Calf Diarrhea: A Brief Resume with Observations on Treatment and Prevention

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During the past two decades intestinal absorptive and secretory functions and the intestinal flora have been significantly clarified. Important concepts of intestinal dysfunction have emerged which have proved of immense clinical value (Smith, H.W., 1965 and 1971; Phillips, 1972; Soergel, 1973; Moon, 1974; Smith, B. P., 1976). Despite this, the medical and economic consequences of diarrhea continue to beset the cattle industry (Barnum, et al., 1967; Marsh, H., 1968; Hubbert, 1974; Vollmar, 1974; White, 1976). Diarrheal disease of the calf occurs at a time of complex developmental, environmental and functional change. The surface defenses and enzyme systems of the neonatal gut are maturing in a protective film of maternal antibody, while undergoing increasing stimulation from environmental microbial challenge. The precarious nature of this defense system is not surprising. It is contingent upon a balance of such changing conditions as maternal antibody quantity, quality and delivery (Bush, et al., 1971), environmental microbial challenge (Smith, H. W., 1965 and 1971), and neonatal immunological and intestinal epithelial maturation (Staley, et al., 1972; Corley, et al., 1977). While both infectious and non-infectious etiologic factors are involved (Barnum, et al., 1967), the former in particular (*Escherichia coli, Salmonella spp.*, and reo and corona viruses) is the more significant. Enteropathogenic *E. coli* (EPEC), a major contributor to neonatal diarrheal disease, will be discussed primarily. Four syndromes, septicemia, enterictoxemic, local invasive and enterotoxic, have been described (Moon, 1974), and adverse outcomes may result from endotoxic shock and/or hypovolemic shock, from systemic infection (Moon, 1974) and from malnutrition. The clinician is thus faced with the selection of a multifaceted approach to the problem. Avenues of attack, in addition to prophylactic husbandry, include: passive and active immunization, reduction of challenge, specific antimicrobial therapy, and resolution of fluid and electrolyte loss and shock. This presentation includes a brief resume of the calf scour syndrome, together with observations concerning treatment and control. These are based predominantly upon work reported from this laboratory, and include active and passive immunization, antimicrobial therapy, and modification of intestinal fluid loss.

Colibacillosis occurs in all breeds of beef and dairy calves (Barnum, et al., 1967; Blood and Henderson, 1974). Enteric colibacillosis (local invasive and enterotoxic colibacillosis) is characterized by diarrhea, dehydration, loss of weight, depression, anorexia, and weakness (Moon, 1974). The temperature may or may not be elevated, and calves usually die or recover in several days. It is this form of colibacillosis which is considered to be the most common. It frequently occurs as a herd problem in which morbidity and mortality varies from one herd to another (Barnum, et al., 1967; White, 1976).

Enteric diseases attributed to *E. coli* infection are considered by some workers to be secondary to enteric infections induced by other agents (White, 1976). Calves with chlamydia-induced diarrhea have higher numbers of *E. coli* in the abomasum and ileum than calves without diarrhea (Storz, et al., 1971). Mebus, et al., (1971) suggested that enteric disease of calves caused by a reo-like virus was more severe if *E. coli* were also present in the intestine. They suggested that the primary viral damage to the intestinal epithelium predisposed to overgrowth with *E. coli*. White (1976) indicated that a reo-like virus could cause diarrhea in calves within 12 hours of birth, when first introduced into the herd might affect calves up to six weeks of age or older, and depending upon the secondary bacteria present, mortality rates might reach 50%. A corona-virus has also been found to cause scours in calves usually over five days of age and, when the infection first occurs, calves of up to six weeks old may scour (White, 1976). Diarrhea may continue for several days. Mortality ranges from 1 to

25%. The bovine diarrhea virus (BVD) can also cause diarrhea from 1 to 3 days after exposure, and death in young exposed calves (White, 1976). In salmonella infection, calves are usually affected at six days of age or older (White, 1976). Enterotoxemia can also result in young calves from *Clostridium perfringens* types B, C and D toxins. The disease is usually associated with the sudden change in weather, feed or management (White, 1976). In man, enterotoxic colibacillosis was considered a disease of infancy until recently when DuPont, et al. (1971), produced diarrhea disease in healthy adults by feeding EPEC.

While colibacillosis syndromes occur spontaneously in calves, pigs, lambs and man, most attempts to induce the disease with *E. coli* in the absence of host predisposition have been unsuccessful (Logan and Penhale, 1972; Yeoman, 1977). It is well recognized that colostrum-deprived calves are very susceptible to infection, for they are essentially but not completely agammaglobulinemic at birth (Osburn, 1973). Calves exposed to EPEC during the first day of life developed clinical disease whereas those exposed to the same *E. coli* during the third day of life were not affected (Logan and Penhale, 1972), presumably due to the protection of colostrum. Other workers have also found experimental infection difficult to induce in colostrum-fed calves (Logan and Penhale, 1972). Since calves are usually exposed to infection within a very short time after birth, early protection is indicated and it has been demonstrated that the administration of colostral immunoglobulin (Ig.) prior to *E. coli* challenge confers better protection (Corley, et al., 1977).

Functional closure of the intestinal epithelium to the passage of protein macromolecules occurs 24 to 48 hours after birth (Brambell, 1958; Payne, 1962; Pierce, 1967; Staley, et al., 1972). Ingestion of colostral Ig. is thus essential during the first 24 hours of life and preferably within 5 to 10 hours (Bush, et al., 1971; Berman, 1973; Corley, et al., 1977). The quantity of colostral Ig. absorbed is also important (Fey and Margadant, 1962; Fey, 1964). Peak serum Ig. values occur at an average of 24 hours after birth and range from 12 to 48 hours (Bush, et al., 1971). With normal serum values of 7.5 gram IgG and 0.8 gram IgM per 100 ml, colibacillosis has been found unlikely (Penhale, et al., 1970). To attain such protective levels, intake of 50 grams Ig. or 1.43 grams Ig. per kg body weight is necessary (Penhale, et al., 1970). The volume of colostrum needed to achieve such a dose varies markedly due to diverse Ig. concentrations. In one herd a range of 1.7 to 8.7 grams Ig. per 100 ml colostrum was observed at parturition (Bush, et al., 1971). The colostral Ig. content also falls rapidly within 12 to 24 hours of parturition–an additional reason for early nursing (Bush, et al., 1971; Porter, 1973). The cause of the diverse colostral Ig. concentrations is unknown and correlation with maternal serum Ig. levels is minimal (Bush, et al., 1971). Approximately two-thirds of the variation in uptake observed in the calf however is accounted for by the amount of intake (Bush *et al.*, 1971). In several instances calves may fail to absorb Ig. despite known intake (Klaus, et al., 1969). In one study 4 of 27 calves remained hypogammaglobulinemic despite normally adequate intake during the first 24 hours of life (Bush, et al., 1971). While local Ig. in the gut limits intestinal colonization by EPEC, systemic Ig., especially IgM, limits bacterial invasion and septicemia. The local effectiveness of passive antibody against adherence of the bacteria (Berman, 1973) and the enterotoxic effect would seem to indicate potential benefit from continued colostral feeding (Logan and Penhale, 1972). Although both cross protection between various EPEC strains and correlation between maternal serum Ig. and colostral Ig. are limited, protection can be enhanced by vaccination of the dams (Myers, 1976; Wilson, 1976). In swine, the use of an autogenous vaccine has been found to be efficacious for sow vaccination (Kohler, 1976). With the many factors influencing the efficient transfer of maternal antibody to the newborn, it is understandable that such transfer is often inadequate.

Moon (1974) reported that antibody can induce resistance to colibacillosis and that such antibody to *E. coli* occurs widely in normal animals which have not been artificially immunized. Perhaps normal animals are predisposed to this disease during periods of relative antibody deficiency. Kashiwazaka and Namioka (1969) postulated that not only were newborn pigs predisposed to *E. coli* prior to colostrum absorption but also at three weeks of age when passive immunity waned. Enterotoxic and local invasive colibacillosis has been induced by Hamm and Jones (1974) in calves 3 to 4 weeks of age, a time when serum Ig. levels have been found to be the lowest after colostral feeding. The half life of absorbed IgA and IgM has been reported to be 2 and 4, respectively, while that of IgG was 18 days; others report IgG loss in normal calves to be 4 ± 2% per day (Logan and Penhale, 1972; Fisher, et al., 1976).

Passively transferred antibody, especially IgG, is immunosuppressive while IgM appears to enhance the immunologic response (Schultz, 1973). The neonatal calf is able to produce IgM, IgA and IgG (Porter, 1973) and is able to respond to such antigens as parainfluenza-3, BVD, blue tongue, chlamydia and *E. coli* as long as antibodies are not present in the colostrum (Ingram and Smith, 1965; Osburn, 1973; Schultz, 1973). Specific antibodies have been detected in the feces within 48 hours after the oral administration of *E. coli* in colostrum-deprived calves (Corley, et al., 1977). The oral exposure of preruminant calves to bacterial antigens has been shown to reduce the incidence of diarrhea, the need for therapy, and to improve weight gain (Porter, 1973). Similarly the oral use of a combined reo-corona virus vaccine has been found effective in the control of diarrhea due to these infections (White, 1976). The need for protection from infection from birth on, and the immunologic competence of the bovine fetus have

motivated attempts to immunize *in utero* (Gay, 1971; Corley and Jones, 1973). While immunity can be induced by intra-amniotic injection of *E coli*, the need to develop a practical, harmless technique and the limited cross protection between strains have limited further studies (Corley and Jones, 1973).

As well as passive and active immune mechanisms, other defense mechanisms are of significance in the neonate. The germ-free state at birth also probably predisposes the small intestine to colonization by *E. coli* (Jones and Rutter, 1972). This predisposition of the germ-free may be due to sluggish motility, high oxidation reduction potentials, and lack of microbial antagonism. Diet affects porcine intestinal colonization by *E. coli* at weaning. High energy diets, abrupt dietary changes and unrestricted feeding predispose to this syndrome (Kenworthy and Crabb, 1963; Palmer and Hulland, 1965; Smith and Halls, 1968) and overfeeding is frequently said to cause diarrhea in calves. Diarrhea has also been reproduced experimentally by feeding a large amount of sucrose (Whitten and Phillips, 1971). Antibiotic feeding has been reported to predispose the pig intestine to colonization with *E. Coli* (Palmer and Hulland, 1965). Colonization of the gut is certainly facilitated by adhesion. Innate resistance of certain strains of swine to colonization by EPEC with failure of adhesion have been reported (Rutter and Anderson, 1972).

Restriction of colonization of the gut by chemotherapy and antibiotics has been the treatment and often the prophylaxis of choice ever since the introduction of these drugs (Barnum, et al., 1967). Currently, such antibiotics as oxytetracycline, neomycin, chloramphenicol, and ampicillin, along with various sulphonamides and nitrofurans are in common use. Resistance to tetracyclines and sulphonamides are common and numerous instances of resistance to chloramphenicol, neomycin and ampicillin have been reported (Ziv, 1976). The veterinarian therefore has been plagued with the development of resistant organisms, with consequent need to utilize newer, more effective drugs.

The diversity of colibacillosis syndromes also imposes a need to use drugs which are both locally and systemically active. The search for new, efficacious products along with increasing governmental constraints has been made more difficult by the lack of a suitable model (Logan and Penhale, 1972) with optimal reproductibility and minimal variance.

Colibacillosis is easily reproduced in colostrum-deprived calves; the resulting syndrome is variable, usually systemic, and often fatal. Acquisition of calves with assured colostrum deprivation is often difficult. The systemic administration of IgM fraction of colostral whey has permitted the development of a model in which septicemia was excluded (Logan and Penhale, 1972). More recently it has been found possible to reproduce the enterotoxic and local invasive forms of colibacillosis in three-week-old calves (Hamm and Jones, 1974). Utilizing such a model, it has been possible to determine dose responses and demonstrate efficacy of various pharmaceutical products, such as the efficacy of 40 and 80 mg twice-daily doses of gentamicin sulphate in contrast to the lack of benefit of 0 and 10 mg doses (Figure 1) (Hamm and Jones, 1974). Pankhurst (1976) reports the efficacy of a new aminocyclitol antibiotic (apramycin) in clinical cases of pneumoenteritis and scours; Ziv (1976) has produced evidence to support the use of the quindine derivative oxolinic acid; and Keefe (1977) has reported the efficacy of amoxicillin for colibacillosis of calves.

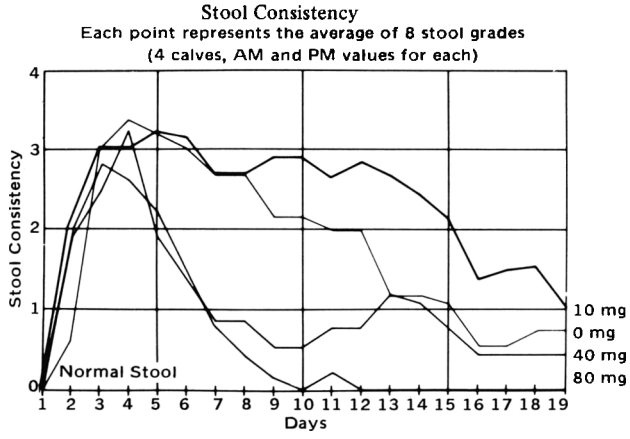

Figure 1. A comparison of 4 treatments (A-0, B-10, C-40, D-80 mg per lb. body wt.). Gentamicin twice daily for 3 days in experimentally induced *E. coli* diarrhea of calves, 4 calves per group. Based upon multivariate comparisons the stool characteristics were significantly improved in Groups C and D in relation to A and B. A tendency for recurrence occurred in Group C.

Diarrhea is especially characteristic of the enterotoxic or locally invasive syndromes of colibacillosis. The ability of the strains of *E. coli* to produce enterotoxin is indicated by injection into ligated intestinal loops and the subsequent fluid accumulation (Moon, 1974). In contrast to enterotoxin, endotoxin does not cause fluid loss by the small intestine following intraluminal exposure (Moon, 1974). Endotoxin is produced by all *E. coli* but detectable amounts of enterotoxin only by certain strains. Absorption of enterotoxin into the blood is not necessary for the induction of diarrhea, presumably does not occur, and in most species there is a gradient with the anterior small intestine being highly sensitive to enterotoxin and the posterior intestine relatively resistant (Moon, 1974). It has been suggested that toxin absorption causes a toxemic form of the disease, the so-called collapse syndrome. It is assumed that the small intestine is the sole site of fluid production in enterotoxic colibacillosis, although the stomach and colon apparently have not been tested (Moon, 1974). The enterotoxin-induced secretions occur across an intact mucosa without alteration and the response to *E. coli* enterotoxin is similar to the response to cholera enterotoxin (Smith, H. W., 1972; Moon, 1974). Soergel (1973) indicated that the resting

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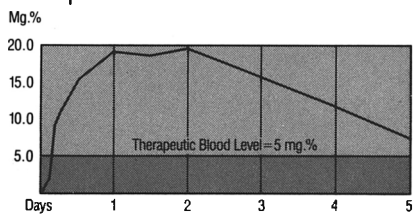

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small intestinal and perhaps colonic mucosa constantly secreted an isotonic protein-free electrolyte solution and this secretion was greatly exaggerated in and responsible for the diarrhea caused by vibrio cholera and enterotoxic *E. coli*. This intestinal secretion is an active energy-requiring process regulated by intracellular availability of cyclic AMP. During *in vitro* studies, agents which increase cyclic AMP synthesis by adenyl cyclase (e.g., prostaglandins) or which inhibit cyclic AMP breakdown by phosphodiesterase (e.g., theophylline) stimulate secretion by the mucosal membrane (Kimberg, et al., 1971). Soergel (1973) stated that these observations have led to the speculation that diarrhea in cholera patients can be treated with salicylates which inhibit local prostaglandin formation. It is probable however that the effect of cholera enterotoxin is not mediated by prostaglandins. Vane (1971), Smith and Willis (1971) and Ferreria, et al., (1971) have all indicated that aspirin inhibits the synthesis of prostaglandins in several *in vitro* systems. Subsequently, Finck, et al. (1972), have reported that 25 mg/kg aspirin administered intravenously significantly depressed fluid output in a feline cholera toxin gut-loop model.

Jacoby, et al. (1972), suggested that an oral drug to reverse the massive loss of fluid and electrolytes by antagonizing the effect of cholera endotoxin on secretory mechanisms of the small intestine would seem a rational means of attacking the cholera problem. They tested aspirin, indomethacin, phenylbutazone, sodium salicylate, dexamethasone, prednisolone and ethacrynic acid in a rat cholera model. The steroid anti-inflammatory agents, dexamethasone and prednisolone, were effective in relatively high doses (4 mg/kg by subcutaneous injection). Of the non-steroids tested, indomethacin was the most active showing 59% inhibition of the cholera toxin effect with a 1 mg/kg dosage subcutaneously and as much as 100% inhibition with 15 mg/kg orally; 50 mg/kg subcutaneously of aspirin provided 99% inhibition; the same dose orally gave 45% of inhibition, and a 100 mg/kg orally gave 90% inhibition; 16 mg/kg of phenylbutazone gave a 68% inhibition. Preliminary evidence (Figures 2 and 3) utilizing a calf enterotoxic colibacillosis model (Hamm and Jones, 1976) would seem to indicate that similar antiprostaglandin treatment with flunixin meglumine (Banamine, Schering Corporation, Kenilworth, New Jersey) can be effective. The report of DuPont and Hornick (1973) sounds a word of caution when controlling diarrhea without suppressing the etiologic agent. They recalled the use of opiates to increase susceptibility to enteric infections in experimental animals and reported human experiments with similar results. In man the use of diphenoxylate hydrochloride and atropine sulphate (Lomotil), alone or with antibiotics, accentuated the systemic response to Shigella enteritis. Flunixin meglumine does not however appear clinically to suppress gut motility (Hamm and Jones, 1976).

Dehydration resulting from scours has been reported to be the most common cause of death (Tennant, et al., 1972). Clinical signs of dehydration first occur when fluid loss reaches 5 to 6% of body weight. The calf becomes moribund when a fluid loss of approximtely 15% of body weight occurs (Robinson, et al., 1974). In addition to antibiotics, the preferred treatment has traditionally been the intravenous administration of lactated Ringer's solution. The amount should be sufficient to replace the deficit plus (depending upon the degree and duration of diarrhea) 4 to 8 liters per day for the next 1 to 4 days (Robinson, et al., 1974). Such a therapeutic regimen comprising antibiotics and parenteral electrolyte solutions has been neither highly efficacious nor entirely practical.

In view of the similarity between cholera and enterotoxic colibacillosis it is pertinent to consider the recent significant advances in practical cholera therapy. The concept that the fluid loss in cholera resulted from exaggeration of normal intestinal

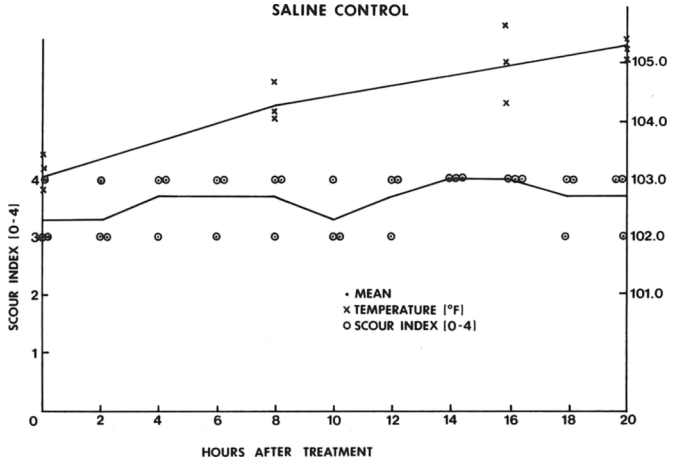

Figure 2. Temperature observations at 0, 8, 16 and 24 hours in 3 calves having experimentally induced colibacillosis. Scour observations every 2 hours in same 3 calves (scour index: 0, normal, to 4+, loose, watery). Placebo treatment was 10 ml physiological saline by intravenous injection.

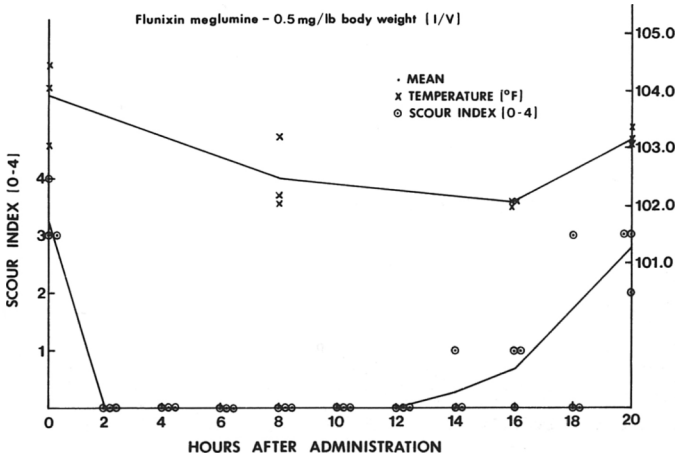

Figure 3. Temperature observations at 0, 8, 16 and 24 hours in 3 calves having experimentally induced colibacillosis. Scour observations every 2 hours in same 3 calves (scour index: 0, normal, to 4+, loose, watery). Treatment was 0.5 mg/lb. body weight flunixin meglumine (SCH 14714) by intravenous injection at 0 hours.

secretory processes was postulated in the 18th century and again in 1889. It was only in the last decade that this was confirmed (Carpenter, 1976). In the normal animal there is a continual flux of water from the blood to the intestinal lumen and an opposed flux from the intestinal lumen to the blood. Thus the net flow in either direction depends on one limb of this flux predominating. In diarrhea, therefore, there is a net flow of water from the blood to the lumen. A similar bi-directional flux holds for electrolytes such as chloride and sodium whose net flow is also altered in diarrhea. Soergel (1973) indicates that water soluble solutes enter the cell primarily by special carrier mechanisms (facilitated diffusion). A reciprocal exchange with the mucosal solution exists for sodium and hydrogen ions, and in ileum and colon for chloride and bicarbonate ions. In addition, a mechanism is present for the entry of sodium ions coupled to those of glucose, galactose, and amino acids.

Based upon the above information, a new therapeutic concept for cholera, the oral administration of an isotonic glucose containing electrolyte solution, was developed (Hirschorn, et al., 1973). It permitted absorption at a rate similar to that of secretion with excellent results. Hynie, et al., (1974), commented upon the similar mechanism of action cholera and coli enterotoxins, and suggested that use of similar therapy in enterotoxic colibacillosis of calves, therapy which was subsequently found efficacious (Raskova, et al., 1976). At a similar time Saperstein (1974) indicated the following justification for an oral electrolyte prescription–facilitation of sodium transport by glucose and certain amino acids, the need for calorie replacement in an animal in which the needs were enhanced, the loss of lactase during scouring with a need to avoid dietary lactose, the loss of carbohydrate, potassium and magnesium. Subsequently, the following oral electrolyte formulation was developed–sodium chloride 11.64%, calcium gluconate 2.2%, magnesium sulphate 0.61%, monopotassium phosphate 8.68%, glycine 21.2%, and dextrose 55.67%. This mixture was added to two quarts of water and fed twice daily instead of milk replacer for up to five days. Antibiotic therapy was used concurrently as indicated. In comparison to a control group receiving traditional therapy, mortality was significantly less (Hamm and Hicks, 1975).

Thus, in addition to the use of the traditional hygienic practices, the control and treatment of colibacillosis in calves should include the early intake (less than 12 hours after birth) of adequate colostral Ig. (51 grams per kg body weight). Therapy should comprise appropriate antibacterial drugs and rehydration with a "cholera-type" oral glucose/amino acid/electrolyte formulation. There is also promise for the potential of new anti-diarrheal anti-prostaglandin drugs and for the development of improved immunizing procedures both of the dam and of the calf, the latter in particular by oral immunization. The etiology of extreme variations in the provision and supply of passive antibody to the calf requires further elucidation, as do the acquisition and inheritance of innate resistance, and the more complex cross protection of vaccines for enteropathogenic *E. coli*.

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