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Antibiotic treatment of metritis in dairy cows—A meta-analysis

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ABSTRACT

The objective of this meta-analysis was to assess the efficacy of the treatment of bovine metritis with common antibiotic and nonantibiotic treatment options. Acute puerperal metritis, a systemic and potentially painful illness with rectal temperature >39.5°C and signs of toxemia due to an infection of the uterus, occurs within 21 d after parturition. Because of the infectious nature, antibiotics are considered beneficial for the treatment of acute puerperal metritis. Each use of an antimicrobial drug, however, is associated with selective pressure for eventual emergence of resistant bacteria. The 23 trials evaluated in the course of a previously conducted systematic review were the basis for meta-analytic investigations. Selected trials were screened regarding their eligibility for the following investigations: (1) comparison of different antibiotic treatments with respect to metritis prevalence at time of re-examination, (2) efficacy of ceftiofur treatment with respect to metritis prevalence at time of re-examination, (3) comparison of efficacy of antibiotic versus nonantibiotic drugs with respect to metritis prevalence at time of re-examination, and (4) equivalence assessment of treatment effects on reproductive performance measures. Where at least 3 trials had investigated the same outcome variable and met the inclusion criteria (inclusion of a control or reference group diagnosed with metritis; reporting means and standard deviation in case of continuous data), meta-analytic investigations were carried out. Due to a shortage of comparable studies, we could not conduct investigations (1) and (3). Ceftiofur treatment of 828 metritic cows was associated with a decrease in the prevalence of metritis following treatment in comparison to 804 untreated cows. In conclusion, meta-analytic investigations uncovered a need for more high-quality studies. Furthermore, a positive effect of the most commonly used antibiotic drug, ceftiofur, for the treatment of bovine metritis could be shown. A comparison with other antibiotic or nonantibiotic treatment options could not be made.
Key words: meta-analysis, acute metritis, antibiotic treatment, dairy cow

INTRODUCTION

Acute puerperal metritis (**APM**), an systemic illness with fever (rectal temperature >39.5°C) and signs of toxemia, occurs within 21 d after parturition and is characterized by an enlarged uterus and by an often fetid watery red-brown fluid to viscous off-white purulent uterine discharge (Sheldon et al., 2006). Depending on the definition for metritis, incidence risks range from 20 to 40% (Haimerl and Heuwieser, 2014). Due to severe detrimental effects on reproductive performance and economics, APM is one of the most important postpartum diseases in dairy cows (Azawi, 2008; Overton and Fetrow, 2008; McLaughlin et al., 2013). A negative effect of APM on reproductive performance has been shown, especially in cases where APM results in endometritis. Increased time to pregnancy and higher culling rates were reported by LeBlanc et al. (2002), and a meta-analysis by Fourichon et al. (2000) found a decreased relative risk of pregnancy by 150 DIM and reduced pregnancy rates. Moreover, resulting reproductive inefficiency, culling, treatment, milk discard, labor, and increased risk of residues in food products cause substantial costs (LeBlanc, 2008).

A colonization of bacteria, such as *Escherichia coli* or *Trueperella pyogenes*, in the postpartum uterus is common (Földi et al., 2006; Miller et al., 2007; Bicalho et al., 2010; Santos et al., 2011). Depending on various factors such as bacterial pathogenicity and the cow's immune status, such colonization might result in an infection (Machado et al., 2014). Due to the mostly bacterial etiology, antibiotics are commonly considered beneficial for the treatment of APM (Beagley et al., 2010; Machado et al., 2012).

Antibiotics commonly used for the treatment of puerperal metritis include penicillin, third-generation cephalosporins, or a combination of ampicillin with oxytetracycline or cloxacillin (Nak et al., 2011). An-

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tibiotic resistance, however, has been recognized as a challenge for public health (Machado et al., 2014). Consequently, and because each application of an antimicrobial drug implies a risk of contributing to the emergence of resistant bacteria (Fishman, 2006; Ozawa et al., 2012), concern is growing regarding the potential effect of extensive antibiotic use in food-producing animals (Machado et al., 2014). Prudent drug use is of tremendous importance, especially concerning antibiotic agents valued for treating serious or life-threatening infections in human medicine.

Ideally, every decision made by a practitioner should be based on the latest and soundest scientific findings available (Glasziou et al., 1998; Arlt, 2016). The amount of available literature, however, is huge, mostly unstructured, and hardly manageable (Buchanan and Wooldridge, 2011). Moreover, usually several treatment options exist for one disorder (Caldwell et al., 2005); hence, information on the comparative effectiveness of treatment alternatives is needed (Pechlivanoglou et al., 2015). To provide such scientific results with the greatest possible reliability, the results of randomized, controlled trials (**RCT**) or meta-analyses of RCT are necessary (Arlt and Heuwieser, 2005).

Meta-analyses are systematic summaries and statistical analyses of a large collection of results from individual studies (Glass, 1976). As pointed out by Askie and Offringa (2015), one of the main reasons for undertaking systematic reviews and meta-analyses is to minimize bias by collating all available evidence on a particular topic. By synthesizing information from the greatest possible number of trials, and hence increasing the amount of available data (and thus statistical power), meta-analyses reduce the effect of randomness.

In a previously published paper on antibiotic treatment of metritis in dairy cows (Haimerl and Heuwieser, 2014) 23 trials were analyzed by means of a systematic review. Overall, the quality of the investigated studies was good, as indicated by a predominantly high evidence level (i.e., 83% were randomized controlled studies). However, the conducted review also revealed suboptimal consideration of critical issues, such as prudent antibiotic drug use, self-cure rates, and bacterial resistance.

Within the 23 trials, 10 different antibiotic agents were applied, with ceftiofur being the most frequent (n = 17). Although efficacy of the antibiotics applied was specified in almost every study (22/23), outcome parameters differed considerably (i.e., 12 and 6 studies assessed the effect on clinical and reproductive parameters, respectively). Even though 7 studies observed clinical improvement, none found improved reproductive performance after an application of ceftiofur in metritic cows compared with the reference group.

Therefore, the overall objective of our study was the meta-analytic investigation of the efficacy of common treatment options. Specifically we set out (1) to compare the effect of various antibiotic treatments on metritis prevalence at time of re-examination after treatment, (2) to investigate the effect of ceftiofur treatment on metritis prevalence at time of re-examination compared with an untreated control, (3) to compare the efficacy of antibiotic with nonantibiotic drugs regarding metritis prevalence at re-examination after treatment, and (4) to compare reproductive performance measures between treated and nontreated cows. As a working hypothesis, we presumed that only a limited number of studies would be comparable concerning study design and measured outcome variables and hence eligible for meta-analytic investigations. Furthermore, we hypothesized a good success rate for treatment with ceftiofur regarding clinical cure and reproductive performance. We did not expect a significant advantage of ceftiofur treatment over other common antibiotic and nonantibiotic treatment options.

MATERIALS AND METHODS

Literature Search

Relevant steps and results of literature retrieval are illustrated in Figure 1. For a previously published review (Haimerl and Heuwieser, 2014), a comprehensive and systematic literature search was conducted on May 23, 2014, utilizing the databases PubMed (http://www.pubmed.gov) and CAB Abstracts (http://ovidsp.tx.ovid.com/) to identify literature focusing on the antibiotic therapy of puerperal metritis in the cow. The subject heading "bovine metritis AND antibiotics" was used to find all trials on this topic written in the English or German language. To assure timeliness of the subsequent meta-analytic investigation, we conducted another literature search on December 6, 2015, utilizing the same databases, search terms, and search operators as in the previous trial.

Inclusion and Exclusion Criteria

As reported previously (Haimerl and Heuwieser, 2014), specific exclusion criteria were defined to exclude articles that did not describe clinical trials (e.g., descriptive or in vitro studies). Also, conference proceedings and review articles were excluded. Furthermore, articles not meeting the inclusion criteria,