

# Antimicrobial Decision Making for Enteric Diseases of Cattle



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## KEYWORDS

• Antimicrobials • Calf diarrhea • Diarrhea • Pharmacology • *Salmonella*

## KEY POINTS

- In general, most enteric diseases of adult cattle would not likely benefit from antimicrobial therapy unless *Salmonella* is suspected.
- Based on current research, the feeding of oral antibiotics to calves to prevent diarrhea cannot be recommended.
- 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 animals that are likely to develop septicemia or have systemic signs of disease.

Diarrhea is the leading cause of calf mortality before weaning in both beef and dairy calves. Therefore, both veterinarians and producers should put some effort into designing rational and efficacious protocols for both 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. Enteric diseases are also common in adult cattle, and both beef and dairy practitioners are often asked to create treatment protocols for diarrhea. As diagnostic testing is often not available, these protocols are generally based on knowledge of the most likely pathogen and the veterinarian's clinical experience. This article reviews existing data on antibiotics given to both calves and adult cattle for the prevention and/or treatment of enteric disease. Based on current research, the administration of oral

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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 animals, antimicrobial therapy should be targeted to specific animals that are likely to develop septicemia or have systemic signs of disease.

## ENTERIC DISEASES OF ADULT CATTLE

There are many causes of diarrhea in adult cattle, and the vast majority of these do not warrant antimicrobial therapy. Common enteric diseases of cattle include simple indigestion, rumen acidosis, parasites, coccidiosis, bovine viral diarrhea (BVD), winter dysentery, *Salmonella*, paratuberculosis (Johne disease), molybdenosis (copper deficiency), and malignant catarrhal fever (MCF), along with a wide range of toxicities including a host of poisonous plants. The only disease on this list that is likely to truly benefit from antimicrobial therapy is *Salmonella* enteritis; however, an argument could be made for BVD and MCF. Both these diseases suppress normal immune function and can lead to an increased occurrence of secondary bacterial infections. It is well understood that BVD is associated with the bovine respiratory disease complex and can lead to higher rates of bacterial pneumonia.<sup>1</sup> However, cases of severe *Salmonella* enteritis have also been reported after BVD infection in cattle causing significant mortality.<sup>2</sup> Therefore, it would not be inappropriate to administer a broad-spectrum antimicrobial to cattle suspected of having BVD or MCF, likely one that is labeled for metaphylactic use in cattle at high risk for developing respiratory disease.

It is also important to note that many toxic cows with severe mastitis, metritis, or peritonitis often have diarrhea that is a direct result of endotoxemia.<sup>3</sup> The mechanism of endotoxin-induced diarrhea is not completely understood; however, it seems to involve both prostaglandins and nitric oxide. The administration of endotoxin leads to abundant accumulation of fluid inside the small intestines of animals, which is thought to be prostaglandin mediated.<sup>4</sup> Endotoxin also increases the enzyme activities of nitric oxide synthase in intestinal smooth muscle, which changes the propagation of jejunal contractions resulting in rapid intestinal transit.<sup>5</sup> The diarrhea observed during endotoxemia in cattle is not profuse but is generally described as low volume. In these cases, choosing to use an antimicrobial would likely not benefit the diarrhea or enteric disease present in the cows but would almost certainly be indicated from the standpoint of treating the primary disease condition.

Despite the limited number of enteric diseases in adult cattle that would benefit from antimicrobial therapy, surveys indicate that diarrhea is a relatively common reason for the use of antibiotics. In the 2007 National Animal Health Monitoring Survey (NAHMS) dairy study, mastitis was the most common reason for antimicrobial use on dairy farms followed by lameness, reproductive diseases (metritis), respiratory disease, and then diarrhea or other enteric disease. Results of the survey showed that about 2% of cattle on dairy farms from the survey population had been treated with an antimicrobial for diarrhea in the preceding 12-month period and 25% of farms said they routinely had cows that received antimicrobial drugs because of diarrhea.<sup>6</sup> Data from the NAHMS 2011 feedlot study indicated that 71% of feedlots reported diarrhea or other enteric disease in calves after arrival with 4.3% of calves showing evidence of diarrhea.<sup>7</sup> Further data from the study indicated that 54% of calves with diarrhea received treatment upon arrival. When the survey looked into what specific therapy was administered, 30% of calves received an injectable antimicrobial, while 51% of the cattle

received an oral antibiotic. When reviewing the data of both the NAHMS dairy and feedlot studies, it becomes clear that enteric disease is not the primary reason for antimicrobial use in adult cattle. However, it is also apparent that diarrhea is one of the top 3 or 4 reasons cattle receive antimicrobials and that at least half of the cattle diagnosed with diarrhea receive either a parenteral and/or an oral antibiotic.

Most of the time dairy or beef cattle have diarrhea, it is not clear what the cause is, and therefore they are empirically treated with antibiotics. The assumption in many cases is that the animal has salmonellosis or some other bacterial enteritis. Although this is certainly true in some cases, it is very likely that most cases of diarrhea are because of simple indigestion caused by an abrupt diet change, moldy feed, spoiled feed, or perhaps a mild grain overload (rumen acidosis). However, simple indigestion is often difficult or impossible to diagnose definitively and therefore cattle are treated empirically with antimicrobials. If *Salmonella* are the main target of antimicrobial therapy in adult cattle with diarrhea, drug selection should ideally be based on the results of susceptibility testing using bacterial strains recovered from that particular dairy or feedlot. Broad-spectrum antimicrobials are usually used pending the availability of susceptibility test results. *Salmonella* show variable resistance patterns to ampicillin, amoxicillin, ceftiofur, florfenicol, neomycin, streptomycin, sulfonamides, tetracycline, and trimethoprim-sulfa and general resistance to penicillin, erythromycin, and tylosin.<sup>8-10</sup> The most recently published data indicated that *Salmonella* isolates from cattle were most commonly resistant to streptomycin, ampicillin, and sulfonamides, whereas resistance to ceftiofur was extremely low.<sup>9</sup> As *Salmonella* are facultative intracellular pathogens, selecting an antimicrobial with good tissue penetration and the ability to attain intracellular therapeutic drug concentrations within macrophages is desirable.

In summary, antimicrobials for the treatment of diarrhea in adult cattle are likely being overused at present in the cattle industry. Although diarrhea occurs fairly commonly, most causes are unlikely to respond to antimicrobials. Treatment should be primarily supportive care, including fluid therapy, anthelmintics if needed, and provision of good-quality pasture or other forages. Mortality rates in most cases of diarrhea in mature cattle are low, and the diarrhea generally resolves within a few days. Diseases such as paratuberculosis would have a higher mortality but would still not be likely to respond to antimicrobial therapy. However, when cattle have signs of systemic infection such as pyrexia or bloody diarrhea, it may be rational to begin antimicrobial therapy, particularly on farms that have a history of salmonellosis. When examining an adult ruminant with enteric disease, the practitioner should consider the age of the animal; the onset, severity, and duration of diarrhea (acute vs chronic); the number of cattle affected (is this an individual animal or a herd problem); clinical signs in the animal other than diarrhea (does the animal show systemic signs of disease); nutritional history (especially recent changes in the diet), and whether there has been an introduction of new animals (BVD). All these help to determine a list of possible causes for the diarrhea and may help reduce the use of antimicrobial drugs in cattle that are unlikely to benefit from therapy. Prudent use of antimicrobial drugs is recommended with an emphasis on establishing a herd diagnosis and conducting susceptibility testing for the specific *Salmonella* serotype or other bacterial pathogen present and choosing an appropriate antibiotic.

## THE USE OF ANTIBIOTICS TO PREVENT CALF DIARRHEA

Calf health should be a priority on both beef and dairy farms. Despite this importance, the United States Department of Agriculture Dairy 2007 study shows a preweaned

heifer calf mortality rate of 8.7% and reports 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 before weaning. In both beef and dairy calves, diarrhea represents the most common reason for loss due to death before weaning. Therefore, practitioners and producers spend a significant amount of time trying to prevent diarrhea and also making sure 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) using a vaccine in late gestation cattle containing enterotoxigenic *Escherichia coli*, rotavirus, and coronavirus; (2) making sure a good colostrum program is in place ensuring adequate intake 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 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 proven to be 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.<sup>11</sup> The investigator concluded that the addition of chlortetracycline and oxytetracycline to milk replacer in the first 8 weeks of life decreased the incidence and severity of diarrhea. The minimum daily doses necessary for efficacy in this study were 0.15 to 0.20 mg/lb, 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 a previous review article, there were several studies done in the 1960s and the 1970s using various antibiotics (including ampicillin, chlortetracycline, furazolidone, neomycin, oxytetracycline, and streptomycin) to prevent diarrhea in calves.<sup>12</sup> Although the results of these studies varied, only 1 study documented a decrease in mortality rate from diarrhea due to prophylactic oral administration of chlortetracycline.<sup>13</sup> A few studies did find a decrease in the total number of days of diarrhea associated with antibiotics<sup>12</sup>; however, other studies (particularly with neomycin) found increased rates of diarrhea in antibiotic-treated calves.<sup>14,15</sup> Quite a few of these older studies found that oral administration of various antibiotics did not change the incidence of diarrhea in calves when compared with untreated controls.<sup>16</sup>

More recent studies have found that 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, whereas another group was fed lasalocid and chlortetracycline (Aureomycin) for the first 12 weeks of life (in addition to nonmedicated milk replacer or whole milk). Antibiotic-treated calves had no difference in average daily gain, feed efficiency, or the proportion of calves treated for diarrhea.<sup>17</sup> In another study, Holstein heifers were fed milk replacer medicated with oxytetracycline and neomycin or an unmedicated milk replacer that contained a probiotic (Enteroguard—no longer commercially available). Once again, body weight gain, feed efficiency, and the incidence and severity of diarrhea were similar between groups.<sup>18</sup> 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 the treatment of diarrhea (referred to as conventional therapy); medicated milk

replacer for the first 14 days of life, bismuth pectin for diarrhea, and other antibiotics only in cases of fever or depressed attitude (targeted therapy); nonmedicated milk replacer with antimicrobial treatment of diarrhea (same treatments as the conventional therapy group above); and nonmedicated milk replacer with targeted therapy.<sup>19</sup> Calves fed a medicated milk replacer had 31% more days with diarrhea when compared with calves fed nonmedicated milk replacer.

In a 2007 survey, about 60% of dairy farms in the United States fed medicated milk replacers to preweaned heifer calves, most commonly a combination of oxytetracycline and neomycin.<sup>6</sup> 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, and 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 the feed and milk replacers for dairy cattle must be sold as nonmedicated, 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 nonmedicated as well. Overall, the conventional practice of adding antibiotics to milk or milk replacers for prophylactic use is being discouraged worldwide. Most modern studies fail to find any benefit of using antibiotics as a prevention for diarrhea, and their use in this manner should be discouraged.

## THE RATIONALE FOR USING ANTIBIOTICS AS A TREATMENT OF CALF DIARRHEA

The use of antibiotics as a treatment in 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.<sup>20,21</sup> In contrast, other studies have indicated that antibiotics are effective in reducing mortality rate and speeding recovery in calves with diarrhea.<sup>22,23</sup> To begin the discussion, it is important to establish a reason to use antibiotics in calves with diarrhea. The 2 primary treatment goals of an antibiotic in calves with diarrhea would be (1) to prevent bacteremia and (2) to decrease the number of coliform bacteria in the small intestine.

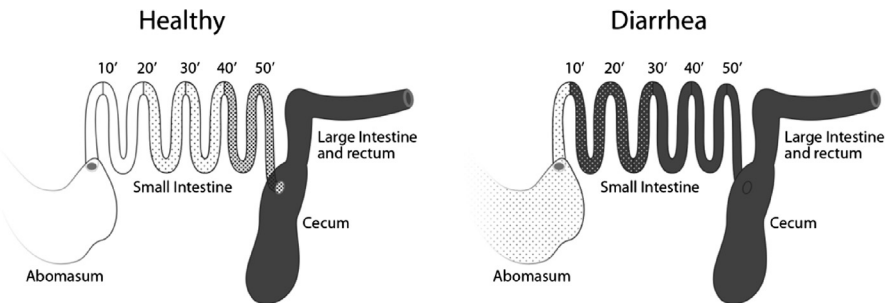
Several studies have reported that a significant number of calves with diarrhea subsequently develop bacteremia. An initial study in the early 1960s reported that colostrum-deprived calves with diarrhea were frequently bacteremic (14/17 calves or 82%).<sup>24</sup> In contrast, none of the diarrheic 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<sup>25</sup>; 129 of the 169 calves (76%) had failure of passive transfer and 47 (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<sup>26</sup>; 78 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%) than in adequate passive transfer group (21/116 or 18%). Taken together these studies indicate that it can be assumed that one-third of the calves with severe diarrhea are bacteremic and that 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.<sup>22</sup>

Another potential reason for antibiotic therapy in calves with diarrhea is coliform overgrowth of the small intestine (Fig. 1). Research conducted in the 1920s documented increased numbers of *E coli* in the abomasum, duodenum, and jejunum of calves with diarrhea.<sup>27,28</sup> 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.<sup>29,30</sup> 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.<sup>22</sup> This small intestinal overgrowth of the intestines with coliform bacteria can persist after the pathogen causing the diarrhea is gone.<sup>30</sup> 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.<sup>31</sup> Therefore there is some logic to the use of antimicrobials in scouring calves to decrease the number of intestinal coliform bacteria. This use 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.<sup>22</sup>

#### 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.<sup>22</sup> This study reviewed articles published since 1950 and included studies with both orally and parenterally administered antibiotics in either naturally acquired or experimentally induced diarrhea. The investigator 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 more than 20 different published studies involving a variety of antimicrobials,



**Fig. 1.** Schematic of the distribution and concentration of *E coli* 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. (Adapted from Constable PD. Antimicrobial use in the treatment of calf diarrhea. J Vet Intern Med 2004;18:9.)

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 alter intestinal flora and thereby induce diarrhea or exacerbate existing diarrhea, (2) antibiotics harm good intestinal bacteria more than bad bacteria, (3) antimicrobial use in calves with diarrhea is not effective, and (4) the use of antibiotics provides a selection pressure on the enteric bacterial population likely leading to increased antimicrobial resistance.<sup>22</sup> There is solid evidence to indicate that the use of antimicrobial drugs can decrease mortality in calves and there is no evidence to support the argument that antimicrobials harm 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. At present, 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 efficacious 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) 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 in the small intestine.

As none of the approved drugs for treating diarrhea in the United States are likely to be effective, extralabel use is likely justified. Some efficacy has been described for oral amoxicillin in the treatment of calves with experimentally induced diarrhea,<sup>16,32</sup> but was not effective in the treatment of naturally acquired diarrhea in beef calves.<sup>33</sup> Amoxicillin trihydrate (10 mg/kg administered orally every 12 h) or amoxicillin trihydrate-clavulanate (12.5 mg combined drug/kg administered orally every 12 h) for at least 3 days is one antimicrobial approach that likely has some efficacy for calves with diarrhea. Amoxicillin is partially absorbed from the calf small intestine with absorption being similar in both milk-fed and fasted calves.<sup>34</sup> High amoxicillin concentrations are found in bile and intestinal contents after oral administration, with lower concentrations in serum.<sup>32</sup> Oral ampicillin could also be used, and its efficacy in one study was shown to be equivalent to that of amoxicillin.<sup>35</sup> Although very popular in the United States, oral sulfonamides cannot be recommended for treating calves with diarrhea because of the lack of efficacy studies. Most antimicrobial susceptibility studies done in the past 30 years indicate that sulfamethazine (and other sulfonamide drugs) would have 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 (2.2 mg/kg given intramuscularly [IM] every 12 h) for at least 3 days. Ceftiofur is a broad-spectrum antibiotic that is resistant to  $\beta$ -lactamase. The labeled

**Table 1**  
**Antibiotics approved in the United States for control and/or treatment of calf diarrhea**

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	22 mg/kg of body weight for 3–5 d orally
Chlortetracycline	Aureomycin 90 Granular or Aureomycin 90 Meal or CLTC 100 MR	Zoetis or Phibro	Treatment of scours caused by <i>E coli</i>	22 mg/kg of body weight mixed or top dressed on feed daily for up to 5 d
Chlortetracycline	ChlorMax 50	Zoetis	Treatment of scours caused by <i>E coli</i>	22 mg/kg of body weight in milk replacer or starter feeds for up to 5 d
Neomycin	Neomed 325 soluble powder	Bimeda	Control and treatment of scours caused by <i>E coli</i>	22 mg/kg of body weight mixed in drinking water, maximum of 14 d
Neomycin	Neomycin oral solution	AgriLabs	Control and treatment of scours caused by <i>E coli</i>	22 mg/kg of body weight given orally divided into at least 2 doses per day, maximum of 14 d
Neomycin-Oxytetracycline	Neo-Terramycin 50/50 or Neo-Terramycin 100/100	Phibro	Treatment of <i>E coli</i> diarrhea	22 mg/kg of body weight fed continuously for a maximum of 14 d
Neomycin-Oxytetracycline	NT concentrate	Land O'Lakes	Treatment and control of <i>E coli</i> diarrhea	Mix in milk replacer to deliver 22 mg/kg of body weight fed continuously for a maximum of 14 d
Oxytetracycline	300 Pro LA	Norbrook	Treatment of <i>E coli</i> diarrhea	6.6–11 mg/kg of body weight daily IM or SC for up to 4 d
Oxytetracycline	Agrimycin 200 or Bio-Mycin 200 or Duramycin 72–200	AgriLabs, Boehringer Ingelheim, or Durvet	Treatment of <i>E coli</i> diarrhea	6.6–11 mg/kg of body weight daily IM or SC for up to 4 d



Oxytetracycline	Calf scours bolus	Durvet	Control and treatment of scours caused by <i>E coli</i> or <i>Salmonella typhimurium</i>	250 mg/45.4 kg of body weight orally every 12 h for up to 4 d (control) or 500 mg every 12 h (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>	5.5 mg/kg of body weight orally every 12 h for up to 4 d (control) or 5 mg/lb every 12 h (treatment)
Oxytetracycline	Terramycin 50, 100, or 200; Terramycin 200 Granular, or Terramycin 100 MR	Phibro	Treatment of <i>E coli</i> diarrhea	22 mg/kg of body weight fed continuously for 7–14 d
Sulfamethazine	SMZ-Med 454 or Sulmet Powder	Bimeda or Boehringer Ingelheim	Treatment of <i>E coli</i> diarrhea	238 mg/kg of body weight on day 1 followed by 119 mg/kg on days 2, 3, and 4, mixed in water
Sulfamethazine	Sulmet Oblets	Boehringer Ingelheim	Treatment of <i>E coli</i> diarrhea	220 mg/kg of body weight on day 1 (given orally) followed by 110 mg/kg on days 2, 3 and 4
Sulfamethazine	Sustain III Boluses	Bimeda, or Durvet, or VetOne	Treatment of <i>E coli</i> scours	352 mg/kg of body weight given orally, given once every 3 d 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 22 mg/kg of body weight for up to 3–5 d
Tetracycline	Tet-Sol 324, Tetramed 324 HCA, Tetra Bac 324, or PolyOtic soluble powder	Zoetis, Bimeda, AgriLabs, or Boehringer Ingelheim	Control and treatment of <i>E coli</i> diarrhea	Dissolve in drinking water to provide daily dose of 22 mg/kg of body weight for up to 3–5 d

The list of trade names is not necessarily complete.  
 Abbreviations: IM, intramuscularly; SC, subcutaneously.

dose maintains plasma concentrations of ceftiofur above the minimum concentration required to inhibit the growth of 90% of *E coli* (MIC<sub>90</sub>) in young calves (0.25 µg/mL). 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 (10 mg/kg IM every 12 h) 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.<sup>36–38</sup> 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 because of 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, and 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 that these calves gain more weight and recover faster than calves not given antibiotics,<sup>22</sup> there are other studies that indicate no benefit to using antibiotics in these cases.<sup>19,20</sup> 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 antibiotics increased the level of resistance to *E coli* isolates; however, the change in antimicrobial susceptibility was only transient.<sup>39</sup>

## ANTIMICROBIAL SUSCEPTIBILITY TESTING

The next logical question is whether or not antimicrobial susceptibility testing should play a role in determining which drug is used to treat calves with diarrhea. Historically, culture and susceptibility results from fecal culture have been routinely used to guide treatment decisions; however, it is not clear whether or not this has any clinical relevance. Research validating susceptibility testing as being predictive of treatment outcome for calves with diarrhea is currently not available. Part of the problem is that our target is coliform bacteria in the blood and small intestine, which are likely different from fecal bacterial flora. Older studies have demonstrated that the predominant strain of *E coli* in the manure of calves with diarrhea usually changes several times during the course of disease.<sup>24,40</sup> These studies also show that about 50% of calves have different *E coli* strains isolated from the upper and lower parts of small intestine.<sup>24</sup> So it is logical to conclude that fecal coliform isolates are not representative of what is happening in the intestine.

Another potential problem with using susceptibility testing to guide antimicrobial selection in cases of diarrhea is that most of the bacterial cultures submitted usually come from dead animals, which represent treatment failures and may have already received antibiotics. Preferential growth of resistant bacterial strains can start within a few hours after antibiotic administration, and therefore culture results from dead calves may not be representative of the actual clinical problem.<sup>41</sup> To the author's knowledge, the only study that has tried to assess the predictive ability of fecal antimicrobial susceptibility testing found that it was an inaccurate predictor of clinical outcome.<sup>42</sup> In a large group of experiments evaluating the efficacy of amoxicillin for treating calf diarrhea, 205 calves were divided into groups that either received amoxicillin or did not. Diarrhea was experimentally induced using enterotoxigenic *E coli* and

rectal swab culture, and susceptibility testing was done. Most calves (80%) developed diarrhea after challenge; however, in only about 25% of cases did calves shed the actual challenge strain of *E coli*. Recovery or treatment success in these studies was defined as normal feces within 4 days after the start of treatment, while treatment failure was defined as death or scouring for more than 4 days. Among calves in which the *E coli* cultured from rectal swabs were susceptible to amoxicillin, 10% died and 62% recovered with 3.3 as the mean number of days scouring. Outcomes were not different in calves that had amoxicillin-resistant strains of *E coli* cultured from rectal swabs with 12% death loss, 60% recovery rates, and 3.6 scouring days. In calves given a placebo instead of amoxicillin, mortality was significantly increased (20%), recovery rates were decreased (34%), and the number of scouring days was longer (5.1). The investigators concluded that amoxicillin had a significant effect on disease by decreasing mortality and number of scouring days; however, treatment success could not be predicted by whether the *E coli* cultured from rectal swabs was susceptible or resistant to the antimicrobial being used.

Two studies have concluded that there was a good correlation between in vitro antimicrobial susceptibility of fecal *E coli* isolates and clinical response to treatment; however, neither study had data to statistically analyze this association.<sup>43,44</sup> In contrast, 2 other studies reported no correlation between in vitro susceptibility results for coliform isolates and response to antimicrobial treatment.<sup>45,46</sup> However, these studies did not differentiate enterotoxigenic and nonenterotoxigenic strains of *E coli* and also failed to do any statistical analysis of the data. There is a significant need for antimicrobial susceptibility data from *E coli* and *Salmonella* isolates collected from the small intestine of untreated calves with diarrhea. Minimum inhibitory concentrations (MIC) could then be compared with free antimicrobial concentrations that are actually achievable in the intestinal tract of calves to determine the best drug to use along with the optimal dosing interval. However, it should be emphasized that antimicrobial concentrations can be altered by multiple variables, such as intestinal pH, which may be quite different between healthy calves and those with diarrhea. Therefore even after establishing MIC values and setting appropriate break-points, these need to be validated through clinical trials examining the use of specific antimicrobial drugs in calves with diarrhea as compared to the pathogen isolated and disease outcome. Until then the use of fecal culture and susceptibility testing to guide antimicrobial selection for treating calf diarrhea is probably of little value. Drug selection is based on knowledge of the likely pathogen (*E coli* in the blood and small intestine), pharmacokinetics of the drug (can it achieve therapeutic concentrations at the site of infection), and evaluation of the response to treatment (does the animal get better). On farms in which *Salmonella* or *E coli* septicemia is a problem, looking at susceptibility results from blood cultures is likely much more appropriate than fecal culture.

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 these drugs 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 toward coliform bacteria in the blood (because of likelihood of bacteremia) and the small intestine (because of bacterial overgrowth). A clinical sepsis scoring system to predict bacteremia based on physical examination does not seem to be sufficiently accurate to guide antimicrobial decision making, and therefore the clinician should assume that 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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