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Effectiveness of collective treatments in the prevention and treatment of bovine digital dermatitis lesions: A systematic review

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ABSTRACT

The collective treatment (CT) of an affected herd is commonly advised to control bovine digital dermatitis (DD). Several CT are commercialized, frequently without major evidence supporting their effectiveness. The objective of this systematic review was to evaluate the published evidence that supports CT in the treatment and prevention of DD lesions in dairy herds. Across the evidence, the main limitations in the studies design were identified and the possible sources of inconsistency were investigated. An extensive literature search of publications through electronic databases and gray literature was conducted between July 2015 and January 2016. Studies that did not include an untreated or placebo control group were excluded from the review. The literature search and screening process identified 13 publications with 24 treatment trial comparisons and 18 prevention trial comparisons. The published evidence included studies mostly considered to have a low or unclear risk of bias. Descriptive analyses were performed according to the prevention and treatment outcomes, and case and success definitions were identified for each study and summarized in odds ratios (OR). Pairwise meta-analyses were conducted according to the prevention and treatment outcomes, comparing directly the intervention used in each study, and ignoring any other differences in the intervention characteristics. The results of the meta-analyses indicated a low degree of heterogeneity across the evidence for the prevention outcome [I^2 = 0%, 95% CI: 0 to 37.2%, 95% prediction interval (PI): 0.72 to 1.74)] and a moderate degree for the treatment outcome (I^2 = 25.3%, 95% CI: 0 to 63%, 95% PI: 0.39 to 3.73). Similarly, appraisal of the graphical L'Abbé plot suggested a considerable degree of heterogeneity across the evidence for the treatment outcome. For both outcomes, the frequent small sample sizes of the trials indicate imprecision across the included studies. Additionally, for the treatment and prevention outcomes, an asymmetric funnel plot suggested possible publication bias. The overall quality of the evidence, for both outcomes (prevention and treatment), was therefore considered to be low, indicating that the true effect of CT may be substantially different from that estimated across the included studies. Consequently, this review and meta-analysis does not support an association between the CT considered in the review and a beneficial effect in the prevention and treatment of DD lesions. The effectiveness of CT therefore remains uncertain, and the epidemiological circumstances in which it can be useful must be investigated. These findings highlight the importance of developing high quality, controlled trials to evaluate the effectiveness of CT for DD control.
Key words: dairy cow, bovine digital dermatitis, collective treatment, meta-analysis, systematic review

INTRODUCTION

Bovine digital dermatitis (**DD**) is a multifactorial contagious disease, with worldwide distribution, characterized by painful and ulcerative lesions in the foot skin (Laven and Logue, 2006; Gomez et al., 2012). This condition is often associated with animal welfare concerns such as lameness (Bruijnis et al., 2012). Digital dermatitis is also related to economic issues such as reduced milk production, impaired reproductive performance, and increased risk of culling (Bruijnis et al., 2010; Ettema et al., 2010; Relun et al., 2013c). The disease affects 70 to 96% of dairy herds in Western Europe and North America, and the within-herd prevalence ranges from 5 to 30% among lactating cows (Brown et al., 2000; Holzhauer et al., 2006b; Cramer et al., 2008).

Despite more than 40 yr of research, the precise pathogenesis of the disease remains unclear. Nevertheless, the presence of specific *Treponema* species on feet suffering from cutaneous maceration is recognized as a major etiological component involved in the development of the disease (Gomez et al., 2012). Current control strategies aim to control the main risk factors of

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DD, such as moist and unhygienic conditions, to limit the spread of the infection. (Palmer et al., 2013; Relun et al., 2013c). These strategies rely particularly on the complementary use of individual medical topical treatment of active lesions and metaphylactic collective treatments (**CT**) of the entire affected herd. However, both approaches are time-consuming practices, presenting economic and environmental challenges for farmers and the veterinary industry (Relun et al., 2013b). Although antibiotics such as oxytetracycline and lincomycin are mainly used as individual treatments and their topical administration is considered effective (Apley, 2015), high rates of lesions recurrence (50%) are reported for some of these products (Berry et al., 2012). The use of antibiotics furthermore should be limited in order to decrease antimicrobial resistance and withdrawal periods for milk. Moreover, the collective administration of antibiotics is no longer advised and such practices are already banned by European Union policies.

Disinfectants such as formaldehyde and copper sulfate ($CuSO_4$) have been used in footbaths as the standard CT in the control of DD. However, formaldehyde is carcinogenic and $CuSO_4$ is toxic for the environment via accumulation in the soil (Ippolito et al., 2010). Moreover, a recent systematic review revealed that the effectiveness of $CuSO_4$ footbaths against DD is not adequately supported by the evidence (Thomsen, 2015). In addition, new evidence suggests possible genetic resistance to copper and zinc in microbiomes associated with DD lesions (Zinicola et al., 2015). Currently, several CT for DD are commercially available, most of which are supported by anecdotal evidence and a few by clinical trials (Laven and Logue, 2006). However, high variability in the efficacy of some of the products evaluated by scientific studies is perceived in practice (Relun et al., 2013b). Last, for most CT, their bactericidal efficacy against DD *Treponema* groups remains uncertain (Hartshorn et al., 2013).

In evidence-based veterinary medicine, randomized controlled trials (**RCT**) are considered the gold standard to guide treatment and prevention decisions. However, under certain circumstances, such as on commercial dairy farms, it can be difficult to conduct RCT for practical reasons. Consequently, part of the existing evidence about CT is based on non-randomized studies (Sargeant et al., 2014). The results of scientific studies on DD are furthermore often difficult to extrapolate to real conditions; this is most likely due to a lack of guidelines for CT use under diverse conditions (Relun et al., 2013b).

An assessment summarizing the scientific evidence concerning existing CT based on an objective procedure is therefore required to assist veterinarians and farmers in their DD control decisions. The main objective of the present systematic review was to evaluate the evidence supporting the use of CT in the treatment and prevention of DD to provide new insights into the design of high-quality DD control effectiveness trials. Data from multiple studies were combined through a meta-analysis to investigate the main sources of heterogeneity between studies and to calculate a summary effect estimate of the effectiveness of CT in the treatment and prevention of DD.

MATERIALS AND METHODS

The review was conducted following the guidelines proposed by Sargeant and O'Connor (2014) for systematic reviews in animal agriculture and veterinary medicine. A protocol was developed a priori that included a detailed description of the review process (Supplemental Data File S1; https://doi.org/10.3168/jds.2016-11875).

Search Strategy

The review questions were designed based on the evidence-based veterinary medicine concept of PICO terms: population (P), intervention (I), comparator (C), and outcomes (O) (Richardson et al., 1995). The study population of interest consisted of dairy cows, including heifers and lactating and dry cows. The intervention was CT, defined as the topical administration on feet of the same treatment (dose and frequencies) at a given time to 2 or more animals without restraining them individually. The comparators were parallel control groups of untreated animals (absence of CT) or groups treated with a water placebo. Two outcomes of interest were defined. The first involved prevention, where the outcome was the incidence, defined as the occurrence of new clinical DD lesions within the follow-up period. The second involved treatment, where the outcome was the healing of DD lesions, defined as the reduction of existent clinical DD lesions within the follow-up period. For both outcomes, the diagnosis and evolution of clinical lesions must be assessed by direct visual diagnosis and measured by an objective methodology (lesion score system). Two clinical questions were therefore defined as follows: "In dairy cows, are collective treatments more effective at preventing the occurrence of clinical lesions of bovine digital dermatitis compared to a placebo or the absence of any collective treatment?" and, "In dairy cows, are collective treatments more effective for the treatment of clinical lesions of bovine digital dermatitis compared to a placebo or the absence of any collective treatment?"