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Invited review: Antibiotic treatment of metritis in dairy cows: A systematic approach

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Abstract

Acute puerperal metritis (APM) is an acute systemic illness with fever ≥39.5°C and signs of toxemia due to an infection of the uterus occurring within 21 d after parturition. Because of the infectious nature of APM, antibiotics are considered beneficial for its treatment. Each use of an antimicrobial drug, however, is associated with selective pressure for the emergence of resistant bacteria. Hence, there is a significant need to encourage prudent use of antibiotics and alternative therapies to antibiotics. Therefore, the objective of this study was to systematically review the current literature on treatment of APM. A comprehensive and systematic literature search was conducted utilizing the PubMed and CAB Abstracts databases to identify literature focusing on the antibiotic therapy of puerperal metritis in the cow. After application of specific exclusion criteria, 21 publications comprising 23 trials remained for final evaluation. Data extraction revealed that the majority of the studies (n = 19) were attributable to the highest evidence level. Of 21 studies controlled, 11 had an untreated group and 3 a positive control group. The majority of the studies (n = 17) applied ceftiofur for the treatment of APM. Concerning the efficacy of ceftiofur, 7 studies observed clinical improvement, whereas none found improved reproductive performance. Fewer than half of the studies (n = 10) performed a bacteriological examination and only 4 implemented an antibiotic susceptibility test. Also, 3 studies (13.0%) described a self-cure rate per se. Little attention was given to the issue of bacterial resistance (n = 3), the need for reducing the application of antibiotics (n = 2), or guidelines for prudent use of antibiotics (n = 1). Our findings demonstrate that implementation of bacteriological examinations, sensitivity testing, and determination of minimum inhibitory concentrations, as well as reporting and discussion of critical issues (e.g., self-cure rates, resistance, prudent drug use), were suboptimal. On the other hand, the quality of studies on the treatment of APM was good, as indicated by evidence level 1. Nevertheless, more high-quality research considering self-cure rates is necessary to address critical issues related to APM and crucial to the dairy industry, such as resistance, prudent use of antibiotics, animal welfare, and cost-benefit ratios.

Key words: acute metritis, antibiotic treatment, systematic review, dairy cow

INTRODUCTION

Definition and Diagnostic Challenges of Acute Puerperal Metritis

Acute puerperal metritis (**APM**) is an acute systemic illness with fever ≥39.5°C and signs of toxemia due to an infection of the uterus, occurring within 21 d after parturition and characterized by an enlarged uterus and a watery red-brown fluid to viscous off-white purulent uterine discharge, which often has a fetid odor (Sheldon et al., 2006, 2009). This definition is well accepted and has been used widely in recent research trials (Dubuc et al., 2011; McLaughlin et al., 2013; Sannmann et al., 2013b). Signs of systemic illness include decreased milk yield, dullness or other signs of toxemia, decreased DMI, elevated heart rate, and dehydration (Sheldon et al., 2008). When applying this definition, the reported incidence rate of APM reaches 20% (Sannmann et al., 2012), but incidence rates up to 40% were reported in older studies (Markusfeld, 1987). Due to its 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).

In both research and practice, the most utilized diagnostic criteria to detect a case of APM are an elevated rectal temperature (≥39.5°C) and fetid, watery, red vaginal discharge (**VD**). A more recent systematic review regarding diagnostic methods for APM demonstrated that these 2 criteria were described in 39 (fever) and 21 (fetid VD) of 48 peer-reviewed research papers, respectively, addressing APM (Sannmann et al., 2012). Therefore, this definition has to be considered the best

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available reference standard. We have emphasized, however, that this definition is empirically based and requires refinement (Burfeind et al., 2014a) as there is no gold standard available (Sheldon et al., 2006). Although evidence exists that VD and body temperature are related (Palenik et al., 2009; Burfeind et al., 2014b) and might therefore be useful to differentiate metritic from healthy cows, both criteria are also imperfect and could introduce bias. Several factors that affect body temperature in dairy cows have been described (Burfeind et al., 2010) and we have proposed increasing the fever threshold to 40.0°C for heat-stressed cows (Burfeind et al., 2012). The sensorial assessment of odor of VD is subjective and error prone (Sannmann et al., 2013a).

The role and potential diagnostic use of acute phase proteins such as haptoglobin (**Hp**), serum amyloid A, and lipopolysaccharide have been comprehensively reviewed (Ceciliani et al., 2012). The most intensively researched acute phase protein in relation to uterine health in dairy cattle is Hp. Although an early study could not find an elevation of plasma Hp concentrations in metritic cows, except for the 3 most severely affected (Hirvonen et al., 1999), an elevated serum Hp concentration (1.06 to 1.90 g/L) has been shown to indicate an acute infectious process in dairy cows (Drillich et al., 2007; Huzzey et al., 2009). This was also supported by Sheldon et al. (2001), who found that acute phase protein concentrations were increased by bacterial contamination.

Reported sensitivities for the detection of metritis (50 to 79%) and specificities (54 to 87%), however, were only moderate (Huzzey et al., 2009; Dubuc et al., 2010; Burfeind et al., 2014b). Furthermore, Smith et al. (1998b) showed a steadily declining Hp concentration during a 5-d antibiotic treatment period. Test characteristic of elevated Hp concentrations might be confounded by the fact that Hp concentration can increase in the first week after calving due to calving-related tissue damage or fatty liver syndrome (Humblet et al., 2006; Silvestre et al., 2011). Therefore, Hp as an indicator of infection should be used with caution in the days following parturition (Humblet et al., 2006).

Considerable self-cure rates (i.e., 15.6 to 55.0%) of cows diagnosed with APM using this definition have been reported (McLaughlin et al., 2012; Sannmann et al., 2013b). It is unclear whether low specificities of the diagnostic methods used to screen cows for APM with a consequently high prevalence of type I errors (i.e., high false-positive rate) might contribute to this self-cure rate.

After calving, the lumen of the uterus is usually contaminated by bacteria (Földi et al., 2006). Specific bacteria identified in the uterus of dairy cattle with APM include *Escherichia coli*, *Trueperella pyogenes*, *Fusobacterium necrophorum*, *Prevotella* spp., and *Bacteroides* spp. (Miller et al., 2007; Bicalho et al., 2010; Santos et al., 2011). According to Noakes et al. (1991), *Fusobacterium nucleatum* and *Proteus mirabilis* are also frequently observed in puerperal uteri. Furthermore, nonbacteriological agents such as bovine herpesvirus 4 can cause endometrial tissue damage (Sheldon et al., 2009). Because of the infectious nature, implications for animal well-being, and a potentially life-threatening course, antibiotics are considered beneficial for the treatment of APM (Beagley et al., 2010; Machado et al., 2012).

Antibiotic Treatment and Resistance

For the treatment of metritis, antibiotics are given by the intrauterine route, systemically, or both (Malinowski et al., 2011). Antibiotics such as penicillin, third-generation cephalosporins, and ampicillin have been systemically administered for the treatment of cows with APM. Furthermore, dairy cows with APM have been treated with systemic penicillin or ampicillin administrations in conjunction with intrauterine instillations of oxytetracycline or ampicillin and cloxacillin (Nak et al., 2011). As shown about 3 decades ago for oxytetracycline and chloramphenicol, no significant differences were observed concerning the distribution of the drug between various tissues or between healthy and infected postpartum cows (Bretzlaff et al., 1983, 1988). The efficacy of these antibiotic drugs, however, is impossible to evaluate conclusively from the literature as different routes, doses, and products were applied and different examinations were performed on farms by farm or study personnel or veterinarians. It is well known that not all infections are eliminated following antibacterial treatment (Malinowski et al., 2011), and definitions of self-cure and cure rates differ widely (Drillich et al., 2001; Galvão et al., 2009).

Each use of an antimicrobial drug is inherently associated with selective pressure for the emergence of resistant bacteria, which stresses the importance of their prudent use (Fishman, 2006; Ozawa et al., 2012). Recently, several publications have demonstrated emerging antimicrobial resistance of zoonotic organisms in food animals worldwide and expressed a potential threat to public health (Tragesser et al., 2006; CVMP, 2009; Mann et al., 2011; Ozawa et al., 2012). It is obvious that increasing antibiotic resistance is associated with decreasing clinical efficacy and could exacerbate animal welfare and economic consequences. It is noteworthy that the antibiotic sensitivity of bacteria from uterine discharges has not been frequently tested (Malinowski et al., 2011). Hence, there is a significant need