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INTRODUCTION

The most important cause of economic loss in the beef and pork industries is infectious neonatal diarrhea. Although diarrhea of man and animals has been studied for hundreds of years very little has been learned about how to control it. In the last 100 years the major advancement in the treatment of diarrhea has been the use of oral glucose and electrolyte solutions for the replacement of fluid losses[21] A variety of chemotherapeutic agents have been developed and employed in an attempt to control the causative agents and cellular mechanisms which lead to diarrhea. The ever growing mass of conflicting data and new information makes the choice of a therapeutic regimen difficult indeed. This paper is an attempt to review and summarize current information regarding the major etiologies, pathophysiology and methods of treatment of infectious diarrhea in the neonatal calf and pig.

ETIOLOGIES

A variety of factors contribute to the pathogenesis of neonatal diarrhea. Under field conditions it is unlikely that any particular case of diarrhea can be said to have a single cause. However, in many cases a major inciting cause may be determined with other contributing factors being identified as secondary. Some researchers and practitioners contend that an etiologic diagnosis of diarrhea is unnecessary because the effect on the victim is essentially the same regardless of the cause. While this may be true for affected animals, diagnosis is imperative for the prevention of future outbreaks from the same cause.

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Factors resulting in diarrhea in baby animals may be either infectious or noninfectious. Since the major economic loss is due to infectious etiologies only those will be discussed here. Although vast amounts of knowledge have been gained about the disease causing mechanisms of infectious agents the methods of control are still elusive. Infectious diarrhea can be divided into three major etiologic classifications: viral, bacterial and protozoal. The first two are being considered the most significant in the neonate. Two field studies have shown *Eschericia coli* to be the major cause of neonatal diarrhea in the calf (Fig. 1).[16] No current data are available for the pig.

Viral causes of enteritis are a growing concern in the beef and pork industries. Coronavirus and rotavirus are the *major* enteric viruses encountered. Coronavirus is the etiological agent for transmissible gastroenteritis (TGE) of swine. Rotavirus, while causing a less severe lesion, is still economically important in both swine and cattle. Parvovirus is important in dogs and cats but does not seem to be a major enteric pathogen of food animals. The smaller viruses, such as the astroviruses and calicivirus-like agents have been implicated in neonatal diarrhea but their pathogenesis and significance is still being worked out. Although BVD is an important diarrheal disease in cattle it is primarily a disease of older calves and adults and not a significant problem in the neonate.

Acute bacterial enteric disease is a major cause of death and economic loss in the food animal industry. As noted above, *E. coli* stands out as the most important cause of neonatal diarrhea. This statistic may, in part, be skewed by the fact that *E. coli* is the easiest of the pathogens to isolate and identify. Many cases of *E. coli* diarrhea may have unidentified primary pathogens which are never suspected

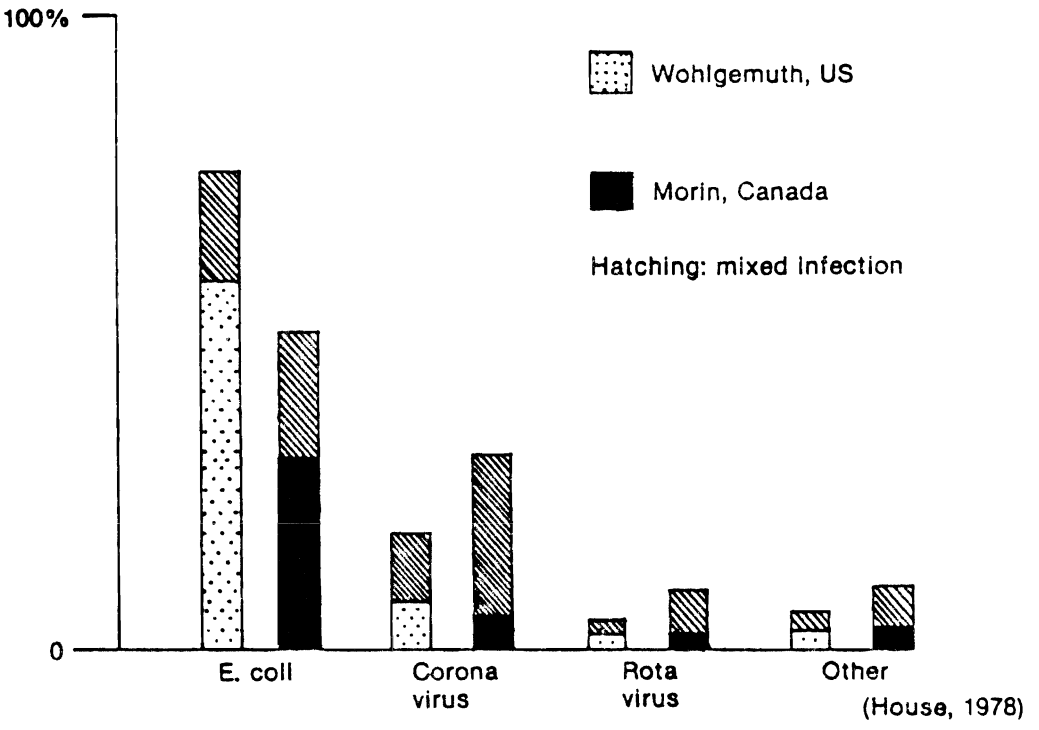

Fig. 1. Calf losses attributed to neonatal disease agents.

possibly because they are never sought. Other bacterial agents important in neonatal diarrhea are *Salmonella* spp. and *Clostridium perfringens* type D in pigs. Mixed infections of various viruses and/or bacteria are commonly encountered.

Two types of pathogenic *E. coli* are found in enteric disease: an invasive type which penetrates the mucosa and may cause septicemia and endotoxic shock; and a noninvasive enterotoxigenic type which attaches to the mucosal epithelial cells and elaborates a toxin which alters the metabolic processes of these cells without altering their histological appearance. The pathophysiology of enterotoxigenic *E. coli* will be covered in more detail below.

Salmonella is an invasive pathogen, penetrating the intestinal mucosa where it proliferates and produces toxins. These toxins may cause local necrosis or, if high enough concentrations occur in the blood steam, endotoxic shock may result. *Clostridium perfringens* is a noninvasive exotoxin producer which attaches to the villi in much the same manner as the enterotoxigenic *E. coli.* The toxins produced by the *Clostridial* organisms cause necrosis of the mucosa resulting in hemorrhage and bloody diarrhea. Peracute cases of *Clostridial* enteritis may result in sudden death before the development of any other clinical signs.

The last major group of enteric pathogens to be considered are the protozoans. Coccidiosis is the best known of the protozoal enteric diseases. It is a neonatal problem primarily in the pig with cattle being affected only after three weeks of age. In pigs the coccidia attack the intestinal mucosa carrying out their life cycle in or just beneath the mucosal epithelium. Their presence causes destruction of the villous epithelium resulting in a malabsorptive diarrhea or in some cases a protein-losing enteropathy. A recently discovered pathogen of neonatal calves is the protozoan, *Cryptosporidia.* This organism has a life cycle very similar to that of the *Coccidia* spp. but lives on

the luminal side of the villous epithelial cells. In its attachment to the cells it displaces the microvilli of the brush border, leaving a crater devoid of microvilli when it detaches. The mechanism of diarrhea production is felt to be the physical displacement of microvilli, with the ultimate loss of digestive enzymes and absorptive surface area.

PATHOPHYSIOLOGY

The mechanisms by which the pathogens produce disease vary significantly but the systemic derangements which ultimately result in the animals death are very similar. The cause of death in a diarrheic animal is usually dehydration and cardiovascualr collapse. Acidosis, hyperkalemia and hypoglycemia are commonly observed. Acidosis is the result of several factors. Lactic acidosis is a result of anaerobic glycolysis in the tissues of the animal, caused in part by the poor tissue perfusion. Sodium-hydrogen exchange mechanims present in the intestine and the kidney are affected either directly by the toxins or destruction of the cells in the intestine or indirectly by the decreased perfusion of the kidney due to dehydration.

Hyperkalemia is a secondary effect of the acidosis. The high concentration of hydrogen ions in the extracellular fluid causes hydrogen to diffuse into the cells forcing the potassium ions out. A concurrent decrease of intracellular potassium has been documented in diarrheic calves with hyperkalemia.[19,20] Calculations of total body potassium levels show that an actual loss of potassium occurs in diarrhea even though the animals present as hyperkalemic. The potassium imbalance inhibits cellular repolarization thereby causing muscular weakness, paresis and eventually failure of the cardiac muscles. The hypoglycemia which occurs with diarrhea may be due in a large part to the lack of absorption of glucose from the damaged intestine. The actual limitation may come in the digestion of lactose into absorbable monosaccharides. In the terminal stages of diarrhea a failure of gluconeogenesis occurs; glycogenolysis helps to maintain plasma glucose levels for a brief period but severe hypoglycemia develops and the animal becomes moribund[19,20] The ultimate demise of the animal is the cardiovascular collapse resulting from the hypovolemia and potassium imbalance.

The specific mechanisms of each pathogen need to be considered when determining the probable effectiveness of any form of therapy. The first pathogens to be considered are the viruses. Since rotavirus and coronavirus are the most important viral pathogens encountered in neonatal diarrhea, they will be the only ones considered here. The pathophysiology of the diseases caused by these organisms is essentially the same, with the important difference being the location of their attack on the mucosal epithelium. Coronavirus of swine (TGE) attacks almost exclusively the villous epithelium of the small intestine, while the coronavirus of calves may be found in the superficial and crypt eipthelium of the spiral colon as well as the small intestine. The rotaviruses are more selective and attack only the most mature epithelial cell on the distal one-third to one-half of the villus. This difference is important because of the function of the crypt and villous epithelial cells. The mature villous cells carry out the digestive and absorptive functions of the small intestinal tract while the immature crypt cells are primarily secretory in function. Rotaviral infections leave a considerable amount of absorptive epithelium intact allowing for significant absorption of nutrients and fluid even though the absorption may not balance the secretion and diarrhea is occurring. Coronavirus in pigs destroys the entire absorptive portion of the mucosa leaving only the immature, secretory crypt cells functional. The destruction of the villous epithelial cells results in the loss of the digestive enzymes contained in the brush border along with the absorptive function of these cells. This causes two mechanisms of diarrhea to come into play, the first being a simple *malabsorption* of fluid and nutrients due to the lack of functional absorptive cells. The second mechanism is a result of the *maldigestion* which occurs due to the loss of digestive enzymes present in the brush border of the now-destroyed villous epithelium. The maldigestion leaves a hypertonic solution of complex carbohydrates and proteins in the lumen of the intestine. Unless the nutrients are broken down into simple sugars and peptides they are unabsorbable. The presence of unabsorbable solutes in the lumen results in an effective osomotic pressure which will cause water movement from the tissues into the lumen of the intestine. Thus, not only is the animal unable to absorb ingested nutrients,

water and ions, but in addition, fluid is being drawn out of its tissue by osmotic forces. The loss of absorptive cells from the small intestine not only causes a malabsorption of water and nutrients but also destroys part of the mechanism which maintains the acid-base balance in the body. The resultant acidosis is a common factor in neonatal diarrhea as described above.

Any other organism which disrupts the integrity of the mucosal epithelium acts by the same pathophysiological mechanisms as those described for the viruses. The severity of the lesion is directly related to the severity of the resulting disease and inversely related to the effectiveness of many therapeutic measures. Many of the bacterial agents as well as some of the protozoa cause damage to the mucosal epithelium as part of their pathogenesis, either through mechanical invasion or through the elaboration of necrotizing toxins. Malabsorption and maldigestion are only part of the problem caused in these cases. Disruption of cell-to-cell junctions and denuding of areas of submucosa causes alterations in the permeability of the mucosal epithelium resulting in uncontrolled leakage of water and ions into the intestinal lumen. "Holes" in the epithelium may become so large as to allow proteins and even blood to enter the intestinal lumen. In some cases, such as salmonellosis and coccidiosis, these lesions are localized, thereby leaving some areas of intact mucosa which may allow the animal to absorb some of the fluid and nutrients from the lumen. If the lesions are too extensive, however, a disruption of hydrostatic and oncotic forces may occur creating a pressure-induced secretion and preventing any absoption. The specific mechanisms of these organisms will not be discussed here.

The group of organisms which differ drastically in their mechanism of disease production are the enterotoxin-producing bacteria. The most prominent and well studied member of this group are the enterotoxigenic *E. coli* (ETEC). These organisms produce disease without causing any mechanical damage to the mucosal epithelium. They act entirely by altering the metabolic functions of the cells. The first step necessary for disease production by ETEC is the establishment of a population in the mammalian small intestine. Several host resistance factors must first be overcome. Upon entering the digestive tract of a mammal the bacteria quickly encounter the gastric barrier. The high acidity and digestive juices present in the stomach prove to be very effective in reducing the number of bacteria which reach the intestine in a viable state. Unfortunately this barrier is poorly developed in the neonates making them more susceptible to bacterial invasion into the intestinal tract.

The next host factor which the bacteria must overcome is the intestinal motility and the flow of ingesta through the intestinal lumen. Many pathogenic strains of *E. coli* have developed surface structures, known as pili, which allow them to attach to the mucosal surface and resist being swept along with the other luminal contents. This adaptation allows the bacteria to remain in the small intestine long enough to proliferate and produce toxins. It also provides a series of antigens which are helpful in producing immunity against infection.

Three different enterotoxins have been found to be produced by various strains of ETEC. One, a *heat labile* toxin (LT), has a high molecular weight and a structure and mechanism of action similar to cholera toxin. The other two toxins are low molecular weight proteins and are *heat stable* (ST). One of the stable toxins, ST_a, is soluble in methanol while the other, ST_b, is methanol-insoluble. Along with their differences in physical properties comes a difference in their biological activity. ST_a has been found to be active in the neonatal pig and detectable by the suckling mouse assay, while ST_b is active in weaned pigs and not in the suckling mouse. Strains of ETEC isolated from calves appear to produce only ST_a and not ST_b or LT.

All of the enterotoxins act by altering the ion transport mechanisms of the mucosal epithelial cells without causing any histological damage to the cells. LT stimulates the adenyl cyclase system causing the increased production of cyclic AMP. The cAMP mediates intestinal secretion by rearranging sodium and chloride transport mechanisms in the epithelial cels. In contrast, both ST_a and ST_b act by stimulating guanylate cyclase, producing increased levels of cyclic GMP without affecting the cAMP lvels. Cyclic GMP acts primarily by inhibiting the absorptive mechanisms, while cAMP stimulates secretion as well as inhibiting absorption. Both result in net secretion into the intestinal lumen. A diagrammatic summary of the cellular mecha-

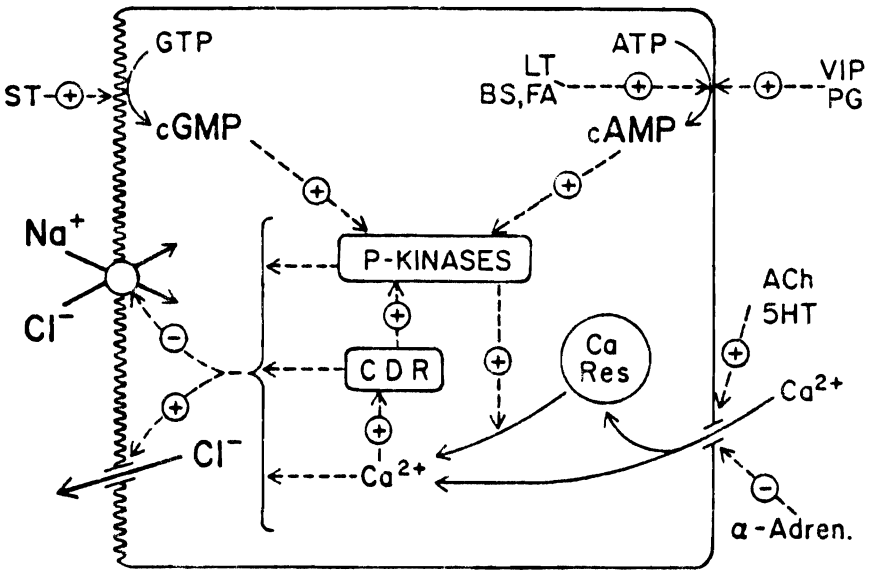

Fig. 2. Postulated intracellular control mechanisms regulating small intestinal ion transport. Stimulation is indicated by a plus and inhibition by a minus. ST, heat-stable *E. coli* enterotoxin; P-kinases, protein kinases; CDR, calcium-dependent regulator protein or calmodulin; CaRes, calcium reservoir; LT, heat-labile *V. cholerae* or *E. coli* entertoxin; BS, bile salts; FA, Fatty acids; VIP, Vasoactive intestinal peptide; PG, prostaglandins; ACh, acetylcholine; 5-HT, serotonin; $^{\alpha}$adren., $^{\alpha}$-adrenergic agonist. Net secretion is thought to involve two separate alterations of luminal (brush-border) membrane permeability: inhibition of NaCl cotransport and an increase in Cl^- conductance. Although depicted in the same cell, these 2 effects may occur in separate cells. Both may occur in response to P-kinase activation, CDR activation, or an increase in cytosolic free Ca. Relative contributions of these 3 effectors to the above 2 permeability changes are not known. Calcium-mediated secretion may occur as a result of ACh- or 5-HT-mediated increases in Ca-gating or cAMP-mediated release of reservoir Ca. According to work with isolated pancreatic islets (24, 142, 218), $^{\alpha}$-adrenergic agonists may inhibit secretion by blocking Ca^{2+} entry. Cyclic AMP-mediated secretion may occur as a result of basolateral membrane adenylate cyclase stimulation by LT, BAS, FA, VIP, or PG or by cAMP phosphodiesterase inhibition (not shown). Cyclic GMP-mediated secretion can occur in response to ST stimulation of brush-border guanylate cyclase. [Powell, *Secretory Diarrhea,* 1980.]

nisms affected by the toxins is presented in Fig. 2.[21]

Toxin effects are not limited to the small intestinal mucosa. It is likely that a normally-functioning colon would be capable of compensating for the additional secretion which occurs in the small intestine under the influence of enterotoxins. However, the toxin-producing *E. coli* are present in the colon as well and the enterotoxins have been shown to inhibit normal colonic function.[3] Thus it seems that the compensating mechanisms of the colon may be impaired.

Enterotoxins produced by ETEC do not directly affect the digestion of disaccharides or the absorption of glucose and amino acids by the small intestinal mucosa, nor the coupling of sodium absorption to these mechanisms. However the total amount of glucose absorbed may be affected by the decreased transit time due to the hypermotility of the gut and also the decreased intake of milk by the weakened calf or pig. The profound dehydration and electrolyte imbalances described above occur in colibacillosis as well. The untreated animal will eventually die from cardiovascular collapse.

APPROACH TO THERAPY: Chemotherapy

1) Immunity

The first logical step in the treatment of neonatal diarrhea is the prevention of infection. Immunity provides a natural defense mechanism and enhancement of this mechanism is the goal of many preventative medicine

programs. It is, for the most part, a function of the dam since the neonates usually do not have time to develop active immunity before they are challenged by pathogens. Vaccination or exposure of the dam to expected pathogens increases the amount of antibodies which are then secreted in the colostrum. Some species transfer antibodies transplacentally, but this is not true of swine or cattle. Therefore ingestion of colostrum is of utmost importance, because without it the newborn calf or pig is totally unprotected until its own immunity develops in two to three weeks. In the case of viral infections vaccination of the dam may be the only effective treatment. Vaccination against pilus antigens provides additional defense against colibacillosis.

2) Antimicrobial and Antiviral Agents

Once infection has occurred the use of chemical agents directed against the invading organism seems to be the defense action prefered by many. This may or may not be an effective plan. In the case of viral infections, there is no effective antiviral agent available for use in animals. This is reasonable considering that viruses are intracellular organisms using normal cellular mechanisms for their replication. Finding an agent which is toxic to a virus and not to a mammalian cell is a considerable challenge.

Antibacterial agents present a different picture. A multitude of antibacterial agents are available for use with an endless variety of specific actions and side effects. Antibiotics were discovered by man many years ago but they have been in existence longer than man himself. Fungi and bacteria have engaged in chemical warfare for ages. The chemical toxins produced by fungi against bacteria have been met by a continually changing set of resistance factors developed by the bacteria. This ability to develop means to resist destruction is just as effective against antibacterial agents produced by man as it is against those elaborated by the fungi. The result of this is the antibiotic resistance which is encountered in both veterinary and human medicine. This resistance has been used as an argument against the use of antibiotics in many situations. Some fear that if the heavy use of antibiotics in veterinary medicine continues a super-resistant bacteria may soon develop and an infection of the human population would be uncontrollable and devastating. As a result of this resistance development many of the drugs which were effective a few years ago no longer seem to have an impact.[26] Some studies have shown greater than ninety percent resistance to commonly used antibiotics by field strains of pathogenic *E. coli*.[19,20] In many cases the drugs which are most effective are not approved for use in food animals. Pharmaceutical companies are making some progress in the development of synthetic antimicrobials which are resistant to many of the known microbial resistance factors.[27] However, there is no reason to believe that the bacteria won't eventually find a way to resist these agents as well.

Besides the problem of resistance, some antimicrobial agents have been shown to cause damage to the intestinal mucosa and may actually exacerbate the disease they are supposed to control.[19,20] In light of all the conflicting evidence involving antibiotic therapy for diarrheal diseases careful consideration should be given to the choice of antibiotics and even as to whether or not they are indicated at all in a particular case.

3) Antitoxins

Specific antitoxins are available for a number of toxin-produced diseases, tetanus being the most well known. Enteric antitoxins are not as common. *Clostridium perfringens,* cholera and heat labile *E. coli* toxins are about the only toxins which are conducive to antitoxin production. The *E. coli* ST's are too small to be antigenic without first binding them to carrier proteins. The use of specific antitoxins in diarrhea is of questionable value. While they appear to be very effective, occasional "breaks" occur in spite of regular use. Also injectable antitoxin might not be of use against the toxins which primarily affect the luminal membrane of mucosal epithelial cells and are not absorbed into the body.

Nonspecific antitoxins exist but are of dubious value. Activated charcoal, kaolin and various clays have been used, charcoal being the most effective of these. Bisumth subsalicylate,[a] besides having some antitoxic properties also has some antibacterial and possibly antiinflammatory effects. Resins may be more effective than nonspecific adsorbants. *In vitro,* cholestyramine is significantly more effective than kaolin in binding toxins. This

[a] Peptobismol, Norwich-Eaton Pharmaceuticals, Norwich, New York.

effect is also present *in vivo,* but is is markedly decreased by the presence of milk.[12] Cost effectiveness of any enteric antitoxin is questionable, but specific antitoxins show considerably more promise than do nonspecific, adsorbant-type compounds.

4) Cell Metabolism Moderators

Since many of the pathogens cause diarrhea by affecting the cellular metabolic processes in the mucosal epithelium, a logical approach to the control of diarrhea is through control of these mechanisms. So far no major breakthroughs have come in this area although considerable research is being done. A number of products have been somewhat effective in controlling diarrhea but there is a need to determine the mechanism of action of these agents, their side effects and contraindications. Nicotinic acid is one compound found to be at least partially effective in controlling secretory diarrhea. It acts by inhibiting the adenyl cyclase activity, the mechanism which is stimulated by LT and cholera toxin. Chlorpromazine and melperone are two compounds which act by blocking calmodulin (CDR), a calcium-dependent regulatory protein which controls cellular secretion among several cellular metabolic functions.

Anticholinergics are a group of compounds which were originally used in treatment of diarrhea because of their effect on gut motility. It has since been determined that they also effect intestinal absorption by actively decreasing the secretory component of the diarrhea. Unfortunately this antisecretory action also affects the gastric mucosa, decreasing the gastric secretion and with it the effectiveness of the gastric barrier to intestinal invasion. Although they are still used primarily for their antiperistaltic activity, the antisecretory properties of these drugs may prove to be helpful in determining cellular mechanisms and control of diarrhea.

Acidic antiinflammatory agents are the most recent group of drugs to come into use in the treatment of diarrhea. These compounds act by inhibiting prostaglandins. Prostaglandins are known to play a role in the absorptive and secretory mechanisms of the gastrointestinal tract as well as a number of other cellular mechanisms throughout the body. Aspirin, indomethacin and 5-aminosalicyclic acid are a few of the acidic antiinflammatory agents under study. Unfortunately these agents have been only marginally effective and because of the involvement of prostaglandins in body metabolic functions, many side effects are possible with their use. The search continues for drugs which are specific for the GI tract in their mechanism of action. So far no cellular mechanism mediator exclusive to the gut has been determined, making the control of diarrhea without other effects very diffiicult.

5) Antispasmodics and Motility Control

The role of motility in diarrhea has been examined for many years. It was believed for a long period that hypermotility was actually the cause of diarrhea and that if the transit time was increased the diarrhea would be cured. The search for motility-controlling agents led to the use of anticholinergics, opiates and morphine derivatives in the treatment of diarrhea. These drugs proved to be clinically very effective in some cases, useless in others. It has since been determined that diarrhea may be present with not only hypermotility but also with hypomotility and normal motility. It appears now as though motility changes are not the cause of the diarrhea but rather a reaction of the gut to the pathogens which are present. It may, in fact, be a protective mechanism. A secretory type of diarrhea, such as colibacillosis, is often associated with hypermotility, while a malabsorptive type of diarrhea, such as TGE, is commonly associated with hypomotility or normal motility. Teleological speculation is the only explanation for this at present, suggesting that in the presence of a toxin the body is attempting to rid iself of the offending organism and its toxin, while in a malabsorptive situation the gut may actually try to retain material so that the few remaining functional cells have an increased opportunity to absorb water and nutrients from this material. This is, of course, only speculation, but it does help in pointing out a few of the contraindications to this method of treatment.

First, if hypermotility only occurs in some cases of diarrhea, how does one arrive at the decision to use an antispasmodic agent? If the gut happened to be hypomotile an anticholinergic would only exacerbate the situation. Next, controlling motility does little or nothing to stop secretion. The fluid loss into the intestine is still occurring. The animal is still going to die from dehydration even though clinically the diarrhea has improved. The animal derives no benefit from this treatment

and in fact may be suffering from it. As mentioned earlier, scouring may in itself be a protective mechanism, eliminating toxins and organisms by propelling them out of the body. Decreasing the motility will result in all of the fluid, toxins and rapidly proliferating bacteria pooling inside the animal's gut. Another sequela to this treatment is the misinterpretation of the disease state of the animal and premature cessation of supportive therapy. If the amount of fluid loss is determined by the amount of fluid feces present, replacement therapy will be grossly inadequate. Although the antispasmodics have been empirically effective, they offer very little benefit to the animal and may present considerable risk under certain condtions.

Two major drug groups are used to control the transit of ingesta through the intestinal tract. The anticholinergics act to decrease peristalsis and are used primarily for this purpose although they also seem to have some effect on the secretory mechanisms of diarrhea. These drugs were discussed briefly above. The other major group is the opiates and morphine derivatives, such as loperamide. These drugs act on the gut by increasing the segmental contractions. Some of them may also decrease peristalsis slightly. The major purpose of using these drugs is to increase ingesta transit time without halting peristalsis. These drugs also have effects on the absorptive and secretory functions of the mucosal epithelium that are not fully understood. Although they are not used much in veterinary medicine they have been employed extensively in the control of human diarrhea.

Fluid Therapy

The major goals of fluid therapy are to replace the fluid losses, correct electrolyte imbalances and provide energy and nutrients to the disabled animal. The first step in fluid therapy is the assessment of the needs of the animal. The needs include not only the fluid which has already been lost, current dehydration, but also continuing fluid losses through diarrhea, maintenance requirements and electrolyte imbalances. Dehydration is best estimated on the basis of clinical signs such as skin tension, sunken eyes and dry mucous membranes. A table of these signs and the level of dehydration they indicate is included in Figure 3. Laboratory parameters are not very useful in determining the initial state of dehydration because of the wide variation among normal neonates. Monitoring changes in the lab data may be useful in determining progress during therapy. The volume of replacement fluids can be calculated from the weight of the animal and the estimated deficit. Determination of the electrolyte imbalances comes from a knowledge of the pathophysiology of the disease. This aspect was discussed above. Clinical signs of some of the imbalances include rapid respiration in response to acidosis, weakness or general paresis due to the potassium imbalance and hypoglycemic coma. All of these needs should be taken into account when instituting fluid therapy.

The next decision is the route of administration. Subcutaneous fluid therapy is fast and simple but rather ineffective in a severely dehydrated animal. Perfusion of the peripheral parts of the body is generally very poor, resulting in poor absorption of the fluids. The volume of fluids which may be given by this method is limited and may be inadequate. The next possibility is intraperitoneally. This choice presents the risk of causing peritonitis and the amount of uptake by this route is questionable. The best route in the severely dehydrated animal, greater than six percent, is intravenous. Although this route requires considerable care in administration with regard to cleanliness and technique, it offers the best advantage in getting the proper volume of fluid and electrolytes to the area where they are needed most. Intravenous therapy, while medically the best choice, may be economically prohibitive. This is especially true when dealing with a major herd problem or with pigs. Oral fluid therapy seems to be the method of choice when dealing with a large number of individuals which require treatment or when the value of an animal does not warrant the expense involved in intravenous therapy. This is the most economical and effective method of treatment early in the disease. Dry mixes of glucose and electrolytes can be added to the drinking water and the animals can "self treat" as they drink. The need for sterility is eliminated and the treatment can be administered by the owner rather than the veterinarian. There are contraindications for oral therapy however. One is the moribund animal in which oral therapy is simply too slow

Percentage body weight loss	Clinical signs
0-5%	1. Mild depression 2. Decreased urine output
6%-8%	1. Sunken eye 2. Tight skin 3. Depressed but standing 4. Dry mouth/nose 5. Further urine reduction
9%-11%	1. Increase in above 2. Cold extremities 3. Recumbancy
12%-14%	1. Shock 2. Death

Fig. 3. Degree of dehydration—clinical signs.

to save the animal. The other is malabsorptive diarrhea. Consider TGE as an example. If a glucose-electrolyte solution is placed in the gut of an affected pig the glucose and ions would be unabsorbable. Their presence in the lumen would cause water movement out of the tissues and into the lumen in an attempt to equalize the concentrations. Thus, instead of replacing fluid the effect would be an increased loss and accelerated demise of the animal. It is partly because of this that a diagnosis is needed to determine effective therapy. If, as in the case of rotavirus, some of the absorptive cells are still functional oral therapy may be of some use in treatment.

Composition of the fluids must be given some consideration. The exact makeup of the glucose-electrolyte solution is disagreed on by several researchers. The presence of certain elements is necessary however. A solution should contain sodium, potassium, chloride, some form of base and glucose. Approximately 150 meq/1 of sodium should be present. Potassium concentrations may vary from 5 to 35 meq/1 without adverse effects. The base may be in the form of bicarbonate, citrate or lactate. Some feel that bicarbonate is detrimental in oral therapy because it tends to increase gastric pH.[7] Others state that citrate and lactate are of limited usefulness because they must be metabolized in the body before they contribute to the resolution of the acidosis.[19,20] Bicarbonate is also a readily available compound for use in home mixtures, more so than the other two. The amount of glucose in the solution is a point of considerable controversy. It brings into consideration the question of tonicity as well as that of energy requirements.

Although simple saline is helpful in restoring fluid losses of the animal, the need for the other components of the solutions is clear from the pathophysiology. The use of bicarbonate or some other base neutralizes the extracellular hydrogen ions. This allows more hydrogen ions to leave the cells and drives the potassium back into the cells. By this means the bicarbonate helps relieve the hyperkalemia as well as the acidosis. Glucose also aids in the resolution of the hyperkalemia by stimulating the release of insulin which will drive the potassium back into the cell. Even though a hyperkalemia exists there is actually a loss of potassium in diarrhea. For this reason, potassium must be added to the solution.

Osmolarity is an important point to be considered when preparing a solution for therapy purposes. The controversy in this matter occurs primarily in regard to oral therapy. The

osmolarity of intravenous solutions is of little concern if care is taken in their administration. Some investigators contend that a solution for oral therapy should be isotonic. They feel that a hypertonic solution would osmotically induce secretion.[7] This is only true if the components of the solution are unabsorable. With the exception of malabsorptive-type diarrheas, the transport of glucose and electrolytes across the mucosal epithelium is unimpaired. Since the glucose is readily absorbed it cannot contribute to osmotic forces which would draw water out of the tissues and into the lumen. Recent studies have shown that the osmolarity of a solution is actually increased before it leaves the stomach and the use of isotonic or hypotonic solutions increases gastric emptying time.[19,20]

The controversy over tonicity of therapy solutions could be easily solved by simply making them all isotonic since this does not present any particularly harmful possibilities. The osmolarity of the solutions is largely determined by the amount of glucose in the solutions, and this on initial examination would seem to be expendable. The purpose of the glucose in the solutions is twofold, however. Glucose enhances the absorption of water and electrolytes from the lumen and it also provides energy for the debilitated animal. It is the second purpose which drastically increases the need for high levels of glucose in the solutions. Isotonic solutions do not contain more than a fraction of the energy required by a diarrheic animal. If the energy requirements of the animal are not at least partially met the animal may die from starvation or be permanently stunted upon recovery. Studies have shown that diarrheic calves do better during and after treatment if high levels of glucose are added to the solutions.[19,20] The use of intravenous glucose as an adjunct to oral therapy is very helpful.

In addition to adding glucose to therapeutic solutions to meet energy requirements, some investigators propose that actual hyperalimentation may be the best therapy. Addition of amino acids to glucose and electrolyte solutions would provide the animal with all of the basic elements to sustain life during its illness. While this treatment does offer additional advantage to the diarrheic animal it also causes a tremendous increase in the cost of therapy. Even though this should be kept in mind as an option on a highly valuable animal, it is probably cost-prohibitive for routine use.

Other Considerations

A few other possibilities exist for the treatment or prevention of diarrhea. For the most part they are not heavily studied procedures and little hard evidence is available in their support. They are, however, things which may see more use as the understanding of the mechanisms of diarrhea increases.

The first is the use of "biological warfare" within the intestine of the neonate. This involves innoculating newborn animals with nonpathogenic bacteria in the hopes of discouraging colonization by pathogens through competition. Some of the bacteria available for this purpose are believed to have some antipathogenic properties. The innoculation of baby pigs with cultures of Lactobacillus falls into this category.

A procedure which is as yet untried but similar to the one discussed above is actually an attempt to create "age resistance factors" in baby pigs against TGE. While TGE infects all ages of swine it is only the neonates which die from the disease. This may in part be due to their inability to utilize any of the nutrients which pass through their diseased intestine. In the older pigs the carbohydrates in the undigested milk are fermented in the colon by lactose-fermenting bacteria. The resulting volatile fatty acids are readily absorbed by the colon along with a considerable amount of water. It is conceivable that if the baby pigs were innoculated with a culture of nonpathogenic lactose-fermenting bacteria they may have a better chance of surviving the disease. Although it is little more than speculation at this point it is worth some consideration.

One element of animal disease which cannot be ignored is management. No amount of therapeutic drugs or fluids will overcome the effects of poor hygiene and sloppy management of the animals. Prevention of disease is always more effective than cures. Even though additional cost may be incurred by instituting a proper management program, this cost may eventually be recovered in decreased losses from disease.

CONCLUSION

There is much to be learned about the con-

trol of diarrhea in neonatal animals. Progress is slow but it is important for the practitioner to keep in touch with the latest information and to utilize that information for the benefit of his patients and clients. Empirical treatment of disease is no longer a cost effective procedure; if it was the local feed supplier would probably put the veterinarian out of business. The veterinarian must utilize all of his knowledge and training in determining the best treatment for his patients.

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