*Review*

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# Antimicrobial Use in the Treatment of Calf Diarrhea

Peter D. Constable

Calves with diarrhea often have small intestinal overgrowth with *Escherichia coli* bacteria, regardless of the inciting cause for the diarrhea, and 30% of systemically ill calves with diarrhea have bacteremia, predominantly because of *E coli*. Antimicrobial treatment of diarrheic calves should therefore be focused against *E coli* in the small intestine and blood, the 2 sites of infection. Fecal bacterial culture and antimicrobial susceptibility testing is not recommended in calves with diarrhea because fecal bacterial populations do not accurately reflect small intestinal or blood bacterial populations and because the break points for susceptibility test results have not been validated. Antimicrobial efficacy is therefore best evaluated by the clinical response of a number of calves to treatment, with calves randomly assigned to treatment groups. Amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, sulfamethazine, and tetracycline administered PO are currently labeled in the United States for the treatment of calf diarrhea. On the basis of published evidence for the oral administration of these antimicrobial agents, only amoxicillin can be recommended for the treatment of diarrhea. Dosage recommendations are amoxicillin trihydrate (10 mg/kg PO q12h) or amoxicillin trihydrate–clavulanate potassium (12.5 mg combined drug/kg PO q12h) for at least 3 days; the latter constitutes extra-label drug use. Parenteral administration of broad-spectrum β-lactam antimicrobials—ceftiofur (2.2 mg/kg IM or SC q12h) and amoxicillin or ampicillin (10 mg/kg IM q12h)—or potentiated sulfonamides (25 mg/kg IV or IM q24h) is recommended for treating calves with diarrhea and systemic illness; both constitute extra-label drug use. In calves with diarrhea and no systemic illness (normal appetite for milk, no fever), it is recommended that the health of the calf be monitored and that oral or parenteral antimicrobials not be administered.

**Key words:** Antibiotic; *Escherichia coli*; *Salmonella*; septicemia; susceptibility.

Calf diarrhea remains the leading cause of mortality in dairy calves[1] and an important cause of morbidity and mortality in beef calves.[2] Despite the increased availability of vaccines against enterotoxigenic *E coli*, rotavirus, and coronavirus and continued emphasis on optimizing colostral transfer of passive immunity, improved treatment protocols for calf diarrhea are required. Although the administration of intravenous fluids and oral electrolyte solutions plays a central role in treatment, the efficacy of antimicrobial agents in treating calf diarrhea is controversial. The purpose of this article, therefore, is to critically review studies related to the use of antimicrobials in calves with diarrhea and to develop evidence-based recommendations for the use of antimicrobials to treat calf diarrhea. Treatment aspects related to economics, animal welfare, and the potential for promoting antimicrobial resistance are also important but are beyond the scope of this review.

## *Change in Small Intestinal Bacterial Flora in Calves with Diarrhea*

There has been a paradigm shift in the last 40 years toward attributing an episode of calf diarrhea to a specific etiologic agent, such as rotavirus, coronavirus, cryptosporidia, *Salmonella* spp, or enterotoxigenic *E coli*. Although the etiologic approach has correctly focused attention on preventive programs, including vaccination and optimizing transfer of colostral immunity, it has diverted attention from the finding of numerous studies that calves with diarrhea have coliform bacterial overgrowth of the small intestine.[3–8]

Studies completed more than 70 years ago documented increased numbers of *E coli* bacteria in the abomasum, duodenum, and jejunum of scouring calves.[3,4] Moreover, calves severely affected with diarrhea had increased numbers of *E coli* bacteria in the anterior portion of their intestinal tracts, compared with mildly affected animals.[4] More recent studies have consistently documented that calves with naturally acquired diarrhea, regardless of age and etiologic cause for the diarrhea, have altered small intestinal bacterial flora.[5–7] Specifically, *E coli* bacterial numbers are increased 5- to 10,000-fold in the duodenum, jejunum, and ileum of calves with naturally acquired diarrhea,[5–8] even when the diarrhea was not caused by enterotoxigenic strains of *E coli* and when rotavirus and coronavirus were identified in the feces. The largest increase in *E coli* bacterial numbers occurs in the distal jejunum and ileum,[5] whereas the *E coli* or coliform bacterial numbers in the colon and feces are similar or higher for calves with diarrhea than for calves without diarrhea,[5,7] with *E coli* being more numerous in the feces of colostrum-deprived than colostrum-fed calves.[5] Small intestinal overgrowth with coliform bacteria can persist after departure of the initiating enteric pathogen.[7]

In calves with naturally acquired diarrhea, increased small intestinal colonization with *E coli* has been associated with impaired glucose, xylose, and fat absorption.[7] Mixed infections with enteric pathogens are commonly diagnosed in calves with naturally acquired diarrhea,[6,8,9] and the clinical signs and pathologic damage associated with rotavirus infection are more severe when *E coli* is present than when it is absent.[8,10–12] Primary viral morphologic damage to the small intestine also facilitates systemic invasion by normal intestinal flora, including *E coli*.[10]

*From the Department of Veterinary Clinical Medicine, University of Illinois at Urbana-Champaign, Urbana, IL*

*Reprint requests: Dr Peter D. Constable, Department of Veterinary Clinical Medicine, University of Illinois at Urbana-Champaign, 1008 West Hazelwood Drive, Urbana, IL 61802; e-mail: p-constable@uiuc.edu.*

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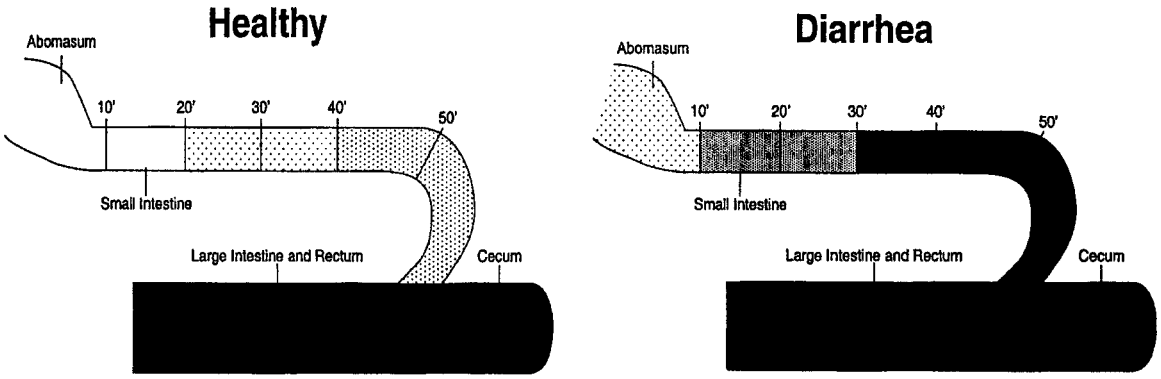


**Fig 1.** Schematic of the distribution and concentration of *Escherichia coli* bacteria in the intestinal tract of a calf with undifferentiated diarrhea and a similarly aged calf without diarrhea. Adapted from Reisinger.[15] The figure indicates that the number of *E coli* in the large intestine of 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.

In calves with experimentally induced enterotoxigenic *E coli* diarrhea, colonization of the small intestine by *E coli* has been associated with impaired glucose and lactose absorption, decreased serum glucose concentration, and possibly increased susceptibility to cryptosporidial infection.[13]

Calves with diarrhea often have increased coliform bacterial numbers in the small intestine, regardless of etiology (Fig 1),[3–8,14] and this colonization is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia. It therefore follows that administration of antimicrobial agents that decrease small intestinal coliform bacterial numbers in calves with diarrhea might prevent the development of bacteremia, decrease mortality, and decrease morphologic damage to the small intestine, thereby facilitating digestion and absorption and increasing growth rate.

### *Incidence of Bacteremia in Calves with Diarrhea*

Calves with diarrhea are more likely to have failure or partial failure of passive transfer, and this group of calves, in turn, is more likely to be bacteremic. This is an additional reason that antimicrobial agents might be indicated in the treatment of calf diarrhea. Smith reported in 1962[5] that colostrum-deprived calves that subsequently developed diarrhea were frequently bacteremic (14/17 = 82%), whereas bacteremia occurred much less frequently in colostrum-fed calves that developed diarrhea (0/26 = 0%). Similar results have been observed in 2 recent North American studies.[15,16] These studies identified bacteremia in calves with a median age of 8 days[15] or a mean age of 9 days[16]; these results were at odds with current dogma that calf septicemia and bacteremia occur most frequently in the 1st few days of life.

Fecteau et al[15] examined 169 dairy calves <20 days old with severe diarrhea or depression on a large California calf-rearing facility; 129 of 169 (76%) of the calves had failure of passive transfer of colostral immunoglobulin, and 47 of 169 (28%) of the affected calves were bacteremic, predominantly with *E coli*. Bacteremia was detected in a significantly ($P = .0010$) greater proportion of calves with failure of passive transfer (44/129 = 34%) than in calves with adequate passive transfer (3/40 = 8%); however, the number of calves with severe diarrhea and bacteremia was not specifically stated.

Lofstedt and her colleagues examined 252 calves <28 days old with diarrhea on Prince Edward Island, Canada.[16] The feces of diarrheic calves were examined for enteric pathogens and were positive for coronavirus (39%), enterotoxigenic *E coli* (38%), cryptosporidia (33%), and rotavirus (12%). Forty-one percent (103/252) of the calves had failure of passive transfer of colostral immunoglobulin, and 31% (78/252) of the calves were bacteremic, predominantly with *E coli.* Bacteremia was detected in a significantly ($P < .0001$) greater proportion of calves with failure of passive transfer (47/103 = 46%) than in calves with adequate passive transfer (21/116 = 18%) and calves ≤5 days old.

The results of these 2 studies[15,16] indicate that veterinarians should assume that, on average, 30% of severely ill calves with diarrhea are bacteremic, that the risk of bacteremia is higher in calves with failure of passive transfer than in calves with adequate passive transfer, and that the risk of bacteremia is higher in calves ≤5 days old. The frequency of bacteremia is sufficiently high that treatment of calves with diarrhea that are severely ill (as manifested by reduced suckle reflex, >6% dehydration, weakness, inability to stand, or clinical depression) should include routine treatment against bacteremia, with emphasis on treating potential *E coli* bacteremia. Veterinarians should also assume that 8%[15] to 18%[16] of diarrheic calves with adequate passive transfer and systemic illness are bacteremic. In the author's opinion, the prevalence of bacteremia is sufficiently high in systemically ill calves that effective antimicrobial treatment for potential bacteremia should be routinely instituted, regardless of passive transfer status and treatment cost. Withholding an effective treatment for a life-threatening condition, such as bacteremia in calves with diarrhea, cannot be condoned on animal welfare grounds.

## Safety and Efficacy of Antimicrobials in Treating Calf Diarrhea

The appropriate use of antimicrobial agents to treat calf diarrhea would be facilitated by publication of controlled, randomized treatment studies in peer-reviewed journals. Unfortunately, the majority of the valuable information

generated by pharmaceutical companies to support their label claim of treating calf diarrhea has not been published and is therefore unavailable for independent evaluation.

On the basis of the previous discussion, the 2 primary reasons for administering antimicrobial agents to calves with diarrhea are (1) to decrease the number of *E coli* bacteria in the small intestine and (2) to treat potential *E coli* bacteremia. It therefore follows that when antimicrobial agents are administered to calves with diarrhea, the antimicrobial should be safe and effective against *E coli* in both the small intestine and blood, which should be regarded as the 2 sites of infection.

### *Antimicrobial Safety*

A number of antimicrobial agents produce deleterious effects on small intestinal function and morphology when administered PO to healthy milk-fed dairy calves. The addition to milk replacer powder of potassium penicillin (11 mg/kg of milk replacer) and procaine penicillin (2–60 mg/kg of milk replacer) increased the incidence and duration of diarrhea and decreased growth rate compared with untreated controls in a total of 36 milk-fed calves.[17] Administration of neomycin sulfate (300 mg PO q24h for the 1st 4 days of life) tended ($P = .060$) to increase the proportion of calves developing diarrhea (99/233 = 43%) compared with the proportion in an untreated control group (58/174 = 33%).[18] Administration of neomycin sulfate (25 mg/kg PO q6h, n = 10), chloramphenicol (50 mg/kg PO q12h, n = 6),[a] ampicillin trihydrate (12 mg/kg PO q8h, n = 6), or tetracycline hydrochloride (11 mg/kg PO q12h, n = 6) for 5 days increased the occurrence of diarrhea and decreased glucose absorption through unknown mechanisms compared with untreated controls (n = 6),[19] whereas 2 other studies found that tetracycline hydrochloride (40 mg PO q12h; 11 mg/kg PO q12h) did not induce diarrhea or alter glucose absorption.[20,21] In a separate study, administration of chloramphenicol (50 mg/kg PO q12h for 3 days) to healthy neonatal calves decreased jejunal villous length and D-xylose absorption and increased breath $H_2$ excretion, indicating small intestinal malabsorption, which was attributed to a chloramphenicol-induced decrease in intestinal epithelium mitochondrial protein synthesis.[22] Other investigators reported that administration of chloramphenicol (50 mg/kg PO q12h) induced diarrhea in 7 of 8 calves within 5 days, although this study did not contain a control group.[23] Finally, administration of chloramphenicol (55 mg/kg PO q12h for 5 days) did not induce diarrhea in 7 calves, but delayed glucose absorption.[21] The effects of prolonged oral chloramphenicol administration in calves raises the question as to whether other antimicrobial agents administered PO induce diarrhea or alter small intestinal function or morphology; such a deleterious effect is less likely to occur after administration of antimicrobial agents with high oral bioavailability.

### *Antimicrobial Susceptibility*

The most important determinant of antimicrobial efficacy in calf diarrhea is obtaining an effective antimicrobial concentration against bacteria at the sites of infection (small intestine and blood). The results of fecal antimicrobial susceptibility testing have traditionally been used to guide treatment decisions; however, susceptibility testing in calf diarrhea probably has clinical relevance only when applied to fecal isolates of enterotoxigenic strains of *E coli* or pathogenic *Salmonella* spp and blood culture isolates from calves with bacteremia. Validation of susceptibility testing as being predictive of treatment outcome for calves with diarrhea is currently lacking.

***Antimicrobial Susceptibility of Fecal* E coli *Isolates.*** The ability of fecal bacterial culture and antimicrobial susceptibility testing by the Kirby Bauer technique to guide treatment in calf diarrhea is questionable when applied to fecal *E coli* isolates that have not been identified as enterotoxigenic, although 2 reports concluded that a ''good correlation'' existed between in vitro antimicrobial susceptibility of fecal *E coli* isolates and clinical response to antimicrobial treatment.[24,25] In contrast, 3 other studies reported no correlation between in vitro antimicrobial susceptibility of fecal *E coli* and *Salmonella* spp isolates and clinical response to antimicrobial treatment,[26–28] although these studies did not differentiate enterotoxigenic and nonenterotoxigenic strains of *E coli.* The only study to statistically test the predictive ability of fecal antimicrobial susceptibility results found that the rectal swab was an inaccurate method of predicting clinical outcome.[28] There do not appear to be any data demonstrating that fecal bacterial flora is representative of small intestinal bacterial flora, which is the physiologically important site of infection in calf diarrhea. Finally, and most importantly, the predominant strain of *E coli* in the feces of a scouring calf can change several times during the diarrhea episode,[5,29] and 9 of 20 (45%) calves with diarrhea had different strains of *E coli* isolated from the upper and lower small intestine,[5] indicating that fecal *E coli* strains are not always representative of small intestinal *E coli* strains.

An additional bias present in most antimicrobial susceptibility studies conducted on fecal *E coli* isolates is that data are frequently obtained from dead calves, which are likely to be treatment failures. The time since death is also likely to be an important determinant of the value of fecal culture because ''such a rapid proliferation of bacteria occurs in the alimentary tract after death that the results of examinations made on dead calves received at the laboratory can have little significance.''[5(p147)] Calves that die from diarrhea are likely to have received multiple antimicrobial treatments, and preferential growth of antimicrobial-resistant *E coli* strains starts within 3 hours of antimicrobial administration.[30] A 3rd concern with fecal susceptibility testing is that the Kirby Bauer break points (minimum inhibitory concentration [MIC]) are not based on typical antimicrobial concentrations in the small intestine and blood of calves. What is urgently needed are studies documenting the antimicrobial susceptibility of *E coli* isolates from the small intestine of untreated calves on the basis of achievable drug concentrations and dosage regimens. Until these data are available, it appears that antimicrobial efficacy is best evaluated by the clinical response of a number of calves to treatment, with calves randomly assigned to treatment groups, rather than the results of in vitro antimicrobial susceptibility testing performed on fecal *E coli* isolates.

***Antimicrobial Susceptibility of Blood* E coli *Isolates.*** The Kirby Bauer technique for the antimicrobial susceptibility test has more clinical relevance for predicting the clinical response to antimicrobial treatment when applied to blood isolates than fecal isolates. This is because the Kirby Bauer break points (MIC) are based on achievable antimicrobial concentrations in human plasma and $MIC_{90}$ values for human *E coli* isolates, which provide a reasonable approximation to achievable MIC values in calf plasma and $MIC_{90}$ values for bovine *E coli* isolates. Unfortunately, susceptibility results are not available for at least 48 hours, and very few studies have documented the antimicrobial susceptibility of blood isolates in calves with diarrhea. In a 1997 study of dairy calves in California, the antimicrobial susceptibility of isolates from the blood of calves with severe diarrhea or illness produced the following results—ceftiofur (19/25 = 76% sensitive), potentiated sulfonamides (14/25 = 56% sensitive), gentamicin (12/25 = 48% sensitive), ampicillin (11/25 = 44% sensitive), and tetracycline (3/25 = 12% sensitive)—although there was a clinically significant year-to-year difference in the results of susceptibility testing that might have reflected different antimicrobial administration protocols on the farm.[16]

### *Success of Antimicrobial Therapy*

The 4 critical measures of success of antimicrobial therapy in calf diarrhea are, 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. Because many of the early studies on antimicrobial treatment in calf diarrhea were uncontrolled, this review of antimicrobial therapy success has been restricted to studies with adequate numbers, random allocation to groups, and inclusion of an appropriate control group.

Success of antimicrobial therapy can vary with the route of administration and whether the antimicrobial is dissolved in milk, oral electrolyte solutions, or water.[31,32] Oral antimicrobials administered as a bolus or contained in a gelatin capsule are deposited into the rumen and therefore have a different serum concentration-time profile to antimicrobial agents dissolved in milk replacer that are suckled by the calf or administered as an oral drench at the back of the pharynx.[24,30,31,33] Antimicrobial agents that bypass the rumen are not thought to alter rumen microflora, potentially permitting bacterial recolonization of the small intestine from the rumen.[30] Finally, when oral antimicrobial agents are administered to calves with diarrhea, the antimicrobial concentration in the small intestinal lumen is lower and the rate of antimicrobial elimination faster than in healthy calves.[30]

Amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, sulfamethazine, and tetracycline administered PO are currently labeled in the United States for the treatment of calf diarrhea. No parenteral antimicrobial agents have a label claim in the United States for treating calf diarrhea.

***Success of Oral Antimicrobials in Treating Naturally Acquired Diarrhea.*** The studies are summarized in chronological order. A 1954 study in California involved 37 dairy calves with *Salmonella enterica* serotype Bredeney diarrhea.[34] The mortality rate in calves treated with streptomycin (500 mg IM and PO once, then 750 mg PO q24h for 3 days) was 45% (10/22), which was significantly ($P = .014$) higher than the mortality rate (1/15 = 7%) in another group of calves treated with chloramphenicol (500 mg PO q24h for 4 days).[34] This study was instrumental in promoting the use of oral chloramphenicol to treat calf diarrhea, particularly diarrhea episodes caused by *Salmonella* spp.

A 1959 study in North Carolina involved 63 dairy calves with diarrhea.[35] Twice daily administration of neomycin sulfate (dose unknown) and nifuraldezone[b] (dose unknown) PO for 2 days did not alter mortality rate (neomycin, 6/21 = 28%; nifuraldezone, 3/21 = 14%) when compared with nonantimicrobial-treated controls (6/21 = 28%). Among surviving calves, the mean duration of diarrhea tended to be shorter in those treated with neomycin (6.5 days) or nifuraldezone (6.2 days) when compared with untreated control calves (9.7 days). Furazolidone (15 mg/kg PO q24h) also had no effect on mortality when compared with untreated control calves in a 1971 study completed in Scotland on 24 male Ayrshire calves with diarrhea.[36]

One of the seminal studies was conducted on 165 beef calves with diarrhea in Saskatchewan, Canada.[37] Ampicillin (12 mg/kg PO q12h for 3–5 days) had no effect ($P = .83$) on mortality rate (26/83 = 31% in ampicillin-treated calves; 27/82 = 33% in control calves). Lack of treatment success in this 1975 study was later attributed to a delay in instituting antimicrobial treatment[38]; antimicrobials were not administered until diarrhea had been present for a number of days. In the same year, a large study was conducted in Europe involving 347 male dairy calves with diarrhea.[39] Apramycin significantly decreased the mortality rate in calves treated at 20 mg/kg PO q24h for 5 days (mortality 10/118 = 9%, $P < .001$) or 40 mg/kg PO q24h (mortality 6/108 = 6%, $P < .001$) when compared with untreated controls (mortality 36/121 = 30%). Apramycin administration PO also increased growth rate in survivors. Apramycin is an aminocyclitol antimicrobial with a predominantly gram-negative spectrum of activity.

One hundred fifty-three dairy calves with diarrhea in Arkansas were administered a potentiated sulfonamide or sulfamethazine and neomycin.[40] Administration of a potentiated sulfonamide (5 mg/kg PO q24h trimethoprim; 25 mg/kg PO q24h sulfadiazine) for 3–5 days had no effect ($P = .17$) on the proportion of calves returning to normal fecal consistency (recovery rate 88/101 = 87%) when compared with a combined treatment of 87 mg/kg PO q12h sulfamethazine and 11 mg/kg PO q12h neomycin sulfate (recovery rate 62/78 = 80%) or with an untreated control group (recovery rate 23/31 = 74%, $P = .097$).

In a 1998 European study, 174 beef and dairy diarrheic calves <5 days old were randomly assigned to treatment with fluoroquinolone marbofloxacin[c] (1 mg/kg PO q24h for 3 days) or amoxicillin-clavulanic acid (12.5 mg/kg PO q12h) as a positive control.[41] Marbofloxacin treatment produced a significantly ($P < .05$) faster return to normal feces (30% by day 1; 73% by day 3) than did amoxicillin-clavulanic acid (10% by day 1; 58% by day 3). *E coli* K99 was isolated from the feces in 51% of the calves, and the superior response to marbofloxacin was similar whether enterotoxigenic *E coli* was detected or not detected in the feces of the scouring calves.

Oral administration of chloramphenicol was effective in treating *S enterica* serotype Bredeney diarrhea, and apramycin and marbofloxacin administered PO were effective in treating undifferentiated diarrhea. Although chloramphenicol and marbofloxacin have demonstrated efficacy, their listing does not condone, support, or suggest that these therapies should be used in the United States.

***Efficacy of Oral Antimicrobials in Treating Experimentally Induced Diarrhea.*** Diarrhea was experimentally induced by intraduodenal inoculation with *S enterica* serotype Dublin in 54 dairy calves aged 1–2 weeks.[42] Treatment began when calves had profuse diarrhea and fever and consisted of administration of 30 mg/kg chloramphenicol, 500 mg furazolidone, 75 mg/kg sulphamethylphenasole, or 500 mg neomycin sulfate PO q12h. Compared with an untreated control group (16/20 = 80% died), the mortality rate was significantly lower in calves treated with chloramphenicol (1/9 = 11% died, $P = .0009$), furazolidone (2/10 = 20% died, $P = .0041$), and sulphamethylphenasole (3/9 = 33% died, $P = .032$). The mortality rate in the untreated control group was similar to that obtained in calves treated with neomycin sulfate (3/6 = 50% died, $P = .29$).

Diarrhea was experimentally induced by oral inoculation with *S enterica* serotype Dublin in 35 dairy calves aged 2–3 weeks.[43] Daily administration of trimethoprim, sulfadiazine, or both (in 1 : 5 ratio) was started 24 hours after inoculation, at which time the calves were slightly subdued but otherwise clinically normal,[44] and continued for 5 days. Compared with an untreated control group (5/7 = 71% died), the mortality rate tended to be lower in calves treated with trimethoprim/sulfadiazine boluses (5 mg/kg trimethoprim and 25 mg/kg sulfadiazine; 1/7 = 14% died, $P = .10$). Similar mortality rates were observed in control calves and calves treated with a lower dose of trimethoprim/sulfadiazine (2.5 mg/kg trimethoprim and 12.5 mg/kg sulfadiazine; 4/7 = 57% died, $P = 1.00$), trimethoprim (10 mg/kg; 4/7 = 57% died, $P = 1.00$), or sulfadiazine (50 mg/kg; 6/7 = 86% died, $P = 1.00$).

Enterotoxigenic *E coli* diarrhea was experimentally induced in 40 calves 5–10 days old, and treatment was administered immediately after diarrhea was detected.[45] The mortality rate was significantly ($P < .05$) lower in calves administered amoxicillin trihydrate in milk replacer (at ~10 mg/kg PO q12h for 4 days; 1/20 = 5%) than in untreated control calves (6/20 = 30%). The duration of diarrhea was significantly ($P < .01$) shorter in calves administered amoxicillin (3.9 ± 0.1 days) than in untreated control calves (5.7 ± 0.2 days).

Diarrhea was experimentally induced in 82 calves by administering an enterotoxigenic strain of *E coli*, although rotavirus was frequently isolated from calves with diarrhea.[46] Treatment was administered immediately after diarrhea was detected. The mortality rate tended to be lower in calves administered amoxicillin (as amoxicillin trihydrate, 10 mg/kg PO q12h for 2 days; 1/21 = 5%), oral electrolyte solution (1/20 = 5%), or oral electrolyte solution and amoxicillin (0/20 = 0%) than in untreated control calves (4/21 = 19%). The duration of diarrhea was significantly ($P < .05$) shorter in calves administered amoxicillin (3.1 ± 1.9 days), oral electrolyte solution (3.1 ± 1.1 days), or oral electrolyte solution and amoxicillin (2.3 ± 1.5 days) than in untreated control calves (4.6 ± 2.3 days).

In a study of forty-three 1-day-old calves with experimentally induced enterotoxigenic *E coli* diarrhea, oral administration of cephamycin C, a broad-spectrum β-lactam antimicrobial that is β-lactamase resistant and not absorbed from the intestine, caused a significant ($P < .0001$) decrease in mortality (3/22 = 14%) in treated calves compared with control calves (19/21 = 90% mortality) and greatly decreased fecal *E coli* bacterial concentrations.[47]

In a related study in thirty-one 1–3-day-old calves with experimentally induced enterotoxigenic *E coli* diarrhea, oral administration of L-640,876, a broad-spectrum, potent β-lactam antimicrobial, caused a significant ($P < .01$) decrease in mortality (1/9 = 11%) in treated calves compared with control calves (9/11 = 82% mortality) and greatly decreased fecal *E coli* bacterial concentrations.[48]

In a 1998 study, enterotoxigenic *E coli* diarrhea was experimentally induced in 30 calves (<1 day old), and calves were randomly assigned to treatment with fluoroquinolone enrofloxacin (5 mg/kg PO q24h for 3 days) or no treatment.[49] Oral administration of enrofloxacin significantly decreased the mortality rate (7/15 = 47% versus 13/15 = 87%, $P = .020$).

Oral administration of chloramphenicol, furazolidone, sulphamethylphenasole, broad-spectrum β-lactam antimicrobials (amoxicillin, cephamycin C, L-640,876), and enrofloxacin was effective in treating experimentally induced enterotoxigenic *E coli* or *S enterica* serotype Dublin diarrhea. Although chloramphenicol, furazolidone, and enrofloxacin have demonstrated efficacy, their listing here does not condone, support, or suggest that these therapies should be used in the United States.

***Efficacy of Parenteral Antimicrobials in Treating Naturally Acquired Diarrhea.*** Chloramphenicol (15 mg/kg IM q24h) had no effect on mortality when compared with untreated control calves in a 1971 study in Scotland involving 20 male Ayrshire calves with diarrhea.[36] Administration of chloramphenicol (20 mg/kg IV q12h) combined with nifuraldezone (60 mg/kg initially, then 30 mg/kg PO q12h for 3 days) also had no effect ($P = .13$) on mortality rate (20/89 = 22% in antimicrobial-treated calves; 27/82 = 33% in control calves) in a study involving 171 diarrheic beef calves in Saskatchewan, Canada.[37]

In a 1975 study conducted in Europe involving 181 male dairy calves with diarrhea,[39] injection of apramycin (20 mg/kg q24h, unstated route, for 5 days) significantly ($P = .030$) decreased the mortality rate (5/90 = 6%) compared with untreated controls (14/91 = 15%). Apramycin injection also increased the growth rate in survivors.[39] A study involving 25 male Holstein calves with diarrhea was conducted in the same year in the United States.[50] Ampicillin trihydrate (400 mg/kg IM q24h) combined with nitrofurazone ([2 oz] 57 g PO q24h) for 5 days improved ($P < .05$) the general appearance (assessed subjectively by appetite, coat condition, morbidity) on day 5 and day 12 when compared with nonantimicrobial-treated control calves.

Twenty diarrheic calves were treated with oral, subcutaneous, and intravenous fluids and trimethoprim/sulfonamide (IM at ''the recommended dose'' for up to 7 days) or no treatment (controls) in a 1980 study conducted in

Scotland.[51] No difference in mortality rate was detected between antimicrobial-treated (6/10 = 60%) and control (4/10 = 40%) calves.

Another seminal study was conducted in 1987 at multiple locations in Europe involving 318 diarrheic calves.[38] Calves were randomly assigned to 1 of 3 treatment groups: sulbactam-ampicillin (9.9 mg/kg IM q24h; 10/105 = 10% mortality), ampicillin (6.6 mg/kg IM q24h; 15/107 = 14% mortality), or untreated control (28/106 = 26% mortality). Treatment was instituted immediately on detection of diarrhea. This study indicated a lower mortality rate in calves treated with sulbactam-ampicillin ($P = .0014$) or ampicillin ($P = .024$) and provided strong support for the routine parenteral administration of broad-spectrum β-lactam antimicrobials in the treatment of undifferentiated calf diarrhea. The study also indicated that administration of sulbactam (penicillinic acid sulfone), which is a potent irreversible inhibitor of β-lactamase, increased the treatment efficacy of parenteral ampicillin.[38]

Parenteral administration of apramycin or the β-lactam antimicrobial ampicillin was effective in treating naturally acquired diarrhea, and treatment efficacy of ampicillin was increased with β-lactamase inhibition.

***Efficacy of Parenteral Antimicrobials in Treating Experimentally Induced Diarrhea.*** A study was conducted in 38 male dairy calves aged 1–2 weeks with experimentally induced enterotoxigenic *E coli* diarrhea.[52] After diarrhea induction, calves were randomized into 3 treatment groups consisting of danofloxacin,[c] a fluoroquinolone antimicrobial (1.25 mg/kg IM q24h for 3 days), a positive control baquiloprim/sulphadimidine (10 mg/kg IM q24h for 3 days), or untreated controls. Although most calves developed only mild diarrhea and did not become severely ill (all calves survived), danofloxacin decreased the time taken to recover to a normal demeanor and prevented development of mild metabolic acidosis. Compared with potentiated sulfonamide–treated calves, danofloxacin increased weight gain.

Diarrhea was experimentally induced by oral inoculation with *S enterica* serotype Dublin in 58 dairy calves aged 2–3 weeks.[43] Daily administration of trimethoprim/sulfadiazine (in a 1:5 ratio) was started 24 hours after inoculation, at which time the calves were slightly subdued but otherwise clinically normal,[44] and continued for 5 days. Compared with untreated controls (19/22 = 86% died), the mortality rate was significantly lower in calves treated with trimethoprim/sulfadiazine (20 mg/kg sulfadiazine and 4 mg/kg trimethoprim IV; 2/14 = 14% died, $P < .0001$), trimethoprim/sulfadiazine (20 mg/kg sulfadiazine and 4 mg/kg trimethoprim IM; 1/14 = 7% died, $P < .0001$), or a lower dose of trimethoprim/sulfadiazine (10 mg/kg sulfadiazine and 2 mg/kg trimethoprim IV; 1/7 = 14% died, $P = .0011$). Administration of either sulfadiazine or trimethoprim alone was associated with high mortality rates, demonstrating marked synergism of trimethoprim and sulfadiazine in vivo.[43]

Early IV or IM administration of trimethoprim/sulfadiazine was effective in treating experimentally induced *S enterica* serotype Dublin diarrhea, and danofloxacin was effective in treating experimentally induced mild enterotoxigenic *E coli* diarrhea. Although danofloxacin has demonstrated efficacy, its listing does not condone, support, or suggest that this therapy should be used in the United States.

## Evidenced-Based Recommendations for Antimicrobial Administration

The current recommendation by some veterinarians that oral or parenteral antimicrobials should not be used for treating calf diarrhea is not supported by a critical evidenced-based review of the literature. The arguments used to support a nonantimicrobial treatment approach are that (1) antimicrobials administered PO alter intestinal flora and function and thereby induce diarrhea, which has been documented on more than 1 occasion with chloramphenicol,[20,22–24] neomycin,[19,20] and penicillin[18,53]; (2) antimicrobials harm the ''good'' bacteria more than the ''bad'' bacteria in the small intestine (an undocumented claim in the calf); (3) antimicrobials are not effective (a statement that is clearly not supported by the results of some published peer-reviewed studies); and (4) antimicrobial administration promotes the selection of antimicrobial resistance in enteric bacteria.

Oxytetracycline and sulfachloropyridiazine administered parenterally and amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, sulfamethazine, and tetracycline administered PO are currently labeled in the United States for the treatment of calf diarrhea. Of the 8 antimicrobials administered PO, only amoxicillin has been shown to be efficacious in studies that were conducted with appropriate control groups and published in peer-reviewed journals. In general, the 2 parenteral and 8 oral antimicrobials have been labeled by the U.S. Food and Drug Administration for the treatment and aid in the control of bacterial enteritis (scours, colibacillosis) caused by *E coli* bacteria susceptible to the antimicrobial. Unfortunately, data supporting the efficacy of parenteral oxytetracycline and sulfachloropyridiazine and of oral amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, sulfamethazine, and tetracycline in treating calves with naturally acquired diarrhea do not appear to have been published in peer-reviewed journals, and the Freedom of Information summary (www.fda.gov/cvm/efoi) does not supply sufficient information for an independent conclusion of efficacy to be made. Chlortetracycline, neomycin, oxytetracycline, and tetracycline were originally approved as safe for use in the 1950s. Subsequently, the National Academy of Sciences/National Research Council reviewed the available data from 1969 to 1971 and concluded that chlortetracycline, neomycin, oxytetracycline, and tetracycline were probably effective for oral treatment of animal diseases when such diseases were caused by pathogenic microorganisms sensitive to the drug (www.fda.gov/cvm/efoi).

Oral amoxicillin has documented efficacy in the treatment of experimentally induced diarrhea,[45,46] but amoxicillin administered PO was not efficacious in the treatment of naturally acquired diarrhea in beef calves.[37] Extra-label antimicrobial use (excluding prohibited antimicrobials) is therefore justified in treating calf diarrhea because of the apparent lack of published studies documenting clinical efficacy of antimicrobials with a label claim and because the

health of the animal is threatened and suffering or death might result from failure to treat systemically ill calves.

Because the 2 sites of infection in calf diarrhea are the small intestine and blood, administered antimicrobials should have both local (small intestinal) and systemic effects. In addition, the antimicrobial must reach therapeutic concentrations at the site of infection for a long enough period and, ideally, have only a narrow gram-negative spectrum of activity to minimize collateral damage to other enteric bacteria.[15] In general, oral and parenteral administration of broad-spectrum β-lactam and fluoroquinolone antimicrobials have proven efficacy in treating naturally acquired and experimentally induced diarrhea; parenteral administration of trimethoprim/sulfadiazine has proven efficacy in treating experimentally induced *S enterica* serotype Dublin (although efficacy has only been demonstrated when antimicrobial administration starts before diarrhea is present); and oral administration of the predominantly gram-negative antimicrobial apramycin has proven efficacy in treating naturally acquired diarrhea. Because use of fluoroquinolone antimicrobials in an extra-label manner is illegal in the United States and apramycin is an aminocyclitol antimicrobial that is poorly absorbed after oral administration (oral bioavailability <15%) and has relatively high MIC values against *Salmonella* spp and *E coli* ($MIC_{90}$ >3 μg/mL) in the calf,[54] treatment recommendations will focus on the use of broad-spectrum β-lactam antimicrobials such as amoxicillin, ampicillin, ceftiofur, and potentiated sulfonamides (trimethoprim/sulfadiazine).

### *Administration of Oral Antimicrobials to Treat* E coli *Overgrowth of the Small Intestine*

In enteric infections, it is desirable that high intestinal luminal antimicrobial concentrations are maintained with some degree of drug penetration through the intestinal wall.[55] Accordingly, in preruminant calves with diarrhea and mild systemic illness (defined as depressed suckling but normal rectal temperature, hydration status, and heart rate), the veterinarian should continue to monitor the calf's health or administer amoxicillin trihydrate (10 mg/kg PO q12h) or amoxicillin trihydrate-clavulanate potassium (12.5 mg combined drug/kg PO q12h) for at least 3 days; the latter constitutes extra-label drug use. Amoxicillin trihydrate (10 mg/kg PO q12h in milk replacer) was efficacious in decreasing mortality rate and duration of diarrhea in 2 studies in which diarrhea was experimentally induced with enterotoxigenic *E coli* bacteria.[45,46] Amoxicillin trihydrate is 30% absorbed from the calf small intestine, with absorption being similar in milk-fed and fasted calves.[55] After administration of amoxicillin trihydrate (7 mg/kg PO in milk replacer), high antimicrobial concentrations are present in the bile and intestinal contents, with lower antimicrobial concentrations in serum,[45] although serum amoxicillin concentration exceeded 0.5 μg/mL for the duration of treatment.[55] Concurrent feeding of milk and amoxicillin does not change the bioavailability of amoxicillin, although it is absorbed faster when dissolved in an oral electrolyte solution than in milk replacer[32] and absorption is slowed during endotoxemia, presumably because of a decrease in the abomasal emptying rate.[56] Amoxicillin trihydrate is preferred to ampicillin trihydrate for oral administration in calves because it is labeled for the treatment of calf diarrhea in the United States and is absorbed to a much greater extent.[32,55,57] However, a field study comparing amoxicillin (400 mg PO q12h) and ampicillin (400 mg PO q12h) treatments for diarrhea reported similar proportions of calves with a good to excellent clinical response (49/62 = 79% for amoxicillin bolus, 59/74 = 80% for amoxicillin powder, 47/65 = 65% for ampicillin bolus, $P > .30$ for all comparisons).[58] The addition of clavulanate potassium to amoxicillin trihydrate is recommended because clavulanate potassium is a potent irreversible inhibitor of β-lactamase, increasing the antimicrobial spectrum of activity.

Oral administration of potentiated sulfonamides is not recommended for treating calf diarrhea because of the lack of efficacy studies. No other antimicrobial administered PO currently available in the United States is likely to be effective in treating calves with diarrhea, even though gentamicin (50 mg/calf PO q12h) markedly decreased *E coli* bacterial concentrations in the feces of healthy calves.[59] Despite 1 study that reported gentamicin (40–80 mg q12h for 3 days, route not stated but presumed to be oral) improved stool consistency in calves with experimentally induced *E coli* diarrhea,[60] administration of gentamicin PO is not recommended because antimicrobial agents administered to calves with diarrhea should have both local and systemic effects and gentamicin administered PO is poorly absorbed. An additional problem with gentamicin is the prolonged withdrawal time for slaughter, even after oral administration.

Fluoroquinolones clearly have proven efficacy in treating calf diarrhea, and a label indication exists in Europe for oral and parenteral enrofloxacin and oral marbofloxacin for the treatment of calf diarrhea. In those countries where their administration is permitted to treat calf diarrhea, oral fluoroquinolones are recommended because of their high oral bioavailability. However, it must be emphasized that extra-label use of the fluoroquinolone class of antimicrobials in food-producing animals in the United States is illegal and obviously not recommended.

In calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever), the author recommends that the clinician monitor the health of the calf and not administer oral antimicrobials.

### *Administration of Parenteral Antimicrobials to Treat* E coli *Bacteremia*

In calves with diarrhea and moderate to severe systemic illness, the positive predictive value (.65) of clinical tests (sensitivity [Se] = .39, specificity [Sp] = .91) and the positive predictive value (.77) of clinicopathologic tests (Se = .40, Sp = .95) for detecting bacteremia are too low assuming reasonable estimates for the prevalence of bacteremia (30%).[17] Accordingly, it is recommended that clinicians routinely assume 30% of ill calves with diarrhea are bacteremic and that bacteremia constitutes a threat to the life of the calf. Parenteral antimicrobial treatment is required for these calves.

The most logical parenteral treatment is ceftiofur (2.2 mg/kg IM/SC q12h) for at least 3 days. Ceftiofur is the

most appropriate antimicrobial because it is a broad-spectrum β-lactam antimicrobial that is resistant to the action of β-lactamase; the $MIC_{90}$ for *E coli* is <0.25 μg/mL[61]; the recommended dosage schedule maintains free plasma β-lactam antimicrobial concentrations at the desired 4 times above the $MIC_{90}$ value for the duration of treatment in 7-day-old calves; and 30% of the active metabolite of ceftiofur (desfuroylceftiofur) is excreted into the intestinal tract of cattle,[62] providing antimicrobial activity in both blood and small intestine. Moreover, ceftiofur hydrochloride (2 mg/kg IM once and 0.5 mg/kg PO once) decreased the mortality rate and the severity of diarrhea in pigs with experimentally induced enteric colibacillosis, although these pigs were not suspected to be bacteremic.[63] The beneficial effects of parenteral ceftiofur in these pigs was attributed to decreasing intestinal luminal concentration of pathogenic *E coli*.[63] Ceftiofur sodium (<5 mg/kg PO q24h) was also effective in treating mice with experimentally induced enteric colibacillosis.[61] Administration of ceftiofur to treat bacteremia and diarrhea in calves constitutes extra-label drug use, and ceftiofur should not be administered to calves to be processed as veal.

Another recommended treatment is parenteral amoxicillin trihydrate or ampicillin trihydrate (10 mg/kg IM q12h) for at least 3 days. Although parenteral ampicillin has proven efficacy in treating naturally acquired diarrhea,[38] whereas ceftiofur has unproven efficacy, the broad-spectrum β-lactam antimicrobials amoxicillin and ampicillin are theoretically inferior to ceftiofur because parenterally administered ampicillin and amoxicillin reach lower plasma concentrations, require a higher MIC than ceftiofur, and are not β-lactamase resistant.[61] Amoxicillin or ampicillin should be injected into the neck musculature because this site provides the greatest absorption[62] and minimizes damage to more valuable areas of the carcass. Amoxicillin and ampicillin should not be administered subcutaneously because the rate and extent of absorption is reduced relative to intramuscular injection.[64]

A 3rd recommended treatment is parenteral potentiated sulfonamides (20 mg/kg sulfadiazine with 5 mg/kg trimethoprim IV or IM, depending on the formulation characteristics, q24h for 5 days). Efficacy of potentiated sulfonamides has only been proven when treatment began before clinical signs of diarrhea were present.[43,44] It is therefore unknown whether potentiated sulfonamides are efficacious when administered to calves with diarrhea and depression, although it is likely that potentiated sulfonamides are efficacious in the treatment of salmonellosis.

Oral administration of potentiated sulfonamides and apramycin is not recommended for the treatment of bacteremia because of poor oral bioavailability. Oxytetracycline or chlortetracycline also are not recommended for the treatment of bacteremia, although tetracyclines might have some efficacy for treating *E coli* bacterial overgrowth of the small intestine. Tetracycline antimicrobials are bound to calcium, and oral bioavailability when administered with milk is 46% for oxytetracycline and 24% for chlortetracycline.[65] Schifferli et al[65] calculated that oxytetracycline would need to be administered at 20 mg/kg PO q12h to achieve the minimal serum concentrations necessary to treat *E coli* bacteremia ($MIC_{50}$ = 4 μg/mL).

In the past, gentamicin has been "considered an appropriate alternative drug for use in calf diarrheas and pneumonias when other antimicrobial agents are unsatisfactory."[66(p2461)] Parenteral administration of gentamicin and other aminoglycosides (amikacin, kanamycin) cannot currently be recommended as part of the treatment for calf diarrhea because of the lack of published efficacy studies; prolonged slaughter withdrawal times (15–18 months); potential for nephrotoxicity in dehydrated animals; and availability of ceftiofur, amoxicillin, and ampicillin.

A label indication exists in Europe for parenteral enrofloxacin in the treatment of calf diarrhea. In those countries where administration is permitted to treat calves with diarrhea, parenteral fluoroquinolones are recommended because of their broad-spectrum bactericidal activity, particularly against gram-negative bacteria. However, it must be emphasized that extra-label use of the fluoroquinolone class of antimicrobials in food-producing animals in the United States is illegal and obviously not recommended.

Chloramphenicol had proven efficacy in treating calf diarrhea due to *S enterica* serotype Bredeney and Dublin,[34,42] although its use is now illegal in the United States. The related antimicrobial florfenicol achieves high concentrations in the small intestinal lumen and is 89% absorbed when administered PO to milk-fed calves[67]; however, florfenicol is not the most appropriate antimicrobial for treating calf diarrhea because the $MIC_{90}$ for *E coli* is very high at 25 μg/mL,[68] and florfenicol (11 mg/kg PO or 20 mg/kg IM) failed to reach the $MIC_{90}$ value in plasma, whereas florfenicol (11–20 mg/kg IV) only exceeded the $MIC_{90}$ value for <60 minutes.[67,69,70]

In calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever), the author recommends that the clinician monitor the health of the calf and not administer parenteral antimicrobials.

## Footnotes

[a] The use of chloramphenicol in food-producing animals in the United States is prohibited by law because of the occurrence of non–dose-related aplastic anemia in 1 in 10,000–50,000 exposed humans.

[b] The administration of nifuraldezone and furazolidone in food-producing animals in the United States is prohibited by law because of concerns regarding nitrofuran-induced mutagenicity and carcinogenicity.

[c] Extra-label administration of fluoroquinolones in food-producing animals in the United States is prohibited by law because of concerns regarding facilitating the emergence of bacteria with multiple antimicrobial resistance, particularly pathogenic enteric bacteria in humans.

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