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Fluid Therapy for Diarrheic Calves

What, How, and How Much

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Fluid therapy for diarrheic neonatal calves is increasingly recognized as the most appropriate and practical solution for providing life support. Restoration and maintenance of fluid and electrolyte balance as well as energy provision are necessary considerations. To be maximally effective, fluid therapy for diarrheic calves or other neonates must fulfill several criteria. Dehydration must be reversed and adequate fluid provided for normal body water turnover plus continued diarrheal fecal losses. From the animal's point of view, the optimum therapeutic approach would be a continuous fluid input at a rate equal to body losses, a condition best provided by slow intravenous administration.[29,54,69] This is not a practical approach under many field conditions. As an alternative, subcutaneous fluid administration can be effective for providing a sustained fluid input, because subcutaneous fluids are slowly absorbed over several hours.[7]

Over the past several years, the major emphasis on fluid and electrolyte maintenance for diarrheic calves has become focused on the use of oral fluids. A basis for this has been the outstanding success of oral glucose-electrolyte therapies for the treatment of *Vibrio cholera* and infant diarrhea in humans. Associated with this beneficial effect is the recognition that the mechanism by which *Escherichia coli* enterotoxin induces diarrhea is analogous to the pathogenesis of *V. cholera* diarrhea as well as diarrhea induced by other enterotoxigenic bacteria. Increased secretory activity is the initiating cause, yet absorption may continue and even be increased.[3,10,41,68] However, the simplistic assumption that, during diarrhea, absorption is normal or increased as is seen with many bacterial diarrheas,[21] may be fallacious when considering the spectrum of diarrheal etiologies.

Motility changes may also modify gastrointestinal function.[58] Increased motility due to inflammation, local irritation, or other activation of smooth muscle may increase transit rate and diminish the time available for nutrient exposure to the enteric surface, thereby limiting absorption. Conversely,

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flaccid paralysis can occur, creating a dilated open tube. Without the numerous constrictions imposed by contraction of the enteric circular muscle, fluid contents move more rapidly through the system, causing diarrhea. Although motility during diarrhea has not been commonly measured, it appears that hypomotility is a more frequent occurrence than hypermotility.

Viral diseases that cause significant changes in both individual epithelial cells and in villous morphology[9,41,56,57,70] have been associated with inhibited absorptive capacity. Most evidence supports the thesis that decreased absorption is the principal basis for the onset of viral diarrheas.[1,9,32,37] Malabsorption of sugars and lipids is well recognized in many diarrheal diseases.[53] However, increased secretion may be an additional complicating factor in viral diarrhea. The mechanism is not clearly identified, but it has been hypothesized that more immature crypt cells, which are secretory in function, are present on the villi, and that this leads to a transition from net absorption to net secretion.[13]

The use of oral antibiotics has been linked to malabsorption syndromes (diarrhea) in domestic and laboratory animals and in humans. Several antibiotics known to cause malabsorption are commonly used in veterinary medicine as prophylaxis or therapy of neonatal diarrheas. For example, oral neomycin, chloramphenicol, ampicillin, and tetracycline have all been incriminated as causing malabsorption. When they are administered orally at the upper level of recommended dosage to calves, a malabsorptive diarrhea with villus and enterocyte morphologic and functional changes results.[38,51] A more detailed description of antibiotic-induced malabsorption in calves is presented in the article "Malabsorption Due to Selected Oral Antibiotics." When malabsorption causes the diarrhea, particularly if glucose absorption is limited,[37] oral therapies may be ineffective and actually exacerbate the diarrhea by providing an increased supply of energy-rich substrate for bacteria in the terminal portions of the small intestine and in the large intestine. A secondary consequence of bacterial fermentation is the creation of excessive osmolality in the lower bowel. A number of the antibiotic-induced malabsorption syndromes in humans are associated with colonic overgrowth of *Clostridium difficile* and other gram-positive enterotoxigenic organisms.[24] Neither *C. difficile* nor the lesions of pseudomembranous colitis were noted in neonatal calf-antibiotic-induced malabsorption.[38]

DIARRHEAL LOSSES AND IMBALANCES

The composition and volume of supportive fluid therapy should be based on several factors—a principal one being the quantity of fluids and electrolytes lost. An important concept is that diarrheic animals needing fluid, electrolyte, and energy support will have the same requirements, regardless of the route of administration. The goal is to provide sustenance in an effective yet feasible manner.

Diarrheic animals quickly become dehydrated. It is not uncommon to find that neonatal calves have lost 6 to 12 per cent of the body fluids. Therefore, therapeutic provision of large quantities of water is necessary. Unfortunately, water losses are not evenly distributed through body water

pools.[43] The greatest loss is from the extracellular fluid (ECF), and blood volume is most severely depleted.[34,44,46] Decreases up to 50 per cent of blood volume have been reported. Such severe losses of blood cause peripheral vasoconstriction and result in hypovolemic shock. The rest of the ECF is also decreased but not to the same extent.[46] Only small changes are seen in the size of the intracellular water pool, which may in fact be increased in volume.[46] The inward shift in fluids is due in part to decreased cellular metabolism causing alterations in energy charge and ion transport, increased intracellular osmolality, and cellular swelling.[66] Because fluid loss is essentially from the ECF, the ionic composition of fluid replacement therapy should be similar to the ECF.[43] This is necessary so that crystalloids will remain after energy substrates are utilized, otherwise there will not be sufficient water retention.

Major whole-body losses of sodium, potassium, chloride, and bicarbonate occur during diarrhea.[34,41,60] Clinical assessment of electrolyte status is dependent on measurement of plasma or serum ion concentrations, but these values are not necessarily indicative of fecal and urinary losses. Further, they may give false impressions of whole-body electrolyte status. This is particularly true for potassium, which may be significantly increased in the blood and other extracellular fluids, reaching cardiotoxic levels.[23,35,43,50,63] At the same time, a whole-body potassium deficit is present (Fig. 1).[23,34,63] Potassium accumulation in extracellular fluids is a complex phenomenon associated with hyponatremia, changing osmolality, developing acidosis, and cellular energy imbalances.[8,26] Fecal sodium and bicarbonate loss, anaerobic lactate production, and decreased renal function due to hypovolemia and hypotension are all involved. Potassium-hydrogen and other ion shifts occur, owing in part to increased potassium permeability across cellular membranes. The decrease in intracellular potassium with a resultant increase in extracellular potassium causes myocardial and skeletal muscle dysfunction due to a decreased resting membrane potential.[23,34,35,66] A paradox develops in which a whole-body potassium deficit is present in concert with hyperkalemia.[23,34] Because the volume of the vascular and ECF pools are decreased owing to extracellular dehydration, the total plasma potassium content as well as the total intracellular potassium content are often diminished (see Fig. 1). This facet is often not appreciated in developing a rationale for effective restoration of electrolyte normalcy. A working basis for understanding the misbehavior of body fluid (electrolytes) during the development of enteric diseases[39] is shown in Figure 2. The bottom line is that lost ions and fluids must be replaced and intracellular and extracellular imbalances must be corrected.

ENERGY STATUS

The maintenance metabolic rate of neonatal calves is a function of body weight (W). This maintenance requirement will be increased by the metabolic demands of growth and fever. Kleiber established a general formula for metabolic body size; using this formula, maintenance requirements may be calculated (Fig. 3). Maintenance (kcal per day) equals $140 \times W$ in $kg^{.75}$.[33]

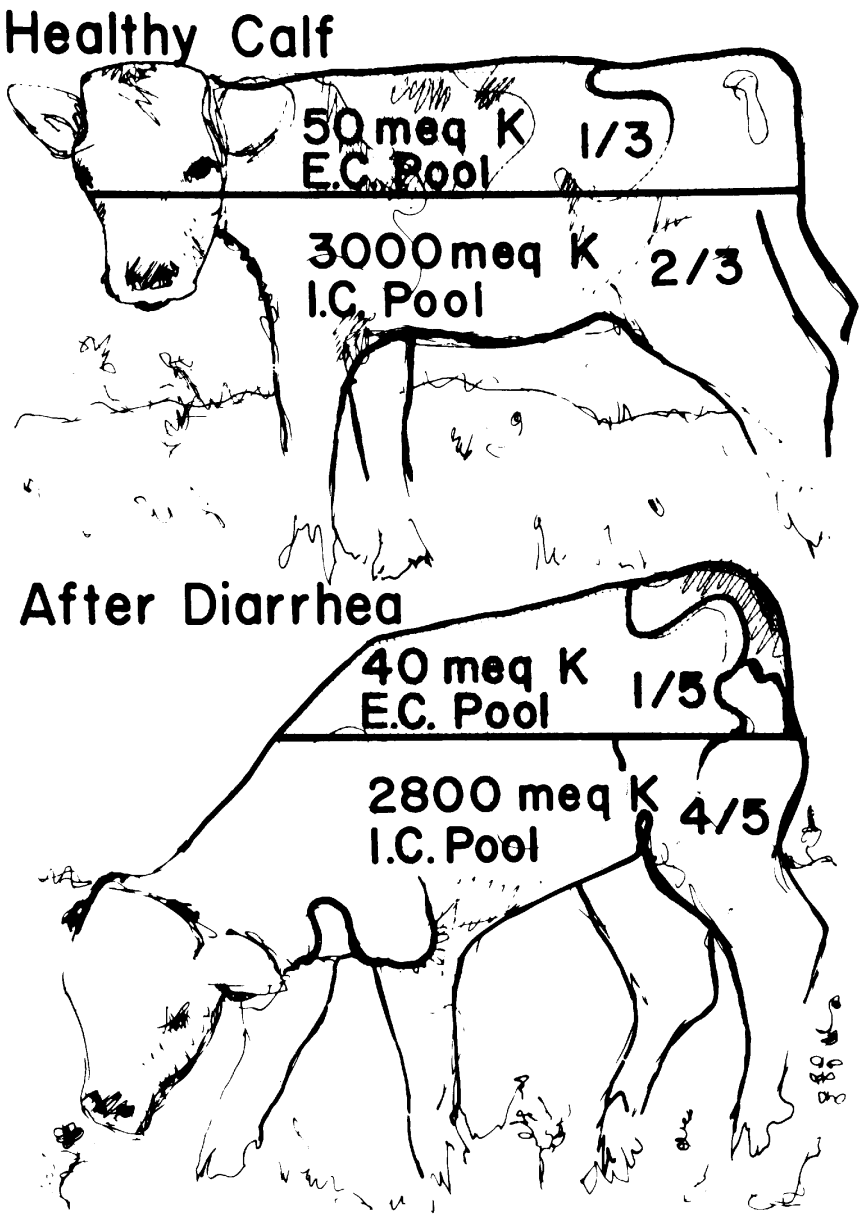

Figure 1. Changes in the calf's extracellular fluid (*E.C.*) and intracellular fluid (*I.C.*) potassium pools as a result of diarrhea. Both pools decrease in total potassium content but the *E.C.* decrease is masked by an increase in plasma potassium concentration.

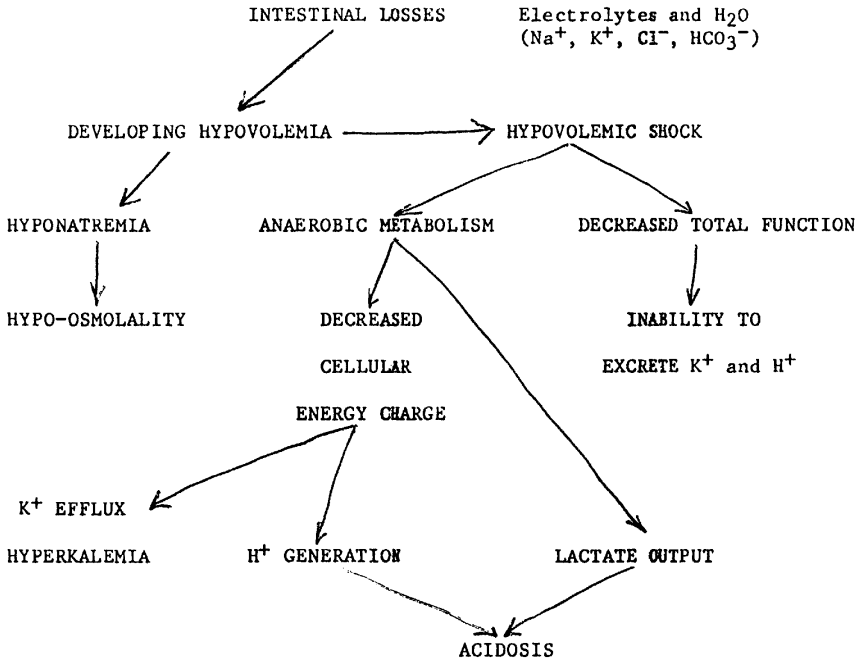

Figure 2. Fluid and electrolyte imbalances that occur as diarrhea develops.

Published data[2] indicate that the resting metabolic rate of growing 40-kg calves less than 1 week of age is 2213 kcal per day. Using the Kleiber formula (140 kcal per $kg^{.75}$) for these same calves it would be 2226 kcal per day. A simple, but less accurate, alternative linear estimate of metabolic rate can be utilized. It is based on 50 kcal per kg, which is a reasonable approximation in the size range of neonatal calves.[45] Figure 4 is a plot of this simple straight line method as a ratio with the requirements derived using the Kleiber metabolic body size formula. Using 50 kcal per kg as a base, the straight line method underestimates requirements in smaller animals. Both methods would underestimate actual metabolic rate of dietary energy requirements in rapidly growing or febrile calves.

During diarrhea, many animals have a decrease in food intake, a decreased net absorptive function, and an increase in metabolic rate associated with fever. The combination of these three events can result in a significant negative energy balance. In calves or other neonates, this is potentially more serious because they have meager energy reserves. Only about 1.8 per cent of the body weight of neonatal calves is adipose tisuse, and a significant proportion of that is brown adipose tissue (BAT).[2] BAT is helpful in maintaining normal body temperature in neonates but is not of value in supplying free fatty acids (FFAs) for general metabolic utilization during periods of reduced food intake. Neonatal calves do not have high levels of circulating FFAs except in the peripartum period.[17] Also, plasma FFAs are not increased in diarretic calves with hypoglycemia due either to the low reserves or to

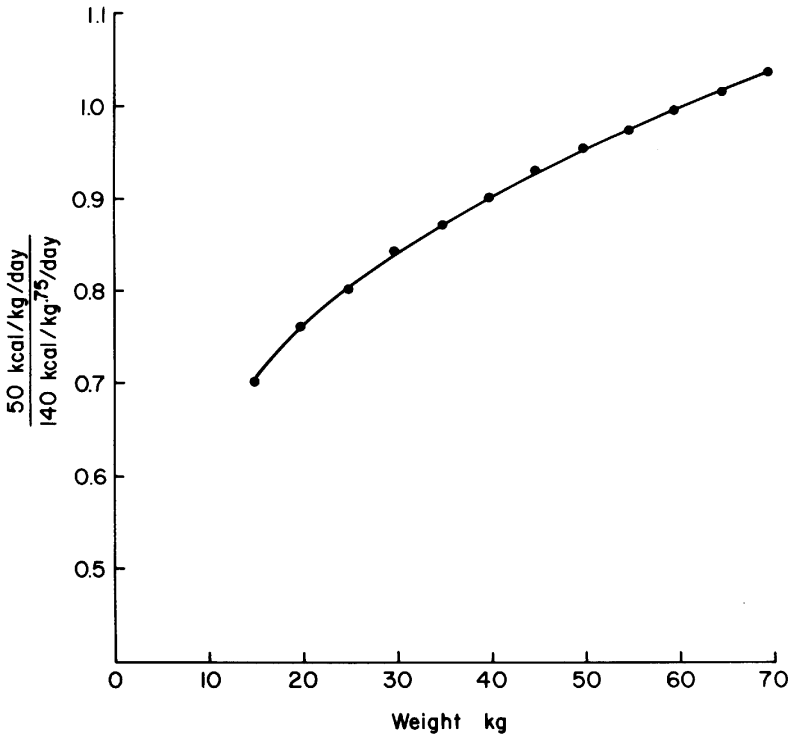

Figure 3. Maintenance energy required as a function of increasing body size from 15 to 17 kg using metabolic body size (140 kcal per $kg^{.75}$) and straight line (50 kcal per kg per day) method.[33,45]

an inability to mobilize triglycerides.[18] From a practical standpoint, this means that care should be taken to ensure that young diarrheic calves receive adequate energy orally or parenterally in a utilizable form.

In severely diarrheic calves, hypoglycemia and lactic acidosis are an almost constant finding.[14,18,49,60] Hypoglycemia and lactic acidosis are also pathognomonic signs of endotoxemia.[28] Similar blood levels of glucose, lactate and potassium are seen in diarrheic and in endotoxemic calves.[14,18,46,49,60,62] These similarities have led to the tenet that diarrheal damage to the intestinal epithelial barrier, whether from viruses, bacteria, or other agents, allows endotoxin and/or bacteria to enter the vascular system in increased quantities and that endotoxemia commonly accompanies diarrhea. The hypoglycemia, hyperlactatemia, and hyperkalemia seen in diarrheic neonates may represent a combination of anorexia with decreased intake, altered epithelial transport, and developing endotoxic-septic shock. However, the relative role of each is not known.

In summary, during diarrhea, dehydration occurs with the greatest losses from the extracellular pool. The initial hypovolemia may lead to hypovolemic shock and increased anaerobic metabolism. Acidosis is seen due to the anaerobiasis as well as intestinal bicarbonate loss and renal insuffi-

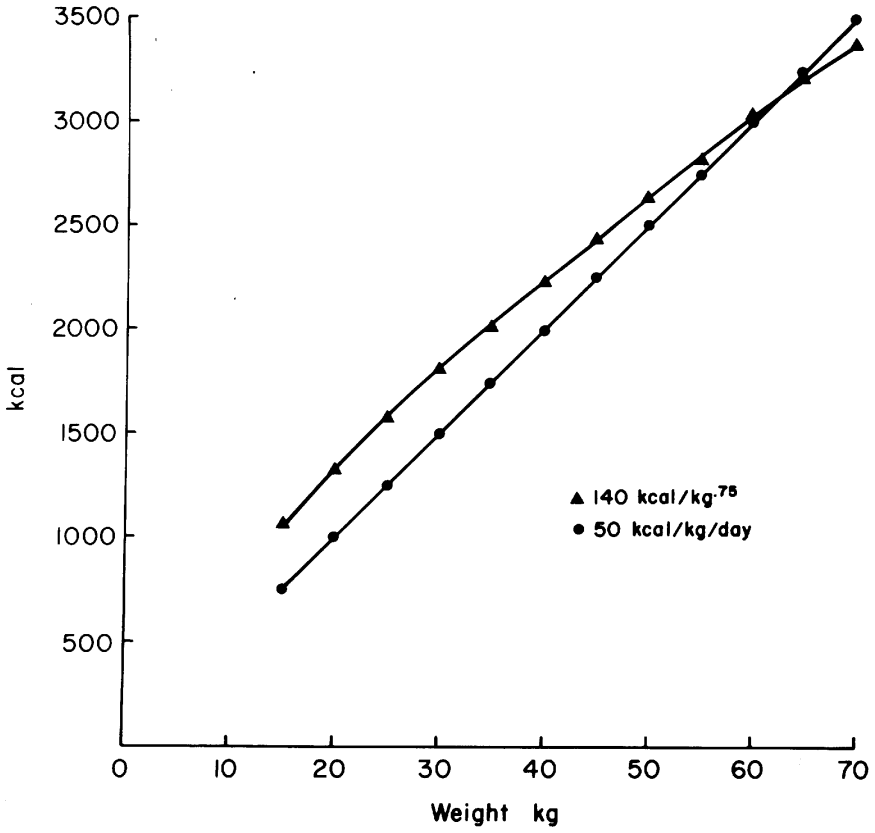

Figure 4. Effectiveness of the straight line (50 kcal per kg per day) method of energy provision as a percentage of metabolic body size determination of energy requirements. In smaller animals (15 kg), only 70 per cent of maintenance is provided. At approximately 60 kg, they are equivalent.

ciency. Hypoglycemia is common, and major losses of sodium, chloride, and potassium occur. Intracellular-extracellular potassium imbalance may become severe, resulting in a reduced resting membrane potential and altered cardiac and skeletal muscle contractile ability.[43] Finally, the effects of decreased nutrient energy input are compounded by the scant energy reserves found in neonates.

INTESTINAL FUNCTION

Some concepts of normal gastrointestinal function may aid in developing a basis for oral therapy. The gastrointestinal tract normally serves as a barrier that essentially eliminates the opportunity for microbial entry into the body. Conversely, it is a transport system in that absorption and secretion are continually occurring across the mucosal epithelium. The enterocytes that

make up the epithelium are formed in the crypts and move rapidly up the villi over a period of several days. In calves, the life span of an epithelial cell from formation to sloughing at the villous tip is about 48 hours.[40] The intestinal epithelial cells have several functions, and these functions change as they mature during migration up the villus. In the crypts, immature cells are secretory, whereas mature villous cells are absorptive. These cells serve as the barrier, limiting entry of organisms and toxins into the body and preventing loss of body substance to the gut. In the small intestine, this barrier is somewhat leaky, as water and some solutes can pass in a paracellular manner. The junctional complexes between epithelial cells are functionally important structures. They are similar to a fence because they prevent molecular movement; to a gate because they allow certain substances to pass; and to a bridge because adjacent cells may interact directly via gap junctions.[20] Like many barriers, the one between cells is not absolute, and normally some bacteria and bacterial toxins enter the portal blood.[30] During diarrhea, significant changes occur in the magnitude of directional transport and the integrity of the barrier causing the loss of fluids and body constituents, which is an increase in the gate function. Also, with barrier modification, it is easier for intestinal microorganisms and toxins to enter the body at an increased rate, which is a decrease in fence function. This may lead to endotoxemia and septicemia with potentially lethal consequences. The apparent damage to the epithelial barrier is much greater with viral than bacterial diarrhea; therefore, septicemia and its resultant hypoglycemia may be more severe in viral than bacterially induced diarrheas.

NUTRIENT ABSORPTION

Most absorption occurs in the small intestine, and intestinal epithelial cells transport many nutrients. For this discussion, nutrients will include water, electrolytes, and energy-yielding substrates such as carbohydrates, amino acids, and lipids. Absorptive transport is primarily via the more mature cells near the villous tip, which also have the greatest degree of contact with intestinal contents.

The villus is the functional unit of the small intestine. It is comprised of a vascular and lymphatic core, smooth muscle, and supportive connective tissue surrounded by absorptive epithelial cells. The vessels are arranged so that a countercurrent flow pattern is established.[27] The central arteriole in each villus can be compared to a fountain that sprays capillaries that descend toward the base of the villus adjacent to the epithelial cells (Fig. 5).[59] Absorbed nutrients enter descending capillaries, causing an increase in osmolality. The diffusion pattern is such that water leaves the ascending arterioles and enters capillaries while absorbed nutrients diffuse from capillaries to arterioles. Together these effects create an increasing concentration gradient in the ascending arteriole and increased osmolality at the villous tip (Fig. 6).[27] Conceptually, it is similar to the countercurrent exchange system that develops in the loop of Henle in the renal medulla. During active absorption, the osmolar gradient may reach 600 mOsm or roughly twice body-fluid osmolality. An additional osmotic gradient develops in the

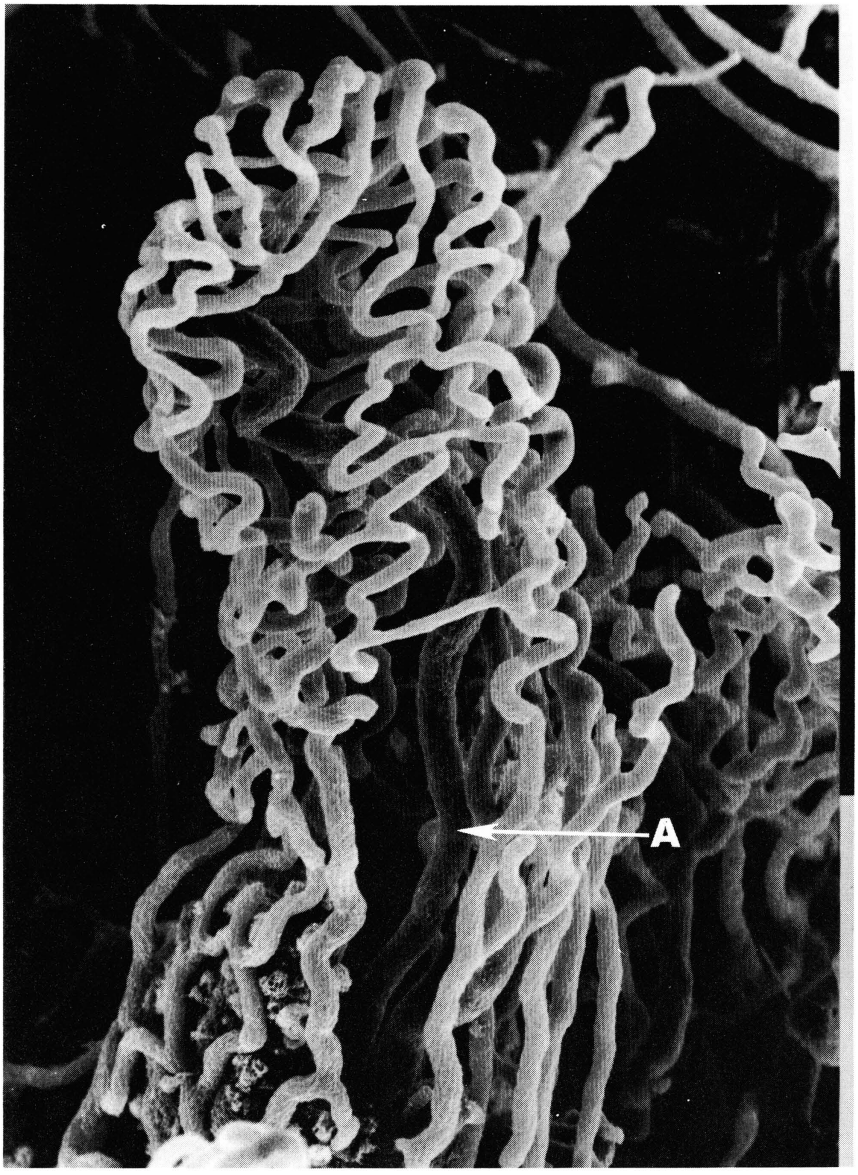

Figure 5. Scanning electron micrograph of villous vasculature of a calf's small intestine. The villous vascular network is such that a central arteriole (A) ascends to the tip and branches into a "spray" of capillaries that descend toward the base of the villus, creating a countercurrent flow system.

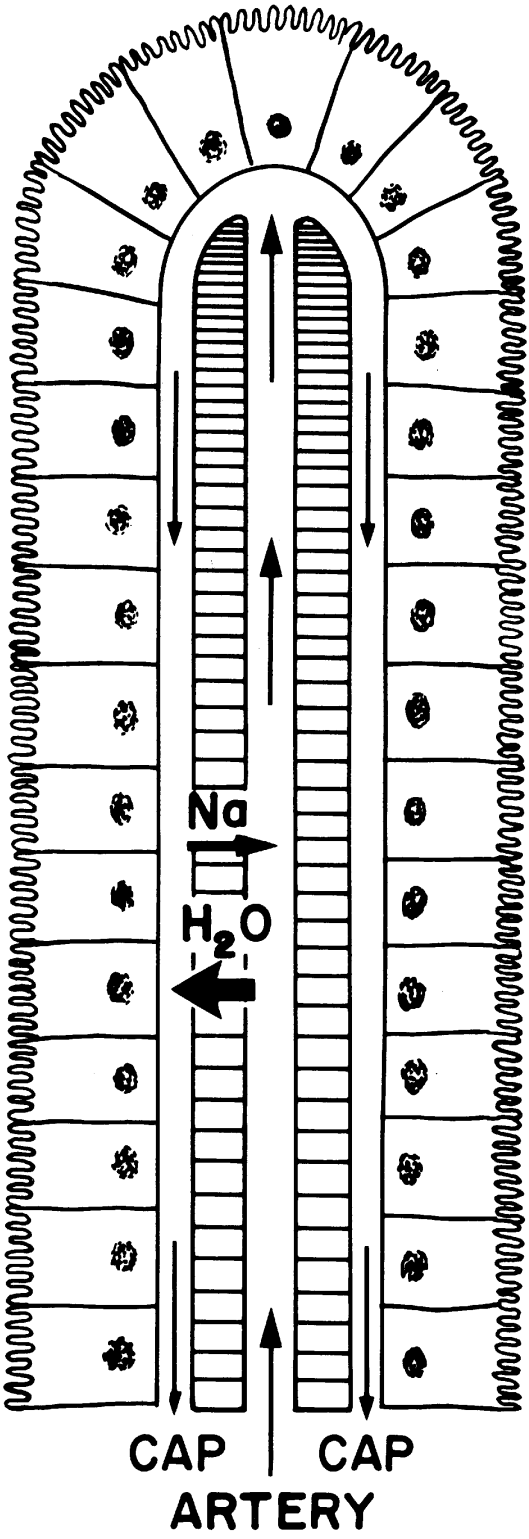

Figure 6. The villous countercurrent multiplier system is depicted. During absorption, there is net water diffusion from the ascending arteriole to the descending capillary. Some solute diffuses in the opposite direction. The result is an increasing osmotic gradient at the villous tip. (Modified from Hallback, D.A., Hulten, L., Jodal, M., et al.: Evidence for the existence of a countercurrent exchanger in the small intestine in man. Gastroenterology, *74*:683–890, 1978.)

lateral intercellular space between epithelial cells when they are absorbing, which aids solute flux to the capillaries. These two osmolar gradients are believed to enhance nutrient absorption. This same countercurrent system allows free diffusion of oxygen and carbon dioxide between the ascending arteriole and the descending capillaries. As a result, oxygen leaves the ascending arteriole and the villous tip cells are prone to suffer from anoxia in low flow states, such as the hypovolemia induced by acute diarrhea.

During absorption, nutrients cross the microvillous brush border, enter the cell, and then leave via the lateral cellular membrane. The mechanisms involved in this process are similar for glucose, galactose, amino acids, and short peptides, although peptides are hydrolyzed in the epithelial cell. Glucose transport has been most extensively studied and will be used as an example. A microvillous membrane receptor binds both sodium and glucose. They enter the epithelial cell together based on the sodium diffusion potential. These cells, like others, have only a minimal intracellular Na^+ concentration, and a constant diffusion gradient exists for sodium to move from the intestine into the epithelial cell. Electrochemical neutrality is maintained by cotransport of a negative ion, generally Cl^- or HCO_3^-. Sodium is then pumped by active transport into the lateral intercellular space below the junctional barrier. Again, the anion follows, maintaining electrochemical neutrality. Glucose is believed to diffuse out, with minimal metabolism occurring during the absorptive process.[6] Sodium, anion, and glucose increase in concentration in the lateral intercellular space, effecting an increase in osmolality. Water diffuses into this space from adjacent cells and by paracellular movement from the intestinal lumen across the leaky junctional complex. Diagrams of resting and absorbing intestinal epithelial cells in relation to both transepithelial and vascular fluxes are shown in Figures 7 and 8.[25,27] The lateral intercellular space at the apex of cell near the villous tip would normally have a high osmolality during active absorption. The continuing solute and solvent movement into the lateral space near the apex of the cell causes a flow from apex to base carrying the absorptive products. In the lamina propria at the base of the cell, the absorbed nutrients diffuse into the descending capillary network and help develop the villous countercurrent osmolar gradient system.[27] Absorption across the epithelial cells also increases tissue hydrostatic pressure and lymphatic flow as illustrated in Figures 7 and 8. Absorbed lipid with subsequent chylomicron formation, which is not shown, would also increase lymphatic flow.

THE CALF

In the normal calf, nutrient delivery to the intestine and the rate of subsequent absorption is controlled largely by gastric emptying. In milk-fed calves, the conversion of soluble casein to insoluble paracaseinate greatly decreases gastric emptying rate. Bell and Razig[4,5] have studied factors modifying abomasal emptying in calves. They found that highly hypertonic pure solutions of electrolytes or carbohydrates will delay emptying. Their data indicate that maximal gastric emptying of NaCl and $NaHCO_3$ solutions in calves occurs at an osmolality of 400 to 600 mOsm per L (Fig. 9), well above

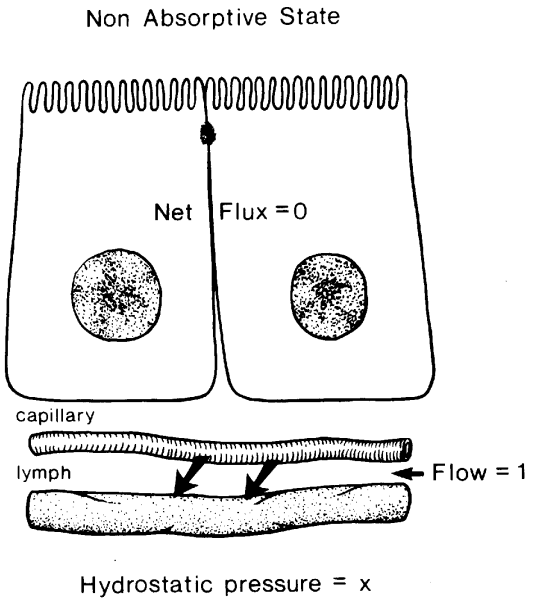

Figure 7. In a resting intestinal epithelial cell, there is no net absorptive cellular flux. The lateral intercellular space is collapsed. Some lymph flow is present due to capilllary leakage.

body fluid osmolality of 290 mOsm per L, but similar to the villous vascular osmolality when absorption is occurring.[4,5] In a study with young adult pigs using fluid diets ranging from 250 to 700 mOsm per L, it was found that duodenal contents equilibrated at 450 to 500 mOsm per L with declining intestinal content osmolality as transit through the intestine occurred.[15]

The optimal rate of gastric emptying for providing normal nutrient uptake for calves has not been determined. Although gastric emptying may be slower with a hypertonic glucose-electrolyte solution. This does not provide a basis for using more isotonic oral fluid therapy. If gastric emptying is slowed, more total carbohydrate could be provided to the small intestine over a longer period.[4,5] Rapid gastric emptying may not be of benefit; in fact, one is tempted to ask why it should be considered beneficial, if a sustained fluid input to the absorptive surface of the small intestine is a valid therapeutic goal. Delayed gastric emptying by feeding hypertonic solutions would tend not to overload the small intestine's absorptive capacity and would also provide more total nutrients and more energy, particularly if tonicity is increased by adding energy-yielding absorbable nutrients. In a study with calves, the addition of 80 mOsm per L of NaCl to a 10 per cent glucose solution enhanced glucose absorptive rate, yet increased osmolality from 555 to 715 mOsm per L.[16]

Cow's milk is an isosmotic fluid when secreted. During digestion, the breakdown of milk protein and lactose causes an increase in luminal osmolality. For example, 6 hours following milk ingestion by normal or diarrheic calves, upper small intestine osmolality was greater than blood osmolality (Figs. 10*A* and *B*).[67] Finally, it has been reported that increasing the dry-matter content of calves' diets, which presumably increases gastrointestinal osmolality, resulted in a decreased incidence of diarrhea.[55]

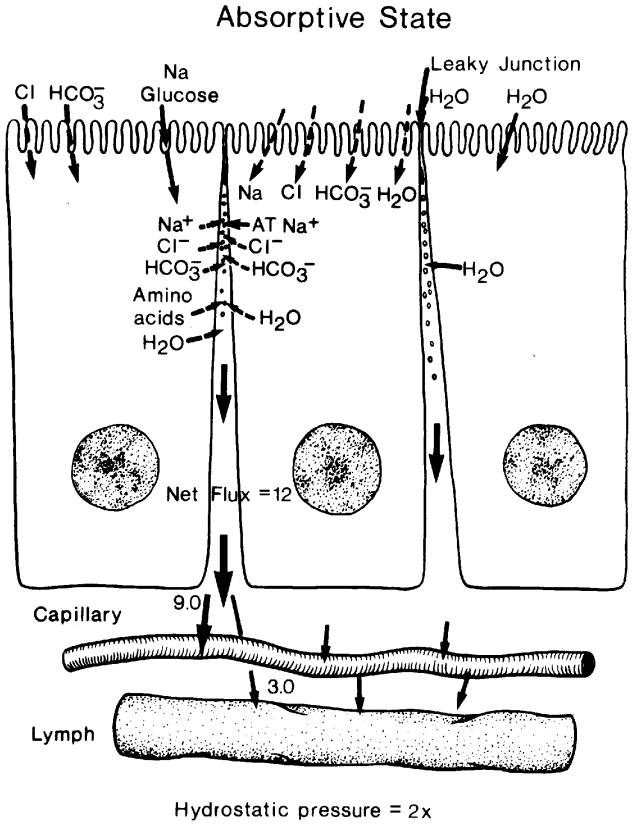

Figure 8. In active intestinal epithelial cells, net absorption causes a solute and solvent flow from cell apex to base. There is net uptake by capillaries, and due to increased hydrostatic pressure, an increase in lymph formation. (Modified from Granger, D.N.: Intestinal microcirculation and transmucosal fluid transport. Am. J. Physiol., *240*:G343–349, 1981.)

Based on the absorption rates of glucose following either oral glucose or lactose administration and calculated rates of glucose transport,[10,11,65] the calf's small intestine can absorb larger quantities of glucose and amino acids than are presented by most oral therapies. In the normal state, this must occur because milk contains a higher percentage of both carbohydrate as lactose and amino acids as protein. To achieve the necessary provision of adequate energy substrates to the young calf, the most appropriate approach physiologically is to have a slow, constant flow of nutrients from the stomach.

Several conclusions can be made concerning osmolality:

1. During absorption, the environment of the upper small intestine, both contents and mucosa, is hyperosmotic compared to body fluids, and hyperosmolar gradients that develop during absorption are normal and beneficial to the absorptive process.
2. The rate of gastric emptying is in part controlled by gastric and intestinal

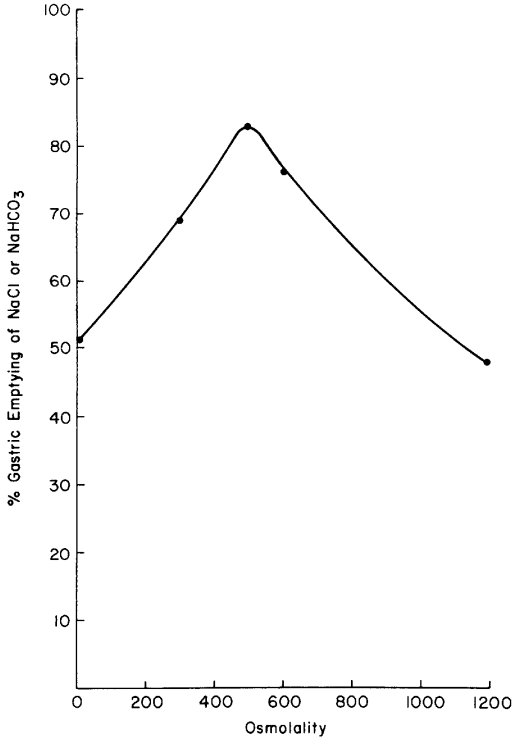

Figure 9. The effect of varying osmolality of NaCl or $NaHCO_3$ on rate of abomasal emptying. (Calculated from Bell, F.R., and Razig, S.A.D.: Gastric emptying and secretion in the milk-fed calf. J. Physiol., 228:499–511, 1973; and Bell, F.R., and Razig, S.A.D.: The effect of some molecules and ions on gastric function in the milk-fed calf. J. Physiol., 228:513–526, 1973.)

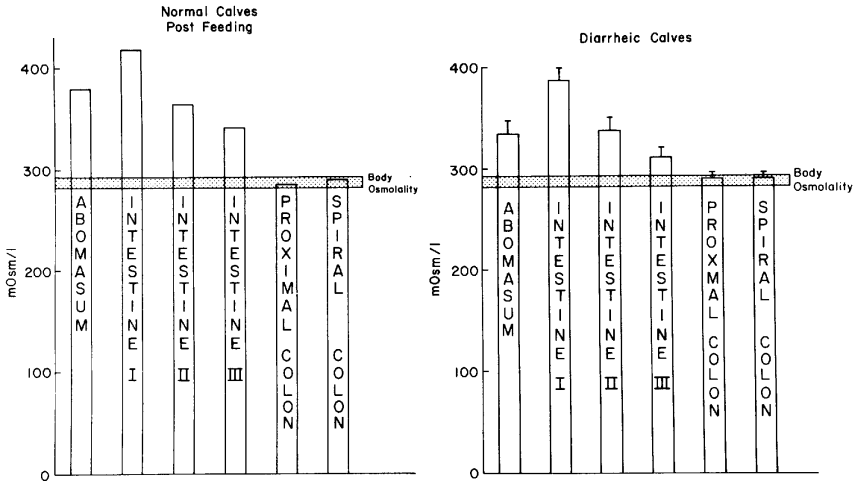

Figure 10. *A*, Intestinal osmolality of normal calves 6 hours after a milk meal. *B*, Intestinal osmolality of diarrheic calves 6 hours after a milk meal. (Modified from Ward, D.E.: Pathophysiology of enteric colibacillosis in the intact neonatal calf. Ph.D. thesis, Cornell University, 1976.)

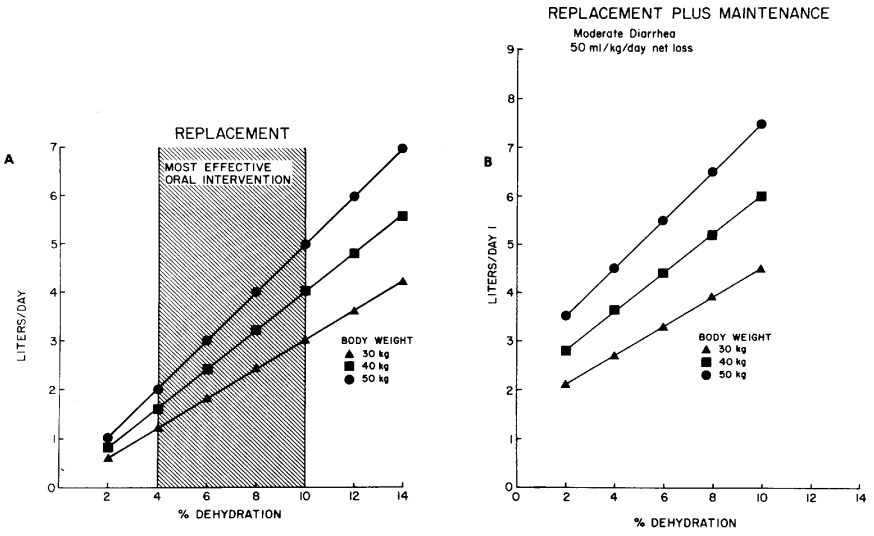

Figure 11. *A*, Fluid-replacement requirements for varying degrees of dehydration and body size as well as the degree of dehydration at which oral fluid therapy may be most effective are shown. *B*, Daily fluid replacement plus maintenance requirements for a calf with moderate fluid loss of 50 ml per kg per day.

osmolality, and increased osmolality of ingested fluid above 500 mOsm per L should provide a more prolonged nutrient input to the intestines.

3. By increasing osmolality with energy-rich substrates, the calf's metabolic requirements will be more nearly met. The result is less loss of body weight due to fluid administration.[22]

FLUID THERAPY

The use of fluid therapy during diarrhea represents a combination of replacement and maintenance.[39,54] The elements comprising that fluid and the quantity administered will be roughly equivalent, regardless of the route of administration, because they are based on the animal's needs. The replacement component fulfills the important requirement of re-establishing normal body-water, electrolyte and energy substrate status. The quantity of water administered is based on the estimated degree of dehydration. For instance, a 40-kg calf that was 10 per cent dehydrated would require 4 L of fluid. If diarrhea is still present, daily net loss must also be considered. It may range from negligible quantities to 7.5 per cent of body weight per day or more, which could result in a daily loss of 3 L in a 40-kg calf. Fluid required for replacement plus maintenance for three sizes of calves with varying degrees of initial dehydration and a continuing loss of 50 ml per kg per day is plotted in Figure 11. If dehydration is cured, the required volume will be less on succeeding days. Excess fluids that are administered and absorbed will be excreted via the kidneys.

Next, what should be added to the water in order to provide maximum support for the calf? Important considerations and components include the following:

1. Ion replacement
   Na^+, K^+
   Cl^-, HCO_3^-
2. Acid-base correction
   HCO_3^- or bicarbonate equivalent, such as acetate, citrate, or L-lactate
3. Energy maintenance
   Glucose, amino acids, lipids

On the basis of fecal losses and changes in the size of the ECF pool, the replacement fluid should essentially have the composition of the ECF with regard to ions—that is, it should contain sodium at 120 to 140 mEq per L, chloride at 30 to 40 mEq less than sodium, and either bicarbonate or a bicarbonate equivalent such as acetate, citrate, or L-lactate. Bicarbonate added directly will have the most immediate benefit. Conversely, a bicarbonate equivalent can provide additional energy. Both acetate and citrate can be recommended, for they can be more readily utilized than lactate, which is an isomeric mixture one half of which (D-lactate) is poorly utilized. Further, the diarrheic calf is often suffering from hyperlactatemia with a decreased lactate utilization rate.[14] Reports have been published of the beneficial effect on intestinal absorption of both acetate[19] and citrate.[11,12] Studies on optimal concentrations of either ion are not available. However, the rationale for their inclusion seems valid, if they are present in sufficient quantities. For instance, provision of 4 gm of Na acetate to a 40-kg calf would only yield an increase of 2 to 3 mEq of HCO_3^- per L if every molecule of carbon was converted to HCO_3^-. It is more likely that one half as much could be gained—that is, one HCO_3^- per Na^+. Therefore, 4 gm of Na acetate would not materially affect acid-base status and HCO_3^- deficit in a 40-kg calf. Similar calculations can be made for citrate and lactate. Na citrate would be roughly as effective as acetate, but lactate contains less sodium per gram and would be a less efficient source of bicarbonate buffer on a gram basis. Citric acid, by itself, has no alkalinizing effect, because it is completely oxidized to carbon dioxide and water. The alkalinizing power of small quantities of the sodium or potassium salt of any organic acid should be considered negligible. Table 1 lists the alkalinizing potential of several products currently available on the market.

Potassium should be present to restore whole-body potassium deficits, remembering that the potassium deficit is coupled with a hyperkalemia. Both glucose and bicarbonate or an equivalent that will be rapidly oxidized to bicarbonate are essential additions. Both will facilitate potassium entry into cells. The safety and efficacy of administering solutions high in potassium, either parenterally or orally, to hyperkalemic calves has been clearly demonstrated.[31,47,49] In all cases, there were significant decreases in plasma potassium following administration. With intravenous administration, K^+ concentration decreases as the fluid is administered.[47,49]

An available energy supply in the form of glucose is an important component for several reasons. Diarrheic calves are hypoglycemic, glucose is

Table 1. *A Comparison of Volume, Osmolality, Alkalinizing Potential, and Energy Content of Some Oral Therapies Currently Available in the United States*

PRODUCT	VOLUME* (ml/day)	HCO_3^-† (mEq/L)	mOsm/L	kcal/L
Biolyte	3784	76.0	698	288
Electroplus A	6000	40.0	323	65
Ionaid	3784	4.0	515	142
Lifeguard	5676	71.0	490	173
Resorb	4000	0.6	340	96
Revive	3784	57.0	705	285

Label recommended administration rate per calf per day. Note that mOsm per L and kcal per L have been calculated from label ingredients or manufacturer's literature.

*Maximum per calf per day or per 40-kg calf per day.

†Alkalinizing potential either as HCO_3^- or bicarbonate equivalent assuming complete oxidation of organic anions.

readily absorbed in most cases, and following absorption, glucose will facilitate movement of potassium into cells, correcting the hyperkalemia. Other carbohydrate sources may be of less value. Neonatal calves do not have sucrase, nor do they have significant quantities of maltase in the brush border[64]; therefore, sucrose and maltose will not be digested and absorbed.[16] Their inclusion is of negligible value and may be detrimental. Sucrose can even be utilized to induce diarrhea in calves. Lactose would seem to be a logical choice, but lactase in the brush border is a particularly fragile enzyme, and it tends to be diminished in activity in many diarrheal diseases. Therefore, glucose appears to be the carbohydrate of choice for inclusion in therapies.

Glycine has also been shown to stimulate overall intestinal absorption of sodium and water and is incorporated in many therapies for this purpose. Amino acids in general would seem to be of more questionable benefit than carbohydrates. Under the conditions associated with diarrhea, such as anorexia, dehydration, hypoglycemia, and acidosis, the calf is unlikely to utilize amino acids for growth. It is more likely under these conditions that amino acids will be oxidized for energy. In so doing, they would potentially have a protein-sparing effect. However, if oxidized, they will contribute to increased urea synthesis, potentially compounding the uremia that is present owing to decreased renal function. Lipids could be considered of possible benefit owing to their high energy content. However, lipids tend to be less stable, and it appears that little information is available on their absorbability during diarrheal diseases.

Many of the oral therapies currently on the market in the United States have been formulated on the hypothesis that it is desirable for such solutions to be reasonably isosmotic with regard to body fluids. The basis for this view is the supposition that hyperosmotic fluids will remove water from the body by increasing gastrointestinal secretory activity. This appears fallacious and is not supported by data published in the literature.[16,31] Unfortunately, this concept has resulted in the preparation of a great many products that provide only minimal energy input (Fig. 12). This figure presents the available energy

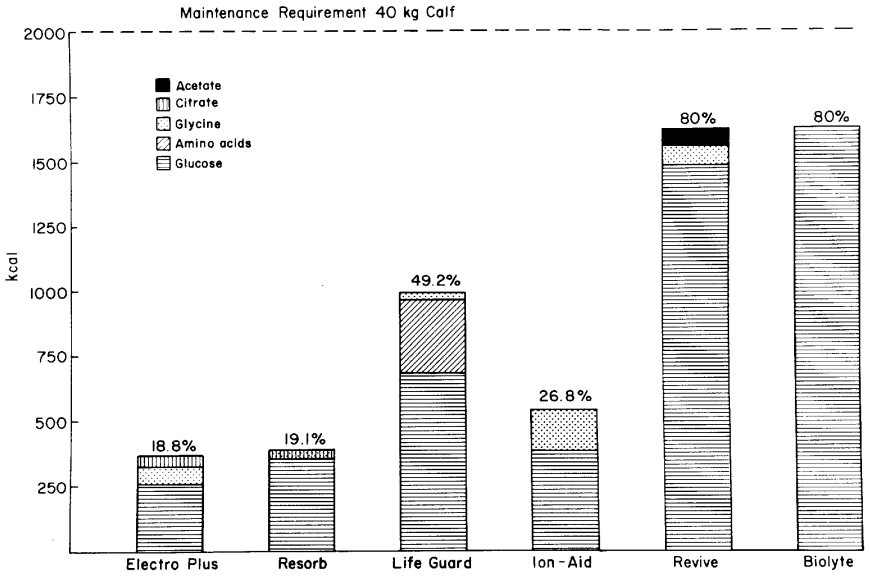

Figure 12. A summation of maximum energy yield by substrate from several commercial therapies currently marketed in the United States. The minimal maintenance requirement of neonatal calves is listed at the top and percentage of maintenance is provided, utilizing the manufacturer's label instructions.

by nutrient source in a number of products currently being marketed in the United States. Osmolality, volume, and relative energy provision of a number of oral therapies are also presented in Table 1. The majority provide sufficient water to combat dehydration if used at the manufacturer's maximum recommended level (Fig. 11 and Table 1). The greatest deficit of most of the products is in energy, and several contain negligible alkalinizing potential. Using a conservative maintenance estimate for a 40-kg calf of 2000 kcal per kg per day versus the calculated and measured values of over 2200 kcal per kg per day, the highest energy provisions (Biolyte* and Revive†) represent 80 per cent, whereas the other products are more deficient in providing a maintenance energy level (Fig. 12).

A word of caution regarding oral therapy: The gastrointestinal tract may not be capable of absorbing when villous atrophy is present,[40] and the villous countercurrent flow system is destroyed; also, it may not be capable of absorbing when there are changes in epithelial cell transport function.[1,52,53] The use of oral therapies during a malabsorptive diarrhea may exacerbate the problem by providing an additional growth medium to intestinal microbes. Under these conditions, parenteral therapy should be used. However, the general assumption that oral fluids are of benefit is sound, for clinical results indicate that most diarrheic neonates can absorb significant quantities of nutrients from the gastrointestinal tract. Many manufacturers

*The Upjohn Company, Kalamazoo, Michigan.
†Tech America Group, Inc., Elwood, Kansas.

of oral products suggest that their solutions be mixed half and half with milk after several days as the calves are being moved back to a normal diet. This may be an inappropriate step. In preliminary studies using normal calves, there was a threefold increase in the number of animals diarrheic after 2 days of such half-and-half feeding.[22] Our preliminary belief is that dilution may prevent rennin's formation of a casein clot, which would result in too rapid gastric emptying of the mixture and a nutritional diarrhea.

In conclusion, it appears that (1) many available oral therapies for treating neonatal calf diarrhea are woefully inadequate in energy; (2) undue attention has been given to providing isosmotic fluids with no valid basis for that approach; and (3) the potential for acid base correction has not been incorporated in several therapies. Based on these conclusions, more effective oral therapies can be provided for diarrheic calves. The more effective therapies will be hyperosmotic and have a composition that is similar to ECF but with added energy. At least a portion of that energy will be in the form of glucose and provide significant alkalinizing potential.

PARENTERAL THERAPY

Today, intravenous, subcutaneous, and intraperitoneal administration of supportive therapy is not as common as oral administration—with good reason. In most cases, effective results can be obtained using oral fluids. However, there are still circumstances in which parenteral administration should be the method of choice.[39,54] Many "homemade" parenteral concoctions have been utilized over the years as well as standard solutions such as Ringer's lactate or one half saline and one half dextrose. Both of these would be beneficial, but the Ringer's lactate would probably be less so owing to the relative inhibition of gluconeogenesis and hyperlactatemia frequently seen in diarrheic calves.[14,60] Also, the Ringer's lactate is a racemic mixture, and the D-lactate is poorly utilized. The one half saline and one half dextrose would provide more energy but would not address the acidosis or the total body potassium deficit.

To the best of the author's knowledge, only one product has been prepared and marketed for parenteral administration to diarrheic calves. It (Biolyte) can also be utilized orally, and some characteristics are presented in Table 1 and Figure 12. When Biolyte is given intravenously or orally, hyperkalemia is reduced in spite of the high potassium content.[31,47,49] When given intravenously, good results have been obtained with the hypertonic high-energy solution. For subcutaneous or intraperitoneal use, it should be diluted 2½ times to isotonicity. The FDA has recently requested that the manufacturer not market the product for parenteral use.

In any case, parenteral fluid administration can be recommended where good facilities are available and in animals that have become more seriously ill, are comatose, severely hypoglycemic or hypothermic. Once some degree of return toward normal function has occurred, it may be easier and more practical to switch to oral support.

Adequate and conscientious use of appropriate fluids is the most effective means of combating neonatal enteritis. Until more marked success is

achieved in preventing diarrhea in young animals, fluid administration will continue to be a valuable tool for preserving the life of calves and other domestic neonates. For further information concerning parenteral fluid therapy, the reader is referred to the appendices in this symposium.

REFERENCES

1. Abel, J.H., Phillips, R.W., and Lewis, L.D.: Intestinal mucosal enzymatic and histochemical changes during infectious diarrhea in calves. Am. J. Dig. Dis., *17*:423–429, 1972.
2. Alexander, G., Bennett, J.W., and Gemmell, R.T.: Brown adipose tissue in the newborn calf (*Bos taurus*). J. Physiol., *244*:223–234, 1975.
3. Argenzio, R.A.: Physiology of diarrhea: Large intestine. J. Am. Vet. Med. Assoc., *173*:667–672, 1978.
4. Bell, F.R., and Razig, S.A.D.: Gastric emptying and secretion in the milk-fed calf. J. Physiol., *228*499–511, 1973.
5. Bell, F.R., and Razig, S.A.D.: The effect of some molecules and ions on gastric function in the milk-fed calf. J. Physiol., *228*:513–526, 1973.
6. Bjorkman, O., Crump, M., and Phillips, R.W.: Intestinal metabolism of orally administered glucose and fructose in Yucatan miniature swine. J. Nutr., *114*:1413, 1984.
7. Buck, D., and Phillips, R.W.: Unpublished observations.
8. Busa, W.B., and Nuccitelli, R.: Metabolic regulation via intracellular pH. Am. J. Physiol., *246*:R409, 1984.
9. Butler, D.G., Gall, D.G., Kelly, M.H., et al.: Transmissible gastroenteritis: Mechanisms responsible for diarrhea in an acute viral enteritis in piglets. J. Clin. Invest., *53*:1335–1342, 1974.
10. Bywater, R.J.: Some effects of *E. coli* enterotoxin on net fluid, glucose and electrolyte transfer in calf small intestine. J. Comp. Pathol., *80*:565–573, 1970.
11. Bywater, R.J.: Evaluation of an oral glucose-glycine-electrolyte formulation and amoxicillin for treatment of diarrhea in calves. Am. J. Vet. Res., *38*:1983–1987, 1977.
12. Bywater, R.J.: Comparison between milk deprivation and oral rehydration with a glucose-glycerin-electrolyte formulation in diarrhoeic and transported calves. Vet. Rec., *107*:549–551, 1980.
13. Bywater, R.J.: Pathophysiology and treatment of calf diarrhoea. *In* Proceedings of the World Congress on Diseases of Cattle, Amsterdam, 1982.
14. Case, G.L., Phillips, R.W., and Cleek, J.L.: Lactic acid and glucose metabolism in healthy, lactic acid infused and diarrheic calves. Am. J. Vet. Res., *41*:1035–1038, 1980.
15. Case, G.L., Lewis, L.D., Phillips, R.W., et al.: Effects of osmolality of liquid nutrient diets on meal passage and nutrient absorption in Yucatan miniature swine. Am. J. Clin. Nutr., *34*:1868–1878, 1981.
16. Cleek, J.L., Phillips, R.W., and Johnson, B.D.: Availability of oral carbohydrates in neonatal calves. J. Am. Vet. Med. Assoc., *174*:373–377, 1979.
17. Demigne, C., and Remesy, C.: Fetal and postnatal metabolism in the calf. Ann. Biol. Anim. Biochim. Biophys., *19*:159–165, 1979.
18. Demigne, C., and Remesy, C.: Evolution of the postnatal metabolism in the healthy or diarrhoeic calf. Ann. Rech. Veterinarmed., *20*:12–31, 1979.
19. Demigne, C., Remesy, C., Chartier, F., et al.: Effect of acetate or chloride anions on intestinal absorption of water and solutes in the calf. Am. J. Vet. Res., *42*:1356–1359, 1981.
20. Diamond, J.M.: The epithelial junction: Bridge, gate and fence. Physiologist, *20*:10–18, 1977.
21. Donaldson, R.M., Jr.: Role of enteric microorganisms in malabsorption. Fed. Proc., *26*:1426–1431, 1967.
22. Fettman, M.J., Brooks, P.A., Burrows, K.P., et al.: Comparative evaluation of commercial oral replacement formulae in healthy neonatal calves. J. Am. Vet. Med. Assoc., *187*: (in press), 1985.
23. Fisher, E.W.: Hydrogen ion and electrolyte disturbances in neonatal calf diarrhea. Ann. N.Y. Acad. Sci., *176*:223–230, 1971.

24. George, W.L., Rolfe, R.D., and Finegold, S.M.: Treatment and prevention of antimicrobial agent-induced colitis and diarrhea. Gastroenterology, *79*:366–372, 1980.
25. Granger, D.N.: Intestinal microcirculation and transmucosal fluid transport. Am. J. Physiol., *240*:G343–349, 1981.
26. Grantham, J., and Linshaw, M.: The effect of hyponatremia on the regulation of intracellular volume and solute composition. Circ. Res., *54*:483–491, 1984.
27. Hallback, D.A., Hulten, L., Jodal, M., et al.: Evidence for the existence of a countercurrent exchanger in the small intestine in man. Gastroenterology, *74*:683–890, 1978.
28. Hinshaw, L.B.: Concise review: The role of glucose in endotoxic shock. Circ. Shock., *3*:1–10, 1976.
29. Hoffsis, G.F., Gingerich, D.A., Sherman, D.M., et al.: Total intravenous feeding of calves. J. Am. Vet. Med. Assoc., *171*:67–70, 1977.
30. Jacob, A.I., Goldberg, P.K., Bloom, N., et al.: Endotoxin and bacteria in portal blood. Gastroenterology, *72*:1268–970, 1977.
31. Jones, R., Phillips, R.W., and Cleek, J.L.: Hyperosmotic oral replacement fluid for diarrheic calves. J. Am. Vet. Med. Assoc., *184*:1501–1505, 1984.
32. Kerzner, B., Kelly, M.H., Gall, D.G., et al.: Transmissible gastroenteritis: Sodium transport and the intestinal epithelium during the course of viral enteritis. Gastroenterology, *72*:457–461, 1977.
33. Kleiber, M.: The Fire of Life. New York, John Wiley & Sons, Inc., 1961.
34. Lewis, L.D., and Phillips, R.W.: Water and electrolyte losses in neonatal calves with acute diarrhea. A complete balance study. Cornell Vet., *62*:596–607, 1972.
35. Lewis, L.D., and Phillips, R.W.: Pathophysiologic changes due to coronavirus-induced diarrhea in the calf. J. Am. Vet. Med. Assoc., *173*:636–642, 1978.
36. Lewis, L.D., and Phillips, R.W.: Diarrheic induced changes in intracellular and extracellular ion concentrations in neonatal calves. Ann. Rech. Vet., *4*:99–111, 1973.
37. McClung, H.J., Butler, D.G., Kerzner, B., et al.: Transmissible gastroenteritis: Mucosal ion transport in acute viral enteritis. Gastroenterology, *70*:1091–1095, 1976.
38. Mero, K.N.: Antibiotic-induced malabsorption: Morphologic and microbiologic alterations. Ph.D. thesis, Colorado State University, Fort Collins, Colorado, 1984.
39. Mitchell, A.R.: Understanding fluid therapy. Irish Vet. J., *37*:94–103, 1983.
40. Moon, H.W., and Joel, D.D.: Epithelial cell migration in the small intestine of sheep and calves. Am. J. Vet. Res., *36*:187–189, 1975.
41. Moon, H.W.: Mechanisms in the pathogenesis of diarrhea. A review. J. Am. Vet. Med. Assoc., *172*:443–448, 1978.
42. Mitchell, A.R.: Body fluids and diarrhoea: Dynamics of dysfunction. Vet. Rec., *94*:311–315, 1974.
43. Phillips, R.W.: Water and electrolyte imbalances in diarrhea. *In* Woodard, J.C., and Bruss, M. (eds.): Nutritional and Metabolic Diseases. Boca Raton, Florida, CRC Press, Inc., 1982.
44. Phillips, R.W., Lewis, L.D., and Knox, K.L.: Alterations in body water turnover and distribution in neonatal calves with acute diarrhea. Ann. N.Y. Acad. Sci., *176*:231–243, 1971.
45. Phillips, R.W., and Lewis, L.D.: Milk replacers: Evalaution and use. Bovine Pract., *7*:28–33, 1972.
46. Phillips, R.W., and Lewis, L.D.: Viral induced changes in intestinal transport and resultant body fluid alterations in neonatal calves. Ann Rech. Veterinarmed., *4*:87–98, 1973.
47. Phillips, R.W., and Lewis, L.D.: Intravenous high potassium therapy for diarrheic calves. *In* Proceedings of the International Congress on Diseases in Cattle, 1981, pp. 1529–1536.
48. Phillips, R.W., Huffman, E.M., Cleek, J.L., et al.: The effect of oral chloramphenicol in neonatal calves. *In* Proceedings of the Congress of the European de Pharmacologie et Toxicologie Veterinaires, Toulouse, September, 1982.
49. Phillips, R.W., and Case, G.L.: Altered metabolism, acute shock, and therapeutic response in a calf with severe coronavirus-induced diarrhea. Am. J. Vet. Res., *41*:1039–1044, 1980.
50. Radostits, O.M.: Treatment and control of neonatal diarrhea in calves. J. Dairy Sci., *58*:464–470, 1975.
51. Rollin, R.E.: Clinical and functional changes associated with antibiotic-induced diarrhea

and malabsorption. Ph.D. thesis, Colorado State University, Fort Collins. Colorado, 1984.
52. Rollin, R., Levine, K., Mero, L.N., et al.: Structural and functional changes seen in chloramphenicol-induced malabsorption in calves. *In* Proceedings of the World Congress on Diseases of Cattle, Amsterdam, 1984.
53. Rosenberg, I.H., Solomons, N.W., and Schneider, R.E.: Malabsorption associated with diarrhea and intestinal infections. Am. J. Clin. Nutr., *30*:1248–1253, 1977.
54. Roussel, A.J., Jr.: Principles and mechanics of fluid therapy in calves. Comp. Vet. Med. Ed., *5*:S332–S339, 1983.
55. Stiles, R.P., Grieve, D.G., Butler, D.G., et al.: Effects of fluid intake level and dry matter concentration on the incidence of scours in milk replacer-fed claves. Can. J. Anim. Sci., *54*:73–78, 1974.
56. Storz, J., Collier, J.R., Eugster, A.K., et al.: Intestinal bacterial changes in *Chlamydia*-induced primary enteritis of newborn calves. Ann. N.Y. Acad. Sci., *176*:162–175, 1971.
57. Storz, J., Doughri, A.M., and Hajer, I.: Coronaviral morphogenesis and ultrastructural changes in intestinal infections of calves. J. Am. Vet. Med. Assoc., *173*:633–635, 1978.
58. Summers, R.W.: Role of motility in infectious diarrhea. Gastroenterology, *80*:1070–1071, 1981.
59. Swan, K.G., Spees, E.K., Reynolds, D.G., et al.: Microvascular architecture of anthropoid primate intestine. Circ. Shock, *5*:375–382, 1978.
60. Tennant, B., Harrold, D., and Reina-Guerra, M.: Hypoglycemia in neonatal calves associated with acute diarrhea. Cornell Vet., *58*:136–146, 1968.
61. Tennant, B., Harold, D., and Reina-Guerra, M.: Physiologic and metabolic factors in the pathogenesis of neonatal enteric infection in calves. J. Am. Vet. Med. Assoc., *161*:993–1007, 1972.
62. Tennant, B., Reina-Guerra, M., and Harrold, D.: Metabolic response of calves following acute experimental endotoxemia. Ann. Rech. Veterinarmed., *4*:135–147, 1973.
63. Tennant, B., Ward, D.E., Braun, R.K., et al.: Clinical management and control of neonatal enteric infections of calves. J. Am. Vet. Med. Assoc., *173*:654–661, 1978.
64. Toofanian, F., Hill, F.W.G., and Kidder, D.E.: The mucosal disaccharidases in the small intestine of the calf. Ann. Rech. Veterinarmed., *4*:57–69, 1973.
65. Toofanian, F.: Small intestinal infusion studies in the calf. Br. Vet. J., *132*:215–220, 1976.
66. Trump, B.F., Croker, B.P., Jr., and Mergner, W.L.: The role of energy metabolism, ion and water in the pathogenesis of cell injury. *In* Richter, G.W. and Scarpelli, D.G. (eds.): Cell Membranes, Biological and Pathological Aspects. Baltimore, Williams & Wilkins, 1971.
67. Ward, D.E.: Pathophysiology of enteric colibacillosis in the intact neonatal calf. Ph.D. thesis, Cornell University, Ithaca, New York, 1976.
68. Whipp, S.C.: Physiology of diarrhea: Small intestines. J. Am. Vet. Med. Assoc., *173*:662–666, 1978.
69. Willoughby, R.A., and Butler, D.G.: An apparatus for the continuous administration of fluid and electrolytes in large animals. Can. Vet. J., *8*:70–74, 1967.
70. Woode, G.N., Smith, C., and Dennis, M.J.: Intestinal damage in rotavirus infected calves assessed by D-xylose malabsorption. Vet. Rec., *102*:340–341, 1978.

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