



Efficacy of ampicillin trihydrate or ceftiofur hydrochloride for treatment of metritis and subsequent fertility in dairy cows

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ABSTRACT

Our objectives were to evaluate the efficacy of ampicillin trihydrate for the treatment of metritis in dairy cows compared with ceftiofur hydrochloride and the subsequent effects on pregnancy at first insemination (P/AI). Cows in the first 12 d in milk (DIM) with a uterine discharge score of 5 (watery, reddish or brownish discharge of foul smell) and rectal temperature $<39.5^{\circ}\text{C}$ were diagnosed with metritis based on the fetid discharge, and cows with metritis and rectal temperature $\geq 39.5^{\circ}\text{C}$ were diagnosed as having puerperal metritis. Cows with metritis ($n = 528$) were blocked by parity and type of metritis as fetid discharge or puerperal metritis and, within each block, assigned randomly to receive 11 mg/kg of ampicillin ($n = 259$) or 2.2 mg/kg of ceftiofur ($n = 269$) once daily for 5 d. Day of diagnosis of metritis was considered study d 1. A cohort of 268 cows without metritis was selected randomly at 12 DIM. Rectal temperature was measured in cows with metritis on study d 1 to 7, and 12, and vaginal discharge was scored on study d 5, 7, and 12. Metritis cure was characterized by vaginal discharge score of <5 or by vaginal discharge score of <5 and no fever. At 32 ± 3 DIM, vaginal discharge was scored for diagnosis of purulent vaginal discharge. At 39 ± 3 DIM, endometrial cytology was performed. At 53 ± 3 and 67 ± 3 DIM, ovaries were scanned to determine estrous cyclicity. Pregnancy was evaluated after the first AI. Cure of metritis based on vaginal discharge <5 was greater for ampicillin than ceftiofur on d 5 (37.1 vs. 25.2%) and 7 (57.2 vs. 46.3%), but not on d 12 (82.0 vs. 85.0%). Cure of metritis based on vaginal discharge <5 and no fever was greater for ampicillin than for ceftiofur only on d 7 (50.4 vs. 37.9%), but not on d 5 (23.1 vs. 17.6%) and 12 (66.1 vs. 67.4%). Cows with puerperal metritis had

reduced cure compared with cows with fetid discharge on d 5 (30.5 vs. 12.8%), 7 (55.2 vs. 33.6%), and 12 (72.0 vs. 61.1%). The proportion of cows with fever on any day after therapy started did not differ between treatments. Fifty-three percent of cows with metritis based on fetid discharge developed fever after initiating antimicrobial therapy. Cows receiving ampicillin had less prevalence of purulent vaginal discharge than those treated with ceftiofur (57.7 vs. 67.8%), but they were both greater than cows without metritis (21.9%). Prevalence of cytological endometritis did not differ between ampicillin and ceftiofur (30.0 vs. 25.4%), but they were both greater than cows without metritis (14.5%). The proportion of estrous cyclic cows (75.0%) and P/AI did not differ among treatments (ampicillin = 28.0% vs. ceftiofur = 28.3% vs. without metritis = 30.5%). Clinical cure was faster for ampicillin than for ceftiofur, but on study d 12 both treatments resulted in similar cure. Clinical cure was less for cows with puerperal metritis than for cows with fetid uterine discharge. Despite differences in uterine health, P/AI at the first insemination did not differ among treatments. **Key words:** ampicillin, ceftiofur, metritis, pregnancy

INTRODUCTION

Metritis is a prevalent uterine disease that affects early postpartum dairy cows characterized by an abnormally enlarged uterus and a fetid, watery red-brown fluid to viscous off-white purulent uterine discharge that can be accompanied or not by fever within the first 21 d postpartum (Sheldon et al., 2006). The incidence of metritis in dairy cows ranges from 10 to 36% (Goshen and Shpigel, 2006; Santos et al., 2010; Chapinal et al., 2011) and is more frequently diagnosed during the first week postpartum (Sheldon et al., 2006).

The economic losses caused by metritis are striking calculated at \$380 per affected cow, and the losses are caused by reduced milk production, delayed pregnancy, treatment, and increased culling and death (Drillich et al., 2001). Additionally, cows diagnosed with metritis have an increased risk to develop both clinical and cy-

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tological endometritis (Galvão et al., 2009; Martinez et al., 2012). The main bacteria isolated from cases of uterine infection include *Escherichia coli*, *Trueperella* (formerly *Arcanobacterium*) *pyogenes*, and anaerobic bacteria such as *Prevotella* (formerly *Bacteroides*) species and *Fusobacterium necrophorum* (Griffin et al., 1974; Noakes et al., 1989; Sheldon et al., 2002). Thus, it is reasonable to suggest that the use of antimicrobials with broad spectrum activity against these utero-pathogenic bacteria is the preferred choice for therapy of metritis.

Ampicillin is a β -lactam antibiotic that binds to specific penicillin-binding proteins in the inner surface of the bacterial cell wall acting as an irreversible inhibitor of dd-transpeptidase, an essential enzyme that bacteria use to synthesize peptidoglycan and other components of the cell wall (Prescott and Baggott, 1993; Chambers, 2007). Disruption in cell wall synthesis ultimately leads to cell lysis and death of the bacteria. The amino group in the chemical composition of ampicillin is thought to facilitate binding and penetration into the outer membrane of gram-negative bacteria, thereby increasing the spectrum of action when compared with penicillin. Ampicillin received approval in 1998 for use in dairy cattle in the United States (Center for Veterinary Medicine, Food and Drug Administration new animal drug application 200–180; FDA, 1998) and it is indicated for therapy of infections caused by *E. coli* (Burrows et al., 1993; Lehtolainen et al., 2003), but it is also efficacious against other gram-negative bacteria and those associated with metritis (Simon, 1977; Malinowski et al., 2011).

Most bacteria associated with metritis are susceptible to ceftiofur (Malinowski et al., 2011), and administration of ceftiofur hydrochloride has been shown to be an efficacious therapy for puerperal metritis in dairy cows (Chenault et al., 2004). Although ceftiofur is unique in that amounts of residue appearing in milk are below the tolerance for human consumption, so no withholding is required when used as indicated in the label, 23 to 35% of the cows treated with ceftiofur hydrochloride had failure to cure metritis (Chenault et al., 2004). Additionally, because ceftiofur is the only third-generation cephalosporin labeled in the United States to treat metritis, pneumonia, necrotizing pododermatitis, and mastitis, it might lead to selection pressure, which has been suggested to be involved with emergence and dissemination of β -lactamase CMY-2, a major mechanism of third-generation cephalosporin resistance (Jiang et al., 2006; Tragesser et al. 2006). Thus, an alternative treatment for metritis that either improves cure rates or offers an escape therapy for cows that failed to cure metritis is warranted. Moreover, having alternative therapies for metritis can potentially mitigate the se-

lection pressure caused by widespread use of ceftiofur. To date, no published study has evaluated efficacy of systemic administration of ampicillin for treatment of metritis in dairy cows.

We hypothesized that ampicillin would be an effective therapy for metritis, resulting in similar clinical cure and subsequent reproductive performance compared with cows treated with ceftiofur, a common antibiotic labeled and prescribed for treatment of metritis in the United States. The objectives of the present study were to evaluate the efficacy of ampicillin trihydrate for treatment of metritis in dairy cows compared with ceftiofur hydrochloride and subsequent effect on pregnancy to the first postpartum AI (P/AI).

MATERIALS AND METHODS

The University of Florida Institute of Food and Agricultural Sciences Animal Research Committee approved all procedures involving animals in the current study.

Cows, Housing, and Diets

The present study was conducted on a single dairy farm located in central Florida. The lactating herd was composed of approximately 5,270 lactating cows during the study period with a yearly rolling herd average milk yield of approximately 11,000 kg. A total of 528 cows diagnosed with metritis (264 primiparous and 264 multiparous) were enrolled in the study from October 10, 2012, to January 5, 2013. Those cows represent all cows diagnosed with metritis in the dairy during the enrollment period. Additionally, 268 herdmates (134 primiparous and 134 multiparous) without metritis were enrolled on d 12 postpartum. The cows without metritis were selected randomly and retrospectively based on the same day of calving and parity to match herdmates diagnosed with metritis.

Cows were housed in freestall barns with sand-bedded stalls and equipped with sprinklers and fans for forced evaporative cooling. The study was conducted when environmental temperature and humidity were not conducive of heat stress in dairy cows and unlikely to have altered body temperature measurements. The temperature and relative humidity data were obtained from the Florida Automated Weather Network (<http://fawn.ifas.ufl.edu>) from October 2012 to January 2013, approximately 40 km from the experimental location. Average daily temperature-humidity index (THI) was calculated as $\text{THI} = \text{temperature } (^{\circ}\text{F}) - [0.55 - (0.55 \times \text{relative humidity})] \times (\text{temperature} - 58)$. The mean daily THI averaged 65.6, 61.4, 58.7, and 60.1 for the months of October 2012 to January of 2013.

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