PEER REVIEWED

Use of Antibiotics to Prevent Calf Diarrhea and Septicemia

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Abstract

This article reviews studies related to the use of antimicrobial agents to prevent calf diarrhea and septicemia, and discusses whether prophylactic administration of antibiotics in neonatal calves is effective and indicated. Orally administered chlortetracycline, oxytetracycline, tetracycline and neomycin have label claims in the US for the "control" or "aid in the control" of calf diarrhea caused by bacteria susceptible to the antibiotic. Chlortetracycline and oxytetracycline (0.15 to 6.0 mg/lb [0.32 to 13.2 mg/kg], q 24 h, PO) are efficacious for preventing calf diarrhea and increasing growth rate in milk-fed calves, and chlortetracycline (3 mg/lb [7 mg/kg], q 12 h, PO) is efficacious for decreasing mortality when administered to prevent diarrhea in neonatal calves. There are no antibiotics with a label claim for prevention of calf septicemia. Because of the apparent lack of efficacy studies for tetracycline and neomycin, and because extra-label use of drugs for routine disease prevention and for increasing weight gain and feed efficiency in calves is prohibited under the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994, only oral chlortetracycline or oxytetracycline should be administered to prevent calf diarrhea.

Résumé

Cet article fait le tour des études portant sur l'utilisation des antibiotiques pour la prévention de la diarrhée et de la septicémie chez les veaux et discute de la valeur de l'administration prophylactique d'antibiotiques chez les veaux nouveau-nés. Aux Etats-Unis, les étiquettes des antibiotiques administrés par voie orale, telle que la chlortétracycline, l'oxytétracycline, la tétracycline et la néomycine, promettent le contrôle ou l'aide au contrôle de la diarrhée causée par des bactéries susceptibles aux antibiotiques chez les veaux. La chlortétracycline et l'oxytétracycline (0.15 to 6.0 mg/lb [0.32 to 13.2 mg/kg] au 24 h, per os) sont efficaces dans le traitement de la diarrhée chez les veaux et permettent un accroissement du taux de croissance des veaux nourris au lait. De plus, la chlortétracycline permet la diminution du taux de mortalité lorsque administrée chez les veaux nouveau-nés pour prévenir la diarrhée. Il n'y a pas d'antibiotiques qui promettent de prévenir la septicémie chez les veaux. Parce qu'il ne semble pas exister d'études sur l'efficacité de la tétracycline et de la néomycine et parce que l'utilisation hors homologation des médicaments n'est pas permise pour la prévention routinière des maladies ou l'augmentation du taux de croissance et du taux de conversion alimentaire, selon le code de l'AMDUCA de 1994, seule l'administration orale de chlortétracycline et d'oxytétracycline est recommandée pour la prévention de la diarrhée chez les veaux.

Introduction

Calf diarrhea is the leading cause of mortality in dairy calves[31] and an important cause of morbidity and mortality in beef calves.[32] The three principle methods used to reduce the incidence and severity of calf diarrhea are: 1) administration of enterotoxigenic *Escherichia coli* (ETEC), rotavirus and coronavirus vaccines to cows and heifers in late gestation, 2) ensuring adequate transfer of passive immunity by optimizing colostral immunoglobulin administration and absorption, and 3) decreasing enteric pathogen load in the environment. A fourth but non-approved method for preventing calf diarrhea is the administration of oral antibiotics in an extra-label manner to prevent diarrhea and thereby decrease mortality in newborn calves. The purpose of this review is to critically examine studies related to the use of antibiotics to prevent naturally acquired diarrhea and septicemia in calves, and to discuss the appropriate use of antibiotics to prevent calf diarrhea and septicemia.

Antibiotics with a Label Claim to Prevent Calf Diarrhea

Only four orally administered antibiotics (chlortetracycline, oxytetracycline, tetracycline and neomycin) are currently labeled in the United States for the "control" or "aid in the control" of calf diarrhea caused by bacteria (*E. coli* and *Salmonella spp.*) susceptible to the antibiotic (Table 1; the list of trade name products is not exhaustive). The tetracycline group of antibiotics can be administered to dairy, beef and veal calves, whereas neomycin can only be administered to dairy and beef calves. There are no parenterally administered antibiotics with a label claim for prevention of calf diarrhea, and no antibiotics have a label claim for prevention of calf septicemia.

Antibiotic Efficacy for Preventing Calf Diarrhea

The five critical measures of antibiotic efficacy in preventing calf diarrhea are, in descending order of

Table 1. Antibiotics with a label claim for the control or aid in the control of bacterial diarrhea in calves less than 1 month of age. The list of trade name products is not exhaustive.

Formulation	Dosage schedule	Product
chlortetracycline hydrochloride		
powder	5 mg/lb, q 12 h PO in solution for up to 5 days[a]	Aureomycin Soluble Powder Concentrate, Fort Dodge; CTC Soluble Powder Concentrate, Durvet; Purina Chek-R-Mycin 10X, Purina Mills
tablet	5 mg/lb, q 12 h PO for 3 to 5 days[a]	Aureomycin Tablets, Fort Dodge
powder	0.25 mg/lb, q 12 h PO in milk replacer or feed	Aureomycin 90 Granular Type A Medicated Article, Aureomycin 100 Granular Type A Medicated Article, Alpharma; CLTC 100 MR, Philbro; CTC 5, Alpharma
oxytetracycline hydrochloride		
powder	10 mg/lb, PO daily in water for up to 5 days[e]	Terramycin-343 Soluble Powder, Pfizer Animal Health
tablet	2.5 mg/lb, q 12 h PO for up to 4 days	Terramycin Scours Tablets, Pfizer Animal Health
powder	0.5 mg/lb, q 12 h PO	Terramycin Soluble Powder, Pfizer Animal Health
powder	0.25 mg/lb, q 12 h PO	TM-50D, Philbro; Aureomycin 50 Granular Type A Medicated Article, Alpharma
feed additive	50 g oxytetracycline/ton	OTC 50, Durvet
tetracycline hydrochloride		
bolus	5 mg/lb, q 12 h PO for 3-5 days[a,d,e]	5-way calf scour bolus, Agrilabs; Polyotic Oblets, Fort Dodge
powder	5 mg/lb, q 12 h PO for 3-5 days[a,d,e]	Tetracycline Hydrochloride Soluble Powder-324, AgriLabs, AgriPharm, Butler, RXV, Vedco, WVS; Tetrasure 324, Fermenta; Tet-sol 324, A.H.A; Duramycin 10 & Duramycin-324, Durvet; Fermycin Soluble, Fermenta; Polyotic Soluble Powder, Fort Dodge
powder	100-200 mg/gallon drinking water[f]	Tetra-324, Premier Farmtech
powder	100-200 mg/gallon drinking water[g]	Tetracycline Hydrochloride Soluble Powder, Butler; Solu/Tet, Vedco
neomycin sulfate		
liquid	5 mg/lb, q 12 h PO for up to 14 days[b,c]	Biosol Liquid, Pharmacia; Neomycin 200, Aspen; Neomycin Oral Solution, Durvet; Neomycin Oral Solution, Phoenix; Neovet Neomycin Oral Solution, RXV.
liquid	not stated[b]	Neo-128, TriBio
powder	5 mg/lb, q 12 h PO for up to 14 days[b,c]	Neomix 325 Soluble Powder and Neomix Ag 325 Soluble Powder , Pharmacia; Neomycin 325 Soluble Powder, Rhone Merieux
oxytetracycline hydrochloride & neomycin sulfate		
milk replacer additive	(100 mg oxytetracycline & neomycin)/gallon	Neo-Terramycin 50/50D, Philbro
milk replacer additive	(50-100 mg oxytetracycline & 100-200 mg neomycin)/gallon	Neo-Terramycin 100/50D, Philbro
milk replacer additive	(125 g oxytetracycline & 250 g neomycin)/ton	Land O'Lakes Instant Amplifier Max NT, Select NT, & Maxicare NT, Land O'Lakes
calf starter additive	(50 g oxytetracycline & 35 g neomycin)/ton	Neo-Terramycin 50/50, Philbro; Moormans NT 10/10, Moorman
calf starter additive	(50 g oxytetracycline & 70 g neomycin)/ton	Neo-Terramycin 100/50, Philbro

[a]Administer 1 hour before or 2 hours after feeding milk or milk replacer.
[b]Can be administered in milk or milk replacer.
[c]If signs such as fever, depression, or going off feed develop, oral neomycin is not indicated as the sole treatment since systemic levels of neomycin are not. obtained due to low absorption from the gastrointestinal tract. If symptoms persist after using the preparation for 2 or 3 days, consult a veterinarian. Treatment should continue 24 to 48 hours beyond remission of disease symptoms.
[d]If improvement is not noted in 3-4 days, consult a veterinarian.
[e]Do not mix with milk or milk replacer.
[f]No label claim for use in milk or milk replacer.
[g]Do not administer to calves being fed milk or milk replacer.

importance: 1) mortality rate, 2) weight gain in survivors, 3) severity of diarrhea, 4) incidence of diarrhea, and 5) duration of diarrhea. Because many of the early studies were uncontrolled, this review of antibiotic efficacy has been restricted to peer-reviewed published studies with adequate numbers, random allocation to groups and inclusion of an appropriate control group.

Efficacy of oral antibiotics

In an extensive 1955 review of the efficacy of antibiotics for preventing diarrhea and increasing weight gain in milk-fed calves, Lassiter concluded that the addition of chlortetracycline and oxytetracycline to milk replacer in the first eight weeks of life increased weight gain and feed consumption, and decreased the incidence and duration of diarrheal episodes.[17] The minimum daily oral doses of chlortetracycline and oxytetracycline required to achieve these beneficial effects were 0.15 to 0.20 mg/lb (0.33 to 0.44 mg/kg) body weight. This conclusion led to the routine addition of chlortetracycline and oxytetracycline to milk replacer in the United States. Unfortunately, none of the references cited by Lassiter reported that oral administration of chlortetracycline and oxytetracycline decreased mortality, which is the most important measure of efficacy. The principal benefits of chlortetracycline and oxytetracycline administration were higher weight gain,[4,19,20,21,23,28] improved coat appearance,[22,28] and decreased severity and duration of diarrhea.[19,27] As all of this research was completed more than 45 years ago, it is unknown whether these beneficial effects are observed today.

In a comprehensive 1960 study involving 280 male Ayrshire calves with unknown status of passive transfer of colostral immunity, different antibiotic treatments were administered twice daily for 15 successive days, beginning at 3 to 7 days of age.[8] Streptomycin administration (3.2 mg/lb [7 mg/kg], q 12 h, PO) resulted in a significant (P = 0.02) reduction in the total number of days with diarrhea in one trial but not in a second trial, but neither trial showed that streptomycin altered mortality rate or weight gain. Penicillin G (3,600 IU/lb [8,000 IU/kg], q 12 h, PO), or neomycin (3.2 mg/lb [7 mg/kg], q 12 h, PO) had no effect on mortality rate, weight gain, or the total number of days with diarrhea. Oxytetracycline (3.6 mg/lb [8 mg/kg], q 12 h, PO) did not alter mortality rate in three studies, but caused a significant (P = 0.001 and P = 0.002) reduction in the total number of days with diarrhea in two studies, but not in a third study. Chlortetracycline (3.2 mg/lb [7 mg/kg], q 12 h, PO) significantly (P = 0.029) decreased mortality rate in one study (0/10 = 0% in chlortetracycline-treated calves; 8/20 = 40% in milk-fed calves), resulted in a significant (P = 0.01, 0.002, 0.01) reduction in the total number of days with diarrhea in three studies, but had no effect on the duration of diarrhea in a fourth study. The postulated mechanism for the beneficial effect of prolonged oral administration of chlortetracycline and oxytetracycline on the incidence and duration of diarrhea was decreased concentrations of *E. coli* in the small intestine and feces.[8] The 1960 study by Dalton *et al*[8] appears to be the only study documenting that prophylactic administration of oral antibiotics decreased mortality.

The daily oral administration of ampicillin (50 to 200 mg by syringe) for 14 days significantly (P = 0.0092) decreased the infection rate with *Salmonella enterica* serotype Dublin in milk-fed calves (ampicillin treated, 0/30 infected; controls, 3/9 infected) and significantly (P = 0.0006) decreased the incidence of diarrhea (ampicillin treated, 2/30 scoured; controls, 6/9 scoured).[16] Oral administration of ampicillin increased weight gain but did not alter mortality rate (ampicillin, 0/30 died; controls, 1/9 died).

In a 1971 study of 10 neonatal Ayrshire male calves in Scotland, furazolidone (6.8 mg/lb [15 mg/kg], q 24 h, PO) used as a preventative had no effect on mortality rate when compared to untreated control calves.[10] The administration of furazolidone in food-producing animals in the US is prohibited by law.

Oral administration of neomycin sulfate (300 mg) daily for the first four days of life tended (P = 0.06) to increase the proportion of calves developing diarrhea (99/233 = 43%), compared to the proportion of untreated calves (58/174 = 33%).[30] Oral administration of neomycin sulfate (11.4 mg/lb [25 mg/kg], q 6 h, n = 10) and tetracycline hydrochloride (5 mg/lb [11 mg/kg], q 12 h, n = 6) for five days increased the occurrence of diarrhea compared to untreated controls (n = 6),[26] whereas two other studies found that oral administration of tetracycline hydrochloride (40 mg, q 12 h; 5 mg/lb [11 mg/kg], q 12 h) did not alter the incidence of diarrhea.[3,23]

In summary, of the five critical measures of antibiotic efficacy, only one study reported a decrease in mortality rate following prophylactic oral antibiotic administration (chlortetracycline, 3.2 mg/lb [7 mg/kg], q 12 h, PO),[8] seven studies reported an increase in growth rate (chlortetracycline and oxytetracycline, (0.15 to 6.0 mg/lb [0.32 to 13.2 mg/kg], q 24 h, PO),[4,8,19,20,21,23,28] very few studies commented on the incidence and severity of diarrhea, and 10 studies reported a decrease in the total number of days with diarrhea.[8,19,27] Interestingly, the efficacy of orally administered neomycin for preventing diarrhea does not appear to have been demonstrated in a study published in a peer-reviewed journal.

Efficacy of parenteral antibiotics

In studies involving male Ayrshire calves without diarrhea (unknown status of passive transfer of colostral immunity), oxytetracycline and streptomycin (3.2 mg/lb [7 mg/kg], q 12 h, IM administered on 15 succes-

sive days, starting at 3 to 7 days of age) had no effect on mortality rate, weight gain, or the total number of days with diarrhea.[8]

In a 1970 study involving 72 Holstein bull calves purchased at one week of age and housed for eight weeks, combined preventive and therapeutic antibiotic administration of one or more antibiotics administered as parenteral oxytetracycline, procaine penicillin or dihydrostreptomycin (mean of 3.5 parenteral treatments/calf), and an oral tablet containing neomycin, polymixin B, sulfathazole and sulfamethazine or an oral tablet of erythromycin (mean of 7.3 oral treatments/calf), significantly (P = 0.0002) decreased the mortality rate (0/18 = 0%) compared to an untreated control group (mortality, 10/18 = 56%).[17] Obviously, such a polypharmaceutical approach cannot be recommended.

Evidenced Based Recommendations for use of Antibiotics to Prevent Diarrhea

The two primary reasons for administering antibiotics to prevent diarrhea in calves are: 1) to decrease *E. coli* bacterial numbers in the small intestine, and 2) to prevent *E. coli* bacteremia, which presumably occurs following translocation of bacteria from the small intestinal lumen.[6] It therefore follows that when antibiotics are administered to calves to prevent diarrhea, the antibiotic should be effective against *E. coli* in the small intestine. The ideal antibiotic should reach therapeutic concentrations in the small intestinal lumen for a long enough period, have some degree of drug penetration through the intestinal wall,[33] and have only a narrow gram negative spectrum of activity in order to minimize potential collateral damage to other enteric bacteria.[25]

Four orally administered antibiotics (chlortetracycline, oxytetracycline, tetracycline and neomycin) are the only antibiotics that can be legally used to prevent calf diarrhea in the United States. Extra-label use of any other antibiotic (or dose, frequency, or route of administration) is not permitted, as extra-label drug use is limited to **treatment** modalities when the health of an animal is threatened, or suffering or death may result from failure to treat. Extra-label use of drugs for routine disease prevention and for increasing weight gain and feed efficiency is therefore prohibited under AMDUCA.

Orally administered chlortetracycline and oxytetracycline can be recommended for preventing calf diarrhea, because a number of studies have been published in peer-reviewed journals documenting efficacy. Only chlortetracycline (3.2 mg/lb [7 mg/kg], PO, q 12 h) has been reported in peer-reviewed studies to decrease mortality rate, whereas both oxytetracycline and chlortetracycline have been documented to decrease the duration of diarrhea.[8] The major drawback with higher oral doses of chlortetracycline is the label requirement that treatment must be administered one hour before or two hours after feeding milk or milk replacer (Table 1), which makes antibiotic administration impractical. The highest label dose of oxytetracycline (10 mg/lb [22 mg/kg], PO daily) must also be administered separately from milk replacer, although not at a specified time interval (Table 1). This requirement is because tetracycline antibiotics as a group are irreversibly bound to calcium, leading to inactivation. Although orally administered chlortetracycline and oxytetracycline are partially absorbed from the small intestine, absorption is reduced when the antibiotic is fed with milk replacer (oral bioavailability when administered with milk is 24% for chlortetracycline[24] and 46% for oxytetracycline[29]).

Orally administered tetracycline and neomycin cannot be recommended for **preventing** calf diarrhea, primarily because of the apparent lack of published efficacy studies with adequate control groups in peer-reviewed journals. In general, tetracycline and neomycin have been labeled by the Food and Drug Administration as being effective for the control of bacterial enteritis (scours, colibacillosis) caused by *E. coli* bacteria susceptible to the antibiotic. Unfortunately, data supporting the treatment efficacy of these antibiotics does not appear to have been published in peer-reviewed journals.

Efficacy of Antibiotics in Preventing Calf Septicemia

Recent studies in lambs[5,9,11,13,14] indicate that oral antibiotic administration can prevent or decrease mortality due to neonatal *E coli* bacteremia (colisepticemia). Studies in piglets[1,12,22] indicate that oral antibiotic administration can decrease mortality due to post-weaning ETEC diarrhea (post-weaning colibacillosis). Similar studies do not appear to have been completed in calves.

"Watery mouth" is a colloquial expression used in Great Britain to describe a collection of clinical signs in neonatal lambs which include lethargy, presence of excessive saliva around the mouth (hence the name), fluid distention of the abomasum and small intestine, and retained meconium.[5,9,11,13,14] Watery mouth is a common cause of death in lambs less than 48 hours of age in Great Britain. The risk of developing watery mouth is increased with intensive indoor lambing systems and when colostrum ingestion is delayed, and *E. coli* bacteremia is frequently present in affected lambs.[5,9,11] It is currently believed that watery mouth occurs when *E. coli* bacteria from a heavily contaminated environment are ingested before the lamb receives significant quantities of colostrum.[13,14] The incidence of watery mouth is greatly decreased when oral antibiotics are administered within 15 minutes to two hours of birth,[9,13] and oral antibiotics are commonly administered to newborn lambs in Great Britain to prevent cases of watery mouth.

In a field study of 204 lambs in Scotland, the oral administration of 80 mg of amoxicillin trihydrate significantly ($P < 0.05$) decreased the incidence of watery mouth (treated, 1/45 = 2%; control, 10/53 = 19%), and in a related study, the oral administration of 140 mg of neomycin sulfate and 140 mg of streptomycin sulfate also significantly ($P < 0.001$) decreased the incidence of watery mouth (treated, 1/57 = 2%; control, 11/49 = 23%). Oral antibiotics were administered within 15 minutes of birth.[9] An experimental study in Scotland demonstrated that prophylactic oral administration of spectinomycin (50 mg, PO once 2 h after birth) decreased the mortality and incidence of bacteremia in colostrum-deprived neonatal lambs,[13] but only to the same level as that observed in colostrum-fed lambs. It is important to note that oral administration of ewe colostrum (23 ml/lb [50 ml/kg] bodyweight) is an effective measure against watery mouth, and commercial colostrum substitutes are also effective.[13] The preference for oral antibiotic administration in Great Britain to prevent watery mouth in lambs is therefore based on convenience and practicality, rather than a demonstrated superiority of oral antibiotics over colostrum and decreased environmental contamination.

Colibacillosis in weaned pigs results from colonization of the small intestine with enterotoxigenic strains of *E. coli*,[22] and therefore has some similarities to watery mouth in lambs, with the major difference being that swine colibacillosis occurs most commonly after weaning. Apramycin (5.7 mg/lb [12.5 mg/kg], PO daily) is approved for the control of *E. coli* diarrhea in pigs in the United States, and results of field trials indicated that apramycin controlled post-weaning colibacillosis when added to the drinking water for 7 to 14 days immediately after weaning.[1,12,22]

It is widely accepted that septicemia is more likely to occur in colostrum-deprived calves, and experimental infection with *E. coli* is considerably more difficult after calves have been fed colostrum.[7] Colostrum appears to confer protection by preventing transepithelial bacterial migration and facilitating phagocytosis of invading bacteria through opsinization.[7] However, the presence of high intestinal bacterial concentrations decreases the efficiency of colostrum absorption in the calf, either by decreasing the permeability of intestinal epithelial cells to immunoglobulin, or enhancing the replacement of permeable cells by cells incapable of macromolecular uptake.[15] Accordingly, the emphasis on preventing colisepticemia in calves should be on ensuring adequate and timely colostrum administration and decreasing environmental contamination. There is currently no evidence to support the administration of oral antibiotics to prevent colisepticemia in calves, and administration of oral or parenteral antibiotics to prevent septicemia in healthy calves is illegal in the United States.

Conclusions

Antibiotic use in milk-fed calves has focused on three main areas: 1) treatment of spontaneous cases of diarrhea (decreasing mortality rate, diarrhea severity and duration), 2) prevention of diarrhea (decreasing mortality rate and the incidence, duration and severity of diarrhea), and 3) increasing weight gain and feed conversion efficiency. The efficacy of antibiotics in the treatment of calf diarrhea has been discussed previously.[6] The evidence supporting prophylactic oral administration of chlortetracycline and oxytetracycline to decrease mortality rate and prevent diarrhea is strong but at least 40 years old. In view of the increasing concern regarding transferable resistance amongst enteric bacteria, and the lack of contemporary studies documenting antibiotic efficacy in preventing diarrhea, the administration of antibiotics in milk replacer and calf starter rations should be re-evaluated.

The conclusion of a 1956 editorial regarding the use of antibiotics to prevent calf diarrhea stated that "it must be emphasized that antibiotic prophylactic treatment cannot be a substitute for better husbandry".[2] This conclusion remains valid. When confronted with a calf diarrhea problem, veterinarians and agricultural producers should continue to emphasize implementation of an effective vaccination program, optimizing colostral transfer of immunoglobulins, sanitizing feeding utensils and decreasing environmental contamination with enteric pathogens, in conjunction with appropriate use of intravenous fluids and oral electrolyte solutions. Finally, the appropriate use of antibiotics to prevent calf diarrhea would be facilitated by publication of controlled, randomized treatment studies in peer-reviewed journals. Unfortunately, most of the data generated by pharmaceutical companies to support their label claim for the "control" or "aid in the control" of calf diarrhea caused by bacteria (*E. coli* and *Salmonella spp.*) susceptible to the antibiotic has not been published and is therefore unavailable for independent evaluation.

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Abstract

An Investigation Into the Possible Relationships Between BVD and TB in Practice

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Outbreaks of both Tuberculosis (*Mycobacterium bovis*) and Bovine Virus Diarrhoea (BVD) were investigated in 2 Gloucestershire herds. One a 60 cow suckler beef unit and the other a 100 cow dairy herd. The study followed the course of both of these diseases in these herds to investigate the proposal that BVD may be producing immuno-suppression and predisposing or exacerbating the effects ofTB within a herd. The conclusions from the beef unit are based on retrospective sampling of animals for evidence of BVD. These results indicated a high level of persistently infected (PI) animals that subsequently became TB reactors and suggests an increased susceptibility to TB was being produced by the PI status. The dairy herd was being monitored in an ongoing vaccine trial when there was both a TB and BVD breakdown. As the evidence was based on contemporary sampling the results here strongly support the proposal that TB could be encouraged by active BVD infection entering the herd. There is some suggestion that the accuracy ofTB testing could be influenced by the presence of BVDV.