
Technical Bulletin



A Non-inferiority Trial Comparing a First-Generation Cephalosporin with a Third-Generation Cephalosporin in the Treatment of Non-severe Clinical Mastitis in Dairy Cows

Schukken YH, Zurakowski MJ, Rauch BJ, et al. *J Dairy Sci* 2013;96(10):6763–6774.

Key Points

- No significant difference in overall bacteriologic cure risk between treatments.
- No significant difference in bacteriologic cure risk between treatments for clinical mastitis caused by Gram-positive bacteria.
- Cephapirin showed a significantly lower bacteriologic cure risk for Gram-negative bacteria.
- No significant difference in clinical cure risk between treatments for Gram-positive and Gram-negative cases.
- Study results can be used as the basis to develop farm-specific treatment protocols for clinical mastitis.

Introduction

Clinical mastitis is an important disease of dairy cattle, requiring dairy producers to make treatment decisions, upon observation of symptoms, to minimize production and milk quality losses. Several treatment options are available to dairy producers; however, most efficacy information available evaluates a treatment against a negative control. Comparative studies evaluating one registered intramammary (IMM) treatment against another are lacking in the U.S., but clearly would be valuable to information-based treatment decisions.

Although Gram-negative bacteria are important causes of clinical mastitis in some well-managed dairies, Gram-positive infections and clinical mastitis with culture results of 'no growth' often represent the majority of clinical cases in many other dairies.¹ Blanket use of extended-therapy protocols with third-generation cephalosporins may not have an economical advantage over short-duration protocols with a first-generation cephalosporin. Additionally, recent concerns have arisen over the extra-label use of third- and higher-generation cephalosporins in food-producing animals.²

Cattle First.



Study Objective

To compare the treatment efficacy of a one-day, 12-hour interval treatment with ToDAY® (cephapirin sodium) to a five-day, 24-hour interval treatment with Spectramast® LC (ceftiofur hydrochloride).

Materials and Methods

The study design was a non-inferiority study. To disprove the null hypothesis, ToDAY could not be inferior to SPECTRAMAST LC by more than 15%. The margin of 15% was chosen because of the economic advantage of a short-duration protocol with ToDAY over an extended-therapy protocol with SPECTRAMAST LC.

Farms with at least 200 cows, milking twice daily and participating in monthly Dairy Herd Improvement Association (DHIA) testing, including somatic cell counting (SCC), were eligible. For enrollment in the study, cows must have had a parity fewer than seven, were more than 25 days from dry-off, had no clinical mastitis or antimicrobial treatment for any reason within the prior 30 days, and had clinical mastitis in only one quarter that was classified as mild or moderate.

Upon identification of clinical mastitis, farmworkers obtained a milk sample for culture, recorded a clinical score and treated the animal with the test treatment as randomly assigned upon opening of a numbered study envelope.

Milk samples for culture were taken and clinical scores recorded approximately 10 (+/-2) and 17 (+/-2) days after onset of treatment. Milk culture and pathogen identification techniques were in accordance with National Mastitis Council guidelines. Bacteriologic cure was defined as the absence of the organism present in the pre-treatment sample from both of the post-treatment samples. Clinical cure was defined as clinically normal milk and a normal gland at both of the post-treatment scorings.

Statistical Analysis

Statistical analysis of the primary outcomes (bacteriologic and clinical cures) was done using a generalized linear mixed model, including co-variates such as parity, days in milk at the time of treatment and quarter location. A second model was used to evaluate the impact of the bacterial groups (Gram-negative versus Gram-positive) on cure. All analyses were done in SAS 9.2, Proc Glimmix and Proc Lifetest.

Results

Seven farms in New York met eligibility requirements and were included in the study, contributing a total of 321 cases. Twenty-five cases were considered ineligible (failure to collect initial milk sample, failure to adhere to protocol, loss of records), resulting in 296 enrolled cases. No difference in age, days in milk or affected quarter existed between the treatment groups.

Culture results ($n = 296$) from the initial milk samples taken at the time of first treatment are shown in Figure 1. Pathogen distribution differed among herds, indicating important differences in intramammary ecosystems (Figure 2). For most of the herds included, Gram-positive cases and cases with a culture result of 'no growth' predominated.

Figure 1. Intramammary Infection Status at Time of First Treatment

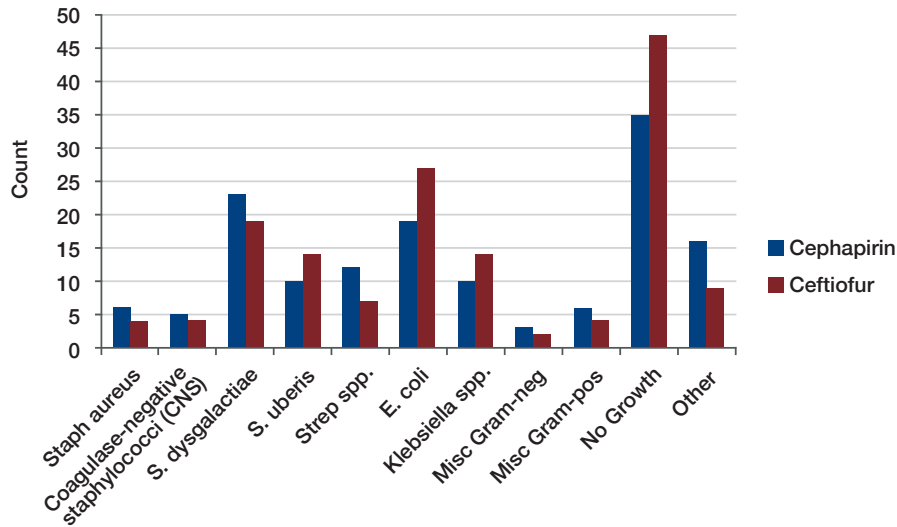
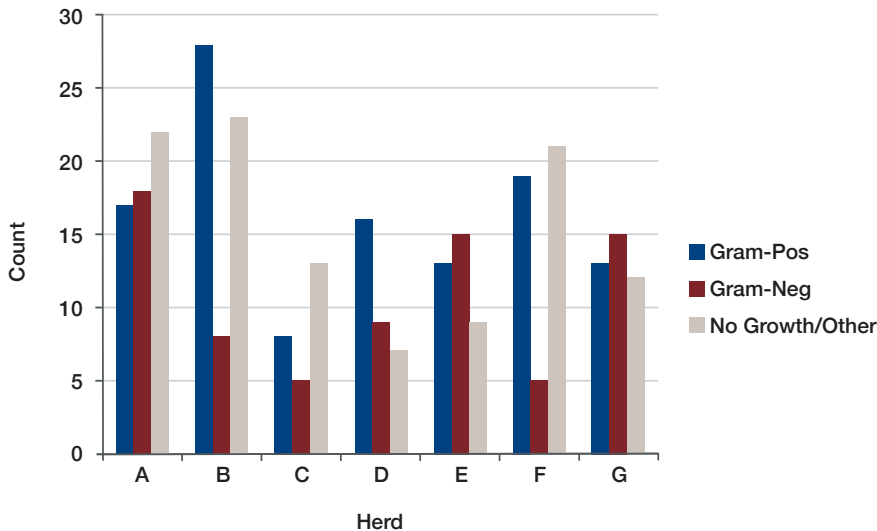


Figure 2. Distribution of Culture Results Within Herds



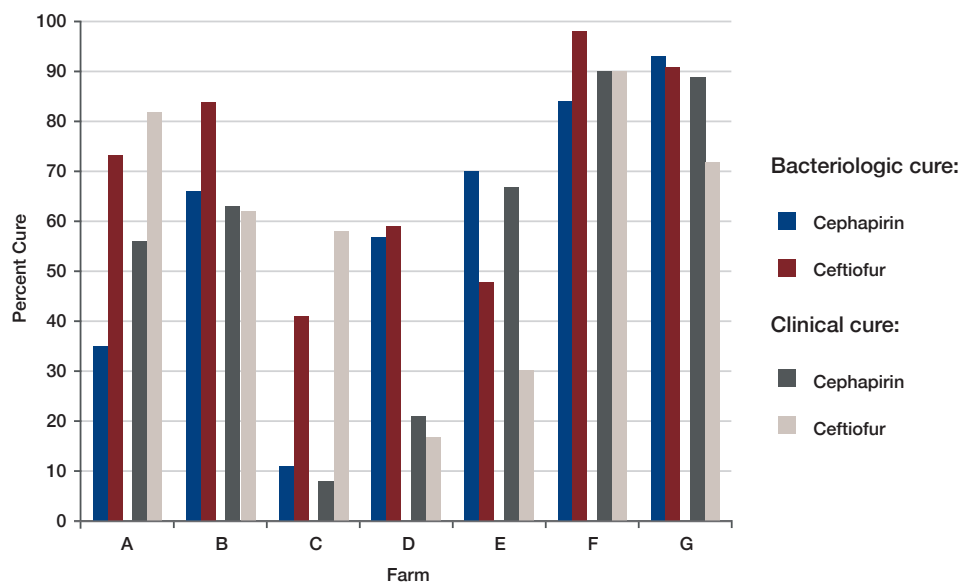
Cases were only eligible for bacteriologic cure if the quarter was culture-positive at study entry; 193 cases (97 in the ToDAY® (cephapirin sodium) group and 96 in the Spectramast® LC (ceftiofur hydrochloride) group). Overall, bacteriologic cure was 67%: 61% for ToDAY and 73% for SPECTRAMAST LC. This difference between treatments was not statistically significant ($p = 0.08$). Results were also analyzed by Gram-positive or Gram-negative status. For Gram-positive cases, there was no difference in bacteriological cure risk between ToDAY® (cephapirin sodium) (68%) and Spectramast® LC (ceftiofur hydrochloride) (67%). A significant difference in bacteriologic cure risk was demonstrated for Gram-negative infections: 79% for SPECTRAMAST LC and 50% for ToDAY.

Clinical cure was observed for 184 out of 296 cases, and there was no difference between treatments. Overall, clinical cure was 62%: Clinical cure for ‘no growth’ samples was 71%, 63% for Gram-positive cases and 49% for Gram-negative cases. When analyzed by treatment, clinical cure for ToDAY for Gram-negative cases was 56%, and for SPECTRAMAST LC, 44%. For Gram-positive cases, 65% of ToDAY cases showed clinical cures, and 62% for cases treated with SPECTRAMAST LC.

Bacteriologic- and clinical-cure comparisons, by farm, are included in Figure 3. Cure risk varied widely among farms, and did not seem to be associated with the predominant pathogen type in the dairy (Gram-positive or Gram-negative).

Time in the study was also evaluated, and was defined as the time between study enrollment and the time that the animal was removed from the study, either because all observations were completed or there was an adverse event or a decision made by the herd manager to remove the cow. Forty-eight cows were removed from the study: 18 for ceftiofur and 30 for cephalosporin; however, this difference was not significant. All were considered bacteriologic and clinical non-cures. One farm (C) removed a greater proportion of animals relative to other herds. Because this was a non-blinded study, herd managers may have been biased against the shorter protocol.

Figure 3. Comparison of Bacteriologic and Clinical Cure by Farm



Discussion

This positive-control, randomized trial evaluated the difference in treatment efficacy between ToDAY® (cephapirin sodium) and Spectramast® LC (ceftiofur hydrochloride) for non-severe clinical mastitis. There was no difference between treatments for bacteriologic cure of all cases, bacteriologic cure of clinical mastitis due to Gram-positive pathogens, and clinical cure.

Although SPECTRAMAST LC showed an advantage in the treatment of non-severe clinical mastitis caused by Gram-negative organisms, the need for antimicrobial treatment of mild and moderate cases of coliform mastitis is debated because of a high level of spontaneous cures associated with these infections.³ No negative-control group was included in this study, in order to determine the spontaneous cure risk for untreated infections.

Similar to other studies, just 25% of clinical cases were caused by Gram-negative organisms, and 28% had culture results of ‘no growth.’ Intramammary antimicrobial therapy does improve cure risk for clinical mastitis caused by Gram-positive organisms over no treatment, and so is economically justified.⁴

First-generation cephalosporins have an excellent Gram-positive spectrum of activity, with limited Gram-negative activity, whereas third-generation cephalosporins have reduced spectrum of activity against Gram-positive organisms, but perform better against Gram-negative organisms.⁵

Pathogen distribution differed among herds in this study: Four herds had predominantly Gram-positive bacteria, and three herds had equal distributions of Gram-positive and Gram-negative results. Similarly to previous studies, differences in intramammary ecosystems exist, and this information should be utilized to determine herd-specific protocols. For herds that do not utilize a culture-based approach for treatment of clinical mastitis, there is economic benefit to choosing a tube with a shorter period of nonsalable milk as the first treatment option.

Using a five-day extended-therapy approach for the treatment of all mastitis cases may not be economically justifiable when cost of the intramammary tubes, labor, total milk discard and time in the hospital pen are considered. A protocol implementing ToDAY would result in a 108-hour milk discard versus a 168-hour milk withhold for a five-day protocol with SPECTRAMAST LC. Nonsalable milk may retain value for dairies that use this milk as calf feed, since it reduces the costs associated with purchased milk replacer. According to label cautions, use of nonsalable milk from SPECTRAMAST LC-treated cows is prohibited for use as calf feed. The recent FDA ruling [21 CFR Part 530] specifically states that there can be no ELDU (deviation from the label) for third-generation cephalosporins.

Conclusions

Milk that has been taken from animals during treatment and for 96 hours after the last treatment must not be used for food. Treated animals must not be slaughtered for food until four days after the last treatment. Administration of more than the prescribed dose may lead to residue of antibiotic in milk longer than 96 hours.

ToDAY RESIDUE WARNING: Results indicate that ToDAY is not inferior to SPECTRAMAST LC with regard to clinical cure of all cases and bacteriologic cure of Gram-positive cases. SPECTRAMAST LC showed a higher bacterial cure of mild and moderate Gram-negative cases. These results can be the basis for developing farm-specific mastitis treatment protocols.

References

- ¹ Apparao MD, Ruegg PL, Lago A, et al. Relationship between in vitro susceptibility test results and treatment outcomes for Gram-positive mastitis pathogens following treatment with cephapirin sodium. *J Dairy Sci* 2009;92(6):2589–2597.
- ² Greko, C. Reflection paper on the use of third and fourth generation cephalosporins in food producing animals in the European Union: Development of resistance and impact on human and animal health. *J Vet Pharmacol Ther* 2009;32(6):515–533.
- ³ Roberson, JR, Warnick LD, Moore G, et al. *J Dairy Sci* 2004;87(3):583–592.
- ⁴ van den Borne *J Dairy Sci* 2010;93:218–233.
- ⁵ Cortinhas, CS, Oliveira L, Hullah CA, et al. Minimum inhibitory concentrations of cephalosporin compounds and their active metabolites for selected mastitis pathogens. *AJVR* 2013;74:683–690.

NADA 097-222, Approved by FDA

ToDAY[®]

(cephapirin sodium)
Intramammary Infusion
For lactating cows only



Description: ToDAY is a cephalosporin which possesses a wide range of antimicrobial activity against Gram-positive and Gram-negative organisms. It is derived biosynthetically from 7-aminocephalosporanic acid.

Each 10 mL disposable syringe contains 200 mg of cephalirin activity in a stable peanut oil gel. This product was manufactured by a non-sterilizing process.

Storage: Store at or below 25°C (77°F). Do not freeze. Avoid excessive heat.

Action: Cephalirin is bactericidal to susceptible organisms; it is known to be highly active against *Streptococcus agalactiae* and *Staphylococcus aureus* including strains resistant to penicillin.

To determine the susceptibility of bacteria to cephalirin in the laboratory, the class disc, Cephalothin Susceptibility Test Discs, 30 mcg, should be used.

Indications: For lactating cows only / For the treatment of bovine mastitis

ToDAY for intramammary infusion should be used at the first signs of inflammation or at the first indication of any alteration in the milk. Treatment is indicated immediately upon determining, by C.M.T. or other tests, that the leukocyte count is elevated, or that a susceptible pathogen has been cultured from the milk.

ToDAY for intramammary infusion has been shown to be efficacious in the treatment of mastitis in lactating cows caused by susceptible strains of *Streptococcus agalactiae* and *Staphylococcus aureus* including strains resistant to penicillin.

Dosage and Directions For Use: Infuse the entire contents of one syringe (10 mL) into each infected quarter immediately after the quarter has been completely milked out. Repeat once only in 12 hours. If definite improvement is not noted within 48 hours after treatment, the causal organism should be further investigated. Consult your veterinarian.

Milk out udder completely. Wash the udder and teats thoroughly with warm water containing a suitable dairy antiseptic and dry, preferably using individual paper towels. Carefully scrub the teat end and orifice with 70% alcohol, using a separate swab for each teat. **Allow to dry.**

ToDAY is packaged with the Opti-Sert[®] protective cap.

For Partial Insertion: Twist off upper portion of the OPTI-SERT protective cap to expose 3–4 mm of the syringe tip.

For Full Insertion: Remove protective cap to expose the full length of the syringe tip.

Insert syringe tip into the teat canal and expel the entire contents of one syringe into each infected quarter. Withdraw the syringe and gently massage the quarter to distribute the suspension into the milk cistern. Do not milk out for 12 hours.

Do not infuse contents of the mastitis syringe into the teat canal if the OPTI-SERT protective cap is broken or damaged.

Reinfection: The use of antibiotics, however effective, for the treatment of mastitis will not significantly reduce the incidence of this disease in the herd unless their use is fortified by good herd management, and sanitary and mechanical safety measures are practiced to prevent reinfection.

Residue Warnings: 1. Milk that has been taken from animals during treatment and for 96 hours after the last treatment must not be used for food. 2. Treated animals must not be slaughtered for food until 4 days after the last treatment. 3. Administration of more than the prescribed dose may lead to residue of antibiotic in milk longer than 96 hours.

Precautions: ToDAY should be administered with caution to subjects which have demonstrated some form of allergy, particularly to penicillin. Such reactions are rare; however, should they occur, consult your veterinarian.

How Supplied: ToDAY for intramammary infusion. Cephalirin sodium equivalent to 200 mg of cephalirin activity per syringe. Each pail contains 144 x 10 mL syringes and 144 convenient single use alcohol pads. NDC 0010-4717-03.

ToDAY is also supplied in cartons containing 12 x 10 mL syringes with 12 convenient single use alcohol pads. NDC 0010-4717-02.

Not for Human Use

Restricted Drug (California) – Use only as directed

Made in Italy

Manufactured for:

Boehringer Ingelheim Vetmedica, Inc.

St. Joseph, MO 64506 U.S.A.

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