
Technical Bulletin



Randomized Non-inferiority Clinical Trial Evaluating Three Commercial Dry-Cow Mastitis Preparations

Based on Publications:

Arruda AG, Godden S, Rapnicki P, et al. Randomized non-inferiority clinical trial evaluating three commercial dry-cow mastitis preparations: I. Quarter-level outcomes. *J. Dairy Sci* 2013;96(7):4419–4435.

Arruda AG, Godden S, Rapnicki P, et al. Randomized non-inferiority clinical trial evaluating three commercial dry-cow mastitis preparations: II. Cow health and performance in early lactation. *J Dairy Sci* 2013;96(10):6390–6399.

Overview

A large clinical trial was conducted to compare the treatment efficacy of three dry-cow formulations: ToMORROW[®] (cephapirin benzathine), Spectramast[®] DC (500mg ceftiofur HCL) and Quartermaster[®] (1 x 10⁶ units penicillin G and 1g dihydrostreptomycin). The study was conducted across multiple states: WI (2), MN (1), IA (1) and CA (2), with 1,091 cows (4,364 quarters). All quarters were also infused with Orbeseal[®].

There was no difference among the preparations in the following quarter-level outcomes:

- The prevalence of intramammary infections (IMI) post calving
- Ability to cure preexisting IMI during the dry period
- Ability to prevent new IMI during the dry period
- Risk for a clinical mastitis event between calving and 100 days in milk (DIM)

There was also no difference in the following cow-level outcomes up to 100 DIM.

- Milk production (305ME)
- Linear score
- Risk for a clinical mastitis event
- Risk for leaving the herd
- Risk for getting pregnant

Introduction

Dry-cow mastitis treatment is a well-established management practice, intended to cure existing IMI acquired during lactation and to prevent new IMI in the dry period. The prevalence of subclinical IMI at dry-off can vary between 13 and 35%, and the incidence of new IMI during the dry period can vary from 8 to 25% (Godden, et al. 2003). The majority (50 to 60%) of all new infections, caused by environmental pathogens, occur during the dry period (Bradley and Green 2000).

Cattle First.



Materials and Methods

The study was designed to detect a 10% difference in treatment effects at the quarter level. To qualify for the study, cows had to have four functional quarters, be in good general health, be in a herd undergoing regular Dairy Herd Improvement Association (DHIA) testing, no clinical mastitis at dry-off, and no history of having been treated with antibiotics or anti-inflammatory drugs within 30 days prior to enrollment. All study enrollment and sampling activities were conducted by university technicians who visited the herd on dry-off day each week.

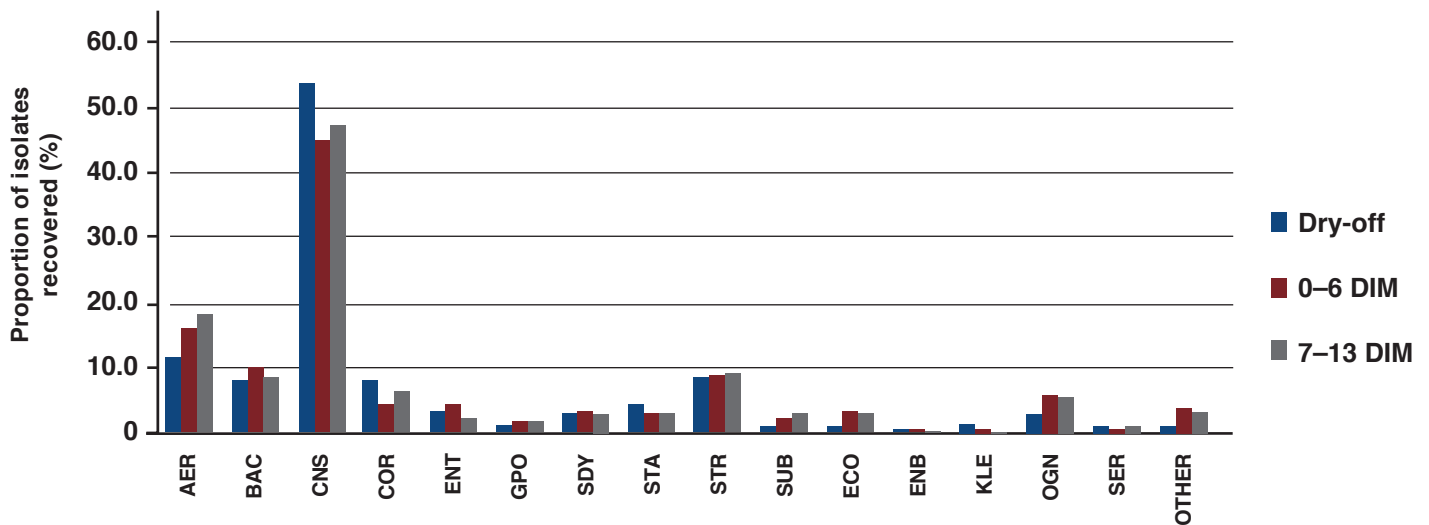
Milk culture and pathogen identification techniques were in accordance with National Mastitis Council guidelines. The definitions for intramammary infection status were as follows:

- Presence of an IMI:
 - Most pathogens: ≥ 1 colony isolated in 10 μ L of milk
 - Coagulase-negative staphylococci ≥ 2 colonies
 - *Bacillus* spp. ≥ 5 colonies
- Bacteriologic cure of an IMI:
 - Disappearance of one or two pathogens that were previously isolated at the dry-off milk sample from both post-calving samples
- New IMI:
 - Growth of one or two pathogens in either the 0-6 DIM or 7-13 DIM sample that had not been previously isolated from the dry-off sample

Results

The IMI pathogens isolated during the study are displayed in Chart 1:

Chart 1



AER (*Aerococcus* spp.), BAC (*Bacillus* spp.), CNS (*Coagulase-negative staphylococcus*), COR (*Corynebacterium* spp.), ENT (*Enterococcus* spp.), GPO (Other Gram-positive), SDY (*Streptococcus dysgalactiae*), STA (*Staphylococcus aureus*), STR (Other streptococci), SUB (*Streptococcus uberis*), ECO (*Escherichia coli*), ENB (*Enterobacter* spp.), KLE (*Klebsiella* spp.), OGN (Other Gram-negative), SER (*Serratia* spp.)



Boehringer
Ingelheim

Cattle First.

Statistical analysis of the results was performed with SAS 9.2. A logistic regression model was used for risk of IMI at calving, risk of developing new IMI, and cure. A mixed linear model was used for milk production and linear score to 100 DIM. Survival analysis was used for risk of clinical mastitis, risk of leaving the herd, and risk of becoming pregnant by 100 DIM.

At dry-off, 94.4% of the IMI were Gram-positive and 4.9% Gram-negative. After calving (0–6 DIM), 89.7% of the IMI were Gram-positive and 7% Gram-negative. The culture results were consistent with the pathogen profiles from dry-off and freshening cows in the modern dairy industry; the majority of isolates were environmental Gram-positives, with CNS spp. predominating. Contagious pathogens, which traditionally have been the major target for dry-cow therapy, were either totally absent (*Streptococcus agalactiae*) or were a very small percentage of isolated IMI (*Staphylococcus aureus*, 2.5% and 1.3% at dry-off and 0–6 DIM).

A comparison of prevalence of IMI at dry-off, cure and new IMI among the three dry-cow therapies are shown in Table 1:

Table 1

	ToMORROW® (cephapirin benzathine)	Quartermaster® (penicillin- dihydrostreptomycin in oil)	Spectramast® DC (ceftiofur hydrochloride)	P*
IMI present at Dry-off	20.7%	18.8%	18.2%	0.73
IMI present at 0–6 DIM	15.3%	15.4%	13.4%	0.34
IMI present at 7–13 DIM	13.7%	15.4%	15.0%	0.37
Cure	89.7%	88.9%	88.0%	0.79
New IMI at 0–6 DIM	13.8%	14.1%	11.9%	0.27
New IMI at 7–13 DIM	12.6%	14.2%	13.5%	0.6
Risk of clinical mastitis in qtr to 100 DIM	4.1%	5.3%	3.8%	0.27

*Significance declared at $P < 0.05$

Cow level variables analyzed are shown in Table 2:

Table 2

	ToMORROW® (cephapirin benzathine)	Quartermaster® (penicillin- dihydrostreptomycin in oil)	Spectramast® DC (ceftiofur hydrochloride)	P*
Risk of mastitis to 100 DIM	15%	14.8%	12.7%	0.8
305ME (kg)	11,540	11,587	11,463	0.31
Linear score	1.7	1.9	2.0	0.12
Risk of leaving herd to 100 DIM	10.3%	7.5%	9.2%	0.55
Risk of pregnancy by 100 DIM	26.9%	31.5%	26.1%	0.26

*Significance declared at $P < 0.05$.

Discussion

This study, which was designed as a non-inferiority study, demonstrated no significant difference among the three dry-cow intramammary preparations.

The majority of pathogens isolated in this study were CNS spp., and the results reflect the preponderance of this organism in all sampling stages. Although the numbers are small, the biggest disparity in cure rates by pathogen was for *Staphylococcus aureus*. The number of quarters at risk of a cure and the cure rate (CR) are as follows for each treatment: QM ($n = 5$); CR = 80%; SP ($n = 7$); CR = 42.9%; TM ($n = 9$); CR = 88.9%. ToMORROW® (cephapirin benzathine), a first-generation cephalosporin, has a more robust Gram-positive spectrum than a third-generation cephalosporin. ToMORROW's cure rate for *S. aureus* at 88.9% approached statistical significance (one-sided p -value <0.08) when compared to Spectramast® DC's (ceftiofur HCL) cure rate at 42.7%.

The factors (cure rate, prevention of new infections, risk of clinical mastitis, milk production, linear score, and risks for culling and pregnancy) examined in this study are the most economically important to consider in selecting a dry-cow intramammary preparation. However, given that all these preparations yielded similar results, other factors would need to be considered in herds that have a similar pathogen profile.

These factors include judicious use of antimicrobials, milk withhold after calving, meat withhold times and the cost of dry-cow therapy.

From the point of view of judicious use of antibiotics, the authors suggest that the veterinary community should consider the use of first-generation cephalosporins over the use of third-generation cephalosporins.

The cost of the different dry-cow preparations with regard to milk withhold depends on available uses for milk from treated animals. This nonsalable milk can be very valuable if fed to calves, so the cost may in fact be zero or minimal, depending on the market milk price and the cost of milk replacer powder.

The milk withhold (hours nonsalable) difference between two products should be calculated as the time difference to when milk is marketed. Most dairies still collect colostrum from zero-milk-hold dry-cow therapies, and it may be 12 to 24 hours before these cows actually have milk marketed.

A dairy manager may elect to sell a cow after treatment with a dry cow preparation due to abortion or other problems. These cows need to clear the meat residue withhold times before sale. However, because these cows represent a very small percentage of all the cows dry-treated, the cost is minimal.

Conclusion

There were no significant differences among the three dry-cow preparations. As such, dairy producers could potentially put aside concerns about differences in product efficacy, and instead base their selection decision between these three products on other characteristics, such as milk and meat withholding time, targeted dry-period length, and cost. From the standpoint of promoting prudent use of antimicrobials, the veterinary community might consider recommending the use of the older, simpler antimicrobials as a first choice among dry cow therapy products.

References

- ¹ Godden S., Rapnicki P, Stewart S, et al. Effectiveness of an Internal Teat Seal in the Prevention of New Intramammary Infections During the Dry and Early-Lactation Periods in Dairy Cows when used with a Dry-Cow Intramammary Antibiotic. *J Dairy Sci* 2003;86(12):3899–3911.
- ² Bradley AJ, & Green MJ. A Study of the Incidence and Significance of Intramammary Enterobacterial Infections Acquired During the Dry Period. *J Dairy Sci* 2000;83(9):1957–1965.