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Effect of extended cefquinome treatment on clinical persistence or recurrence of environmental clinical mastitis

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ABSTRACT

The effectiveness of antibiotic treatment of clinical mastitis (CM) is classically evaluated using bacteriological cure, which provides a concise and objective way of assessing efficacy but does not reflect the situation in the field where persistence or recurrence of clinical signs lead to perceived treatment failure. If clinical signs persist or recur, intramammary (IMM) treatment is often extended or supplemented with parenteral therapy in the expectation of a more efficient elimination of clinical signs or a lower probability of recurrence.

The objective of this study was to evaluate the efficacy against clinical persistence or recurrence of three cefquinome treatment regimes, standard 1.5-day intramammary (SIMM), 5-day extended intramammary (EIMM) and combination of EIMM plus 5-day extended parenteral (ECOMBO) treatment. The study was conducted on three dairy farms with a high recurrence rate of environmental mastitis. Efficacy was evaluated using a multi-level model at the quarter and at the cow level, based on the persistence or recurrence of clinical signs at any time during a 105-day period following the end of the initial treatment, independent of pathogen.

The most prevalent pathogens were *E. coli* (16.9%) and *S. uberis* (11.97%). EIMM and ECOMBO significantly decreased the persistence or recurrence of CM by 8% and 6% at the quarter level and by 9% and 8% at the cow level, respectively. ECOMBO may not reduce the persistence or recurrence of CM beyond EIMM. Whilst extended treatment regimens offered an improved outcome in this study, the producer and practitioner need to carefully consider such regimens from the perspective of prudent antibiotic use.

Introduction

Environmental pathogens, particularly *Streptococcus uberis* and *Escherichia coli*, can be a cause of persistent intramammary infection (Van Eenennaam et al., 1995; Döpfer et al., 1999; Bradley and Green, 2001). On some farms, with a low bulk milk somatic cell count (BMSCC) and high incidence of clinical mastitis (CM), a significant proportion of CM may occur in a limited number of animals as a result of a high level of recurrence (Houben et al., 1993; Lam et al., 1996; Zadoks et al., 2001). Recurrent CM cases have been described as being as severe as index cases, with comparable impact on milk yield and probability of death (Bar et al., 2007). Moreover, cows with recurrent CM are at a higher risk for culling (Bar et al., 2008).

Recurrent CM is usually defined by initial disappearance and subsequent re-occurrence of clinical signs after a preset number of days. Using this definition, recurrent CM can be due to a recrudescence of a persistent IMM infection due to failure to cure (Pinzón-Sánchez and Ruegg, 2011), or as a result of re-infection of the quarter after successful cure. However, differentiating between persistence of infection and re-infection is not possible in the field. Generally, in practice, the disappearance of clinical signs is considered as a cure, whereas persistence or recurrence of clinical signs is considered as a treatment failure. This treatment failure is what is evaluated in this study.

One of the consequences of successful elimination of the causative bacteria is a shortened timeframe during which infection can spread to other cows in the herd via the milking machine, the milker or the environment. Potentially, improving bacteriological cure rates decreases the infection pressure on healthy cows and so prevents new CM cases. At the same time bacteriological cure also prevents the recrudescence of persistent infections (Van Eenennaam et al., 1995). These indirect effects of cure may play a role in decreasing the overall incidence of CM.

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A number of approaches to improve CM bacteriological cure have been evaluated, such as extending treatment duration (Sol et al., 2000; Oliver et al., 2004; Milne et al., 2005) and additional parenteral therapy (Shpigel et al., 1997; Erskine et al., 2002; Wenz et al., 2005). However, such studies have not evaluated the long-term outcome of treatment, nor do they necessarily accurately reflect the field situation where CM treatment outcomes are assessed by the elimination of clinical signs, such as abnormal milk, swelling or redness of the udder. In the field, if clinical signs persist or recur, IMM treatment is often extended or reinstated with parenteral treatment in the expectation of a more effective elimination of clinical signs, leading to the use of additional antibiotic on farm. However, there are few reports on the effects of extended treatment, with or without parenteral treatment, on CM persistence or recurrence.

Clinical mastitis can be treated with different types of antibiotics. Cefquinome is a broad-spectrum β-lactam antibiotic for the treatment of CM, via the IMM and parenteral routes and is licensed as a combination therapy for *E. coli* mastitis in the UK. Concurrent use of IMM and parenteral cefquinome in CM has been evaluated (Shpigel et al., 1997; Ehinger et al., 2006). In herds in which environmental mastitis predominates, the aetiology is necessarily diverse thereby demanding a broad-spectrum antibiotic for first treatment of CM in the absence of previous identification of the causative pathogen.

The aim of this study was to evaluate the effect of different cefquinome treatment regimes in a field based context on the likelihood of clinical persistence or recurrence of CM in dairy herds with high recurrence rates of environmental mastitis.

Material and methods

Farms

Three commercial dairy farms in Somerset, UK, were selected on the basis of access to electronic records, a history of a high rate of recurrence of CM and a predominance of environmental mastitis (Table 1). CM cases were sampled from August 2009 until November 2010. Monthly milk production, individual cow somatic cell counts (SCC) and all CM cases had been recorded for at least 12 months prior to the start of the study. Milking protocols were comparable between farms, post milking teat disinfection, pre-dipping or pre-wiping and inspection for CM was practiced on all farms in all cows throughout lactation. Milking procedures and equipment did not change during the study period. All three farms used blanket antibiotic dry cow treatment.

Animals

Lactating Holstein Friesian dairy cows with CM in one or more quarters were enrolled. Animal parity, yield, historic SCC, CM history, treatment history and relevant clinical data were recorded contemporaneously onto data capture forms or retrieved from on-farm software.

Inclusion and exclusion criteria

Cows were eligible for the study if they were in good general health and had four functional quarters free from clinically significant udder, teat and teat orifice lesions. Cows were followed for 105 days after treatment and when cows were dried off or removed from the herd earlier, right censoring was used. Data from animals that were dried off or removed from the herd due to death or culling were analyzed until the day of dry off or removal.

Table 1
The characteristics of the 3 herds involved in the study.

Farm ID	C	H	S
Number of dairy cows	560	239	308
BMSCC (×1000 cells/ml)	248	201	158
ICRM	85	116	76
Predominant housing	Cubicles	Cubicles/pasture	Cubicles
Predominant breed	HF	HF	HF
Approx 305 day yield (L)	9159	9003	11,309
Milking frequency/day	2×	2×	3×

BMSCC, bulk milk somatic cell count, 12 months rolling mean; IRCM, incidence rate of clinical mastitis (number of quarter cases per 100 cows per year); HF, Holstein Fresian.

Treatment allocation

Cows were randomly allocated to a treatment group, by the herdspersons based on line numbers. Line numbers were allocated randomly on farm at the moment animals joined the herd. Cows that developed CM were sampled aseptically before treatment, according to their pre-assigned treatment group. When clinical signs did not resolve ('treatment failure') during the 105 day period after the last treatment of an animal's first enrolled clinical case, or if clinical signs disappeared and recurred at any time point during that period, the cows were treated again with the same treatment regime on all subsequent occasions.

Treatment

All treatments were administered by farm personnel and three different regimes were evaluated: (1) 1.5-day IMM treatment with cefquinome 75 mg (Cobactan LC, MSD Animal Health), twice on the first day, at two consecutive milkings and once, at the morning milking on the following day (SIMM); (2) 5-day IMM treatment with cefquinome 75 mg, six times, twice on the first day, at two consecutive milkings, four times once a day, at the morning milking (EIMM); (3) 5-day combination treatment with cefquinome 75 mg IMM, six times, twice on the first day at two consecutive milkings and once, at the morning milking on the following 4 days, plus cefquinome sulphate suspension (1 mg/kg, Cobactan 2.5%, MSD Animal Health) by intramuscular injection five times at 24-h intervals (ECOMBO).

Post admission withdrawal

Animals were withdrawn post admission due to missing data, injury or disability or abnormalities, or concomitant disease or disease other than CM requiring antibiotic or anti-inflammatory treatment.

Detection of CM, persistence of clinical signs and milk sampling

CM was defined as a quarter with any visible change of milk aspect and was identified by farm personnel, who had been trained and assessed in the detection, classification and sampling of CM. Individual cases were assessed for persistence or recurrence of clinical signs at every milking (twice daily on two units and three times daily on one unit). The severity of CM was classified using a three-grade scale: Grade 1, mild (only clots in the milk); Grade 2, moderate (milk aspect changes in colour and/or consistency and/or presence of clots, heat, pain and/or swelling of the udder); and Grade 3, severe (milk aspect changes in colour and/or consistency and/or presence of clots, fever, depression, anorexia, very swollen udder).

Any concurrent treatments were also recorded. Prior to treatment farm personnel collected milk samples from affected quarters. Milk samples were frozen (−20 °C) and collected for submission to the laboratory on a weekly basis.

Laboratory methods

Microbiological investigation and SCC were carried out using the standard milk sample examination techniques, according to the standard recommended by the International Dairy Federation (Bulletin 132, 1981), International Standard 13366-1:1997 (E) and 13366-2:1997 (G). More specifically, three plates were used and 10 μL of secretion were inoculated onto sheep blood agar and Edward's agar, and 100 μL of secretion were inoculated onto MacConkey agar to enhance the detection of *Enterobacteriaceae* before incubation at 37 °C. All plates were read at 24, 48, and 72 h. Organisms were identified and quantified using standard laboratory techniques (NMC, 1999; Quinn et al., 1994). *E. coli* was identified by colony morphology, oxidase, and indole tests; other *Enterobacteriaceae* were identified using a microtube identification system (RapiD 20 E).

Efficacy of treatment

Treatment was considered effective if clinical signs had resolved after the last treatment and did not recur in the 105 day period after treatment, independent of the bacteria involved. To allow assessment of the potential benefits of systemic treatment on concurrently infected (but not clinically affected) quarters, efficacy was assessed at the quarter and cow level. At the quarter level, lack of efficacy was based on clinical persistence or clinical recurrence of CM in the same quarter. At the cow level, lack of efficacy was based on clinical persistence or clinical recurrence of CM in the same cow, irrespective of the quarter involved.