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Treatment of Diarrhea of Neonatal Calves

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In our quest for order and simplicity, we often dissect complex disease syndromes into simpler components. This article does the same by discussing the causative agents, pathogenesis, and therapeutic agents separately; however, we hasten to remind the reader that in reality, disease is seldom that simplistic. Instead, many cases and outbreaks of neonatal diarrhea are associated with multiple pathogens, and most pathogens cause diarrhea by more than one mechanism. In some cases, it is important to know the etiologic agent because specific therapy can be directed against it; in other cases, nonspecific, symptomatic and supportive therapy is the only alternative. Although our therapy should be directed against specific pathogens if they are known or suspected to be involved, the greatest success in treating diarrheic calves comes when treatment regimens reverse pathophysiologic abnormalities associated with most or all diarrheas of calves, regardless of cause.

CAUSATIVE AGENTS

In some instances it is more important to know the diarrhea-causing agent than it is in others. *Escherichia coli, Salmonella* sp, and *Giardia duodenalis* respond to specific therapy, whereas viruses and *Cryptosporidium muris* do not. Because cryptosporidia can cause disease in human beings, however, it is important to establish a diagnosis of this organism. In most instances, treatment of a single patient or the initial treatment of a herd outbreak must be initiated without confirmation of an etiologic diagnosis. Medical history of the herd, age at onset of diarrhea, characteristics of feces, and accompanying clinical signs often can be used to establish a presumptive etiologic diagnosis.

Therapy can be directed against specific known or suspected pathogens;

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however, therapeutic success will be achieved more consistently when regimens are used that reverse pathophysiologic abnormalities, regardless of cause.

Enterotoxigenic *E. coli*

Infection with entereotoxigenic *E. coli* (ETEC) causes acute severe watery diarrhea and dehydration and often results in death of calves younger than 10 days of age. Most severe cases occur in calves younger than 1 week of age. To cause diarrhea, ETEC must possess an adherence factor (pili) and secrete enterotoxin.[13] The most frequently identified type of pilus is K-99 (also known as F-5), although F-41 is also found on ETEC from calves.[83] Thermostable enterotoxin (STa) is produced by ETEC isolated from calves. Diagnosis of colibacillosis is confirmed by isolating *E. coli* from the feces and identifying the K-99 pilus antigen. A small percentage of ETEC may possess other pilus antigens and cause disease, but these are encountered infrequently and should be suspected only if K-99 ETEC are not isolated but clinical signs and signalment are typical of colibacillosis. *Remember,* E. coli *may be isolated from almost every calf in the world. Escherichia coli* are normal inhabitants of mammalian large intestines, and isolation of them from the feces without identification of the pilus antigen or enterotoxin has very little pathogenic significance. Misunderstanding of that fact has led to tremendous misuse of antimicrobial drugs in diarrheic calves.

Salmonella sp.

Of some 1500 serotypes of salmonella, the only four that are isolated frequently from cattle are *S. typhimurium, S. dublin, S. muenchen,* and *S. copenhagen.*[66] Unlike ETEC, salmonellae are invasive. Calves from 10 days to 3 months of age are most susceptible to salmonellosis.[66] Because salmonella are invasive, severe mucosal damage, infection of lymph nodes, and bacteremia may result. The feces can vary from slightly loose to voluminous and may be foul-smelling with blood or strands of fibrin and mucus. In contrast with most other causes of diarrhea in neonatal calves, salmonellosis often causes fever, anorexia, and depression, with or without concomitant dehydration.

Other Bacteria

Enteropathogenic *E. coli* have recently been isolated from calves with enterocolitis.[35,50,62] These bacteria, also called "attaching" and "effacing," adhere closely to the enterocytes, effacing the microvilli from the attachment site. Some strains produce a Shigella-like toxin but do not produce enterotoxin. Lesions primarily are in the colon, and dysentery is the most prominent clinical sign. The prevalence and importance of this pathogen as a cause of diarrhea of calves are unknown.

Campylobacter jejuni has been isolated from calves with diarrhea, and infection of experimental calves results in mild diarrhea.[54] However, the frequency of isolation of *C. jejuni* from diarrheic and from healthy calves is not different.[54] Therefore, the significance of this bacterium as a cause of clinical disease in calves is questionable.

Cryptosporidium muris

Once thought to be a nonpathogenic protozoa, *Cryptosporidium muris* is now considered a major contributing cause of some outbreaks of diarrhea in calves between 1 and 3 weeks of age.[43] The prevalence of infection on dairy farms is high (64% in one study), but infection does not always cause diarrhea.[4] With most natural infections in calves, the ileum and distal jejunum are the sites of infection. The lesions consist of villous blunting, infiltration of the lamina propria with inflammatory cells, and bridging of adjacent villi.[43] Concurrent infections with viruses are common; therefore, fecal characteristics are variable.

One of the authors (AJR) has observed several calves with physical, hematologic, and biochemical abnormalities that were consistent with malnutrition/malabsorption due to severe villous atrophy. Those calves were 2 to 3 weeks of age, emaciated, comatose, hypoglycemic and/or hypothermic, but only mildly to moderately dehydrated. All dramatically but temporarily responded to intravenously administered glucose and/or restoration of body temperature. Cryptosporidia were observed in the feces of these calves, which was usually mucoid and loose but not voluminous or watery.

Cryptosporidial oocysts are extremely resistant to the environment and to disinfectants. Most mammals, including humans, are susceptible to infection. In immunocompetent people, signs of infection can be mild to moderate diarrhea and flu-like symptoms. Cryptosporidiosis can be disabling or fatal to immunocompromised people, including patients with AIDS, those receiving immunosuppressive drugs, radiation therapy, and so forth.

Giardia duodenalis

Giardia duodenalis is a flagellated protozoa that has been found in the small intestine of several domestic species, including cattle.[42,76] Naturally infected calves ranged in age from 12 days to 12 weeks. Clinical signs included diarrhea that sometimes became chronic, mucoid feces, and poor weight gain. The disease has been transmitted experimentally by inoculation of oocysts into calves.[87]

Viruses

Viruses are the most frequent cause of diarrhea in neonatal calves.[83] Although rotavirus and coronavirus are the most familiar viral pathogens, astrovirus,[89] Bredavirus,[90,60] calici-like virus,[10] and parvovirus have been isolated from diarrheic calves and have caused diarrhea in experimental calves. The significance and prevalence of viral diarrhea are yet to be determined. The less known viruses receive little attention from diagnostic laboratories, so their prevalence is probably underestimated.

Viral infection can occur at almost any age. Herd immunity and environmental contamination may be important determinants of the age of onset in a particular herd. Rotavirus usually affects younger calves (3 days to 3 weeks), causing mild to moderate diarrhea if there are no complications.[80] Villous atrophy first occurs in the orad half of the jejunum, and later spreads to the rest of the small intestine.[80] Coronavirus can result in more serious disease because it affects a grater portion of each villus and because of its propensity to infect the large intestine as well as the small intestine.[80] Bredavirus also causes lesions in both small and large intestines.[60] Clinical signs of viral enteritis are nonspecific but include watery-to-mucoid diarrhea (without blood), dehydration, and depression.

The importance of determining the specific viral pathogen involved in a case or outbreak of diarrhea is debatable. No specific therapy is currently available, and the efficacy of viral vaccines has been questioned.[85] When considering therapeutic strategies, the identity of the virus involved in diarrhea is relatively unimportant. The following are arguments against committing significant resources in an attempt to identify viral pathogens: (1) no specific antiviral therapy is currently available; (2) intermittant shedding and mixed infections render it difficult to isolate all potential viral pathogens involved; and (3) viruses are almost ubiquitous and can be isolated from calves during most outbreaks of diarrhea of calves older than 1 week. Identification of viral pathogens may be important for prevention, especially if highly effective vaccines are developed, but from a therapeutic standpoint, diagnostic efforts may be directed towards identification of those pathogens that would indicate need to alter therapeutic protocols, namely ETEC, *Salmonella*, and *Giardia*, and *Cryptosporidium* because of its zoonotic potential.

PATHOPHYSIOLOGY

Many adjectives, such as secretory, osmotic, malabsorptive, maldigestive, and nutritional, have been used to describe types of diarrhea based on pathologic mechanisms. A simple yet complete scheme for classifying diarrhea according to mechanism was proposed by Argenzio in 1985.[5] Because it is easily adapted to a discussion of therapy, we will use that classification.

Secretion Caused by Bacterial Enterotoxins

At present, the only enterotoxin of proven import as a cause of diarrhea in calves is the STa of *E. coli*. The STa induces net secretion of Na^+ and Cl^- by activating guanylate cyclase.[20] The role of intracellular Ca^{++} and calmodulin is still controversial.[20,33] Release of arachidonic acid and formation of prostaglandin also may occur.[79] The Na^+-Cl^- cotransport system in the enterocyte's membrane is disabled by STa. The membrane-bound Na^+-glucose cotransport system remains functional and provides an excellent opportunity to utilize Na^+ and glucose in orally administered rehydration solutions to enhance water absorption.[28] Although the major lesion caused by ETEC is biochemical, morphologic changes have been reported;[8] however, the general absorptive capacity of the intestine is probably less affected by ETEC than it is by other pathogens.

An enterotoxin has been isolated from a strain of *Salmonella typhimurium* of equine origin.[55] It is reasonable to suspect that salmonellae of bovine origin also may elaborate enterotoxins.

Secretion and Malabsorption Due to Inflammation

Inflammation is probably a component of the pathophysiology of nearly all infectious diarrheas. Invasive organisms such as salmonellae incite a more intense inflammatory response than do viruses or cryptosporidia; however, as previously cited, even ETEC-induced diarrhea may have an inflammatory component. Several mediators of inflammation, including 5-hydroxytryptamine, histamine, and prostaglandin, have an effect on intestinal transmembrane ionic flux and are probably involved in the pathogenesis of diarrhea induced by inflammation.[56,81]

Accompanying inflammation is the loss or disruption of normal villous architecture. Enterocytic necrosis, submucosal inflammatory infiltrate, and villous atrophy contribute to malabsorption during salmonellosis.[66] Villous atrophy, fusing of villi, and inflammatory cell infiltrate are typical lesions caused by viruses and cryptosporidia. When brush-border enzymes (particularly lactase) are lost, lactose is not degraded in the small intestine. Likewise, other nutrients are not absorbed by the small intestine when villous atrophy occurs. Those undigested nutrients entering the large intestine become substrate for colonic bacteria that degrade large molecules into small ones. The osmotic effect of these particles exacerbates the diarrhea. Because organic acids are produced during colonic fermentation, the feces in malabsorptive diarrheas are often acidic.

Malabsorption Caused by Villous Atrophy

Villous atrophy caused by viral, bacterial, or protozoal enteric infection results in decreased intestinal surface area for absorption. In addition, the brush-border enzymes located in the tips of the normal villus are lacking, resulting in maldigestion. The severity of maldigestion and malabsorption is related to the severity of the villous atrophy and the location and extent of the lesion in the gut. Because diarrhea due to malabsorption and maldigestion is a result of passage of undigested food into the colon followed by bacterial fermentation, purely malabsorptive diarrhea can be eliminated by fasting the patient. However, in infectious diarrheas of calves, pure malabsorptive diarrhea seldom exists.

Severe villous atrophy likely alters absorption of drugs from the gut, but the authors are unaware of studies using calves to demonstrate this phenomenon. If systemic concentrations of drugs are desired, however, it is not advisable to rely on orally administered drugs in calves with diarrhea.

In addition to infectious causes of villous atrophy, antimicrobial agents also can cause malabsorption in healthy calves.[51,69] After 5 days of oral treatment with therapeutic doses of chloramphenicol, neomycin, ampicillin, or tetracycline, calves developed diarrhea, had abnormal oral glucose tolerance tests, and had microscopic evidence of villous atrophy. In addition to the lack of anti-diarrheal efficacy of antimicrobial drugs, villous atrophy produced by these compounds is another reason to avoid orally administered antimicrobials when treating diarrheic calves.

Abnormal Intestinal Motility and Diarrhea

Without doubt, intestinal motility is altered in animals and people with diarrhea. However, there is much confusion about the changes of motility associated with diarrhea. In the small intestine, diarrhea is associated with prolonged Phase II of the migrating myoelectrical complex (MMC), appearance of minute rhythms, or disorganization of the MMC.[12] None of these phenomena can be viewed as decreased intestinal motility. However, diarrhea is associated with decreased short spike bursts in the colon (thought to be stationary contractions that impede flow).[11] If these segmental contractions are not present in the colon, normal or even infrequent long spike bursts (or peristaltic contractions) are capable of moving ingesta rapidly through the colon. Therefore, a single dogmatic statement about "increased" or "decreased" motility during diarrhea cannot be applied to the entire intestinal tract. It is generally accepted that "hypermotility" is seldom a significant cause of diarrhea and that drugs that generally inhibit intestinal motility are seldom indicated as a part of antidiarrheal therapy.

PHARMACOLOGIC AGENTS

This section discusses the pharmacologic management of calves with diarrhea. Perhaps more appropriately, we should focus on the "logical" management of the patient, for it seems that as veterinarians we sometimes get preoccupied with the "pharmaco" and forget the "logic" of treatment.

There are several impediments to successful treatment of diarrheal diseases of calves. Firstly, we seldom have the advantage of knowing the exact etiologic agent, at least at the commencement of therapy. Even with the resources available to physicians, an etiologic diagnosis is accomplished in fewer than half of human diarrheic patients.[39] Furthermore, even when we know the etiologic agents, there are only a few pathogens against which we can direct specific therapy, namely ETEC, *Salmonella*, and *Giardia*. The second impediment to successful treatment is incomplete understanding of the pathogenesis of diarrhea. Except for secretory diarrhea associated with ETEC in which the mechanism is well-defined, the relative importance of inflammation and its various mediators and pertubations of gut hormones and motility is unknown. Finally, the excessive emphasis on the character and quantity of the feces rather than the general condition of the patient is an impediment. An interesting perspective was presented by Ludan; in infectious enteritis, acute diarrhea per se is, with its cleansing effect, physiologic with beneficial effects. The acute dehydration that accompanies diarrhea is pathologic.[48] Unfortunately, in bovine practice we are not able to routinely supply all the necessary supportive care to maintain calves while the diarrhea runs its course and the calf's intestine heals. Therefore, the search continues for a cure for the diarrhea itself. Although this may prove to be life-saving, we should also remember that an extremely successful antidiarrheal agent may have serious side effects if diarrhea is, in fact, a beneficial physiologic process.

Fluid and Electrolyte Therapy

It is beyond the scope of this article to discuss the principles of fluid therapy of diarrheic calves. However, it is essential to remember that replacement of fluid and electrolytes is the cornerstone of medical management of the diarrheic calf. In most calves with diarrhea, it is the only therapy necessary. Therefore, all further comments about pharmacologic management of diarrhea are made under the assumption that fluid and electrolyte replacement was the first therapeutic priority and has been accomplished.

For a complete discussion of fluid therapy in cattle, please refer to *Veterinary Clinics of North America: Food Animal Practice*, 6:1, March, 1990.

Antimicrobial Drugs

The most widely used, and probably the most overused, drugs for treatment of diarrhea of calves are undoubtedly the antimicrobial agents. The first identified cause of diarrhea of calves was *E. coli*,[3] and *E. coli* was isolated from nearly every diarrheic calf. Therefore, it seemed sensible to treat every diarrheic calf with antimicrobial drugs that were effective against *E. coli*. Our understanding of the cause and pathophysiology of diarrhea of calves has advanced remarkably, but the far-too-common practice by owners and (to some degree) veterinarians of treating diarrheic calves with antimicrobial drugs does not reflect these advances. The high incidence of mild-to-moderate, self-limiting diarrhea of neonatal calves has perpetuated the practice of administering a few "scour pills" to every calf with loose feces. Because the vast majority of cases are self-limiting, the success of treatment with *anything* will be high. Therefore, the misuse goes on and the potential to create highly resistant bacterial populations increases.

Because ETEC are noninvasive, the oral route for administration of antimicrobial drugs is preferred. If another bacterial disease is recognized or suspected, parenteral administration of antimicrobial agents is also recommended. The extent to which antimicrobials are absorbed across the diseased intestine is not known; therefore, one should not rely on absorption of orally administered antimicrobial drugs to achieve adequate systemic concentrations of the drug. Listed below are the antimicrobial agents approved in the United States for use in calves with diarrhea.

Amoxicillin trihydrate
Ampicillin trihydrate

Chlortetracycline HCl
Furamazone
Neomycin sulfate
Oxytetracycline HCl
Sodium sulfachlorpyridazine
Streptomycin
Sulfabromethazine sodium
Sulfaethoxypyridazine
Sulfamethazine sodium
Tetracycline

Although the results vary among studies, *E. coli* from diarrheic calves appear to be fairly resistant in vitro to all approved drugs (Table 1). The fact that some of the isolates in these studies were from calves previously treated with antimicrobial agents may have biased the results toward greater antimicrobial resistance. Data from these studies showed that gentamicin and nitrofurans were active against greater than 90% of the bovine isolates of enteric *E. coli*. In two other reports of susceptibility of bovine isolates of *E. coli* not exclusively from diarrheic calves, 91% and 98%[31,75] showed in vitro susceptibility to sulfachlorpyridazine. In experimental ETEC infections of calves, cephamycin C and amoxicillin administered orally each have been shown to reduce mortality.[38,57] Treatment of calves with spontaneous ETEC with sulfachlorpyridazine administered orally resulted in 87% survival.[84] One of the authors (AJR) has successfully halted outbreaks of ETEC diarrhea with potentiated sulfonamides (960 mg orally twice-daily for the first 3 days of life) until products that contained specific antibody were secured.

In humans, ETEC is an important cause of travelers' diarrhea. Potentiated sulfonamides, doxycycline, and some of the quinolones are preferred drugs for treatment of that condition. They are 70% to 90% effective as preventatives and also are effective for reducing the duration of diarrhea after it has begun.[72]

Salmonellosis is less likely than colibacillosis to be a purely enteric disease in calves, which makes parenteral antimicrobial therapy rational for treatment of salmonellosis. The objective of antimicrobial therapy in salmonellosis is not

Table 1. *Susceptibility In Vitro of* E. coli *Isolated from Diarrheic Calves*

	PERCENT SUSCEPTIBLE			
	*Survey 1**	*Survey 2†*	*Survey 3‡*	*Survey 4§*
Ampicillin	32	93	17	41
Neomycin	22	73	21	34
Streptomycin	5	13	0	14
Tetracycline	8	27	0	14
Triple sulfa	5	0	5	14

**Data from* Coates SR, Hoopes KH: Sensitivities of *Escherichia coli* isolated from bovine and porcine enteric infections to antimicrobial antibiotics. Am J Vet Res 41:1882–1883, 1980

†*Data from* Lopez A, Kadis S, Shotts E: Enterotoxin production and resistance to antimicrobial agents in porcine and bovine *Escherichia coli* strains. Am J Vet Res 43:1286–1288, 1982

‡*Data from* Prescott JF, Gannon VP, Kittler G, et al: Antimicrobial drug susceptibility of bacteria isolated from disease processes in cattle, horses, dogs and cats. Can Vet J 25:289–292, 1984

§*Data from* Portnoy B, DuPont H, Pruitt D, et al: Attaching and effacing bacteria in the intestines of calves and cats with diarrhea. Vet Pathol 24:330–334, 1987 to eliminate the organism from the gut or to eliminate the diarrhea it causes but rather to eliminate systemic infection. Table 2 lists susceptibilities (in vitro) of *Salmonella* isolated from cattle to antimicrobial drugs. Of those approved for parenteral use in cattle in the United States, cephalothin, sulfachlorpyridazine, and, perhaps, ampicillin, are the only antimicrobial drugs with sufficient activity in vitro to be recommended for use in patients suspected of having salmonellosis while awaiting results of susceptibility test with organisms isolated from the patient.

In these studies, 89% to 100% of isolates were susceptible to gentamicin and 92% (one study only) were susceptible to potentiated sulfonamides. In experimentally induced salmonellosis of calves, trimethoprim (4 mg/kg) with sulfadiazine (20 mg/kg) administered either intramuscularly or intravenously very effectively reduced mortality.[86] The challenge organism was susceptible in vitro to these drugs.

In one study of chronic salmonellosis in 11 children, 9 responded within 72 hours of initiating therapy with amikacin and either nalidixic acid or norfloxacin.[41] The other 2 children died of complications on day 5 and 6, but the diarrhea had resolved. In another study of chronic human carriers of *Salmonella*, treatment with potentiated sulfonamide eliminated the carrier state more rapidly than did no treatment.[15]

Well-controlled clinical trials evaluating the efficacy of antimicrobial agents for the treatment of spontaneous, nonspecific diarrhea of calves are scarce. In two studies,[19,58] treatment with antimicrobial agents was beneficial, whereas in a third study[65] no benefit was realized.

In several studies of acute undifferentiated diarrhea of humans, treatment

Table 2. *Susceptibility In Vitro of* Salmonella *Isolated from Cattle to Injectable Antimicrobials*

	PERCENT SUSCEPTIBLE			
	*Survey 1**	*Survey 2†*	*Survey 3‡*	*Survey 4§*
Ampicillin	52	72	69	45
Cephalothin	NR	88	NR	87
Erythromycin	0	40	50	1
Gentamicin	89	100	100	98
Penicillin	37	0	20	1
Sulfachlorpyridazine	96	NR	67	NR
Streptomycin	22	NR	32	23
Tetracycline	47	40	43	37
Trimethoprim sulfa	NR	92	NR	NR
Triple sulfa	NR	48	48	43

NR = not reported

**Data from* South Dakota Animal Research and Diagnostic Laboratory Annual Report. Brookings, SD, 1978

†*Data from* Prescott JF, Gannon VP, Kittler VP, et al: Antimicrobial drug susceptibility of bacteria isolated from disease processes in cattle, horses, dogs and cats. Can Vet J 25:289–292, 1984

‡*Data from* Glisan G, Steele J, Whitford H, et al: Antimicrobial resistance and susceptibility in five bacterial pathogens: A comparison of susceptibility in 1974 and 1978. J Am Vet Med Assoc 180:665–668, 1982

§*Data from* Blackburn B, Schlater L, Swanson M: Antibiotic resistance of members of the genus *Salmonella* isolated from chickens, turkeys, cattle, and swine in the United States during October 1981 through September 1982. Am J Vet Res 45:1245–1250, 1984 with antimicrobial agents resulted in faster resolution of clinical signs and fewer post-treatment "positive" stool cultures.[32,45,68] Interestingly, response to treatment to was not different in those patients from whom pathogenic bacteria were isolated prior to treatment and those with negative cultures.

Giardia duodenalis infection of dogs is treated by oral administration of metronidazole, quinacrine, milibis, or furozolidine.[6] The following drugs have been used for treatment of giardiasis of cattle, reportedly with "good" clinical results: quinacrine HCl 1 mg/kg orally twice daily for 7 days;[87] furazolidone;[42] dimetridazole 50 mg/kg orally once or twice daily for 5 days.[42,76] None of these drugs is approved for treatment of food-producing animals in the United States.

Antisecretory Drugs

A number of drugs have shown antisecretory activity in vitro. Non-steroidal antiinflammatory drugs (NSAIDS), alpha-adrenergic agonists, calcium channel blockers, opiates, phenothiazines, and other compounds reduce net loss of intestinal fluid in vitro.

It is logical that NSAIDS reduce secretion resulting from prostaglandin-induced inflammation. However, there may be a second mechanism by which the NSAIDS decrease diarrhea. Salicylates, phenylbutazone, flunixin meglumine, and indomethacin effectively reduce the secretion induced by enterotoxins, which primarily is noninflammatory.[27,40,70,88] Flunixin meglumine (1.1 mg/kg IV) reduced diarrhea in experimental calves challenged with live ETEC, and 2.2 mg/kg intramuscularly reduced total fecal output of calves receiving partially purified STa.[40,70] Intravenously administered sodium salicylate, but not orally administered aspirin, reduced STa-induced secretion in intestinal loops of experimental calves.[88]

Numerous studies have demonstrated the benefits of bismuth subsalicylate as a preventative and treatment for diarrhea of humans. Proposed mechanisms of action include (1) binding of the enterotoxin, (2) prevention of attachment, (3) antimicrobial activity of bismuth, (4) antisecretory activity of salicylate, and (5) binding of bile acids.[34,74] The most frequently reported use of bismuth subsalicylate is for the prevention and treatment of travelers' diarrhea in humans. The usual dose for treatment is 30 mL every 30 minutes for 8 doses.[21,23,24,78] In general, bismuth subsalicylate was more effective at preventing diarrhea than at treating it, but most authors reported improvement in clinical signs of humans receiving bismuth subsalicylate compared with those receiving placebo.[21,23,24,78] In one study,[24] therapeutic success was greater in patients from whom ETEC was isolated. In three studies, loperamide was superior to bismuth subsalicylate.[78,23] Bismuth subsalicylate also effectively treated acute and chronic diarrhea in children.[74,34] Although widely used in veterinary medicine, bismuth subsalicylate has not, to our knowledge, been evaluated in a controlled clinical trial with calves.

Alpha-adrenergic agonists reduce secretion by decreasing intracellular cyclic adenosine monophosphate.[27] Lidamidine is an alpha-2 agonist that has demonstrated antisecretory activity in a porcine model using STa as the secretagogue.[52] The pigs were anesthetized, so the degree of sedation produced by the drug was not evaluated. Clonidine, a similar alpha-2 agonist, did not reduce diarrhea or the incidence of death of pigs with experimentally induced mixed (viral and ETEC) enteritis.[17]

Calcium channel blockers diminish net efflux of ion and water by modulating the concentration of intracellular calcium; however, because STa-induced secretion may not be mediated by Ca^{++}; there may be a second mechanism that also was blocked.[27] Loperamide, which has several anti-diarrheal properties, also blocks calcium channels and has been widely used for treating diarrheic patients.

Loperamide, as well as other opiates, can reverse the secretory action of secretagogues. The mechanism of action is unknown, but the fact that tetrodotoxin blocked the action of morphine suggests that opiates work indirectly through a neural mechanism.[82] Loperamide is marketed over-the-counter for use in humans and has been studied in many clinical trials; it is well-tolerated and reduced frequency of defecation and time to cessation of unformed stools[21,22,23,26] in human patients with acute diarrhea. When compared with diphenoxylate plus atropine (Lomotil), attapulgite, or bismuth subsalicylate, loperamide was superior.[21-23,26] To our knowledge, no studies evaluating the antisecretory effects of loperamide have been conducted using calves. Although the adverse effects of loperamide are minimal, it is not recommended for infants because it was associated with necrotizing enterocolitis in two infants.[14,48] Loperamide is one of three drugs, available over the counter in the United States for human use that are considered "safe and effective" by the Food & Drug Administration (FDA).[25] Loperamide has very little potential for abuse.

Diphenoxylate (with atropine) is another opiate with proven clinical efficacy.[49] The atropine is added to reduce the potential for abuse of the product. In a comparison study diphenoxylate with atropine was inferior to loperamide.[26]

Adsorbants

Kaolin (a clay) and pectin (a derivative of fruit) have been accepted treatments for diarrhea in human beings as well as in domestic animals. Although kaolin and pectin improve the consistency of feces, they do not reduce the loss of water or ions.[61] In fact, data from studies using rats showed that diarrheic animals receiving kaolin-pectin lost 185% more potassium and 103% more sodium than did controls.[48] Based on these data, the use of combinations of kaolin and pectin should be discouraged in calves because depletion of potassium is a frequent feature of neonatal diarrhea. Activated attapulgite is another of the three drugs sold over the counter in the United States for use in human patients that are considered safe and effective by the FDA. A recent study showed attapulgite to be inferior to loperamide for the treatment of acute diarrhea of humans.[22]

Motility Modifying Drugs

The intuitive linkage among intestinal transit time, fecal volume, and intestinal motility has led veterinarians and physicians to assume that reducing intestinal motility would reduce diarrhea. In fact, induction of complete intestinal paralysis would be a successful treatment of diarrhea if success were measured in terms of fecal production. The cumulative effect of such therapy would be disastrous, however, because reduced motility would allow accumulation of toxins and pathogens within the intestinal lumen, which may exacerbate toxigenic and invasive enteritides. Remember: diarrhea may be physiologic; dehydration is pathologic. Perhaps more germane to the issue of modification of intestinal motility of diarrheic patients is the fact that the pertubations of motility during diarrheal disease are poorly understood. It is not easy to restore a physiologic function to normalcy if one does not know the nature of the abnormality or even know if an abnormality exists. Therefore, in view of what is known and not known about motility in diarrheal disease, most authors do not recommend anticholinergic drugs that "paralyze" the gut for treatment of diarrheal diseases. Opiates, however, are effective antidiarrheal drugs. Previously described as an antisecretory drug, loperamide is thought by some to exert its antidiarrheal effect primarily through its motility modifying properties.[73] Loperamide induced changes in motility of the gastrointestinal tract of healthy calves, but it did not attenuate changes induced by mannitol or castor oil.[29] It did, however, delay the onset of diarrhea induced by mannitol or castor oil. The authors of that study concluded that the antidiarrheal effect of loperamide was not due to its effect on motility.

Other Treatments

Chlorpromazine, a phenothiazine derivative, may exert its antidiarrheal activity through its effect on calmodulin, cyclic AMP, or membrane stabilization.[46,49] Reduction in STa-induced secretion and diarrhea has been demonstrated in mice and piglets.[1,46,67] Duration of diarrhea in a field outbreak of diarrhea in piglets was shortened when piglets received 1 mg chlorpromazine/kg body weight intramuscularly.[46] Higher doses in experimental pigs resulted in greater efficacy, but marked sedation occurred. The authors are unaware of the use of chlorpromazine in calves.

Niacin and nicotinic acid were shown to be antisecretory in experimental entertoxigenic diarrhea, but their efficacy has been disappointing in human clinical trials.[71] Berberine is an extract of a plant that has been used for centuries in the Far East to treat diarrheal disease. It possesses antisecretory and antimicrobial properties. In human patients, berberine remarkably reduced fecal volume in ETEC-induced diarrhea.[64]

In a clinical trial in the Netherlands, disodium cromoglycate (200 mg fed twice daily) reduced the severity of diarrhea in veal calves.[30] Nutmeg, fed daily to calves for 3 to 4 days after birth, was credited with the absence of diarrhea for 2 years on one farm.[77]

Acupuncture was found to be equally effective as gentamicin for treatment of undifferentiated diarrhea in piglets[44] and was equal to neomycin for treatment of ETEC in piglets.[36]

The use of probiotics has been advocated for prevention of diarrhea when fed before disease is present, and as an aid in enhancing recuperation if fed during convalescence.[7] Theories proposed to explain the potential benefit of probiotics include alteration of pH in the intestinal lumen, production of enzymes, B vitamins and antibiotics, alteration of intestinal flora through competition and more.[91] Lactobacilli reduce the population of *E. coli* in the small intestines of mice.[37] Cell-free broth from cultures of *L. bulgaricus* showed significant anti-entertoxin activity in pigs, whereas *Str. fascium* broth had strong inhibitory activity against *E. coli*.[53] Several other strains had little or no activity against toxin or the organism. Therefore, it is unwise to generalize about "probiotics" just as it is unwise to generalize about antibiotics. They apparently are not all the same.

In a study using a commercial product that contained *L. acidophilus*, *L. casei*, *Torulopsis*, and *Aspergillus*, convalescing calves fed this product during recovery from diarrhea gained more weight than did those that did not receive the product.[7]

SUMMARY

Therapeutic strategies for the treatment of diarrhea of neonatal calves should be logical and should be targeted at correction of physiologic dysfunction. Appropriate, specific antimicrobial or antiprotozoal therapy should be instituted when colibacillosis, salmonellosis, or giardiasis is confirmed or suspected. All calves with diarrhea should be rehydrated if necessary, and proper nutritional support should be provided. Antisecretory agents such as flunixin meglumine and bismuth subsalicylate may be beneficial for treatment of calves with colibacillosis and salmonellosis. Adsorbants, such as attapulgite and bismuth subsalicylate, also may reduce loss of fluids. Perhaps loperamide or a similar drug will be proven effective in calves in the future.

Potentially harmful drugs include several antimicrobial agents when they are administered orally, because they result in malabsorption; kaolin and pectin, which increase loss of ions during diarrhea; and motility modifiers that cause a decrease in all types of intestinal motor function.

Finally, success should be measured by indicators of production such as survivability, days treated, weight gained, and net profit. Our goal should be to restore and maintain the health of the calf, not simply to alter the volume and consistency of the feces.

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