Therapeutic and Management options for Postpartum Metritis in Dairy Cattle

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Productos de Agrovet Market relacionados:

ANTIBIÓTICOS: Agrogenta® 11, Agromox 15 L.A.; Agromycin 11; Diflovet® 10; Duramycin® 300; Enroflox® 10; Enroflox® 20 L.A.; Metri-cef 3® ; Proxifen® 23 L.A.; Qrex®

HORMONALES: Lutaprost® 250; Oxyto-Synt® 10.

ABSTRACT:

The treatment goal for postpartum metritis (e.g., endometritis, postpuerperal metritis, toxic puerperal metritis, pyometra) is to facilitate the timely clearance of the infection and return the animal to a normal reproductive state. Clinical signs associated with postpar- tum metritis range from temporary and self-limiting signs to chronic or life-threatening ones. Choosing an appropriate treatment for postpartum metritis depends on understanding the classification scheme for the disease. Treatment of cows with postpartum metritis generally involves hormonal and antibiotic therapy alone or in combination. Current efforts to promote prudent use of antibiotics have created renewed interest in the disease. Successful resolution of postpartum metritis can be accomplished by relying on the use of multiple diagnostic meth- ods to accurately classify postpartum metritis, the incorporation of health-monitoring proto- cols for fresh cows to help prevent it, and the use of hormonal and antimicrobial therapy to help resolve it.

Effective treatment of postpartum metritis (e.g., endometritis, postpuerperial metritis, toxic puerperal metritis, pyometra) in dairy cows remains a controversial topic. Monitoring programs for cows inmediately after parturition have aided in classifying postpartum metritis metritis, thereby facilitaring the development of preventive protocols and selection of appropriate therapy. Depending on the form of postpartum metritis diagnosed, there are several treatment options. Treatment of cows with postpartum metritis generally involves hormonal and antibiotic therapy alone or in combimation.

Cattle suffering from less severe forms of postpartum metritis (e.g., endometritis, pyometra) are more likely to be treated with hormones, but many are also treated with antimicrobial

agents. Clinical opinion varies on whether to treat cows with nontoxic metritis (e.g., endometritis, postpuerperal metritis).[1] Clinical trials that evaluated agents, doses, routes of administration, and timing of nonantibiotic treatment in relation to days after parturition have given conflicting results.[2–5] The apparent discrepancy in results can be attributed to such factors as clinical criteria used to diagnose metritis and performance measures that were evaluated.

There is little argument that cows with toxic puerperal metritis showing signs of pyrexia, anorexia, dehydration, or shock should be minimally treated with antimicrobial drugs. Other types of treatment for these more seriously infected cattle include antiinflammatory agents, steroidal agents, and supportive agents (e.g., fluids). Cattle diagnosed with postpuerperal metritis or toxic puerperal metritis can be treated either with systemic antimicrobial agents or locally by intrauterine infusion of antimicrobial agents. This article discusses treatment options, including hormonal and antimicrobial therapy, for cows diagnosed with postpartum metritis.

HORMONAL THERAPY

The objective of hormonal therapy in resolving postpartum metritis is to induce estrous cycles, thereby increasing estrogen levels. Estrogen may affect the uterus in the following ways:

- Stimulating uterine tone to aid in evacuating abnormal uterine contents
- Increasing production of mucus that contains host defense compounds
- Inducing estrus, which reduces progesterone levels, thereby markedly inhibiting neutrophil phagocytosis and resistance of the uterus to infection.

Drug compounds, such as estrogens and prostaglandin F2a (PGF2a), have been incorporated into treatment protocols for cows suffering from postpartum metritis. The effect of these compounds on uterine motility and defense mechanisms makes them useful treatment alternatives to antimicrobial agents.

Estrogens

Since the 1960s, estradiol cypionate (the oil-based 17-cyclopentyl propionate ester of a-estradiol) has been the only approved estrogen for lactating dairy cows in the United States.[1] It provides estradiol-17ß—one of the most potent estrogens.[6] It is FDA approved for treating anestrus and persistent corpus luteum. It is also indicated for expelling purulent material from the uterus of cows with pyometra and stimulating uterine expulsion of retained fetal membranes (RFMs) in lactating dairy cows.[6] There is a clear association between RFMs and

postpartum metritis. Therefore, estrogens may actually prevent postpartum metritis as a result of their positive effect in removing RFMs.

Estradiol cypionate has been used for treating dairy cows affected with metritis or endometritis but has not been approved for this use.[7] The protocol for the extralabel use of estradiol cypionate is 4 mg IM to cows that have postpartum reproductive problems during the first 10 to 25 days after calving. The treatment is based on the assumption that cows under the influence of estrogens are more resistant to uterine infection. This assumption is based on the observation that cows that cycle regularly after parturition are less likely to develop postpartum metritis than those that do not cycle and that administering estradiol pro-motes neutrophil phagocytosis in the uterus. [8]Furthermore, it has been suggested by various clinical reports that estradiol enhances uterine resistance to infection by increasing uterine motility as well as mucus production and flow, which collectively promote the evacuation of purulent material from the uterus and may enhance uterine involution.[9,10]

The use of estrogens for preventing postpartum metritis is not without controversy. The value and benefit of estradiol cypionate treatment in cows suffering from postpartum complications have not been substantiated by objective research. Furthermore, it has been reported that the use of estrogens during the postpartum period may be contraindicated. The postpartum use of estrogens has been associated with severe infection of the oviducts and increased incidence of cystic ovarian degeneration.[11] The lack of scientific evidence on the efficacy of this hormone coupled with the potential for public concern with the spurious use of hormones in lactating dairy cows are compelling reasons to conduct controlled clinical trials on using estradiol to treat postpartum metritis.

PGF2a and Gonadotropin-Releasing Hormone

PGF2a and its analogues have been advocated in managing postpartum metritis. The rationale for using PGF2a includes stimulation of uterine contraction, which aids in expulsing purulent uterine fluid and debris[12,13]; stimulation of leukocytes[14,15]; and luteolysis with induction of an estrous cycle, which consequently reduces progesterone and increases estrogen levels.[8] Numerous studies have been conducted to determine the value of administering PGF2a to abnormal cows (e.g., cows with dystocia, RFMs, postpartum metritis) during the immediate postpartum period.[2,4,12,13,16,17] The inconsistent findings from these studies have resulted in confusion and skepticism regarding the use of PGF2a in treating cattle diagnosed with

postpartum metritis. Therefore, it is difficult to come to a definitive conclusion on the value of PGF2a in treating cows diagnosed with postpartum metritis.

Olson[18] reviewed 25 trials that evaluated the use of PGF2a for treating metritis during the postpartum period. No noticeable difference was seen in days open between treated and untreated herd mates in these trials. However, when days open were compared between treated and untreated cows in the trials using cows considered to be at high risk for postpartum metritis resulting from RFMs or dystocia, there was an insignificant reduction of 5.3 days open for treated cows. When the difference in average days open was examined by type of trial (normal versus abnormal postpartum period), only routine treatment of cows with abnormal postpartum periods apparently had the potential of being economically justifiable.

Other treatment regimens using gonadotropin-releasing hormone (GnRH) and PGF2a have been developed for cows during the immediate postpartum period. To initiate estrous cyclicity in the early postpartum period and help improve fertility, treatment with GnRH and PGF2a has been evaluated. Fertility was not improved in cows with either an abnormal[2] or normal[3] puerperium that were treated with GnRH early after parturition, followed by PGF2a 10 days later. In one study, the interval from calving to conception was reduced in cows that had a normal puerperium and were treated with GnRH in combination with PGF2a after parturition.[4] In another study in which cows with either a normal or abnormal puerperium were treated with GnRH followed by PGF2a, inseminations per conception were reduced.[5] The discrepancy in study results is related to the diagnostic criteria used to define an abnormal puerperium, days after parturition when the treatments were initiated, reproductive response criteria evaluated, and unknown management factors. The inconsistent findings in many research trials using GnRH or PGF2a alone or in combination do not allow for a clear conclusion on the effectiveness of these hormones in resolving postpartum metritis.

In a field trial, 445 Holstein cows that had experienced dystocia, RFMs, or both (abnormal calvings) at parturition were used to determine the effects of postpartum treatment with GnRH, PGF2a, or both on various reproductive measurements.[16] Dystocia and RFMs were chosen as the criteria for identifying cows with an abnormal puerperium to avoid possible bias introduced in the diagnosis of metritis. Conception rate after first insemination was higher for cows treated with PGF2a at 12 and 26 days after parturition. Cows affected with these conditions and treated early after parturition with GnRH alone or followed 10 days later with PGF2a did not have improved reproductive performance. In these cows, treatment with GnRH may have resulted in ovulation or luteinization of follicles concurrent with uterine infection. A progesterone-

dominated uterus could have exacerbated the uterine infection and reduced fertility. The investigators expected that GnRH treatment would hasten ovulation and establish a corpus luteum that could be lysed when PGF2a was administered. This induction of a new estrous cycle could aid uterine involution, reestablish cyclicity, and improve fertility. In some cows, however, uterine involution may not have been improved despite initiation of an estrous cycle after luteolysis, or an estrous cycle may not have been initiated. In postpartum dairy cows, a significant increase in luteolysis after PGF2a for cows previously treated with GnRH 10 days earlier was not detected.[5] The corpus luteum (formed after GnRH treatment 10 to 14 days after parturition) exhibited only a 47% luteolytic response to an injection of PGF2a 20 to 24 days after parturition.5 The improved reproductive performance seen in this research trial17 suggests a benefit from treating cows with two PGF2a shots at 12 and 26 days in milk. These findings are significant because this research trial is the largest recorded to date; it was conducted on cows that were diagnosed with an abnormal postpartum period; and it compared, head to head, three hormonal treatment regimens used in the early postpartum period.

The following guidelines are suggested for using PGF2a and GnRH during the postpartum period for treating or preventing postpartum metritis and improving reproductive function.

At what day after parturition should prostaglandin be given?

The general opinion is that the benefit derived from PGF2a treatment is regression of the corpus luteum, which brings a cow into estrus. With this premise in mind, it has been documented that most dairy cows, including those with an abnormal parturition, have a corpus luteum responsive to PGF2a by day 26 to 30 after parturition.[16] PGF2a around 30 days' postpartum can be used to treat uterine conditions that may be present, such as endometritis, postpuerperal metritis, or pyometra, by promoting an estrous event. However, the effect of PGF2a in postpartum cows may be independent of corpus luteum presence. Prostaglandin may stimulate leukocyte function, improving postpartum metritis recovery.[14,15] Various studies have also shown a beneficial effect independent of progesterone concentration.[16,17]

What are the number and frequency of prostaglandin treatments?

Because the study by Risco et al 16 did not evaluate a single PGF2a treatment at day 12 or 26, the researchers concluded that treatment with PGF2a early after parturition (around day 12), followed by a second injection 14 days later (day 26), improved first-service conception rates in dairy cows with RFMs. Other studies that did evaluate single or multiple PGF2a treatments

showed little effect of treatment on abnormal cows during the immediate postpartum period.[19,20] Because of the equivocal results from many research trials using prostaglandin in postpartum cows, it is difficult to determine the number and frequency of treatments.

Should prostaglandin be used routinely in all cows or only in those with abnormal parturition?

There is sufficient evidence to suggest that prostaglandin treatment of cows with peripartum health disorders, including RFMs, dystocia, or both, is likely to benefit their reproductive performance. Conversely, early postpartum treatment (days 12 to 21) with prostaglandin in cows with a normal peripartum period is less likely to be beneficial to reproductive performance.[21]

GnRH Treatment

Because of the cost of GnRH and conflicting results regarding its effectiveness in increasing fertility, it is difficult to make general recommendations for the use of this agent. Two postpartum conditions that could affect the efficacy of GnRH treatment are negative energy balance and postpartum metritis. Treatment with GnRH around day 14 after parturition results in luteinizing hormone secretion from the pituitary and induces either follicular luteinization or ovulation of recruited follicles from the first postpartum wave, altering the circulating estradiol: progesterone ratio. In dairy cows experiencing negative energy balance early after parturition, however, the ovaries may be inactive (absence of follicles) and luteinization or ovulation of follicles may not occur. Furthermore, luteinization of the follicle or corpus luteum induction may be detrimental to an infected uterus. In our opinion, the use of GnRH should commence later in the postpartum period when a reproduction management protocol is being followed.

ANTIMICROBIAL THERAPY

There are extensive arguments concerning the treatment of specific forms of postpartum metritis with antimicrobial agents. Antimicrobial agents may be needed to control infection caused by bacteria and prevent the progression of disease.22–25 Compounds from numerous antimicrobial families (e.g., sulfonamides, tetracyclines, ß-lactams, aminoglycosides, cephalosporins) have been used singularly or in combination for treating postpartum metritis.

The use of antibiotics in dairy cattle could result in a milk-residue violation, a human health risk, and/or bacterial resistance. A major consideration when using antibiotics in dairy cattle is

drug residues. Currently, oxytetracycline is the only antimicrobial agent approved by the FDA for use in lactating cows and thus labeled for the treatment of postpartum metritis.26 Oxytetracycline is specifically labeled for acute or toxic puerperal metritis caused by strains of staphylococci and streptococci.[26] All other antimicrobial agents are not labeled for treating any form of postpartum metritis. Because of potential drug residues from extralabel drug use, the US Dairy Quality Assurance Program was developed to ensure food safety. When treating postpartum metritis, various treatment routes, such as local (i.e., intrauterine) or systemic (i.e., IV, IM, SC), are available.

Intrauterine Therapy

Nonantibiotic Treatment

Antiseptic agents, such as iodine, chlorhexidine, and saline, have been infused into the uterus, but there have been few studies to determine the efficacy of these compounds on postpartum metritis.[23] The only approved nonantibiotic antimicrobial drug for intrauterine treatment in the United States is chlorhexidine.[27] The irritating nature of such solutions is thought to increase uterine tone, blood flow, and defense mechanisms.[27] The induced inflammatory response of the uterus is thought to reduce the bacteria level within the uterus and aid in evacuating abnormal uterine fluid. Cattle infused with an irritating chemical reportedly had a shortened estrous cycle (8 to 10 days) when the solution was administered early in the diestrous period.[28] In general, the infusion of nonantibiotic substances into the postpartum uterus is not recommended. This method of treatment can lead to iatrogenic mechanical trauma to the genital tract and secondary bacterial infection through iatrogenic contamination of the genital tract.

Antibiotic Treatment

The infusion of antibiotic agents into the uterus is a common therapy used on all four forms of postpartum metritis. Local treatment involving intrauterine antibiotic infusion aims to produce an even distribution of an active drug throughout all layers of the uterus, limited systemic absorption, low tissue irritation, and high antibacterial activity within the uterine environment. Many antimicrobial agents are readily absorbed systemically from the uterus, including sulfonamides, tetracyclines, penicillins, nitrofurazone, aminoglycosides, and

chloramphenicol.[1,8] However, it is important to understand that intrauterine use of all these antibiotics is off label.

Days postpartum, uterine condition, uterine tissueabsorptive capabilities, and drug distribution are the major factors affecting the efficacy of most drugs infused into the postpartum uterus.[31,30] The molecular structure of the antimicrobial agent and the vehicle used to deliver the drug influence its absorption into the uterine tissue after local uterine infusion.1 The completely involuted uterus has better absorptive capabilities than the immediate postpartum uterus.[31] Endometritis also results in poor concentration of drugs within the uterine tissue after intrauterine treatment.[31–33] The result of poor local uterine absorption is a high concentration of drug on the endometrium but an inadequate concentration in the subendometrial tissues, vagina, cervix, ovaries, and oviducts.[1] Also, the high concentration of drug on the endometrium may result in local irritation of the uterine lining.[34]

The environment of the postpartum uterus diminishes the efficacy of many drugs. Such factors as low oxygen tension, antibiotic-degrading enzymes, mucopurulent discharge, and organic debris could lead to poor efficacy of certain antimicrobial agents infused into the postpartum uterus.[34,35] In addition, infusion of antimicrobial agents has been shown to adversely affect leukocyte function and cause contamination of meat and milk products.[34]

A mild case of endometritis may be the only form of postpartum metritis in which intrauterine treatment is justified.[1] However, diagnosing mild endometritis is difficult in clinical practice. More severe pathologic changes, such as those seen in cows with postpuerperal metritis, toxic puerperal metritis, and pyometra, may not respond to treatment by intrauterine infusion. One reason could be that these disease conditions greatly reduce uterine tissue uptake of the antimicrobial agent.[32,33] Because of the many acknowledged shortcomings of intrauterine antibiotics, it is believed that intrauterine infusion alone often fails as a therapy for postpartum metritis.[1]

Systemic Therapy

Systemic treatment of all forms of postpartum metritis may be more advantageous than intrauterine treatment. Systemic treatment provides better drug distribution to all layers of the female genital tract and ovaries.[31–33] It prevents iatrogenically induced contamination of the uterus and injury to the uterine endometrium.[34] Systemic treatment of postpartum metritis also avoids interference of leukocyte function.[36–38] This could be the most valuable reason to choose systemic over local antimicrobial treatment. In addition, systemic antimicrobial treatment using

drugs, routes, and doses approved for other disease indications allows the establishment of milk and meat withholding times.

Penicillin administered systemically is a treatment option for endometritis, postpuerperal metritis, and toxic puerperal metritis. Penicillin is preferred to other antibiotics because its distribution to all layers of the uterus is excellent,[1,39] it is inexpensive, and it has established milk and meat withholding times when used according to label. Unfortunately, treating postpartum metritis with penicillin is an off-label use because the drug is not indicated for the disease and the dosage of 9,000 to 18,000 U/lb IM once or twice daily is three to six times higher than what is recommended on the label. There is no known withholding time for using penicillin in an off-label manner. However, having an available, easy-to-use residue test kit helps make penicillin a preferred treatment of postpartum metritis.

Oxytetracycline is also used to treat postpartum metritis. It is most often used in cows suffering from less severe forms of metritis (i.e., endometritis, postpuerperal metritis).8 There are many concerns about treating postpartum metritis with systemic oxytetracycline. Research by Bretzlaff et al 29 revealed that 11 mg/kg IV q12h rather than q24h was needed to pro-vide uterine tissue concentrations that would combat infection. This is an impractical regimen. Because of these concerns, the use of systemic oxytetracycline has not been considered the preferred choice for treating postpartum metritis even though it is the only antimicrobial agent approved by the FDA for this treatment.

Antimicrobial agents have been used in combination to treat certain forms of postpartum metritis. Some authors have recommended systemic penicillin in conjunction with intrauterine oxytetracycline for treating toxic puerperal metritis.[35,40] However, the combination of penicillins and tetracyclines has resulted in residues in milk for excessively long periods.[41] This results in discarded milk for a prolonged period, thereby decreasing milk revenues. Furthermore, the failure of dairies to heed milk withholding times or perform milk antibiotic residue tests may lead to antibiotic contamination of milk.

Because of concern over antibiotic residues, a reevaluation of the current approach to treating cows affected with metritis is needed. A reliable treatment alternative that controls the effects of postpartum metritis and avoids the problem of milk antibiotic residues is needed. The use of ceftiofur sodium (which has a zero milk withdrawal time at the recommended label indication, dose, and route) for treating toxic puerperal metritis has been evaluated. It is important to note that ceftiofur sodium is not labeled for treating cows diagnosed with postpartum metritis. Therefore, its use is considered extralabel.

Smith et al[42] studied the effect of ceftiofur sodium on toxic puerperal metritis. Postpartum dairy cows diagnosed with toxic puerperal metritis based on rectal temperature, milk production, and uterine discharge characteristics were assigned to three different antibiotic groups. The results of this study showed that all groups had a favorable clinical response to treatment based on changes in milk production and rectal temperature. Statistically, no difference in milk yield, rectal temperature, or serum haptoglobin was seen between treatment groups. The study found no difference in treatment efficacy among penicillin, oxytetracycline, or ceftiofur in cows with toxic puerperal metritis. Several studies have since shown that ceftiofur given at 1 mg/kg/day IM or SC for 3 to 5 days is an effective antimicrobial choice for treating cows diagnosed with toxic puerperal metritis.[43–45] Postpartum metritis could be effectively treated with ceftiofur because the antibiotic is known to concentrate in infected tissues in vivo.[46] Also, in a study by Schmitt et al,[45]concentrations of ceftiofur and active metabolites in plasma, uterine tissues, and lochial fluid exceeded the reported mean inhibitory concentrations of the causative organisms (e.g., Escherichia coli, Fusobacterium necrophorum, Arcanobacterium pyogenes) most often isolated from cows diagnosed with toxic puerperal metritis.[43]

Bovine metritis responds favorably to systemic antimicrobial treatment,[8] providing better drug distribution to the entire female genital tract.[32,46] Uterine tissue concentration needed to be effective against the most common bacterial pathogens causing postpartum metritis can be attained through the systemic use of such antibiotics as penicillin and ceftiofur. Also, systemic treatment eliminates the risk of endometrial trauma and mechanical interference by fetal membranes and abnormal exudates.[1] However, it is important to understand that modifications to treatment doses and frequency of administering penicillin and oxytetracycline may be necessary to attain therapeutic levels. These modifications result in extralabel use of these drugs. Also, consideration of drug residues and overall cost are important issues when choosing a method of treating postpartum metritis.

Intrauterine or Systemic Antibacterial Agents

A large number of antimicrobial agents have been used to treat postpartum metritis in dairy cattle. A number of factors influence treatment success. Selection of therapy for postpartum metritis should be based on causative agent, sensitivity patterns of causative agents, interaction of drugs and uterine environment, pharmacokinetics of drugs, host defense mechanisms, and antimicrobial residues in milk and meat. Because of these factors, selecting an antibiotic to treat bovine metritis can be difficult. Table 1 depicts the different classes of antimicrobial agents available for treating bovine uterine disease.

SUMMARY

Postpartum metritis is a well-recognized and serious problem for the dairy industry. Currently, monitoring programs have been developed to help identify cows suffering from postpartum metritis. These programs may also help uncover factors that could lead to better methods of preventing and treating postpartum metritis. The first step in successfully resolving uterine infections in cows is to accurately diagnose which type of postpartum metritis is affecting the cow. The second step is to correctly choose a method of treatment that corresponds to the type of postpartum metritis diagnosed. Treatment methods can be hormonal or antimicrobial.

Hormonal treatment with estrogens, PGF2a, and GnRH is commonly used in cattle with endometritis, postpuerperal metritis, and pyometra. These hormones can be used singularly or in combination. Many studies have investigated the use of hormone therapy in the immediate postpartum period. However, the results of studies addressing the benefits of treating postpartum metritis with hormones are equivocal.

Currently, oxytetracycline is the only FDAapproved drug with a label recommendation for treating lactating cows diagnosed with postpartum metritis. There are many concerns about treating postpartum metritis with antimicrobial agents. One serious concern is antimicrobial residues in the food supply. Continued effort is needed to further develop and modify treatment options used in lactating dairy cattle diagnosed with postpartum metritis. When considering antimicrobial treatment options for cows affected with postpartum metritis, the following points should be emphasized:

- Cows with metritis that have fever and systemic signs should be systemically treated with penicillin, oxytetracycline, or ceftiofur.
- Cows with metritis without fever do not require antibiotic treatment and can be managed with hormones.

Table 1. Systemic and Intrauterine Antibacterial Agents Used to Treat Bovine Metritis

Antibacterial Class	*Lactating Cattle for Use in FDA Approved*	*Mechanim of Action*	*Consideratins*	*Reasons Not to Use*
Aminoglycosides	No	Bactericidal; Inhibition of bacterial protein synthesis	Intrauterine or systemic; needs oxygen-dependent transport system to cross cytoplasmic membrane[47]	Anaerobic uterine environment; drug residue problems; negative effects on fertility[40]
Sulfonamides	Yes	Bacteriostatic; interferes with bacterial synthesis of folic acid, leading to a reduction of substrates needed for bacterial cell growth and reproduction	Intrauterine or systemic; readily absorbed from postpartum uterus	Reduced efficacy in the presence of pus and tissue debris; drug residue problems
β-lactams	Yes	Bactericidal; interferes with normal cell wall synthesis by inhibiting transpeptidase enzyme activity	Penicillin is primarily used; not hindered by environmental considerations of low pH, low oxygen tension, pus, or tissue debris; successful against the bacteria commonly causing bovine metritis; high uterine tissue levels with systemic use; intrauterine therapy is rarely chosen	Poor response of intrauterine treatment due to β-lactamase-producing organisms that are abundant within first 30 days postpartum[48]; drug residue problems
Tetracyclines	Yes	Bacteriostatic; inhibits bacterial protein synthesis	Needs an energy-dependent transfer pump to become intracellular; slightly inhibited by pus; not affected by low oxygen tension[45]; effective treatment levels are reached with intrauterine therapy[32,34]; systemic therapy is rarely chosen	Parenteral treatment when used according to label is ineffective; intrauterine treatment adversely affects the uterine defense mechanism[39]; incomplete tissue distribution following intrauterine treatment[32,33]; drug residue reservations
Cephalosporins	Yes	Bactericidal; interferes with normal cell wall synthesis by inhibiting transpeptidase enzyme activity	Systemic therapy only; effective against most organisms cultured from the uterus; excellent distribution throughout body tissues and fluids; no meat or milk withholding times when used according to label[50]	Poor response to intrauterine treatment due to β-lactamase-producing organisms that are abundant within 30 days postpartum[48]

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