A randomized field study comparing differences in core body temperature, health, and performance in crossbred beef heifers administered 2 antimicrobial products given upon arrival at a stocker facility¹

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ABSTRACT

Antimicrobial metaphylaxis is an important tool used for the prevention of bovine respiratory disease complex, an economically important disease that typically affects newly weaned beef calves that are marketed and transported a distance from their origin. An experiment was conducted to determine the effects of administering 2 different metaphylactic products [tulathromycin (TULA) and gamithromycin (GAMI)] on differences on core body temperature, health, and performance on 284 highly stressed

stocker calves. Calves were procured and delivered (transient time = 13.5 h average) from a southeastern United States order buyer in 3 truckload lots during a 6-d period in October 2011. The core body temperatures in nonmorbid calves in the TULA calves were greater compared with the GAMI calves the first 2 h after administration and at multiple time points on d 4 through 6 of the experiment ($P < 0.05$). Calves receiving TULA experienced less morbidity ($P < 0.01$) and less chronicity ($P < 0.05$) when compared with GAMI calves. Calves in the TULA group had greater ADG ($P < 0.001$) from arrival to d 45 compared with calves injected with GAMI. This experiment indicated that metaphylactic products may affect core body temperature differently, which may be an important consideration when managing the health of high-risk calves. Moreover, both

health and performance differences may exist among calves administered different metaphylactic products. Therefore, product selection is an important decision when managing high-risk calves.

Key words: beef calf, metaphylaxis, core body temperature, health, performance

INTRODUCTION

Bovine respiratory disease complex (BRDC) remains an important disease in weaned beef calves (Smith, 1998; NAHMS, 2011c). Multiple management practices including nutrition, environment, and immunization are used to help control this disease process (Snowder et al., 2006). In addition, metaphylaxis, the mass administration of antimicrobial

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products to animals upon arrival at stocker and feedlot operations, is sometimes used for control of BRDC in high-risk cattle, and approximately 42% of all incoming cattle in feedlots with a capacity of less than 1,000 head and 26.0% of all incoming cattle in feedlots with a capacity of 1,000 or more head receive an antimicrobial injection upon initial processing in feedyards (NAHMS, 2011a,b).

The objective of this research was to determine whether crossbred beef heifer calves administered 2 different antibiotics commonly used for metaphylaxis, tulathromycin (TULA, Draxxin, Pfizer Animal Health, New York, NY) and gamithromycin (GAMI, Zactran, Merial Animal Health, Duluth, GA), differed in core body temperature, health, and performance. The metaphylaxis products were chosen on the basis of their recent introduction into the animal health market at the time of the experiment. It was hypothesized that core body temperature may be affected by different metaphylactic products, and these differences may be important considerations when diagnosing BRDC. It was also hypothesized that differences may exist concerning health and performance in calves administered different antibiotics commonly used for metaphylaxis.

MATERIALS AND METHODS

Animals

This experimental protocol was approved by the Kansas State University Animal Care and Use Committee, Protocol #2910. Crossbred beef heifer calves ($n = 284$; BW = 229 ± 21.9 kg) were procured through a livestock order buyer at various auction markets in Alabama and Tennessee in October 2011 and transported to Dickinson, Tennessee. All cattle were then transported, within one day after arrival from the Tennessee facility, to the Kansas State University Beef Stocker Unit (KSBSU), Manhattan, Kansas. Before being transported to Kansas, all calves were provided ad libitum access to long-stem grass hay

and water. The approximate transit time from the order buyer barn departure to arrival at KSBSU for all truckloads was 13 to 14 h. Cattle were mixed continental breeds ranging in hide colors from yellow to black. Three truckloads containing approximately 90 calves per load arrived at the study facility over a 6-d period. Arrival dates were October 19, 21, and 26, respectively. Calves from each truckload were housed within a separate string of pens (8 pens per load; 4 pens per treatment).

Housing and Environment

Calves were housed in 24 identical pens measuring 9.1 m by 15.2 m. Each pen was soil surfaced with a concrete fence line feed bunk measuring 9.1 m long, which also included a 3.6-m concrete apron. No shade was present. Average weekly precipitation, in centimeters, measured within 1.6 km of the research facility was as follows: 0.00, 0.03, 0.53, 0.00, 0.10, 0.28, and 0.00 cm for wk 1 to 7, respectively (Weather Source LLC, 2015). Maximum daily temperatures, also measured 1.6 km from the facility, during the study were as follows: 12.2, 13.9, 22.8, 21.1, 26.7, 28.9, and 26.1°C for d 1 to 7, respectively (Weather Source LLC, 2015).

Experimental Design

Upon arrival at the KSBSU, calves were weighed individually and administered a visual “dangle”-style ear tag. Each calf was assigned to a pen using a commercial random number generator program (Excel, Microsoft Corporation, Redmond, WA). Pens were then balanced for arrival weight. A coin flip at every other pen was used to allocate the treatment for that pen with the subsequent pen receiving the alternative treatment allocation. Therefore, 4 pens within each truckload were assigned to each treatment, resulting in 12 pens assigned to each treatment. All 8 pens within the third truckload were selected to participate in the core body temperature portion of the study. The selection of this

subgroup of pens was based on convenience and proximity to the working facility.

Treatment Administration

The day after arrival (d 1), calves within each load were administered their assigned metaphylactic antimicrobial product. Calves assigned to TULA received tulathromycin (Draxxin; Pfizer) at 2.5 mg/kg of BW and calves assigned to GAMI received gamithromycin (Zactran; Merial Limited, Duluth, GA) at 6.0 mg/kg of BW subcutaneously in the left cervical area, cranial to the scapula, ventral to the nuchal ligament, and dorsal to the vertebrae according to beef quality assurance guidelines (Beef Quality Assurance, 2016). Treatments were administered to all calves by the same individual according to labeled instructions. All calves at the time of treatment administration also received a modified-live vaccine containing infectious bovine rhinotracheitis virus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza virus (Bovishield Gold 5; Pfizer) subcutaneously in the right cervical area, as described above, and a parasiticide (Ivomec Pour-On; Merial Limited) according to label instructions. Additionally, each calf was administered, subcutaneously in the right cervical area, as described above, a toxoid containing *Clostridium chauvoei*, *Clostridium perfringens*, *Clostridium septicum*, *Clostridium novyi*, and *Clostridium sordellii* (UltraChoice 7; Pfizer) the day after arrival and on d 28 per labeled instructions. At the time of antibiotic administration, an ear biopsy was collected from the left ear of each calf and submitted to the Kansas State Veterinary Diagnostic Laboratory for bovine viral diarrhea virus PCR analysis.

Core Body Temperature Assessment

Calves in 8 pens and from within one truckload (third arrival load) were monitored for core body tem-

perature via vaginal temperature over the first 7 study days after antibiotic administration. Vaginal temperature was captured using stainless steel temperature loggers (U12–015 HOB0; Onset, Bourne, MA) attached to non-hormonally impregnated controlled internal releasing devices (CIDR; Pfizer). The intravaginal devices were inserted in each calf when allocated treatments were administered on d 1. Vaginal temperature was logged every 10 min, and data were averaged over 1-h periods. To allow the temperature device to come to equilibrium, the first 20 min of recordings after initial insertion were not used in the analysis. The intravaginal devices were removed on d 8. For the core body temperature portion of the study, temperature values were averaged across pens, and only data from nonmorbid calves were analyzed and included 43 TULA and 44 GAMI calves. Data from 2 calves in TULA and 3 calves in GAMI were excluded from the analysis because the data logger was not retained for the entire study period. Data from 2 additional calves in GAMI were removed from the study because the data logger stopped recording during the study. There was approximately a 2.1-h time span from the insertion of the vaginal device in the first calf to the insertion of the vaginal device in the last calf within this subset.

Health Monitoring

Calves were observed by KSBSU animal caregivers twice a day to determine health status. The caregivers were blinded to the treatment allocation for each pen. A 5-d post-metaphylactic antimicrobial treatment moratorium was used in this experiment. At the end of the moratorium, a clinical illness scoring system of 1 to 4 (1, normal; 2, mild depression, gaunt; 3, severe depression, labored breathing; and 4, moribund, near death, little response to human approach) was used to determine health status. Calves with a score greater than 1 were taken to the working facility for examination. Those calves with a

clinical illness score >1 and a rectal temperature $\geq 40^{\circ}\text{C}$ taken during the examination and not presenting signs indicative of nonrespiratory disease were determined to be experiencing BRDC. Bovine respiratory disease complex calves were administered antibiotics according to the KSBSU standard operating procedure. The treatment regimen for BRDC was first illness, florfenicol (Nuflor; Merck Animal Health, Madison, NJ) at 40 mg/kg of BW; second illness, enrofloxacin (Baytril; Bayer Health Care LLC, Animal Health, Pittsburgh, PA) at 10 mg/kg of BW; third illness, oxytetracycline (Biomycin 200; Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO) at 4 mg/kg of BW. Calves continuing to express a clinical illness score >1 and a rectal temperature $\geq 40^{\circ}\text{C}$ on d 3 after first or second treatment were administered the next scheduled treatment product as described above. A hospital pen was not used in this study; all calves were returned to their original pen after physical examination and medication. Chronic calves were defined as calves experiencing BRDC for the third time. These calves were returned to their home pen and not administered antimicrobials again. Investigated health outcomes included BRDC morbidity, case fatality, chronicity, and mortality.

Performance Assessment

All calves were individually weighed, using a livestock scale (Avery Weigh-Tronix, Model 640, Fairmont, MN), immediately upon arrival (d 0), at revaccination (d 28), and at study completion (approximately d 45). Average daily gain was calculated from individual weights taken immediately upon arrival to the KSBSU to d 28 and from arrival to study completion for all calves. All BW measures were collected before feeding at approximately 0800 h on each respective weigh day. Dry matter intake and G:F were calculated for each pen of heifers and each period (d 0 to 28, 0 to 56). Average daily gain for all time periods was calculated with mortalities removed.

Feeding Program

For the first 2 d upon arrival calves were given ad libitum access to water and to medium quality prairie hay (7.0% CP, 0.44 Mcal/kg NE_g; Table 1). From d 3 to study completion, the calves were fed a TMR consisting of mixed grass hay, alfalfa hay, dry rolled corn, wet corn gluten feed, and a commercial pellet (Cargill Animal Nutrition, Minneapolis, MN; Table 1). Feed bunks were scored twice daily, and subsequent feed amounts delivered were based on the amount of feed not consumed at the previous feeding.

Statistical Analysis

Data were statistically analyzed with pen as the experimental unit using a commercial software program (STATA v. 12.0). The experimental design was a completely randomized, blocked by truck load, blinded clinical study. Generalized estimating equations accounting for repeated measures and pen within truckload as random effects were used to analyze core body temperature data. The fixed effects were treatment, hour, and day; the correlation structure was AR(1) (Dohoo et al., 2003). Logistic regression models were used to analyze health outcome data. Treatment was the fixed effect, and pen within truckload were included as random effects to account for a lack of independence among calves. Generalized mixed models were used to investigate associations between treatment and ADG. Random effects in this model included pen within truckload, and treatment was the fixed effect. A 2-sided *P*-value of 0.05 was considered significant for all models.

RESULTS AND DISCUSSION

Core Body Temperature

In the present study, continuous vaginal temperatures were captured in one truckload of calves (93 head) using data loggers. Multiple studies have concluded that vaginal temperature is

Table 1. Composition (% of DM) of growing diets fed during an experiment comparing 2 metaphylaxis treatments in crossbred beef heifer calves

Item	% of DM, unless shown ¹
Ingredient composition, % of DM	
Dry-rolled corn	28.6
Wet corn gluten feed	30.0
Alfalfa hay	17.5
Prairie hay	17.5
Supplement ²	6.4
Corn gluten feed	1.8
Wheat middlings	3.1
Salt	0.38
Limestone	0.82
Potassium chloride	0.02
Magnesium oxide	0.01
Beef vitamin premix ²	0.001
Ruminant trace mineral ²	0.001
Molasses	0.19
Rumensin ³	0.014
Nutrient composition, analyzed ⁴	
DM	79.3
CP	13.2
Starch	26.5
Ether extract	2.7
ADF	24.7
Ca	0.67
P	0.45
Calculated NE _g , Mcal/kg	1.20

¹Provided 0.5 mg/d of melengestrol acetate (Pfizer Animal Health, New York, NY), which was supplemented through a commercially prepared mineral supplement (Cargill Animal Nutrition, Minneapolis, MN).

²Manufactured by Cargill Animal Nutrition (Minneapolis, MN).

³Diet provided 31 mg/kg of monensin (Elanco Animal Health, Indianapolis, IN).

⁴Analyses conducted at SDK Laboratories (Hutchinson, KS).

an acceptable method to monitor core body temperature in cattle (Davis et al., 2003; Vickers et al., 2010; Burdick et al., 2012). Rectal temperature, not vaginal temperature, is commonly used to measure core body temperature in cattle; therefore, for vaginal temperatures to be of value, their correlation with rectal temperature is important. The correlation between rectal and vaginal temperature was determined to be 0.97 ($P < 0.001$) in a study simultaneously measuring vaginal and rectal temperatures in beef heifers (Burdick et al., 2012).

A diurnal core body temperature pattern was observed through the first 7 study days (Figure 1). This diurnal

pattern was also reported in other studies and is considered to be normal bovine reactions to ambient temperature changes (Lefcourt and Adams, 1996, 1998; Davis et al., 2003). Mean core body temperature was greater for TULA on h 1 and 2 after metaphylactic treatment (Figure 1). Although manufacturers of both antimicrobial products used in this study report transient local tissue reaction may occur immediately following administration, it is possible that one product, possibly either through the active ingredient or proprietary carrier, produces a more intense reaction as measured by core body temperature (Merial Limited, 2012; Pfizer Inc.,

2012). Inflammatory response differences associated with product dosage have been reported; one study reported greater inflammatory response in a greater dose vaccine compared with a lesser dose vaccine (Stokka et al., 1994). This is in contrast to the present study's findings, which suggest the lesser dose product (TULA) may have produced a greater inflammatory response than GAMI as measured by core body temperature. The difference in study findings may be explained by the product differences (vaccines compared with antimicrobials) within the 2 studies. Additionally, TULA core body temperatures were greater at multiple time points including h 84, 85, 106 to 113, 115 to 117, 119 to 120, and 132 to 140 after insertion (Figure 1). These time points coincided with the afternoon time periods of study d 4, 5, and 6. Mean ambient temperature during the first 7 study days was 12.5°C (range: 5.6–23.9°C). It is interesting that mean core body temperatures peaked for one or both treatment groups at or above 40.0°C on days when the ambient temperature peak ranged from 12.2 to 26.1°C (Figure 1). The 40.0°C level is important because it is a value used by many cattle-feeding units, including the KSBSU, to classify calves as BRDC cases. Additionally, the ambient temperatures during these time periods are relatively close to the reported bovine thermoneutral threshold of 15 to 25°C (NRC, 1984). The present study indicates that even on days not considered to be above the bovine thermoneutral zone, core body temperatures above established disease-indicating thresholds can occur in some calves. The results from the present study may suggest that using continuous core body temperature as a criterion for BRDC case definition may have reduced specificity depending on what time of day the temperatures are collected. Some researchers have suggested that BRDC clinical illness recognition by animal caregivers is an insensitive diagnostic tool (Bryant et al., 1999; White and Renter, 2009). Although only calves not classified as BRDC cases during

Figure 1. Model adjusted mean hourly core-temperature patterns for crossbred beef heifer calves administered 2 different metaphylactic products. Model contained program, hour, day, and interaction terms (program $\times$ hour $\times$ day) and accounted for repeated measurements within calves and random effect of pen within truckload. TULA = tulathromycin (2.5 mg/kg); GAMI = gamithromycin (6 mg/kg) * $P \leq 0.05$ for difference in core temperature as measured by vaginal temperature between 2 study groups.

the entire study period were included in the core body temperature portion of the present study, it is possible that some calves in the core body temperature portion of the present study may have been experiencing subclinical respiratory disease on those days when group mean temperatures were elevated. Because other diagnostic tests, including at-slaughter lung scoring, were not used in this study, it is not possible to determine the level of subclinical BRDC occurring in this subset.

Some studies have investigated differences in core body temperature between classes of antimicrobials (Fajt et al., 2004). Because both of the antimicrobials in the present study were macrolides, they would be expected to have similar antimicrobial and immunomodulation properties (Ianaro et al., 2000; Woo et al., 2002). Some researchers have concluded that macrolides can upregulate the innate immune response depending on the active ingredients and concentrations (Woo et al., 2002). Additionally, macrolides have demonstrated immune modifying properties in animal respiratory disease, which may be

important in clinical applications (Woo et al., 2002). It is plausible that TULA has different immunomodulating properties compared with GAMI, including cytokine upregulation, expressed through elevated core body temperature; this may have ameliorated the effects of BRDC associated pathogens (Tizard, 2013). In several studies, administering cytokines before infection with bovine herpes virus 1 was found to reduce clinical signs (Babiuk et al., 1985, 1987, 1991). Therefore, it is also possible, although only calves not recorded as BRDC cases were included in the core body temperature study, that TULA calves expressed less clinical BRDC because of product-associated immunomodulation. The findings presented here suggests that some antimicrobial products may have unmeasured properties that may provide additional health benefits to calves.

Health

No animals were determined to be bovine viral diarrhea virus persistently infected by PCR. Mortality was $2.1 \pm 1.2\%$ (3/141) and $1.4 \pm 0.9\%$

(2/143) for TULA and GAMI, respectively. Case fatality was $5.0 \pm 2.8\%$ (3/60) for TULA and $2.4 \pm 1.7\%$ (2/83) for GAMI. In the multivariable model, morbidity was less ($P = 0.013$) for TULA ($41.6 \pm 4.7\%$) compared with GAMI ($58.3 \pm 4.7\%$; Table 2). The percentage of chronics was less ($P = 0.048$) for TULA calves ($5.7 \pm 1.9\%$) compared with GAMI calves ($12.6 \pm 2.8\%$). There was no statistical difference ($P > 0.40$) between TULA and GAMI calves for either mortality or case fatality rate. The morbidity and mortality results of the present study do not agree with a metaphylaxis study completed in Italy where gamithromycin calves experienced less morbidity and mortality compared with tulathromycin calves (Sgoifo Rossi et al., 2010). In the Italian study very low morbidity (14.6 and 9.3%) and mortality (0.4 and 0.6%) was observed in both groups, which may explain the different findings between these 2 studies. It is also possible that there are geographical differences in pathogen susceptibility patterns or pharmacogenomic differences within cattle populations from different countries, which may help explain the differences in the health outcomes between the 2 studies. These plausible differences may be important to consider when comparing antibiotic effectiveness studies across geographical areas and genetically different animals.

Performance

The ADG from arrival to revaccination (d 28) for TULA was greater ($P < 0.001$) than GAMI: 1.51 versus 1.27 kg/d, respectively (Table 3). Over the entire study period (45 d), TULA also outgained GAMI calves ($P < 0.001$), 1.42 and 1.24 kg/d for TULA and GAMI, respectively (Table 3). Additionally, for calves not designated as chronic, the ADG from arrival to d 28 ADG in calves administered TULA was greater ($P < 0.001$) than GAMI: 1.55 versus 1.34 kg/d, respectively. Additionally, the ADG from arrival to d 45 between nonchronic calves administered TULA (1.41 kg/d) was

Table 2. Model¹ adjusted percentages and *P*-values of health outcomes comparing 2 antimicrobial products in crossbred beef heifer calves

Health outcome ²	Treatment, ³ %		SEM	<i>P</i> -value
	TULA	GAMI		
Morbidity	41.6	58.3	0.03	0.013
Mortality	2.1	1.4	0.10	0.643
Case fatality	5.0	2.4	0.15	0.413
Chronicity	5.7	12.6	0.02	0.048

¹Model included pen within truckload as random effect.²Number experiencing outcome/number at risk.³TULA = tulathromycin (2.5 mg/kg of BW); GAMI = gamithromycin (6 mg/kg of BW).

greater ($P < 0.001$) than GAMI (1.27 kg/d). Given the TULA calves experienced less morbidity and chronicity than GAMI calves, these findings are not surprising and agree with other studies showing the negative effects of BRDC on calf performance (Gardner et al., 1999; Waggoner et al., 2007). No statistical differences in DMI or G:F between TULA calves and GAMI calves were found for time periods arrival to d 28 and arrival to d 45 (Table 3).

IMPLICATIONS

At several time points, calves administered tulathromycin or gamithromycin upon arrival, and not experiencing BRDC, experienced different

core body temperatures. This study suggests that core body temperature may be affected for extended periods of time after metaphylactic product administration, depending on the antimicrobial product. Additionally, healthy calves administered either metaphylactic product experienced peak mean core body temperature levels after administration at or above values commonly considered to be within normal, healthy bovine ranges. This finding may suggest that continuous core body temperature measurement may have reduced BRDC diagnostic specificity; therefore, calves not experiencing BRDC may be falsely identified as positive BRDC calves by caregivers. Additionally, calves administered TULA experienced less BRDC

morbidity and chronicity and greater ADG compared with calves administered GAMI.

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Table 3. Model¹ adjusted ADG, DMI, G:F, SE, and *P*-values of health outcomes comparing 2 antimicrobial products in crossbred beef heifer calves

Time period	Treatment ²		SE	<i>P</i> -value
	TULA	GAMI		
Arrival weight, kg	229.7	229.8	0.98	0.970
ADG, arrival to d 28, kg/d	1.51	1.27	0.03	<0.001
ADG, arrival to d 45, kg/d	1.42	1.24	0.03	<0.001
DMI, arrival to d 28, kg/d	5.47	5.46	0.09	0.983
DMI, arrival to d 45 kg/d	6.47	6.59	0.08	0.384
G:F, arrival to d 28 ³	0.26	0.25	0.01	0.855
G:F, arrival to d 45 ³	0.21	0.20	0.01	0.945

¹Model included pen within truckload as random effect.²TULA = tulathromycin (2.5 mg/kg of BW); GAMI = gamithromycin (6 mg/kg of BW).³Calculated from total gain over total DMI.

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