rccp Revista Colombiana de Ciencias Pecuarias

Antimicrobial use in dairy cattle

Diego E Gómez, DMV, MVSc, MSc, PhD, DACVIM

College of Veterinary Medicine, University of Florida, Gainesville, Florida, USA

Introduction

Antimicrobials are among the most important advances in human and veterinary medicine. However, the use of virtually any antimicrobial that continue to grow leads to some potential for antimicrobial resistance, and concerns about the epidemic of resistance in human and animal pathogens, as well as the environment (Wernli *et al.,* 2011). The impacts of antimicrobial resistance in dairy production are multiple, including treatment difficulties, the need for more expensive drugs or intensive treatments and negative public perceptions. It is well accepted that the main risk factor for this increase in resistance in pathogenic bacteria is the use of antimicrobials, prudent use, overuse and misuse all included (van den Bogaard and Stobberingh, 2000). This review aims to describe the current knowledge regarding appropriate antibiotic usage in calves with diarrhea and bovine respiratory disease and cows with mastitis.

Antibiotic usage in calf diarrhea

Calf diarrhea is the major cause of mortality and use of antimicrobial agents in calves <30 d of age on dairy farms (Constable, 2004). Regardless the cause of diarrhea, antibiotics have been historically recommended as part of the treatment (Constable, 2004). However, on some dairy farms antimicrobial treatments rates in diarrheic calves approach to 100% (Gómez *et al.,* 2017). This is of importance because 30 to 90% of the antibiotics administered to cattle are excreted in feces and urine (Sura *et al.,* 2014). This environmental contamination is of public health concern due to its impact on the development and spread of antimicrobial resistance bacteria (van den Bogaard and Stobberingh, 2000; Wernli *et al.,* 2011). Therefore, practitioners working with cattle have the responsibility to use antibiotics appropriately and to provide oversight of antibiotic use by the farmers.

Use of antimicrobials for prevention of diarrhea. Historically, dairy farmers have fed antibiotics in milk or milk replacer for prevention of diarrhea and reduce mortality in calves. However, this practice is now banned in many countries (Constable, 2003), and the value of feeding antibiotics to calves to prevent diarrhea has not proven to be effective in recent investigations. Early studies demonstrated some benefits (e.g. decreased the incidence and severity of diarrhea) of adding antibiotics (including ampicillin, chlortetracycline, furazolidone, neomycin, oxytetracycline, and streptomycin) to the milk or milk replacer at low concentrations (Constable, 2003), but recent investigations have not replicated these results, instead have documented the opposite effect (Donovan *et al.,* 2002; Higginbotham *et al.,* 2010). Furthermore, recent studies have documented that in some farms diarrhea rates actually increased when feeding antibiotics (Shull and Frederick, 1978). Based on the current knowledge the practice of feeding antibiotics in milk or milk replacer for diarrhea prevention should be discontinued.

Use of antimicrobials for treatment of diarrhea. Antimicrobials have been historically recommended as part of the treatment of systemically ill calves (Constable, 2004; Walker *et al.,* 2012). Reasons for this recommendation include prevention of bacteremia and reduction of number of coliform bacteria in the small intestine (Walker *et al.,* 2012). Regarding bacteremia, two separately studies performed in the 90's reported that approximately 30% of diarrheic calves develop bacteremia (predominantly *Escherichia coli*; Fecteau *et al.,* 1997; Loftstedt *et al.,* 1999). Another hypothetical reason for antibiotic therapy in diarrheic calves is coliform overgrowth in the small intestine. Studies using culture-based (Issacson *et al.*, 1978; Youanes and Herdt, 1987) and —more recently— next generation sequencing technology (Gómez *et al.,* 2017) have identified increased relative abundance of *E. coli* in feces of diarrheic calves regardless of the age of the calf or the cause of the diarrhea. This increase in the abundance of coliform bacteria has been associated with altered function of the gastrointestinal tract, morphologic damage, and increased susceptibility to bacteremia (Reisinger, 1965). Therefore, it appears to be justified administering antibiotics to diarrheic calves to decrease or prevent coliform overgrowth in the small intestine of diarrheic calves. Furthermore, the use of antimicrobials could —theoretically— prevent the development of bacteremia and therefore calf morbidity and mortality (Constable, 2004). However, antimicrobials might not be beneficial in some cases of calf diarrhea (e.g. viral or parasitic infection) and might prolong the recovery time from diarrhea (Berge *et al.,* 2009). Administration of antibiotics also can have a negative impact on gut microbial communities of healthy calves, predisposing them to dysbiosis (imbalance of gut microbial communities), and therefore to diarrhea (Gómez *et al.,* 2017). An additional concern is that in some farms the use of antibiotics for treatment of diarrhea is more common than medically justified (Berge *et al.,* 2009). A recent study demonstrated that antimicrobial treatment rates of diarrheic calves approach to 100% (Gómez *et al.,* 2017). The same study demonstrated that the implementation of a protocol for treatment of diarrhea targeting systemically ill calves (calves with fever and decreased demeanor) resulted in a reduction in antimicrobial treatment rates of approximately 80% (from 96 to 20%), with no identifiable negative impacts on clinical outcome (Gómez *et al.,* 2017). This study demonstrated that targeting antimicrobial therapy to calves that are systemically affected is a feasible approach to reduce and refine the use of antibiotics in diarrheic calves, with possible beneficial effects on calf health (fewer days of diarrhea; Berge *et al.,* 2009; Gómez *et al.,* 2017).

Antibiotic usage in bovine respiratory disease

Bovine respiratory disease (BRD) is a major problem in dairy and beef herds. This disease is of multifactorial disease, and the most common post-mortem diagnosis in calves between one to five months of age. Antibiotic administration is a mainstay in both the control and treatment of acute clinical disease. Therefore, the prudent use of antibiotics in animal health remains the most important element to ensure efficacy of treatment of BRD.

Evidence of the benefits of using antibiotics for BRD. A systematic review of the literature including studies investigating the treatment or control of BRD in randomized, blinded, negative control field trials revealed a median spontaneous recovery rate of 24% (across all studies) in untreated calves, whereas the recovery rate of those calves treated with an antibiotic was 71% (DeDonder and Apley, 2015). Thus, there was an increase of 47% recovery rate with the use of antimicrobials compared with a negative control. The median mortality rate in treated calves was 1%, while in negative controls was 17%. These results indicate that calves clinically affected with BRD benefit from antibiotic therapy.

Factors influencing the selection of antibiotics for treatment of BRD. Different factors including susceptibility of the bacteria causing pneumonia (geographic and herd-specific variation) and the probability of exceeding minimal inhibitory concentration (MIC) for pathogenic bacteria in the respiratory tract should be consider by practitioners when selecting antibiotics for treatment of BRD (Giguere *et al.,* 2006). The probability of reaching adequate MIC is likely higher for florfenicol, ceftiofur, tilmicosin, tulathromycin, and fluoroquinolones, and not expected for β-lactamic antibiotics (e.g. penicillins, amoxicillin and ampicillin; Giguere *et al.,* 2006). Other factors to be considered are cost-benefit ratio, the route, frequency and volume of administration, safety (tilmicosin can be fatal when injected to humans) and withdrawal times (Giguere *et al.,* 2006).

A recent meta-analysis compared the efficacy of antimicrobial treatments of BRD. This study included 60 experiments of active drug to negative controls (no treatment) and 33 assessments of antibiotic-to-antibiotic controls (Constable, 2004). Using different statistical approaches, this meta-analysis indicated that tulathromycin was the most efficacious treatment of BRD, and older antibiotics, such as the ceftiofur, trimethoprim and oxytetracycline were the least efficacious antibiotics for treatment of BRD. This study indicates that molecules recently introduced into the marked (e.g. tulathromycin) could be more effective for the treatment of BRD than antibiotics of high importance in human medicine (e.g. ceftiofur and enrofloxacine), and therefore should be used as a first-line antibiotic therapy in cases of BRD.

Antibiotic usage in bovine mastitis

Use of antibiotics during lactation. Mastitis is the main reason for antimicrobial usage on dairy cattle (Royster and Wagner, 2015). Therefore, it is imperative that farmers and veterinarians follow best practices to use antimicrobials selectively and judiciously. Characteristics or risk factors associated with clinical mastitis and their potential as predictors of outcomes or treatment success include age/parity, stage of lactation (days in milk), somatic cell count, clinical mastitis history, and pathogen factors such as virulence and antibiotic susceptibility (Sol *et al.,* 2000; Constable and Morin, 2002; Bradley and Green, 2009; Pinzón-Sánchez *et al.,* 2011). Taking into consideration these factors, practitioners should decide whether a cow is eligible for antimicrobial treatment using a label prescribes or extra-label protocol or it may be more rational not to treat the mastitis (Giguere *et al.,* 2006). Therefore, antimicrobial therapy should be indicated for animals that are likely to benefit from (Giguere *et al.,* 2006). One study documented that increasing parity, elevated somatic cell counts (SCC) before treatment, and having multiple quarters affected were associated with lower probabilities of cure (Gómez *et al.,* 2017). Likewise, repeated treatment of a recurrent case of mastitis is frequently unrewarding (Gómez *et al.,* 2017). Similarly, the expense and likelihood of treatment failure increases as parity also increases (Gómez *et al.,* 2017). A significant association between previous occurrence of clinical mastitis and decreasing microbiological cure also has been reported (Constable and Morin, 2002; Pinzón-Sánchez and Rug, 2011). In addition to these cow-level factors producers and practitioners should also consider other factors that can affect the probability of a cow to remain in the herd long term before deciding to treat a case of mastitis. For instances, cattle in late in lactation and not pregnant, ill with concurrent diseases, or lame should be considered as potential cull candidates, ratherthan treatment candidates (Giguere *et al.,* 2006; Royster and Wagner, 2015). Microbial culture of mastitis infections could also help to decide whether and how to treat a cow. For instance, mastitis caused by *S. aureus, S. uberis, Prototheca* has lower cure rates compared with that caused by other species of staphylococci and streptococci (e.g. *S. agalactie*; Giguere *et al.,* 2006). Furthermore, some infections are likely to resolve without any treatment, while antibiotics can actually delay resolution in some cases (e.g. yeast; Giguere *et al.,* 2006).

Use of antibiotics during dry period. The purposes of dry cow dry (non-lactating) treatment include treatment of any existing infections present at dry off and preventing new infections that may be acquired during the dry period (Royster and Wagner, 20115). Cure rates for intra-mammary infection (IMI) caused by gram-positive cocci —those that existed before the dry period but were not detected after calving—have been documented on average at 78%, while spontaneous cure (no treatment) is only 46% (Halasa *et al.*, 2009). However, antibiotic dry cow therapy efficacy for eliminating chronic IMI is only about 15 to 30% (Giguere *et al.,* 2006).

Evidence-based decision-making should be applied when selecting an appropriate dry cow therapy. The majority of the intra-mammary products were introduced for treatment of contagious mastitis caused by *Staphylococcus aureus* and *Streptococcus agalactiae* (Royster and Wagner, 2015). Therefore, most of the research evaluating the efficacy ofthose products focused on these two pathogens. However, most subclinical infections present at dry off, as well as new infections acquired during the dry period, are associated with environmental mixed pathogens, such as environmental streptococci and coliforms. Currently, little evidence supports the efficacy of IMI for these pathogens (Royster and Wagner, 2015). These studies suggest that a subset of cows benefit from dry-period antibiotic treatment, however the success rates of cure of cows with chronic mastitis or mastitis caused by mixed pathogens is low.

Conclusion

Antibiotics are commonly used for prevention and treatment of disease in calves and mastitis. However, they can also be overused, leading to increased risks of antibiotic resistance, increased costs and negative public perceptions about food production. Therefore, practitioners working with cattle have the responsibility to use their scientific knowledge regarding disease management, diagnostics, epidemiology and pharmacology to provide appropriate advice to farmers and to assist in disease prevention, control, and management.

References

Berge AC, Moore DA, Besser TE, Sischo WM. Targeting therapy to minimize antimicrobial use in preweaned calves: Effects on health, growth, and treatment costs. J Dairy Sci 2009; 92:4707-4714.

Bradley AJ, Green MJ. Factors affecting cure when treating bovine clinical mastitis with cephalosporin-based intramammary preparations. J Dairy Sci 2009; 92:1941-1953.

Constable PD. Use of antibiotics to prevent calf diarrhea and septicemia. Bovine Pract 2003; 37:137-142.

Constable PD. Antimicrobial use in the treatment of calf diarrhea. J Vet Intern Med 2004; 18:8-17.

Constable PD, Morin DE. Use of antimicrobial susceptibility testing of bacterial pathogens isolated from the milk of dairy cows with clinical mastitis to predict response to treatment with cephapirin and oxytetracycline. J Am Vet Med Assoc 2002; 221:103-108.

DeDonder KD, Apley MD. A review of the expected effects of antimicrobials in bovine respiratory disease treatment and control using outcomes from published randomized clinical trials with negative controls. Vet Clin North Am Food Anim Pract 2015; 31:97-111.

Donovan DC, Franklin ST, Chase CC, Hippen AR. Growth and health of Holstein calves fed milk replacers supplemented with antibiotics or Enteroguard. J Dairy Sci 2002; 85:947-950.

Fecteau G, Van Metre DC, Pare J, Smith BP, Higgins R, Holmberg CA, Jang S, Guterbock W. Bacteriological culture of blood from critically ill neonatal calves. Can Vet J 1997; 38:95-100.

Giguere S, Prescott JF, Baggot JD, Walker RD, Dowling PM. Antimicrobial therapy in veterinary medicine. 4th Ed. Blackwell. 2006.

Gómez DE, Arroyo LG, Costa MC, Viel L, Weese JS. Characterization of the fecal bacterial microbiota of healthy and diarrheic dairy calves. J Vet Intern Med 2017; 31:928-939.

Gómez DE, Arroyo LG, Poljak Z, Viel L, Weese JS. Implementation of an algorithm for selection of antimicrobial therapy for diarrhoeic calves: Impact on antimicrobial treatment rates, health and faecal microbiota. Vet J 2017; 226:15-25.

Halasa T, Osterås O, Hogeveen H, van Werven T, Nielen M. Meta-analysis of dry cow management for dairy cattle. Part 1. Protection against new intramammary infections. J Dairy Sci 2009; 92:3134-149.

Higginbotham GE, Pereira LN, Chebel RC, Lehenbauer TW. A field trial comparing the effects of supplementation with aureomycin plus lasalocid or monensin on the health and production performance of dairy calves. Prof Anim Sci. 2010; 26:520-526.

Issacson RE, Moon HW, Schneider RA. Distribution and virulence of *Escherichia coli* in the small intestine of calves with and without diarrhea. Am J Vet Res 1978; 39:1750-1755.

Loftstedt J, Dohoo IR, Duizer G. Model to predict septicemia in diarrheic calves. J Vet Intern Med. 1999; 13:81-88.

O'Connor AM, Coetzee JF, da Silva N, Wang C. A mixed treatment comparison meta- analysis of antibiotic treatments for bovine respiratory disease. Prev Vet Med 2013; 110:77-87.

Pinzón-Sánchez C, Cabrera VE, Ruegg PL. Decision tree analysis of treatment strategies for mild and moderate cases of clinical mastitis occurring in early lactation. J Dairy Sci 2011; 94:1873-1892.

Pinzón-Sánchez C, Rug PL. Risk factors associated with short-term post-treat- mint outcomes of clinical mastitis. J Dairy Sci 2011; 94:3397-3410.

Reisinger RC. Pathogenesis and prevention of infectious diarrhea (scours) of newborn calves. J Am Vet Med Assoc 1965; 147:1377-1386.

Royster E, Wagner S. Treatment of mastitis in cattle. Vet Clin North Am Food Anim Pract 2015; 31:17-46.

Shull JJ, Frederick HM. Adverse effect of oral antibacterial prophylaxis and therapy on incidence of neonatal calf diarrhea. Vet Med Small Anim Clin 1978; 73:924-930.

Sol J, Campion OC, Barkema HW, Schukken YH. Factors associated with cure after therapy of clinical mastitis caused by *Staphylococcus aureus*. J Dairy Sci 2000; 83:278-284.

Sura S, Degenhardt D, Cessna AJ, Larney FJ, Olson AF, McAllister TA. Dissipation of three veterinary antimicrobials in beef cattle feedlot manure stockpiled over winter. J Environ Qual 2014; 43:1061-1070.

USDA, 2007. Dairy 2007, Part I: Reference of dairy cattle health and management practices in the United States. United States Department of Agriculture Animal and Plant Health Inspection Service Veterinary Services (USDA-APHIS-VS), Fort Collins, CO, USA.

van den Bogaard AE, Stobberingh EE. Epidemiology of resistance to antibiotics. Links between animals and humans. Int J Antimicrob Agents 2000; 14:327-335.

Walker WL, Epperson WB, Wittum TE, Lord LK, Rajala-Schultz PJ, Lakritz J. Characteristics of dairy calf ranches: morbidity, mortality, antibiotic use practices, and biosecurity and biocontainment practices. J Dairy Sci 2012; 95:2204-2214.

Wernli D, Haustein T, Conly J, Carmeli Y, Kickbusch I, Harbarth S. A call for action: The application of The International Health Regulations to the global threat of antimicrobial resistance. PLoS Med 2011, 4:e1001022.

Youanes YD, Herdt TH. Changes in small intestinal morphology and flora associated with decreased energy digestibility in calves with naturally occurring diarrhea. Am J Vet Res 1987; 48:719-725.