on endemically infected farms are exposed to *Salmonella* immediately after birth through ingestion of feces and colostrum of their dams;[88] in the first week of life from the environment and via contaminated colostrum, milk, feeding utensils, and farm personnel;[86] and after weaning by drinking water from a continuously replenished water tank with a pH >8.[89] Cows that are chronically infected may shed up to 10^5 salmonella/mL of milk, with 10^2 to 10^3 being the most frequent.[90] *Salmonella* readily multiply in pooled unrefrigerated waste milk, and outbreaks of salmonellosis in calves have been associated with feeding of unrefrigerated waste milk[86] or colostrum from another cow.[91] One study found that 58% (43/74) of dairy calves on a California dairy shed *Salmonella* in their stool within 24 hours of birth, and 85% shed *Salmonella* within 7 days of birth.[92]

Calves develop an age-dependent resistance to *Salmonella* that appears to be associated with development of a functional rumen, presence of a diverse small intestinal bacterial population, and low abomasal pH.[93,94] The optimum pH for *Salmonella* growth is generally accepted to fall between 6.5 and 7.5,[95] and *Salmonella* are sensitive to destruction by exposure to low pH.[96–98] Abomasal acidity therefore provides a natural barrier to ingested salmonellae.[94] *Salmonella* isolated from a small number of cattle were killed when pH $\leq$ 3.4 and multiplied when pH $\geq$ 5.5.[97] Maintaining a low abomasal pH will therefore decrease the number of viable *Salmonella* bacteria reaching the small intestine, thereby increasing nonspecific resistance to intestinal colonization and decreasing the incidence of infection and clinical disease.

Acetate and propionate inhibit the growth of Salmonella

The presence of bacteria can inhibit the growth of *Salmonella*, and this inhibition appears to be mediated by bacterial metabolic waste products, such as short chain fatty acids.[95,96,99] Acetate, propionate, and butyrate inhibit the growth of *Salmonella*, even in concentrations as low as 20 mmol/L[95,96] that are frequently found in ORT solutions administered to diarrheic calves.[100] This finding suggests that the addition of acetate or propionate may have beneficial effects separate from those obtained

by sodium coupled intestinal absorption, systemic alkalinization, preventing excessive intestinal alkalinization, and being a source of nutrition.[100]

TREATMENTS THAT ARE NOT CURRENTLY RECOMMENDED

Probiotics

Probiotics are lyophilized or live bacterial cultures that are added to animal feeds or administered individually to animals in an attempt to improve performance or increase resistance to enteric pathogens. Probiotics may be more correctly termed as direct-fed microbials. There has recently been an emphasis on differentiating probiotics from prebiotics; the latter are foods that nourish beneficial bacteria that already reside in the digestive tract, such as *Bifidobacteria* and *Lactobacillus* species.

Administration of probiotics to diarrheic calves is done in some dairy herds, but the practice cannot currently be recommended. Daily administration of lyophilized lactic-acid producing bacteria in milk for the first 10 days of life had no effect on *C parvum* infection in dairy calves in California.[101] In calves with spontaneous diarrhea, the administration of *Lactobacillus rhamnosus* GG, an extensively studied probiotic isolated from the human gastrointestinal tract, for therapy of diarrhea did not change the mortality rate of the incidence of diarrhea.[7] Of real concern are the results of a recent study in neonatal foals that indicated administration of a different *Lactobacillus* strain for the prevention of diarrhea was associated with the development of diarrhea and clinical abnormalities requiring veterinary intervention.[102] This foal study contradicts widely held beliefs that ''probiotics can't hurt.''

The results of a recent study under field conditions in Germany indicated that the prophylactic administration of the probiotic bacteria *E coli* strain Nissle 1917 for the first 10 or 12 days of life to calves with unknown status of passive transfer was associated with a significant decrease in the number of calves developing diarrhea.[103] Based on these reports, administration of *E coli* strain Nissle 1917 may be helpful in preventing or treating diarrhea in calves, but additional studies are needed. This product is sold in Germany under the trade name Ponsocol for the prevention of neonatal diarrhea.

Intestinal "Protectants" and "Absorbants"

Administration of intestinal ''protectants,'' such as kaolin (natural hydrated aluminum silicate), activated attapulgite (hydrated magnesium aluminum trisilicate), and pectin (natural polygalacturonic acids) or ''absorbants,'' such as activated charcoal, kaolin, and attapulgite, are not recommended. Protectants are believed to protect damaged intestinal mucosa and absorbants purportedly neutralize luminal toxins by preventing binding to epithelial cell receptors. No data on treatment efficacy is available in calves.[3] More importantly, the results of a recent prospective randomized study indicated that non-antibiotic treatments for calf diarrhea, including bismuth, kaolin-pectin, activated attapulgite, and activated charcoal, resulted in a longer duration of treatment and increased risk for morbidity and mortality, compared with oral antibiotics in milk replacer (neomycin sulfate and chlortetracycline hydrochloride) and parenteral administration of ceftiofur hydrochloride (2.2 mg/kg, 3 to 5 days).[36]

Gastrointestinal Motility Modifiers

Intestinal motility is altered in diarrhea, but this change does not mean that abnormal motility is deleterious and that therapeutic manipulation of intestinal motility in calves with diarrhea will be beneficial. Drugs that inhibit intestinal motility are not indicated as part of the routine treatment of calf diarrhea, even though induction of complete

intestinal paralysis may be viewed as a successful treatment of calf diarrhea if success were measured on the basis of fecal production.[104] Indeed, if the daily volume of feces is an important criterion of treatment success, then mere starvation of the calf would be viewed as an excellent therapy! Reduction of intestinal motility means that toxins and bacteria present in the intestinal lumen are not flushed away, increasing their local concentration and the possibility of a pathogenic effect.

Administration of agents that decrease intestinal motility, such as hyoscine N-butylbromide or atropine, are not recommended, despite their widespread use. No data on their treatment efficacy in calves with naturally acquired diarrhea is available.[3] One study in calves with nutritional diarrhea caused by sucrose administration found that hyoscine/dipyrone caused a modest reduction in fecal water losses.[105] Combined administration of the centrally acting muscarinic antagonist dexetimide (Benzetimide; 15 μg/kg bodyweight IM) and antibiotics caused a faster resolution of diarrhea in calves than did administration of antibiotics alone.[106] Dexetimide has been widely used to treat neuroleptic-induced Parkinsonism in humans, and its role, if any, in the treatment of calf diarrhea remains unclear.

Parenteral Administration of Mycobacterial Cell Wall Extracts

A product that was derived from mycobacterial cell wall extracts was developed in the 1990s in the United States. Parenteral administration of the product (Immunoboost, Bioniche Animal Health USA, Inc) during the first 24 hours of life purportedly decreased the prevalence of diarrhea,[107] suggesting that the product may have some efficacy as an ancillary treatment for calf diarrhea. However, peer-reviewed publications documenting treatment efficacy do not appear to be available.

Homeopathic Treatments, Such As Podophyllum or Oregano

Veterinary homeopathy is increasing in popularity, particularly in Europe, where priority is often given to veterinary homeopathic treatment rather than allopathic veterinary medicine on organic farms.[11] The homeopathic agent podophyllum is derived from *Podophyllum peltatum* (mayapple), and it has been used as a medicine by Native American Indians as a laxative or a treatment for intestinal parasites. The results of a double-blind placebo-controlled clinical trial of podophyllum (dose not stated) in 44 calves with diarrhea in Sweden indicated that podophyllum had no effect on the duration of diarrhea or the presence of depression, inappetance, and fever.[11]

Allicin, a sulfur-containing component of garlic that prevents the growth of some bacteria, fungi, viruses, and protozoa, had no effect on weight gain or duration of diarrhea due to *C parvum* in calves.[108] Anecdotal reports of the use of nutmeg as a treatment for calf diarrhea exist,[109] but treatment efficacy has not been formally evaluated.

Oregano contains oils (carvacrol and thymol) that have antimicrobial activity. The effects of oral administration of oregano essential oils (10 mg/kg bodyweight by mouth daily) was compared with that of a purported positive control (oral neomycin, 10 mg/kg bodyweight by mouth daily) in calves with naturally acquired diarrhea in Greece.[110] No difference in duration of diarrhea or severity of diarrhea was observed between the two treatments. Because a study documenting the efficacy of oral neomycin at labeled doses in treating calves with naturally acquired diarrhea does not appear to have been published in a peer-reviewed journal,[1] oregano cannot be recommended as an adjunct treatment for calf diarrhea.

SUMMARY

Adjunct treatment of calves with diarrhea should be routinely undertaken in all calves with systemic signs of illness, manifest as fever, inappetance, or lethargy. Ancillary treatments with documented efficacy in undifferentiated calf diarrhea include: parenteral administration of antimicrobials with a predominantly Gram-negative spectrum of activity; parenteral administration of the NSAID agents meloxicam and flunixin meglumine; and continued feeding of cow's milk. This recommended adjunct treatment protocol is similar to that used by a leading dairy veterinarian in Europe.[111] Finally, because halofuginone and azithromycin have documented efficacy in calves with diarrhea caused by *C parvum*, their administration may be considered in calves documented or suspected to have cryptosporidiosis.

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