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## **Invited review: A systematic review and qualitative analysis of treatments other than conventional antimicrobials for clinical mastitis in dairy cows**

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### **ABSTRACT**

Clinical mastitis is an important disease in dairies. Its treatment is mainly based on the use of antimicrobial drugs. Numerous non-antimicrobial drugs and treatment strategies have already been reported for clinical mastitis treatment, but data on their efficacy have never been collated in a systematic way. The objective of this systematic review was to identify treatments other than conventional antimicrobials for the treatment of clinical mastitis in lactating dairy cows. A systematic review was performed with studies written in English or French selected from CAB Abstracts, PubMed, and Web of Science from January 1970 to June 2014. Controlled clinical trials, observational studies, and experimental challenges were retained. Lactating dairy cows with clinical mastitis were the participant of interest. All treatments other than conventional antimicrobials for clinical mastitis during lactation were retained. Only studies comparing the treatment under investigation to a negative or positive control, or both, were included. Outcomes evaluated were clinical and bacteriological cure rates and milk production. Selection of the study, data extraction, and assessment of risk of bias was performed by 3 reviewers. Assessment of risk of bias was evaluated using the Cochrane Collaboration tool for systematic review of interventions. A total of 2,451 manuscripts were first identified and 39 manuscripts corresponding to 41 studies were included. Among these, 22 were clinical trials, 18 were experimental studies, and 1 was an observational study. The treatments evaluated were conventional anti-inflammatory drugs (n = 14), oxytocin with or without frequent milk out

(n = 5), biologics (n = 9), homeopathy (n = 5), botanicals (n = 4), probiotics (n = 2), and other alternative products (n = 2). All trials had at least one unclear or high risk of bias. Most trials (n = 13) did not observe significant differences in clinical or bacteriological cure rates in comparison with negative or positive controls. Few studies evaluated the effect of treatment on milk yield. In general, the power of the different studies was very low, thus precluding conclusions on noninferiority or nonsuperiority of the treatments investigated. No evidence-based recommendations could be given for the use of an alternative or non-antimicrobial conventional treatment for clinical mastitis. However, probiotics and oxytocin with or without frequent milk out should not be recommended. We concluded that homeopathic treatments are not efficient for management of clinical mastitis.

**Key words:** systematic review, lactating dairy cow, clinical mastitis, non-antimicrobial therapy

### **INTRODUCTION**

Clinical mastitis (CM) has important deleterious effects on dairy herd productivity, longevity, and profitability because of decreased milk production, decreased reproductive performance, costs associated with treatments, and the increased risk of culling and death of affected animals (Halasa et al., 2007). In 2 recent studies conducted on Canadian dairies, most the participants (71 and 54%) stated that they were worried by the cost of mastitis on their farm (Dufour et al., 2010; Francoz et al., 2011). Mastitis was reported to be the most important cause of antimicrobial drug use in dairy herds with close to half of the antimicrobials used on dairies being used for mastitis control, mainly for treatment of CM cases (Saini et al., 2012).

For certification, organic dairies have to meet specific requirements and the use of conventional treatments

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(i.e., antimicrobials) is limited. In cases of clinical diseases, alternative treatments must be instituted first and conventional treatments must only be used when alternative treatments are not successful (Agriculture and Agri-Food Canada, 2012). Moreover, the use of antimicrobials are also scrutinized in conventional dairies and even restricted in some European countries (Santman-Berends et al., 2016). Consequently, conventional dairy producers also have a growing interest in non-antimicrobial therapies.

The use of numerous non-antimicrobials CM treatments has been reported in organic and in conventional dairies. For simplicity, in the remainder of the manuscript non-antimicrobial treatments will be divided in 2 categories: (1) alternative treatments (i.e., alternative to the mainstream allopathic medicine); and (2) non-antimicrobial conventional treatments (i.e., mainstream allopathic treatments that do not directly affect microorganisms). Alternative treatments mainly include homeopathy, biologics (products derived from live organisms that can be used to treat or prevent a disease), botanicals (i.e., aromatherapy, phytotherapy), probiotics, and acupuncture (Karreman, 2009; Ruegg, 2009; Ameloot, 2010).

Evaluation of CM treatment efficacy is a difficult task. First, efficacy can be evaluated based on clinical or bacteriological cures, or both. Furthermore, the effect on milk production is important for determining marketability of a treatment. Second, following initial in vitro and in vivo experimental studies, treatment efficacy should ultimately be evaluated in a randomized controlled trial (RCT; i.e., the gold-standard for evaluating the effect of medical treatments). For CM treatment, because a relatively high rate of spontaneous resolution is expected (>30%; (Hektoen et al., 2004)), the treatment under investigation must be compared with one or many control groups. Optimally, at least 3 different treatment groups would be included in a RCT: a negative control group (no treatment; when justifiable, for instance for less severe cases), a positive control group receiving currently recommended treatment (an antimicrobial, for instance), and the tested treatment group (the non-antimicrobial treatment in this case). Moreover, persons responsible for treatment administration and for evaluation of health outcomes, caregivers, and analysts should be blinded to group allocation. To date, very few alternative treatments have been formally evaluated in RCT. Consequently, recommendations frequently conveyed in the dairy organic sector on use of some alternative treatments are not based on data of efficacy and are often questionable. Additionally, results on the efficacy of these approaches for CM treatment have never been collated in a coherent whole and compared. To our knowledge, only 2

narrative literature reviews have been published on CM alternative treatment (Ruegg, 2009; Ameloot, 2010). These reviews were not systematic reviews (SR) or meta-analyses (Sargeant et al., 2006), and all the different alternative products were not reviewed. Thus, the efficacy of the non-antimicrobial CM treatments available have never been evaluated in a systematic manner. Providing evidence-based advice on non-antimicrobial treatments of CM is, therefore, a difficult task for dairy practitioners and extension agents. A rigorous and exhaustive evaluation of these treatments would help inform the development of standard operating procedures for the treatment of CM in organic dairy. Furthermore, alternative treatments showing unequivocal efficacy could also be used in conventional dairies and would potentially help decrease use of antimicrobials.

Therefore, the objectives of the current study were to identify and report efficacy results of alternative and non-antimicrobial conventional therapies for treatment of CM in dairy cows that have already been studied in RCT, non-RCT, observational studies, or experimental studies using mastitis models. The aim of the study was to determine the therapies that have demonstrated efficacy in scientifically sound research protocols or that have shown consistent results across the available literature, or both.

## MATERIALS AND METHODS

The chosen study design was a SR of the literature. Systematic reviews aim at collecting, analyzing, and synthesizing multiple research studies. This methodology can provide an exhaustive summary of the current literature on a given topic using a detailed and reproducible methodology.

### *Criteria for Considering Studies for the Review*

**Types of Studies.** Study designs such as RCT, non-RCT, observational studies (cohort, cross-sectional, and case-control designs), and experimental challenges using naturally acquired CM or bacterial- or endotoxin-induced CM models were retained. For studies using bacterial- or endotoxin-induced CM models (i.e., experimental challenge), to be included in the review the treatment had to be instituted after onset of clinical signs (vs. the treatment being administered at the time of the challenge or shortly after). Study designs such as case-series, case-report, or expert opinion were not retained. Only studies evaluating the efficacy of a treatment other than conventional antimicrobials for treatment of CM (grade 1 to 3) during the lactating period were included. All studies on the treatment of subclinical mastitis or on dry cow therapy were excluded.

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