Acute puerperal metritis: antimicrobial therapy and the relationship between antimicrobial pharmacodynamics and therapeutic success

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Abstract

Acute puerperal metritis is a common disease in postpartum dairy cattle. This disease causes significant economic losses as affected cows experience reduced milk production, increased culling risk, and impaired reproductive performance. Acute puerperal metritis is invariably associated with bacterial colonization and infection of the uterus. As a result, antimicrobials are a mainstay of therapy for this disease. Optimal dosing of antimicrobial agents is essential to therapeutic success, and designing dosing regimens requires an integration of both pharmacokinetic and pharmacodynamic principles. The goals of this article are to provide an overview of the current state of knowledge of antimicrobial treatment options in cattle with acute puerperal metritis, and review the principles of antimicrobial pharmacodynamics.

Key words: dairy cow, metritis, antimicrobial, therapy

Résumé

La métrite puerpérale aigüe est une maladie fréquente des bovins laitiers en post-partum. Cette maladie entraine des pertes économiques importantes car les vaches affectées produisent moins de lait, ont plus de chance d'être réformées et ont une performance de reproduction altérée. La métrite puerpérale aigüe est invariablement associée à la colonisation et à l'infection de l'utérus par des bactéries. Par conséquent, les antimicrobiens constituent le pilier de la thérapie pour cette maladie. Le dosage optimal des agents antimicrobiens est essentiel pour assurer le succès de la thérapie. De plus, la conception des régimes de dosage nécessite l'intégration des principes de pharmacocinétique et de pharmacodynamique. Le but de cet article est de faire un survol des connaissances actuelles sur les options de traitement antimicrobien chez les bovins avec une métrite puerpérale aigüe et de revoir les principes de pharmacodynamique antimicrobienne.

Introduction

Dairy cattle are susceptible to numerous infectious and metabolic disorders in the immediate post-parturient period. Acute puerperal metritis (APM) is one of the most common clinical conditions seen in modern dairy cattle, affecting 18.3 to 33.5% of all cattle that calve.[26,32,33] Consequences of APM include reduced milk production, impaired reproductive performance, increased culling risk and, in severe cases, death. The economic impact of APM has been studied extensively, and current estimates suggest that the disease can cost individual producers $358/case, and costs the United States dairy industry $650 million annually.[26,32]

After calving, more than 90% of cattle experience some degree of bacterial contamination of the uterine lumen.[11,12] Through the processes of uterine involution and with normal immune function, most cattle clear this contamination and experience no complications. However, cattle with retained placenta, hypocalcemia, and significant negative energy balance fail to clear uterine contamination and develop APM.[25] While certain viruses have been isolated from the uterus of affected cattle, the clinical manifestations of APM are predominantly due to colonization of the reproductive tract with pathogenic bacteria.[7,8,32] Indeed, while a variety of microorganisms may be isolated from the reproductive tract of both healthy post-parturient cattle and cattle with APM, *Escherichia coli* and *Trueperella pyogenes* represent the bacteria most commonly associated with clinical disease.[7,32]

Antimicrobial Therapy and APM

While APM is multifactorial and successful treatment may require multiple different therapeutic modalities, antimicrobials are a mainstay of therapy for cattle diagnosed with clinical disease. In fact, APM is a disease for which parenteral antimicrobials are used frequently on many modern dairy operations.[27] Currently, 3 preparations of 2 different anti-

microbials are labeled for systemic use in cattle with APM in the United States: oxytetracycline dihydrate, ceftiofur hydrochloride, and ceftiofur crystalline free acid. Oxytetracycline dihydrate[a] is the oldest and least expensive of the available compounds still in use. It is labeled for therapy of acute metritis caused by susceptible strains of *Staphylococcus* spp and *Streptococcus* spp at a dose of 5 mg/lb (11 mg/kg) SQ once daily. Intrauterine infusions of tetracycline-based products have been closely evaluated in recent years.[16,34] For example, a study comparing an intrauterine infusion of 6 grams (g) of oxytetracycline to parenteral procaine penicillin G and ceftiofur sodium found no differences in the reduction in rectal temperature over the first 5 days after diagnosis or daily milk yields for 12 days following initiation of treatment.[34] In addition, Goshen and Shpigel evaluated the effect of infusion of 5 g of chlortetracycline into the uterus twice weekly for 2 weeks.[16] Cattle receiving this treatment produced 1,438 lb (654 kg) more milk over the course of lactation, and conceived 29 days sooner than untreated controls. Furthermore, conception risk in treated cattle was 42.5% compared to 38.3% in clinically normal animals and 18% in untreated controls.[16] Assuming treatment with oxytetrayeline would cost $10 per cow and milk would be discarded for 21 days, the overall treatment cost would be $199 (60 lb (27.3 kg)/milk/cow/day X 21 days X $15/cwt). Cows receiving therapy would produce 1,438 lb (654 kg) more milk over the course of a lactation, conceive 29 days sooner than untreated cattle, and represent a return of $237.70/cow ((1,438 lb/100 X 15) + (29 X $2/day open)). As a result, treated cattle would yield a net return to the producer of approximately $74.70/hd, despite the prolonged milk withdrawal required with this therapeutic regimen.[13] Nevertheless, this treatment modality is not approved in the United States and would constitute extra-label drug use, and must be justified by the attending veterinarian.

Ceftiofur, a third-generation cephalosporin, has become the gold-standard therapeutic agent for cattle with APM. Two preparations of ceftiofur—ceftiofur hydrochloride[b] and ceftiofur crystalline free acid[c]—are labeled for use in cattle with APM and have the advantages of short slaughter withdrawal (4 and 13 days, respectively) and no milk withholding. In addition, the effects of ceftiofur on clinical cure and, to some extent reproductive performance, have been thoroughly evaluated.[4,10,15,22,30] Some of the earliest studies to evaluate the effect of ceftiofur in cattle with APM demonstrated that ceftiofur hydrochloride, when given at a dose of 1.0 mg/lb (2.2 mg/kg) IM once daily for 5 days, is effective in reducing rectal temperature and improving the character of uterine discharge in cattle with APM. In this study, vaginal discharge was scored on the basis of odor, color, and general appearance and given a value from 0 to 4. To be considered a cure, cattle had to have a vaginal discharge score of ≤ 3 and characterized as not fetid, but could be purulent, mucopurulent, or chocolate brown.[4] Other work compared the efficacy and economic efficiency of treating cattle diagnosed with APM with either ceftiofur hydrochloride or a combination of intrauterine and systemic antimicrobials.[10] Cattle treated with ceftiofur had rates of clinical cure and reproductive performance similar to cattle in the other groups. Furthermore, economic analysis revealed that costs for the group treated with only ceftiofur were less, primarily as a result of reduced milk withholding times.[10] In a study that compared the clinical efficacy of ceftiofur hydrochloride to oxytetracycline dihydrate in cattle with APM, the risk of clinical cure at day 7 was numerically higher in the ceftiofur group (64.8%) when compared to oxytetracycline-treated cattle (58.1%); however, this difference was not determined to be statistically significant.[30] Between days 2 and 5 after treatment, ceftiofur-treated cattle had significantly lower rectal temperatures than cattle treated with oxytetracycline.[30] Unfortunately, comparisons of milk production and reproductive performance between groups were not evaluated in this study.

Ceftiofur crystalline free acid is labeled for treating APM and is given SQ at the base of the ear at a dose of 3 mg/lb (6.6 mg/kg) every 72 hours for 2 doses. A study that evaluated the effect of 2 doses of CCFA on clinical cure risk in cows with APM found that when compared to a saline-treated control, cows treated with CCFA are more likely to cure (74.3% vs 55.3%, respectively; $P < 0.0001$).[22] Another study evaluated the effects of CCFA on clinical cure risk, milk yield, and reproductive performance and found that CCFA had no influence on clinical cure or milk yield, but did increase risk of pregnancy at insemination (adjusted odds ratio = 2.69).[15]

Work evaluating the potential utility of ampicillin trihydrate[d] as a therapeutic agent in dairy cattle with APM has recently been published.[18] In this study, ampicillin trihydrate was compared to ceftiofur HCL, and the results showed that cattle treated with ampicillin had a faster rate of clinical cure based on vaginal discharge score on day 5 after diagnosis than cattle treated with ceftiofur HCL (37.1% vs 25.2%, respectively; $P < 0.01$).[18] In addition, cattle treated with ampicillin had a significantly lower risk of developing purulent vaginal discharge (PVD) than cows treated with ceftiofur HCL (57.7% vs 67.8%. respectively; $P < 0.03$). There was no difference in the proportion of cattle that developed cytologic evidence of endometritis. For the purposes of this study, cytologic endometritis was defined as ≥ 5% neutrophils from an endometrial cytobrush collected at 39 ± 3 days-in-milk. In addition, pregnancy/AI (P/AI) was similar between treatments.[18] While the results of this study suggest that ampicillin is a potentially useful therapeutic agent for cattle with APM, its use in cattle with this disease is considered extra-label drug use (ELDU) under the Animal Medicinal Use Clarification Act (AMDUCA), and therefore must be justified by the prescribing veterinarian.

Antimicrobial Pharmacodynamics – Relationship to Therapeutic Success

For any disease caused or mediated by an infectious agent, the efficacy of antimicrobial therapy is dependent upon 3 factors. These factors are susceptibility of the pathogen to

the chosen antimicrobial, characteristics of drug exposure necessary for optimum response, and concentrations of free drug at the site of infection.[21]

This relationship, the interaction of systemic drug exposure and corresponding clinical effects, is termed the pharmacokinetic/pharmacodynamic relationship (PK/PD). Here, pharmacokinetics is best defined as the handling of the drug by the host (i.e. what the body does to the drug) while pharmacodynamics is defined as the drug's effect on microorganisms over time (i.e. what the drug does to the bug). It is the pharamacodynamic relationship between a specific antimicrobial and disease-causing microorganism that is the focus of this discussion. Optimal dosing of antimicrobial agents is dependent on both the pharmacokinetic and pharmacodynamic properties of a drug. Currently, the most widely utilized pharamacokinetic input is plasma drug concentration, and the minimum inhibitory concentration (MIC) is considered the primary pharmacodynamic input.[14]

Bacterial antimicrobial susceptibility is determined in vitro using 1 of several available tests. Disk diffusion, concentration-gradient agar dilution, and broth dilution (macro or micro) have all been used to evaluate susceptibility to antimicrobials.[14] Disk diffusion provides mostly qualitative information (susceptible, intermediate, resistant), while both the broth dilution and concentration-gradient agar diffusion tests provide quantitative data (MIC). With these tests, the MIC is defined as the lowest concentration of antimicrobial that inhibits the growth of target bacteria. It is important to note that inhibition of bacterial growth rather than bacterial killing is the primary endpoint. The designation of a microorganism as susceptible or resistant is determined by comparing the organism's MIC to breakpoints established by the Clinical Laboratory Standards Institute (CLSI).[14] Breakpoints are defined as the concentration of drug above and below which specific bacterial isolates are characterized as either susceptible, intermediate, or resistant. These breakpoints are determined utilizing 3 criteria that include the range of in vitro MICs of an antimicrobial for a representative population of specific bacterial pathogens; PK/PD parameters established on the basis of the relationship between drug concentrations and microbial susceptibility; and results of clinical trials in the target species.[14]

When these in vitro susceptibility tests are presented to the clinician or researcher, a pathogen will be designated as susceptible, intermediate, or resistant.[14] Susceptible bacteria are bacteria that may be successfully treated with the recommended dosing regimen of an antimicrobial agent approved for that disease process. Intermediate bacteria can be treated at body sites where drugs are concentrated or when a high dosage can be used. The intermediate designation also represents a "buffer zone" that should prevent minor technical factors from causing major discrepancies in interpretations. Resistant bacteria are not inhibited by typically achievable concentrations of a specific drug with a standard dosing regimen. It is important to note that clinical breakpoints

are only relevant for specific bacteria, a specific drug, and a specific organ system. Thus, breakpoints established for ceftiofur against *Mannheimia haemolytica* in the respiratory tract are irrelevant when that organism is the cause of disease within another body system (mammary gland, uterus). In cattle, few antimicrobials have breakpoints established for bacteria associated with specific diseases, and unfortunately no antimicrobials have valid breakpoints established for the organisms associated with APM. Generally, when species-specific breakpoints are not available for a disease condition, breakpoints are adapted from humans or other domestic animal species. Therefore, the data obtained from these susceptibility tests must be interpreted with caution. In these situations, knowledge of an infecting organism's MIC combined with pharmacokinetic data ideally describing the concentration of drug within the tissue of interest can assist in predicting efficacy.

When evaluating antimicrobials, both the pharmacokinetic and pharmacodynamic properties of the drug of interest must be known to establish optimum doses and dosing intervals.[21] The most important pharmacodynamics parameter determining the efficacy of drugs within the β-lactam, tetracycline, and macrolide classes of antimicrobials is the time that the active drug concentration remains above the MIC of the infecting pathogen (T > MIC, Figure 1).[5,14] With these drugs, increasing drug concentration more than 4-fold above the MIC will not alter the rate of microbial killing. Rather, it is the length of time that bacteria are exposed to concentrations above the MIC that determines efficacy (Table 1). Antimicrobials such as the aminoglycosides and fluoroquinolones are classified as concentration-dependent, and their rate of bacterial killing increases as the plasma concentration increases (Cmax/MIC, Figure 1) (Table 1).[5,14] With these drugs, maintaining concentrations above the MIC between doses is unnecessary and in some cases, can be detrimental.
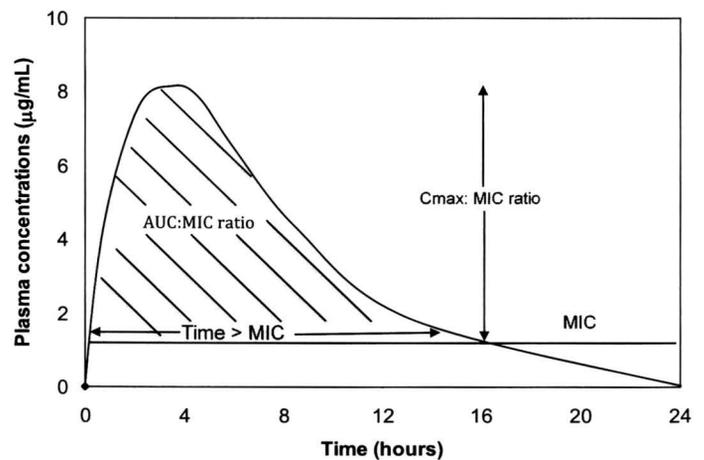

Figure 1. Pharmacodynamic indices determining efficacy for antimicrobials.

Finally, there are certain drugs that have characteristics of both time- and concentration-dependent drugs. For drugs such as rifampin, glycopeptides, certain macrolides, and some fluoroquinolones, the primary determinant of efficacy is the 24-hour plasma area under the curve (AUC) to MIC ratio (AUC_{0-24}/MIC, Figure 1) (Table 1).[5,14] Although many of these drugs are technically time dependent, they generally have prolonged persistent or post-antibiotic effects. These persistent effects result in suppression of bacterial growth for a period of time following antimicrobial administration. Thus, they reflect the time it takes for an organism to recover from the effects of drug exposure. As a result, the goal of an optimum dosing regimen with these compounds would be to ensure adequate concentrations of drug are present to ensure bacterial killing occurs for part of the dosing interval, and no regrowth occurs during the remainder.[5] It is important to note that the primary pharmacodynamic determinant of efficacy is specific for an individual drug, an individual pathogen, and an individual patient. Therefore, a single antimicrobial may be classified in more than 1 way, depending on what pathogen is present and the clinical status of the animal (immunosuppression, neutropenia, etc).[5]

As previously stated, most infections occur in the tissues rather than plasma. Thus, it is logical that an antimicrobial reach the site of infection to be effective. The ability of a specific drug to penetrate extravascular sites is dependent on 5 factors.[23] These include the extent of plasma and tissue protein binding, molecular size, lipid solubility, blood flow at the site of infection, and degree of ionization. In addition, certain sites in the body (central nervous system, prostate, eye) are further restricted by the presence of tight junctions between cells, a factor that further excludes active drug from tissues. For uterine infections caused by extracellular bacteria such as *E. coli*, *T. pyogenes*, *Fusobacterium necrophorum*, and *Prevotella* spp, concentrations of antimicrobial within lochial fluid is likely a better determinant of efficacy than concentrations of drug in plasma or endometrial tissue.[19]

Antimicrobial Disposition in the Bovine Reproductive Tract

While it is apparent that an optimal antimicrobial dosing regimen provides concentrations of active drug at the site of infection at the right concentration for the right duration, there are no current studies directly relating free drug concentrations in lochial fluid or endometrial tissue to clinical outcome. As a result, the optimal drug concentration and/or duration of time above the MIC of infecting pathogens are unknown for cattle with APM. In fact, a recent meta-analysis identified the lack of breakpoints and the inability to reconcile our pharmacokinetic knowledge with available pharmacodynamic data as a serious issue.[17] Nevertheless, despite lacking CLSI breakpoints for the pathogens commonly associated with APM in cattle, numerous pharmacokinetic studies have evaluated the disposition of oxytetracycline, ceftiofur hydrochloride, CCFA, and ampicillin trihydrate in plasma, uterine tissue, lochial fluid, and cotyledonary tissue of both clinically normal cattle and cattle with APM. In addition, several published studies have evaluated MICs of common uterine pathogens (Table 2).[20,28,29,31]

In the early 1980s, 3 separate studies evaluating the disposition of oxytetracyline hydrochloride (OTC) in plasma, uterine tissue, and lochial fluid of healthy and diseased cattle were performed. In the first study the disposition of OTC in the uterine tract of cattle given the drug by 2 different routes (intramuscularly (IM) vs intrauterine (IU)) was investigated.[3] When given IM, OTC concentrations in endometrial tissue (0.43 µg/g) were numerically higher than OTC concentrations in plasma (0.05 µg/ml) 72 hours after dosing.[3] Concentrations of OTC in uterine secretions were sampled at 48 hours after administration and, similar to endometrial tissue, were numerically higher than plasma (0.57 g/ml vs 0.34 µg/ml, respectively). The IU administration of OTC led to high concentrations in endometrial tissue (> 4 µg/g), but no detectable levels of OTC in plasma 72 hours after administration.[3] The second study evaluated the disposition of OTC in genital tissues of healthy postpartum cattle when the drug was given intravenously (IV) or IU.[1] Cattle were given OTC at a dose of 5 mg/lb (11 mg/kg) as a constant IV infusion or at a dose of 2.75 mg/lb (5.5 mg/kg) as a single IU infusion. Similar to the previous study, IU infusion of OTC led to high concentrations in endometrial tissue (> 5 µg/g) at all sampling times.[1] However, concentrations of OTC in plasma, uterine wall, and ovarian tissue of all cattle was low, with the mean concentrations of OTC in these tissues of cows with metritis lower than that of healthy cattle.[1] Computer modeling demonstrated that

Table 1. Classification of antimicrobial agents based on their pharmacodynamic properties.

Time (T > MIC)	Concentration (Cmax/MIC)	Both (AUC/MIC)
β-lactams	Aminoglycosides[*]	Azalides
Tetracyclines	Fluoroquinolones[†]	Ketolides
Macrolides	Metronidazole[‡]	Fluoroquinolones[†]
Lincosamides		Glycopeptides[§]
Fenicols		Streptogramins

[*]Voluntary ban on the use of aminoglycosides in food-producing animals
[†]Extra-label use of fluoroquinolones in food animals prohibited in the United States
[‡]Prohibited from use in food animals in the United States
[§]Prohibited from use in food animals in the United States

when OTC is given IV at a dose of 5 mg/lb (11 mg/kg) twice daily, concentrations of drug in uterine tissues remain above 5 μg/g for the duration of the dosing interval.[1] In the final study, the disposition of OTC in uterine tissues and fluids of healthy and diseased postpartum cattle was investigated using an IV dosing strategy similar to the one used in the second study.[2] Concentrations of OTC in plasma, uterine tissue, and ovaries of healthy and diseased cattle were: plasma (4.95 and 5.23 μg/ml, respectively; $P > 0.28$), uterine tissue (3.65 and 4.18, respectively; $P > 0.28$), and ovarian tissue (4.57 and 4.53 μg/g; $P > 0.28$).[2] Mean plasma to genital ratio of OTC in healthy and diseased cattle was 1.38 and 1.32, respectively. Mean plasma to genital ratio of OTC in uterine tissue of healthy and diseased cattle was 1.38 and 1.31, respectively.[2] Thus, from these studies, it can be seen that systemic administration of OTC at a dose of 5 mg/lb (11 mg/kg) given IV every 12 hours can achieve concentrations > 5 μg/mL in plasma and > 4 μg/g in uterine tissue of cattle with uterine disease.[2] In addition, concentrations of OTC in tissues of animals were similar to concentration of OTC in plasma, suggesting distribution of OTC to the tissues from plasma.[2]

Unfortunately, several studies have shown that resistance to OTC among bacteria commonly involved in the development of APM is widespread.[28,29] One study found that approximately 63.7% of all *T. pyogenes* isolates and 31% of all *E. coli* isolates obtained from the uteri of cattle with APM are resistant to OTC.[20] A separate study demonstrated OTC resistance in 53.7% of all *T. pyogenes* isolated from clinical cases of APM.[28,29] In addition, previous work showed that the MIC$_{90}$ for OTC against *E. coli* and *T. pyogenes* is 32 μg/mL and 16 μg/mL, respectively, concentrations far above what can be achieved in any fluid or tissue at currently labeled dosing regimens.[31] Again, the tetracycline class of antimicrobials is generally considered to be time-dependent, and because of that the primary determinant of efficacy for this class of drugs would be the duration of time that free drug concentration remains above the MIC of the infecting pathogen (T > MIC). Thus, based on the data presented, it is unlikely that OTC would be an effective therapy for cattle with APM as concentration of OTC in most fluids and tissues fail to reach the MIC$_{90}$ of common uterine pathogens at both label and extra-label dosing regimens.

The disposition of both ceftiofur hydrochloride and CCFA in plasma, uterine tissue, and lochial fluid have been evaluated in healthy and clinically ill postpartum cattle. One study evaluating the disposition of ceftiofur hydrochloride in plasma, uterine tissue, and uterine secretions of lactating dairy cattle found that when ceftiofur hydrochloride was given at a dose of 0.45 mg/lb (1 mg/kg) SQ to healthy Holstein cattle within 24 hours of calving, maximum plasma concentrations were 2.85 μg/mL 2 hours after administration.[24] In lochial fluid, maximum ceftiofur concentrations were 0.97 μg/mL at 4 hours and declined to 0.22 μg/mL 24 hours after administration.[24] In uterine tissue, maximum ceftiofur concentrations were 2.23 μg/g, and declined to 0.56 μg/g 24 hours after administration.[24] A second study determined the concentrations of ceftiofur and its derivatives in serum, uterine tissue, cotyledonary tissue, and lochial fluid of cattle following fetal membrane retention.[9] In the aforementioned study, cattle were given ceftiofur hydrochloride at a dose of 0.45 mg/lb (1 mg/kg) SQ once daily for 3 consecutive days. These researchers demonstrated that mean concentrations of ceftiofur derivatives in each fluid and tissue remained greater than the MIC$_{90}$ for common uterine pathogens previously reported.[9] Nevertheless, at each time, single samples were below the MIC$_{90}$ of *E. coli* isolates collected from the uterus of cattle with APM.

Another study evaluated the disposition of CCFA in serum, endometrial tissue, and lochial fluid of healthy postpartum cows after SQ administration.[37] Five days after drug administration, concentrations of ceftiofur derivatives in plasma (1.21 μg/mL), endometrial tissue (0.86 μg/g), and lochial fluid (0.96 ug/mL) were above the MIC$_{90}$ for common uterine pathogens such as *E. coli* and *T. pyogenes*.[37] However, concentrations of ceftiofur derivatives in lochial fluid were quite variable. At points beyond 72 hours following drug administration, numerous animals had concentrations well below the MIC$_{90}$ of *E. coli*, a factor that necessitates that a second dose of CCFA be given 72 hrs following the first.[37]

More recently the disposition of ampicillin trihydrate in plasma, uterine tissue, and lochial fluid of healthy postpartum dairy cattle was investigated.[6] The maximum concentration of ampicillin (55.7 μg/mL) in lochial fluid of cattle given ampicillin trihydrate once daily was obtained 6 hours after

Table 2. Minimum inhibitory concentrations (μg/mL) of various antimicrobials against common uterine pathogens.

Pathogen	Antimicrobial		
	Ceftiofur	Oxytetracycline	Ampicillin*
Escherichia coli	0.5	> 32	8
Trueperella pyogenes	0.125	32	0.25
Fusobacterium necrophorum	0.125	16	N/A

From Sheldon IM, Bushnell M, Montgomery J, et al. Minimum inhibitory concentrations of some antimicrobial drugs against bacteria causing uterine infections in cattle. *Vet Rec* 2004;155:383-387; Wasyl D, Hoszowski A, Zajac M, et al. Antimicrobial resistance in commensal *Escherichia coli* isolated from animals at slaughter. *Front Microbiol* 2013;4:221; Thomson DU, Taylor W, Noffsinger T, et al. Case report – tail tip necrosis in a confined cattle feeding operation. *Bov Pract* 2009;43:18-22; and Yoshimura H, Kojima A, Ishimaru M. Antimicrobial susceptibility of *Arcanobacterium pyogenes* isolated from cattle and pigs. *J Vet Med B Infect Dis Vet Public Health* 2000;47:139-143.

*MIC$_{90}$ of isolates collected from various body sites in cattle

dosing. Twenty-four hours after dosing, concentrations of ampicillin were approximately 7 µg/mL.[6] Also, ampicillin preferentially accumulated in lochial fluid as compared to plasma with a mean ratio of maximum lochial fluid to plasma ampicillin concentration of 5:3.[6] Thus, it appears that when administered at a dose of 5 mg/lb (11 mg/kg) once daily, concentrations of ampicillin in lochial fluid remain above the MIC_{90} of *E. coli* and *T. pyogenes* isolated from various body sites in cattle for a large portion of the dosing interval (8.0 and 0.25 µg/mL, respectively).[6,35,36,38] Nevertheless, the use of ampicillin trihydrate is associated with additional costs when compared to therapy with ceftiofur. The milk withdrawal following administration of ampicillin trihydrate is 48 hours following the last treatment. If waste milk is utilized to feed calves, the total cost of therapy with ampicillin trihydrate is estimated to be approximately $53/case. If waste milk is discarded, the cost of therapy with ampicillin trihydrate is estimated to approach $109/case.

Conclusions

Acute puerperal metritis is a common and economically important disease in dairy cattle. The disease is invariably associated with bacterial infection of the postpartum uterus, and as a result, antimicrobials are a mainstay of therapy. Currently, 3 antimicrobials are labeled for systemic use in cattle with APM, and another has been evaluated for its potential as a therapeutic agent. While current dosing regimens improve clinical cure, and in some cases, reproductive performance, APM remains a disease with significant untoward consequences for both the individual animal and dairy herd as a whole. Optimization of dosing regimens by integrating pharmacokinetic and pharmacodynamic principles has the potential to improve therapeutic success and reduce the risk of the development of antimicrobial resistance. Future studies should be directed at the generation of antimicrobial susceptibility breakpoints for common uterine pathogens. With the knowledge obtained from pharmacokinetic studies, combined with the findings of in vitro pharmacodynamics assessments, our ability to improve outcomes for animals affected with APM is greater than at any time in the past. In addition, the potential for improved antimicrobial stewardship and a reduction in the development of resistance to medically important antimicrobials is a realistic possibility.

Endnotes

[a]Liquamycin LA 200®, Zoetis Inc., Kalamazoo, MI
[b]Excenel® RTU EZ, Zoetis Inc., Kalamazoo, MI
[c]Excede®, Zoetis Inc., Kalamazoo, MI
[d]PolyFlex®, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO

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