

Antibiotic decision making – calf scours

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Abstract

Diarrhea is the leading cause of calf mortality prior to weaning in both beef and dairy calves. Both veterinarians and producers should put some effort into designing rational and effective protocols both for the prevention and treatment of diarrhea. Antimicrobials have long been used to prevent calf diarrhea and are often administered as a treatment. However, it is important to prevent unnecessary use of antibiotics in food animal species to limit the development of resistant bacteria. The purpose of this article is to review existing data on the use of antibiotics given prophylactically for diarrhea prevention and as a treatment for calves with existing disease. Based on current research, the feeding of oral antibiotics to calves to prevent diarrhea cannot be recommended. However, the use of certain antimicrobials to treat select cases of calf diarrhea may be effective in reducing mortality and decreasing the severity and duration of diarrhea. Unfortunately, it is unlikely that any of the antibiotics that are currently approved for the treatment of diarrhea in the United States would be effective. Instead of mass medicating large numbers of calves, antimicrobial therapy should be targeted to specific calves that are likely to develop septicemia or have systemic signs of disease.

Key words: calves, diarrhea, scours, antibiotic, antimicrobial

Résumé

La diarrhée est la cause majeure de mortalité avant le sevrage autant chez les veaux laitiers que chez les veaux de boucherie. Les vétérinaires aussi bien que les producteurs devraient faire un effort pour planifier des protocoles rationnels et efficaces pour la prévention et le traitement de la diarrhée. Les antimicrobiens ont longtemps été utilisés pour prévenir la diarrhée chez les veaux et sont souvent administrés en traitement. Toutefois, il est important de limiter l'utilisation inutile des antibiotiques chez les espèces destinées à l'alimentation afin de freiner le développement de bactéries résistantes. Le but de cet article est de faire un survol des données existantes sur les antibiotiques utilisés prophylactiquement pour prévenir la diarrhée ou administrés sous forme de traitement pour les veaux déjà atteints. Les recherches en cours indiquent que l'utilisation par voie

orale d'antibiotiques pour prévenir la diarrhée chez les veaux ne peut pas être recommandée. Toutefois, l'utilisation de certains antibiotiques pour le traitement de cas particuliers de diarrhée chez les veaux peut efficacement réduire la mortalité et diminuer la sévérité et la durée de la diarrhée. Hélas, il est probable qu'aucun des antibiotiques actuellement approuvés pour le traitement de la diarrhée aux États-Unis ne serait efficace. Plutôt que de viser la médication massive d'un grand nombre de veaux, la thérapie antimicrobienne devrait cibler précisément des veaux qui ont de grande chance de développer une septicémie ou qui montrent des signes systémiques de maladie.

The Use of Antibiotics to Prevent Calf Diarrhea

Calf health should be a priority on both beef and dairy farms. Despite this importance, the USDA Dairy 2007 study showed a preweaned heifer calf mortality rate of 8.7%, and reported that only 40% of farms can supply an adequate number of replacements from their own herd. Although mortality is slightly less in beef calves, 4 to 5% still die prior to weaning. In both beef and dairy calves, diarrhea represents the most common reason for death loss prior to weaning. Therefore, practitioners and producers spend a significant amount of time trying to prevent diarrhea and also ensuring that good treatment programs are in place when diarrhea does occur. The 3 main principles of diarrhea prevention in both beef and dairy cattle include: 1) use of a vaccine in late-gestation cattle containing enterotoxigenic *E. coli* (ETEC), rotavirus, and coronavirus; 2) making sure a good colostrum program is in place, ensuring ingestion of immunoglobulins by the calf; and 3) decreasing the load of enteric pathogens in the environment through sanitation, hygiene, housing, and pasture management.

Historically many producers (particularly in the dairy and veal industries) have used the feeding of oral antibiotics to prevent diarrhea, and hopefully decrease mortality in newborn calves. However, the practice of continually feeding antibiotics to calves is now prohibited in many countries, and the efficacy of feeding antibiotics to calves as a method of diarrhea prevention has not been proven effective in recent studies.

Almost 60 years ago, a thorough review was published on the efficacy of antibiotics for preventing diarrhea and improving weight gain in dairy calves.¹⁵ The author concluded that the addition of chlortetra-

cycline and oxytetracycline to milk replacer in the first 8 weeks of life decrease the incidence and severity of calf diarrhea. The minimum daily doses necessary for efficacy in this study were 0.15 to 0.20 mg/lb (0.33 to 0.44 mg/kg), which led to the routine inclusion of these antibiotics in milk replacers throughout the United States. Unfortunately, this study did not look at critical factors such as mortality rate in calves or incidence of diarrhea. The primary benefits of oral antibiotics were found to be higher weight gain and decreased severity and duration of diarrhea. As discussed in another review article, there were several studies done in the 1960s and 1970s using various antibiotics (including ampicillin, chlortetracycline, furazolidine, neomycin, oxytetracycline and streptomycin) to prevent diarrhea in calves.⁵ Although results of these studies varied, only 1 study documented a decrease in mortality rate from diarrhea due to prophylactic oral administration of chlortetracycline.⁸ A few studies did find a decrease in the total number of days of calf diarrhea associated with antibiotics;^{5,8} however, other studies (particularly with neomycin) found increased rates of diarrhea in antibiotic-treated calves.^{21,22} Quite a few of these older studies found oral administration of various antibiotics did not change the incidence of diarrhea in calves as compared to untreated controls.³

More recent studies have found either oral antibiotics had no effect on decreasing calf diarrhea, or in some cases diarrhea rates actually increased in calves fed antibiotics. For example, a study in California fed 1 group of Holstein heifers monensin in the starter ration as compared to another group that received lasalocid and chlortetracycline (Aureomycin®) for the first 12 weeks of life (in addition to non-medicated milk replacer or whole milk). Antibiotic treatment of calves provided no advantage in average daily gain, feed efficiency or the proportion of calves treated for diarrhea.¹³ In another study, Holstein heifers were fed milk replacer medicated with oxytetracycline and neomycin or an unmedicated milk replacer than contained a probiotic (Enteroguard - no longer on the market). Once again, body weight gain, feed efficiency and the incidence and severity of diarrhea were similar between groups.¹⁰ In a third study, 358 dairy calves were divided into 4 groups: medicated milk replacer (neomycin and tetracycline for the first 14 days of life) plus the administration of trimethoprim-sulfamethoxazole, spectinomycin, penicillin and bismuth-pectin for treatment of diarrhea (referred to as conventional therapy); medicated milk replacer for the first 14 days of life and bismuth-pectin for diarrhea and other antibiotics only in cases of fever or depressed attitude (targeted therapy); non-medicated milk replacer with antimicrobial treatment for diarrhea (same treatments as conventional therapy group above); and non-medicated milk replacer with targeted therapy.²

Calves fed a medicated milk replacer had 31% more days with diarrhea as compared to calves fed non-medicated milk replacer.

In a 2007 survey, about 60% of dairy farms in the United States fed medicated milk replacers to pre-weaned heifer calves, most commonly a combination of oxytetracycline and neomycin.²⁶ However a new federal regulation that began in 2010 restricts the feeding of medicated milk replacers to a period of 7 to 14 days. Thus, continuous feeding of antibiotics in the milk from birth to weaning is no longer permitted. This is meant to transition the use of oral antibiotics in calves from prophylactic to therapeutic. Medicated milk replacers should now be reserved for the treatment of bacterial enteritis (diarrhea) and bacterial pneumonia in dairy calves, and not for prophylactic prevention. Since the late 1990s, the European Union has prohibited the sale of milk replacers and other animal feeds containing antibiotics. All feed and milk replacers for dairy cattle must be sold as non-medicated, and then antibiotics can be added only for therapeutic use (for example, in calves with diarrhea). Australia and New Zealand also have strict laws regarding the importation of any animal feed, and these products are generally non-medicated as well. Overall, the conventional practice of adding antibiotics to milk or milk replacers for prophylactic use is being discouraged worldwide. The majority of modern studies fail to find any benefit to use antibiotics as a prevention for diarrhea and - when using an evidence-based approach - cannot be recommended.

The Rationale for Using Antibiotics as a Treatment for Calf Diarrhea

Use of antibiotics as an ancillary treatment for calves with diarrhea is a controversial topic with strong opinions on both sides. Several articles have been published indicating that antibiotics are contraindicated in calves with diarrhea or that they serve no beneficial purpose.^{9,12} In contrast, other studies have indicated antibiotics are effective in reducing mortality rate and speeding recovery in calves with diarrhea.^{6,7} To begin the discussion, it is important to establish a rationale or indication for the use antibiotics in calves with diarrhea. The 2 primary treatment goals of antibiotics in calves with diarrhea would be 1) to prevent bacteremia and 2) decrease the number of coliform bacteria in the small intestine.

Several studies have reported a significant number of calves with diarrhea subsequently develop bacteremia. An initial study in the early 1960s reported that colostrum-deprived calves with diarrhea were frequently bacteremic (14/17 calves or 82%).²³ In contrast, none of the diarrheic calves in this study that had received colostrum were bacteremic (0.26 or 0%). A study conducted

on a large calf rearing facility in California examined 169 dairy calves with severe diarrhea.¹¹ 129 of the 169 calves (76%) had failure of passive transfer, and 47 of the 169 (28%) calves were bacteremic (predominantly *E. coli*). Another study done in Prince Edward Island, Canada looked at the prevalence of bacteremia in 252 calves with diarrhea.¹⁶ Seventy-eight of the 252 (31%) calves in this study were bacteremic (predominantly *E. coli*). As noted previously, the percentage of calves with bacteremia was significantly higher in the failure-of-passive-transfer group (47/103 or 46%) as compared to calves with adequate passive transfer (21/116 or 18%). Taken together, these studies indicate that we can assume 1/3 of calves with severe diarrhea are bacteremic, and the percentage is likely significantly higher in calves with failure of passive transfer. Although some have argued that antibiotic use in calves with diarrhea is inappropriate and leads to the emergence of resistant bacteria, a case can be made that the use of antibiotics to prevent and/or treat bacteremia in calves with diarrhea and systemic signs of disease is warranted. Withholding effective treatment (antibiotics) for a life-threatening disease, such as bacteremia in calves with diarrhea, should not be condoned on animal welfare grounds.⁶

Another potential reason for antibiotic therapy in calves with diarrhea is coliform overgrowth of the small intestine (Figure 1). Research conducted in the 1920s documented increased numbers of *E. coli* bacteria in the abomasum, duodenum, and jejunum of calves with diarrhea.^{4,24} More recent studies have consistently found increased numbers of intestinal *E. coli* in calves with naturally acquired diarrhea, regardless of the

age of the calf or the cause of the diarrhea.^{14,28} Specifically, the numbers of *E. coli* bacteria increase from 5 to 10,000-fold in the duodenum, jejunum, and ileum of calves with scours, even when rotavirus or coronavirus is identified as the cause of diarrhea.⁶ This small intestinal overgrowth of the intestines with coliform bacteria can persist after the pathogen causing the diarrhea is gone.²⁸ The increased numbers of coliform bacteria in the small intestine of calves with diarrhea is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia.²⁰ Therefore, there is some logic to the use of antimicrobials in scouring calves to decrease the number of intestinal coliform bacteria. This could potentially prevent the development of bacteremia, decrease calf mortality, and decrease damage to the small intestine, facilitating digestion and absorption and increasing growth rate.⁶

Efficacy of Using Antibiotics in Calves with Diarrhea

An extensive review published in 2004 examined the question of whether or not antibiotics were effective in diarrheic calves.⁶ It went back and reviewed articles published since 1950, and included studies with both orally and parenterally administered antibiotics in either naturally acquired or experimentally-induced diarrhea. The author examined the effects of antibiotics on 4 critical measures of antimicrobial success in decreasing order of importance: 1) mortality rate; 2) growth rate in survivors; 3) severity of diarrhea in survivors; and 4) duration of diarrhea in survivors. The review looked at

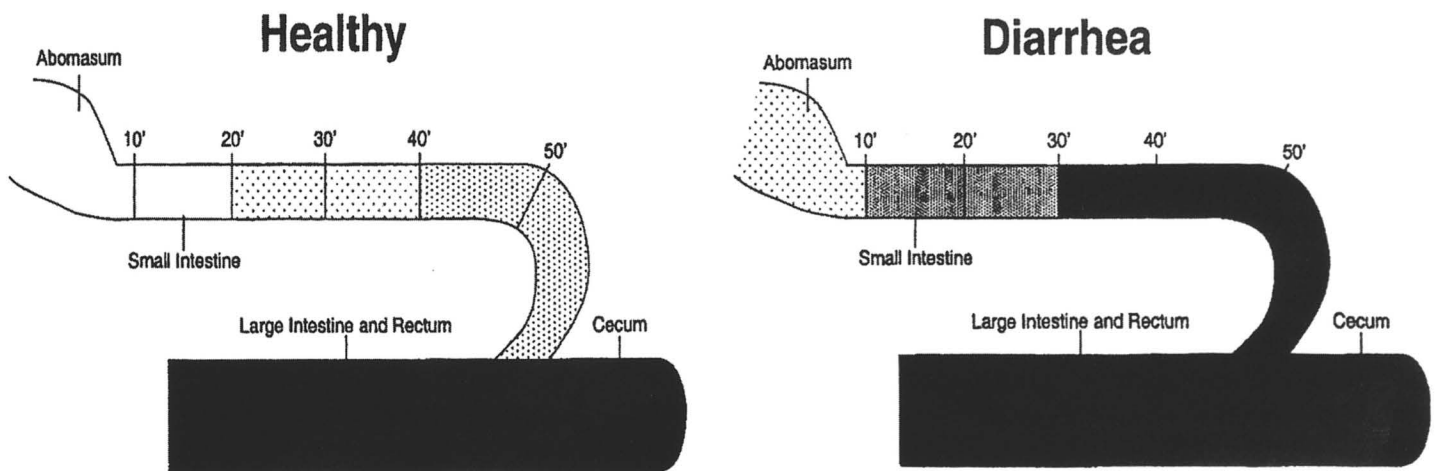


Figure 1. Schematic of the distribution and concentration of *Escherichia coli* bacteria in the intestinal tract of a calf with undifferentiated diarrhea and a similarly aged calf without diarrhea. The figure indicates that the number of *E. coli* in the large intestine of diarrheic and healthy calves is similar, but that diarrheic calves have increased *E. coli* numbers in their small intestine, particularly in the distal jejunum and ileum. Figure reprinted with permission from Constable, 2004.

over 20 different published studies involving a variety of antimicrobials, several of which would be illegal to use in the United States (ie. chloramphenicol, furazolidone, or marbofloxacin). The results indicated that specific antibiotics were effective in reducing mortality and increasing growth rate when administered to calves with diarrhea. Several studies provided evidence that even calves with simple diarrhea (without systemic signs of disease) seemed to recover faster with antibiotics, as opposed to calves that did not receive antibiotics.

Some veterinarians feel that oral or parenteral administration of antibiotics to calves with diarrhea is contraindicated. The arguments most commonly used to support this approach include: 1) oral antibiotics will alter intestinal flora and will thereby induce diarrhea or exacerbate existing diarrhea; 2) antibiotics will harm "good" intestinal bacteria more than "bad" bacteria; 3) antimicrobial use in calves with diarrhea is not effective; and 4) the use of antibiotics will provide a selection pressure on the enteric bacterial population, likely leading to increased antimicrobial resistance.⁶ There is solid evidence to indicate the use of antimicrobial drugs can decrease mortality in calves and there is no evidence to support the argument that antimicrobials "harm the good bacteria more than the bad." However, the emergence of resistant bacteria is certainly serious and is something the veterinarian must take into account before treating calves with diarrhea.

Which Antibiotics Should be Used in Calves with Diarrhea?

Table 1 contains a list of antimicrobials currently approved for the treatment or prevention of diarrhea in the United States. Currently oxytetracycline administered parenterally and chlortetracycline, neomycin, oxytetracycline, sulfamethazine, and tetracycline administered orally, are the only antimicrobials labeled in the United States for the treatment of calf diarrhea. Of these, none have been shown to be consistently effective in peer-reviewed studies. As discussed above, when treating calves with diarrhea the 2 primary goals of therapy are to 1) decrease the number of *E. coli* bacteria in the small intestine and 2) to treat potential *E. coli* bacteremia. With these goals in mind, the target of antimicrobial therapy in calves with diarrhea should be coliform bacteria both in the blood and small intestine.

Since none of the approved drugs for treating diarrhea in the United States are likely to be effective, extra-label use is likely justified. Some efficacy has been described for oral amoxicillin in the treatment of calves with experimentally induced diarrhea,^{3,18} but was not effective in the treatment of naturally acquired diarrhea in beef calves.¹⁹ Amoxicillin trihydrate (4.54 mg/lb or 10 mg/kg PO q12h) or amoxicillin-trihydrate-clavulanate

potassium m(5.7 mg or 12.5 mg combined drug/kg PO q12h) for at least 3 days is one antimicrobial approach that likely has some efficacy for calves with diarrhea. Amoxicillin is 30% absorbed from the calf small intestine, with absorption being similar in both milk-fed and fasted calves.²⁹ High amoxicillin concentrations are found in bile and intestinal contents after oral administration, with lower concentrations in serum.¹⁸ Oral ampicillin could also be used, and its efficacy in 1 study was shown to be equivalent to amoxicillin.¹⁷ Although very popular in the United States, oral sulfonamides cannot be recommended for treating calves with diarrhea due to lack of efficacy studies. Most antimicrobial susceptibility studies done in the last 30 years indicate sulfamethazine (and other sulfonamide drugs) would likely have very poor sensitivity against coliform bacteria in the blood or small intestine.

The most logical antimicrobial for parenteral treatment of calf diarrhea in the United States is ceftiofur (1.0 mg/lb or 2.2 mg/kg IM q12h) for at least 3 days. Ceftiofur is a broad-spectrum antibiotic that is resistant to β -lactamase. The labeled dose maintains plasma concentrations of ceftiofur above the MIC₉₀ value for *E. coli* (0.25 μ g/mL) in young calves. Furthermore, 30% of the active metabolite (desfuroylceftiofur) is excreted into the intestinal tract of cattle, providing activity in both the blood and the small intestine. Parenteral ampicillin (4.54 mg/lb or 10 mg/kg IM, q12h) is another antibiotic that would be likely to have efficacy in calves with diarrhea. In Europe, parenteral enrofloxacin is labeled for the treatment of calf diarrhea, and several studies have documented efficacy with using fluoroquinolone antibiotics in calves with diarrhea.^{25,27} However, it must be emphasized that the extralabel use of fluoroquinolone antibiotics in the United States is illegal and obviously not recommended. Historically, gentamicin was also considered an appropriate treatment for use in calves with diarrhea; however, parenteral administration of aminoglycosides cannot be recommended in calves with diarrhea due to the lack of published efficacy studies, prolonged slaughter withdrawal times (18 months), potential for nephrotoxicity in dehydrated calves and availability of other drugs likely to be equally successful (ceftiofur, amoxicillin, ampicillin).

The issue of whether or not to use antibiotics in a calf with simple diarrhea (without systemic signs of disease) is a little more controversial. Although there have been studies to show these calves gain more weight and recover faster than calves not given antibiotics,⁶ there are other studies that indicate no benefit to using antibiotics in these cases.^{2,9} The clinician must weigh any potential benefit of antimicrobial therapy against the possibility of increasing the population of resistant bacteria on the farm. A fairly recent study demonstrated that individual treatment of sick calves with antibiot-

Table 1. Antibiotics approved in the United States for control and/or treatment of calf diarrhea. The list of trade names is not necessarily complete.

Antibiotic	Trade Name	Manufacturer	Label Claim	Dose
Chlortetracycline	Aureomycin® Soluble Powder Concentrate	Zoetis	Control and treatment of scours caused by <i>E. coli</i> or <i>Salmonella</i> spp	10 mg/lb of body weight for 3 to 5 days orally
Chlortetracycline	Aureomycin® 90 Granular or Meal OR CLTC® 100 MR	Zoetis OR Phibro	Treatment of scours caused by <i>E. coli</i>	10 mg/lb of body weight mixed or top dressed on feed daily for up to 5 days
Chlortetracycline	ChlorMax® 50	Zoetis	Treatment of scours caused by <i>E. coli</i>	10 mg/lb of body weight in milk replacer or starter feeds for up to 5 days
Neomycin	Neomed® 325 Soluble Powder	Bimeda	Control and treatment of scours caused by <i>E. coli</i>	10 mg/lb of body weight mixed in drinking water – maximum of 14 days
Neomycin	Neomycin Oral Solution	AgriLabs	Control and treatment of scours caused by <i>E. coli</i>	10 mg/lb of body weight given orally divided into at least 2 doses per day – maximum of 14 days
Neomycin-Oxytetracycline	Neo-Terramycin® 50/50 or Neo-Terramycin® 100/100	Phibro	Treatment of <i>E. coli</i> diarrhea	10 mg/lb of body weight fed continuously for a maximum of 14 days
Neomycin-Oxytetracycline	NT Concentrate	Land O Lakes	Treatment and control of <i>E. coli</i> diarrhea	Mix in milk replacer to deliver 10 mg/lb of body weight fed continuously for a maximum of 14 days
Oxytetracycline	300 Pro LA	Norbrook	Treatment of <i>E. coli</i> diarrhea	3 to 5 mg/lb of body weight daily IM or SC for up to 4 days
Oxytetracycline	Agrimycin® 200 or Bio-Mycin® 200 or Duramycin 72-200	Agri-Labs OR Boehringer Ingelheim OR Durvet	Treatment of <i>E. coli</i> diarrhea	3 to 5 mg/lb of body weight daily IM or SC for up to 4 days
Oxytetracycline	Calf scours bolus	Durvet	Control and treatment of scours caused by <i>E. coli</i> or <i>Salmonella typhimurium</i>	250 mg per 100 lb of body weight orally every 12 hours for up to 4 days (control) or 500 mg every 12 hours (treatment)
Oxytetracycline	Terramycin® Scours Tablet OR Oxy 500 Calf Bolus	Zoetis OR Boehringer Ingelheim	Control and treatment of scours caused by <i>E. coli</i> or <i>Salmonella typhimurium</i>	2.5 mg/lb of body weight orally every 12 hours for up to 4 days (control) or 5 mg/lb every 12 hours (treatment)
Oxytetracycline	Terramycin® 50, 100, 200 or 200 Granular OR Terramycin® 100MR	Phibro	Treatment of <i>E. coli</i> diarrhea	10 mg/lb of body weight fed continuously for a maximum of 14 days
Sulfamethazine	SMZ-MED 454 OR Sulmet®	Bimeda OR Boehringer Ingelheim	Treatment of <i>E. coli</i> diarrhea	108 mg/lb of body weight on day 1 followed by 54 mg/lb on days 2, 3, and 4 mixed in water
Sulfamethazine	Sulmet Oblets	Boehringer Ingelheim	Treatment of <i>E. coli</i> diarrhea	100 mg/lb of body weight on day 1 (given orally) followed by 50 mg/lb on days 2, 3 and 4
Sulfamethazine	Sustain III® Boluses	Bimeda OR Durvet OR Aspen	Treatment of <i>E. coli</i> scours	160 mg/lb of body weight given orally – given once every 3 days for a maximum of 2 treatments
Tetracycline	Duramycin-10	Durvet	Control scours caused by <i>E. coli</i>	Dissolve in drinking water to provide daily dose of 10 mg/lb of body weight for up to 3-5 days
Tetracycline	Tet-Sol® 324 OR Tetramed® 324 HCA OR Tetra Bac 324 OR PolyOtic Soluble Powder	Zoetis OR Bimeda OR AgriLabs OR Boehringer Ingelheim	Control and treatment of <i>E. coli</i> diarrhea	Dissolve in drinking water to provide daily dose of 10 mg/lb of body weight for up to 3-5 days

ics increased the level of resistance to *E. coli* isolates, however the change in antimicrobial susceptibility was only transient.¹

Conclusions

Certainly the overuse of antibiotics is a concern, and the overall philosophy in veterinary medicine is to use antibiotics conservatively to preserve the efficacy of antibiotics in both animals and humans. Based on the need to minimize the use of antibiotics and because of the lack of any demonstrated recent efficacy, the feeding of antimicrobials to calves as a method of diarrhea prevention is not recommended. However calves with diarrhea and systemic signs of illness should receive antibiotics targeted towards coliform bacteria in the blood (due to likelihood of bacteremia) and the small intestine (due to bacterial overgrowth). A clinical sepsis scoring system to predict bacteremia based on physical examination does not appear to be sufficiently accurate to guide antimicrobial decision making, and therefore the clinician should assume calves are bacteremic when they exhibit inappetence, dehydration, lethargy or fever. In calves with diarrhea and no systemic signs of illness (normal appetite for milk, no fever), evidence suggests that the clinician continue to monitor the health of the calf and not administer antibiotics unless the calf's condition deteriorates.

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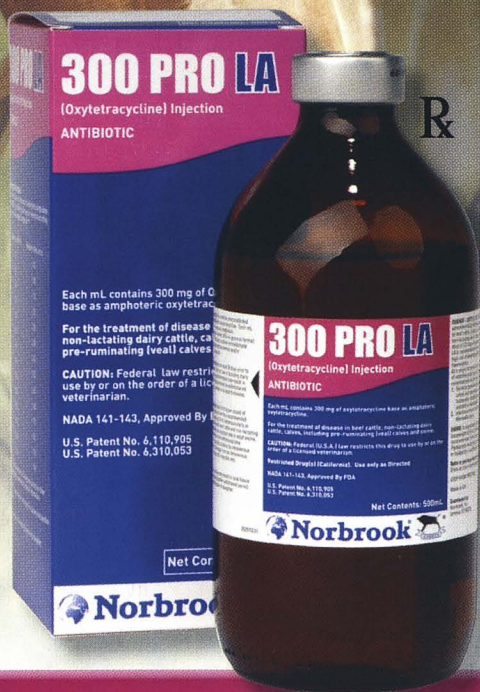
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300 PRO LA Injection is a sterile, pre-constituted solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Each mL contains 300 mg oxytetracycline as base, 40% (v/v) glycerol formal, 10% (v/v) polyethylene glycol 200, 2.7% (w/v) magnesium oxide, 0.4% (w/v) sodium formaldehyde sulphoxylate (as a preservative) and monoethanolamine (as required to adjust pH).

INDICATIONS:

300 PRO LA is intended for use in treatment for the following diseases when due to oxytetracycline-susceptible organisms: *Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves*: 300 PRO LA is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp., and *Histophilus* spp. 300 PRO LA is indicated for the treatment of infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella*

bovis, foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

Swine:

300 PRO LA is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*. In sows 300 PRO LA is indicated as an aid in control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

PHARMACOLOGY:

Oxytetracycline is derived from the metabolic activity of the actinomycete, *Streptomyces rimosus*. Oxytetracycline is an antimicrobial agent that is effective in the treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria. The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates.

Studies have shown that the half-life of oxytetracycline in blood following intramuscular treatment with 300 PRO LA at 5 mg per pound of bodyweight is approximately 23 hours in cattle and 18 hours in swine. Studies have shown when 300 PRO LA is administered once intramuscularly to cattle or swine at 9 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for 3 to 4 days.

Studies have shown when 300 PRO LA is administered once intramuscularly or subcutaneously to cattle at 13.6 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for at least 7 to 8 days.

DOSAGE AND ADMINISTRATION:

Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves: A single intramuscular or subcutaneous dosage of 13.6 mg of oxytetracycline per pound of bodyweight, 300 PRO LA is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (pasteurella) haemolytica*.

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, 300 PRO LA is recommended in the treatment of the following conditions:

- (1) Bacterial pneumonia caused by *Pasteurella* spp (shipping fever) in calves and yearlings where retreatment is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable
- (2) Infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.

For other indications 300 PRO LA is to be administered intramuscularly, subcutaneously or intravenously at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. In treatment of foot-rot and advance cases of other indicated diseases, a dosage level of 5 mg per pound of bodyweight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated.

Do not administer intramuscularly in the neck of small calves due to lack of sufficient muscle mass. Use extreme care when administering this product by intravenous injection. Perivascular injection or leakage from an intravenous injection may cause severe swelling at the injection site.

ADVERSE REACTIONS:

Reports of adverse reactions associated with oxytetracycline administration include injection site swelling, restlessness, ataxia, trembling, swelling of eyelids, ears, muzzle, anus and vulva (or scrotum and sheath in males), respiratory abnormalities (labored breathing), frothing at the mouth, collapse and possibly death. Some of these reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

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