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Antibiotic Treatment of Calves Diarrhea

Hamada Elazazy*; Shaimaa A. Abd Elkader*; Rania, S.M. and Hala S. Abubaker****

*Animal Health Research Institute, Zagazig branch, Agriculture Research Center, Giza, Egypt.

**Bacteriology Department, Animal Health Research Institute, Agriculture Research Center, Giza, Egypt.

Corresponding author:
Rania Saleh Mohammed
E.mail: raania.saleh@yahoo.com

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Abstract

The review discusses the role of antibiotics in treating calf diarrhea, highlighting the need for veterinarians to limit antimicrobial usage to avoid adverse effects on animal and human health. It emphasizes the importance of infection control protocols, diagnostic testing, and monitoring antimicrobial resistance. Despite advancements in vaccines and passive immunity management, antimicrobial treatment remains crucial for managing calf diarrhea, especially when caused by pathogens like *E. coli* and *Salmonella*. The review also covers the limitations of antimicrobial susceptibility testing, particularly in distinguishing between pathogenic and non-pathogenic bacteria. It advocates for evidence-based antimicrobial use and warns against the overuse of broad-spectrum antibiotics, recommending targeted treatments. Furthermore, the review underlines the importance of supportive therapies, such as fluid administration and nonsteroidal anti-inflammatory drugs, to manage the symptoms and complications of diarrhea in calves.

Keywords: *Antibiotic Resistance; Calf Diarrhea; E. coli and Antimicrobial Treatment.*

Introduction

The recommendation encourages veterinarians to limit the use of antimicrobial drugs in order to minimize potential harmful effects on both animal and human health. It also emphasizes the importance of developing formal infection control plans, identifying common conditions like diarrhea or respiratory disease where antimicrobials are often used, and setting clear protocols for antimicrobial usage within the practice. Furthermore, antibiotics should be classified into primary, secondary, and tertiary categories, and appropriate diagnostic and sensitivity testing should be applied. Regular monitoring and surveillance of antibiotic-resistant bacteria, whether within a veterinary practice, on a farm, in a region, or even nationwide, are critical for continually evaluating and improving antimicrobial practices.

Clinical Significance:

For more than 50 years, antimicrobial therapy has played a key role in treating calf diarrhea. Despite this, diarrhea remains the leading cause of mortality among preweaned dairy heifer calves, with no notable reduction in death rates over time **Algammal *et al.*, (2002).** Although vaccines targeting major causes of calf diarrhea such as enterotoxigenic *Escherichia coli*, rotavirus, and coronavirus are widely available, and improvements in passive immunity through colostrum management have been made, both oral and injectable antimicrobial treatments continue to be essential in managing calf diarrhea **Abdelazeem *et al.*, (2020).** Recently, detailed guidelines for the use of antimicrobials in diarrheic calves have been developed, based on a systematic review of randomized controlled studies published in peer-reviewed journals **Aman *et al.*, (2002).**

Causes of Calf Diarrhea:

Diarrhea is often caused by infection with one or more intestinal bacteria such as salmonella spp. rotavirus coronavirus enterotoxigenic *Escherichia coli* or cryptosporidium numerous illnesses can strike the herd on a regular basis and affect both healthy and sick babies in some cases of acute hepatitis salmonella is thought to be critical in the intestines of cows suffering from diarrhea coliform germs are frequently found to predominate despite the presence of other microbes poor intestinal characteristics tissue injury and the potential for bacteremia are associated with the growth of these bacteria **Gharieb *et al.,* (2015); Liu *et al.,* (2007)** since it was discovered that d-lactate plays a role in acidemia in afflicted cows the connection between bacterial overgrowth and diarrhea in cows has garnered attention especially after the discovery of the function of d-lactate in acidemia in affected cows. D-lactic acid is produced by fermentation in the stomach and is often prescribed in toddlers without or with diarrhea. In these cows, it causes acidemia, which regularly causes signs and symptoms including fatigue and loss of coordination **Herrera Luna *et al.,* (2009); Islam *et al.,* (2015).**

Bacteremia in Calves with Diarrhea:

Calves affected by diarrhea are more susceptible to partial or complete failure in passive immunity transfer which significantly increases their risk of developing bacteremia studies indicate that bacteremia primarily caused by *E.coli* is present in roughly 20 to 30 of calves suffering from diarrhea or systemic illnesses due to *E. coli* for calves that are severely ill showing signs such as a weakened suckling reflex dehydration exceeding 6 weakness inability to stand or signs of clinical depression it is recommended to routinely include treatments targeting bacteremia particularly *E.coli* bacteremia due to its high occurrence **Nguyen *et al.,* (2005)** currently it is not recommended to rely on a clinical sepsis score to guide antibiotic treatment in calves until further validation is achieved across different calf-rearing environments **Osman *et al.,* (2012)** while the exact rate of bacteremia in these cases remains undetermined calves showing clinical signs of diarrhea caused by *Salmonella* are also suspected to have bacteremia **Fecteau *et al.,* (2003).**

Antimicrobial Susceptibility Testing:

Salmonella species other than enterotoxigenic *E.coli* are the most commonly identified bacterial enteropathogens in fecal samples and necropsy specimens from calves it is strongly advised to submit appropriate samples for bacterial culture pathogen identification and susceptibility testing using standardized methodologies to facilitate evidence-based drug selection and rationalize antibiotic usage nevertheless there remains a need for the advancement of laboratory techniques and the establishment of standardized breakpoints for numerous bacteria-drug combinations **Randall *et al.,* (2004); Sayed *et al.,* (2002).**

Certain fecal isolates including *E.coli, Clostridium perfringens* type A and Campylobacter species are considered part of the normal intestinal microbiota consequently diagnostic laboratories must effectively distinguish between normal bacterial populations and potential pathogens in fecal cultures particularly when the cultured organisms cannot be differentiated from normal flora based on species identification virulence factors or other markers or when there is clear evidence of bacterial overgrowth **Shahrani *et al.,* (2014)** in instances susceptibility testing can help guide treatment plans and the selection of suitable antimicrobial agents when enterotoxigenic *E.coli* or *Salmonella* is found ensuring appropriate antimicrobial concentrations at the infection sites such as the small intestine and bloodstream is crucial for the successful management of calf diarrhea **Yadegari *et al.,* (2019).**

Testing or fecal antibacterial susceptibility in calves with diarrhea is primarily relevant when dealing with specific pathogens like pathogenic Salmonella species and enterotoxigenic *E.coli* blood culture isolates from calves with confirmed bacteremia may perhaps be taken into the efficacy of current susceptibilitytesting techniques in forecasti ng treatment results for diarrhea in calves

has not been shown for non-enterotoxigenic *E.coli* isolates **Solmaz *et al.,* (2000)** fecal bacteria culture and susceptibility testing specifically the Kirby-Bauer method may be less helpful *Salmonella* isolates and fecal *E.coli* in vitro susceptibility do not appear to be correlated in any way and clinical treatment response results from deceased calves should be interpreted cautiously as they might reflect treatment failures or bacterial overgrowth that doesn't accurately represent the actual in vivo situation **Gupta *et al.,* (2014); Deverdier *et al.,* (2012)** The fact that Kirby-Bauer breakpoints, also known as minimum inhibitory concentrations, are not intended to represent the normal antimicrobial concentrations seen in calves' small intestines and blood is another drawback of fecal susceptibility testing. For this reason, doctors should evaluate the efficacy of antibiotics by monitoring the animal's clinical response to therapy **Cantas *et al.,* (2013)** When assessing blood isolates as opposed to fecal isolates, the Kirby-Bauer technique could be more useful. this is because mic90 values for human *E. coli* isolates, which block 90 percent of the isolates, and Kirby-Bauer breakpoints (minimum inhibitory concentration [MIC]) are based on achievable antimicrobial concentrations in human plasma and MIC_{90} (MIC for 90% of the isolates) 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. **Bradford (2001); Aman *et al.,* (2021).**

Success of Antimicrobial Therapy:

Important aspects of treating calf diarrhea involve strictly following the prescribed guidelines for antibiotic use, selecting an antimicrobial agent with the correct spectrum of activity, and ensuring that the drug reaches and maintains the necessary therapeutic levels at the site of infection. It's also essential to administer the treatment for the appropriate duration while minimizing the risk of adverse local or systemic effects, as well as avoiding the presence of harmful drug residues **Ahmed *et al.,* (2013).** Key measures of success in treating calf diarrhea with antimicrobials include tracking the mortality rate, evaluating the growth rate, and assessing both the severity and length of diarrhea in calves that survive **Addy *et al.,* (2004).** The effectiveness of antibiotic therapy can depend greatly on the method of administration and whether the drug is dissolved in milk, oral electrolyte solutions, or water. For example, oral antibiotics administered in the form of boluses, tablets, or gelatin capsules may end up in the rumen, leading to different serum concentration profiles than those dissolved in milk replacers or given as oral drenches. Antibiotics that bypass the rumen tend to have less impact on rumen microflora, potentially allowing bacterial recolonization in the small intestine. Nevertheless, the normal gut flora is exposed to some level of antibiotics regardless of how the drugs are administered **Alberto, (2022).** Past research has shown that some orally administered antibiotics, like potassium and procaine penicillin, neomycin sulfate, ampicillin trihydrate, and tetracycline hydrochloride, can increase diarrhea occurrence, cause malabsorption, and slow down growth rates in calves **Bradford, (2001); Abd el Azeem *et al.,* (2020).**

Evidence-Based Recommendations for Antimicrobial Administration in Calf Diarrhea:

The U.S. Food and Drug Administration (FDA) has approved several antibiotics for treating and managing bacterial enteritis (scours, colibacillosis) caused by *E. coli* in calves. These include injectable antibiotics such as oxytetracycline and sulfa chlorpyridazine, alongside oral treatments like amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachlorpyridazine, sulfamethazine, and tetracycline **Cantas *et al.,* (2013).** Among these, four antibiotics chlortetracycline, Oxytetracycline, tetracycline, and neomycin are specifically labeled for the treatment or control of bacterial enteritis due to *E. coli* and Salmonella species **CLSI, (2017); Colom *et al.,* (2003).**

However, peer-reviewed research validating the efficacy of many of these antibiotics, particularly injectable oxytetracycline and sulfachlorpyridazine or orally administered options like amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sul-

fachlorpyridazine, sulfamethazine, and tetracycline, in treating naturally occurring diarrhea in calves remains limited **Mona *et al.,* (2023).** Although oral amoxicillin has been effective for experimentally induced diarrhea **Yayesew and Temesgen, (2023),** its effectiveness in treating naturally occurring diarrhea in beef calves has not been established. Given the scarcity of clinical data proving the effectiveness of these antibiotics and considering that untreated diarrhea in calves can lead to serious complications or death, the use of extra-label antimicrobials (excluding prohibited ones) is often justified for treating severely ill calves with diarrhea **Mona *et al.,* (2023).**

Successful treatment of calf diarrhea requires antimicrobials that are effective both locally (in the small intestine) and systemically, as the main areas of infection are the small intestine and the bloodstream. The antibiotic should reach therapeutic levels at the infection site and have a narrow gram-negative spectrum to limit disruption of the natural gut flora **Alberto, (2022).**

Studies show that broad-spectrum β-lactam and fluoroquinolone antimicrobials, whether given orally or by injection, can be effective in managing both naturally occurring and experimentally induced diarrhea. However, extra-label use of fluoroquinolones is prohibited in the U.S. Parenteral treatment with trimethoprim/sulfadiazine and ceftiofur at high extra-label doses has demonstrated effectiveness in experimental infections involving *Salmonella enterica* serotypes Dublin and Typhimurium **Mona *et al.,* (2023).** Orally administered apramycin has also shown promise in treating naturally occurring diarrhea, though its low absorption rate (less than 15%) and high MIC values against *Salmonella* spp. and *E. coli* (MIC90 >3 µg/ml) pose some challenges **Khawaskar *et al.,* (2022).** For these reasons, treatment guidelines often favor broad-spectrum β-lactams like amoxicillin, ampicillin, ceftiofur, and potentiated sulfonamides, such as trimethoprim/sulfadiazine.

Treating *E. Coli* Overgrowth in the Small Intestine with Oral Antimicrobials:

In neonatal calves with mild diarrhea symptoms such as a reduced suckling reflex but maintaining normal body temperature, hydration, and heart rate veterinarians should carefully observe the calf's progress. For treatment, oral administration of amoxicillin trihydrate (10 mg/kg every 12 hours) or a combination of amoxicillin trihydrate with clavulanate potassium (12.5 mg/kg every 12 hours) is advised for at least three days. However, the latter is considered off-label use. Research indicates that giving amoxicillin trihydrate orally at 10 mg/kg every 12 hours for four days can notably reduce mortality rates and the duration of diarrhea in calves experimentally infected with enterotoxigenic *E. coli* **Adzitey *et al.,* (2021).** When administered with milk, around 30% of the dose is absorbed through the small intestine **Alberto, (2022).** High concentrations of the drug are found in bile and the intestines, with lower concentrations in the blood. Although milk does not affect the bioavailability of amoxicillin, the absorption rate increases when dissolved in an electrolyte solution **Solmaz *et al.,* (2000).**

The use of fluoroquinolones in food-producing animals is prohibited in the U.S. due to concerns about antimicrobial resistance **Nguyen *et al.,* (2005).** Additionally, amoxicillin absorption decreases in endotoxemic cases, likely due to slowed abdominal emptying **Groothuis *et al.,* (1978).** Amoxicillin trihydrate is preferred over ampicillin trihydrate for oral use in calves, as it is specifically labeled for treating diarrhea in the U.S. and is more effectively absorbed **Palmer *et al.,* (1983).** However, field studies indicate that oral doses of 400 mg every 12 hours of either amoxicillin or ampicillin result in similar outcomes **Nguyen *et al.,* (2005).** Adding clavulanate potassium to amoxicillin trihydrate is recommended, as clavulanate extends amoxicillin's activity by inhibiting β-lactamase enzymes.

Potentiated sulfonamides are generally not recommended for calf diarrhea due to a lack of data on their effectiveness. Gentamicin is also unsuitable for oral use, as diarrhea treatments need both local and systemic action, but gentamicin is poorly absorbed. No other oral antimicrobials currently available in the U.S. are likely to be effective for treating neonatal calf diarrhea **Khawaskar *et al.,* (2022).**

While fluoroquinolones have shown effective-

ness for treating calf diarrhea, drugs like enrofloxacin, marbofloxacin, and danofloxacin approved in Europe for oral and injectable use cannot be used off-label in food-producing animals in the U.S. **Huehn *et al.,* (2010).**
Salmonellosis in calves is increasingly seen as a systemic infection, not just localized in the intestines, making injectable treatments the preferred option **Huehn *et al.,* (2010).** Moreover, the routine use of antibiotics in milk replacers in the U.S. may contribute to a lower rate of D-lactic acidosis in calves with diarrhea compared to countries like Germany and Canada, where whole milk feeding is more common due to milk quota systems. D-lactic acidosis results from bacterial fermentation of milk in the gut **Adiguzel *et al.,* (2018).** Adding antibiotics to milk replacer may limit D-lactic acid production by promoting the growth of bacteria that do not produce D-lactate.

Parenteral Antimicrobial Use for Colibacillosis and Salmonellosis:
When neonatal calves exhibit diarrhea alongside moderate to severe systemic symptoms such as a reduced suckling reflex while maintaining normal body temperature, hydration, and heart rate the effectiveness of clinical and lab tests for diagnosing bacteremia is often low, with an estimated 20% to 30% prevalence in the field **Alberto, (2022).** Bacteremia significantly increases mortality risk, necessitating parenteral antimicrobial therapy in about 20%-30% of calves with diarrhea.
Ceftiofur is considered the most appropriate injectable antibiotic for *E. coli* bacteremia, given at a dose of 2.2 mg/kg subcutaneously or intramuscularly every 12 hours for at least three days **Adzitey *et al.,* (2021).** For experimentally induced salmonellosis, a higher extra label dose of Ceftiofur (5 mg/kg intramuscularly every 24 hours for five days) is recommended to keep drug concentrations above the MIC90 for *Salmonella enterica* serovar Typhimurium **Huehn *et al.,* (2010).** Since other Salmonella strains on farms may have higher MIC90 values, it is important to determine specific MICs before treatment. Off-label ceftiofur use for *E. coli* bacteremia and salmonellosis should not be used in calves intended for veal production **Huehn *et al.,* (2010).**
Potentiated sulfonamides are typically unsuitable for bacteremia due to poor oral absorption. While oxytetracycline and chlortetracycline may help with *E. coli* overgrowth in the intestines, they are not recommended for bacteremia **Khawaskar *et al.,* (2022).** Tetracycline antibiotics have reduced oral bioavailability due to their binding to calcium. To reach effective serum concentrations for *E. coli* bacteremia (MIC50 = 4 µg/ml), oxytetracycline should be given at 20 mg/kg orally every 12 hours **Schifferli *et al.*, (1982).**
In the U.S., gentamicin and other aminoglycosides like amikacin and kanamycin are not recommended for treating calf diarrhea due to extended withdrawal times before slaughter (15-18 months), the risk of nephrotoxicity in dehydrated calves, and better alternatives like ceftiofur, amoxicillin, and ampicillin. However, studies in Europe found gentamicin to be as effective as danofloxacin or cefquinome in treating calf diarrhea or septicemia **Ji Hyoung *et al.,* (2020).**
In Europe, fluoroquinolones are approved for injectable use in treating *E. coli* diarrhea and salmonellosis in calves. In regions where fluoroquinolones are permitted, they should only be used when culture and sensitivity results confirm their need and effectiveness. Injectable fluoroquinolones should be reserved for critically ill calves, particularly those requiring IV fluids. Their off-label use in food animals is illegal in the U.S.
For calves with diarrhea but no signs of systemic illness, such as normal appetite and no fever, veterinarians should monitor the calf without using injectable antibiotics. A Swedish study found that calves with uncomplicated diarrhea, without additional infections like pneumonia, generally do not benefit from antibiotics **Ana, (2021).**

Supportive Treatments for Calf Diarrhea:
Administering fluids to diarrheic calves, either orally or intravenously, is crucial for rehydration, replenishing blood volume, correcting acidemia, and addressing electrolyte imbalances and energy deficits. This also helps restore the suckling reflex and promotes the healing of damaged intestinal tissues. Oral electrolyte solutions are effective for calves with mild to moderate dehydration, provided they can still suckle. For severely weak calves that cannot

suckle or are recumbent, intravenous fluids are essential for proper resuscitation **Murrary *et al.*, (2003).**

Nonsteroidal Anti-inflammatory Drugs: Flunixin meglumine is commonly used as an anti-inflammatory drug for calves with diarrhea. Administering a single dose of flunixin meglumine (2.2 mg/kg intra muscularly) has been shown to reduce the number of sick days and the need for further antimicrobial treatment, particularly in calves with bloody stools **Khawaskar *et al.*, (2022).** For calves with experimentally induced enterotoxigenic *E. coli* infection, flunixin meglumine (2.2 mg/kg every 8 hours intramuscularly) reduced fecal output, possibly by reducing intestinal secretions (Roussel *et al.,* 1988). For severely ill calves with suspected endotoxemia, flunixin meglumine (2.2 mg/kg every 12 hours) is recommended, as long as hydration is sufficient to avoid kidney damage. It is advised to limit flunixin meglumine administration to one dose of 2.2 mg/kg and no more than three doses to avoid gastrointestinal damage, particularly in farms with a history of abdominal ulcers. Flunixin meglumine has been observed to improve suckling behavior in treated calves, supporting claims of its positive impact on calf well-being **Huehn *et al.*, (2010).**

Motility Modifiers and Intestinal Protectants:

Despite their common use, it is generally not advised to administer intestinal protectants like kaolin-pectin or activated attapulgite, or motility modifiers such as hyoscine N-butylbromide or atropine. Studies have not demonstrated their effectiveness. In fact, one study found that non-antibiotic treatments including bismuth, kaolin-pectin, activated attapulgite, and activated charcoal actually prolonged recovery and increased the risk of illness and death compared to treatment with oral antibiotics (such as neomycin sulfate and tetracycline HCl in milk replacer) along with injectable ceftiofur hydrochloride (2.2 mg/kg) for 3-5 days **Yayesew and Temesgen, (2023).**

Probiotics:

Probiotics are administered to calves with diarrhea on some dairy farms. A field study showed that giving the probiotic *E. coli* strain Nissle 1917 to calves during the first 10-12 days of life, particularly in cases where passive immunity transfer was uncertain, significantly reduced the occurrence of diarrhea **Khawaskar *et al.*, (2022).** However, another study found that providing *Lactobacillus rhamnosus* GG to calves already experiencing diarrhea did not reduce mortality or the severity of scours **Yayesew and Temesgen, (2023).** In a separate study, administering a different *Lactobacillus* strain to neonatal foals intended to prevent diarrhea was actually linked to the development of diarrhea and other complications that required veterinary treatment **Schroeder *et al.*, (2002).**

Conclusion and Recommendations

Calf diarrhea is one of the most frequent health issues in cattle. Any calf displaying symptoms of illness or injury should be treated immediately, and veterinarians should be consulted without delay. The responsibility for selecting appropriate medical treatment usually lies with the attending veterinarian, though farmers may also share this responsibility depending on local regulations. Antibiotics used in livestock must be prescribed by a veterinarian following a thorough clinical examination and diagnosis. Ideally, lab tests such as culture and sensitivity tests should guide antibiotic selection. Veterinarians must weigh the potential benefits and risks to the animal, humans, and the environment before determining the optimal treatment, including drug choice, dosage, and duration. Promoting responsible antibiotic use on farms is a critical part of a veterinarian's role, even when they are not directly administering the drugs.

Antibiotic use should not rely solely on clinical signs or the type of diarrhea. Diagnostic testing is essential. For instance, detecting *Escherichia coli* or bacteremia may warrant antibiotic treatment. Rapid tests are available for identifying fecal pathogens, and a validated test for bacteremia linked to bacteriuria in newborn calves exists, though it is not widely used.

Preventing antibiotic misuse on farms is crucial to reducing the spread of antibiotic-resistant genes. For injectable antibiotics, amoxicillin, ampicillin, and potentiated sulfonamides are first-line options. For oral use, amoxicillin or amoxicillin/clavulanate potassi-

um is recommended. Third and fourth generation cephalosporins, such as ceftiofur and cefquinome, are second-line choices. Fluoroquinolones should be reserved as a last-resort option for treating *E. coli* diarrhea and salmonellosis in calves.

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