

RISKS, REALITIES AND RESPONSIBILITIES ASSOCIATED WITH MASTITIS TREATMENTS

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Introduction

Mastitis remains the most common disease of dairy cows and treatment or prevention of this disease is the most common reason that antibiotics are administered to cows (Pol and Ruegg, 2007, Saini et al., 2012). Mastitis is detected by inflammation that is caused by infection by microorganisms and occurs in both clinical and subclinical forms. Milk obtained from quarters of cows with subclinical mastitis looks normal (even when millions of somatic cells are present) but the milk contains an excessive number of somatic cells, (with or without the detectable presence of pathogenic organisms) (Dohoo and Leslie, 1991). Unless the herd prevalence of subclinical mastitis is high, subclinical infections are usually managed by antimicrobial treatments administered at the end of the lactating period. Inflammation that results in visible abnormalities of milk or the gland is defined as clinical mastitis. Most symptoms of clinical mastitis are quite mild and cannot be detected unless foremilk is observed, thus the perceived incidence of clinical mastitis on individual dairy farms is dependent on the intensity of detection. In a study that enrolled almost 800 cases of clinical mastitis occurring on 50 Wisconsin dairy farms, 50% of clinical cases presented with only abnormal milk, 35% of cases had abnormal milk accompanied by swelling of the affected quarter and only 15% of clinical cases presented with systemic symptoms (Oliveira et al. 2013). In most countries, milk from cows affected with clinical mastitis cannot be sold for human consumption and most farmers administer antimicrobials to affected cows. The use of antimicrobials to treat food animals is under increased scrutiny by consumers, governmental officials and regulatory agencies and must be well justified. The purpose of this paper is to review the risks, realities and responsibilities associated with treatment of clinical mastitis.

Realities of Mastitis Treatments on Modern Dairy Farms

Widespread adoption of the 5-point plan (Neave et al., 1969) has been demonstrated to successfully control contagious mastitis pathogens. As a result, in many developed dairy farm regions, the prevalence of mastitis caused by *Staphylococcus aureus* is minimal and *Streptococcus agalactiae* is virtually eradicated (Table 1; Makovec and Ruegg, 2003; Pitkala et al, 2004). As contagious pathogens have been controlled and herds have adopted intensive management practices, clinical mastitis is caused by an increasingly diverse group of opportunistic pathogens (Table 1). Knowledge of these changes in etiology is important because the pathogenesis, virulence and prognosis of clinical mastitis are influenced by important characteristics that vary among pathogens. Depending on specific virulence factors, organisms infect different locations within the mammary gland, have differing abilities to cause systemic symptoms, vary in the expected duration of subclinical phases of infection and differ in the expected rate of spontaneous bacteriological cure. For example, expectations for spontaneous bacteriological cure of subclinical and clinical mastitis caused by *Staph aureus* are essentially zero (Oliver et al., 2004) while the expectation for spontaneous cure of *E coli* is quite high (Suojala, 2010) and therapeutic cure rates for several

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pathogens (yeasts, pseudomonas, mycoplasma, prototheca etc.) are essentially zero, regardless of treatment.

Table 1. Results of selected studies that describe the distribution of bacteria recovered from milk of cows with clinical mastitis in modern dairy herds located in developed countries (Table adapted from Ruegg et al., 2014).

Country	Herds	Milk Samples ^a	S. aureus	Other staph	Strep agalactiae	Other strep	Coliform	Other	No Growth
Holland (de Haas, 2002)	274	2,737	18%	6%	0%	25%	28%	NR ^b	22%
UK (Bradley, 2007)	90	480	3%	13%	0%	25%	21%	11%	27%
New Zealand (McDougal I, 2007)	28	1,332	19%	7%	0%	45%	NR	4%	27%
Canada (Olde Riekerink, 2007)	106	2,850	11%	6%	0%	16%	15%	5%	47%
USA (Oliveira, 2013)	50	741	3%	7%	0%	11%	36%	16%	27%

^aResults characterized as contaminated and mixed infections were excluded; ^bNR indicates that the study did not report that outcome

More than 80% of cases of clinical mastitis present solely with local symptoms (Oliveira et al., 2013, Oliveira and Ruegg, 2014) and in the U.S. (Richert et al., 2013) (and a number of other countries), very few cases are examined or treated by veterinarians. In many regions, intramammary (IMM) antimicrobial therapy is the usual treatment for mild and moderate cases of bovine mastitis and most cases are treated by farm personnel without determination of etiology (Hoe and Ruegg, 2006; Oliviera and Ruegg., 2014). In spite of considerable changes in the etiology of mastitis, there has been limited innovation in development of mastitis therapies and there is relatively little variation in the types of treatments that are administered. While different countries have various combinations and routes of allowable drugs, most products are β -lactams.

In many countries, almost all approved IMM antimicrobials have label indications primarily for treatment of Streptococci and Staphylococci. In the U.S., there are no approved IMM products for treatment of cases caused by *Klebsiella* spp. nor for many other pathogens that account for most cases of clinical mastitis. In the U.S., 88% of cases of clinical mastitis occurring in 51 larger WI dairy herds received 1st (16%) or 3rd (72%) generation cephalosporin (Oliveira and Ruegg, 2014). About, 35% of these treatments were given to cases which were culture negative at the time of detection and a further 17% were administered to cases for which there are no approved effective antimicrobials. The probability of cure is highly influenced by the characteristics of the pathogen.

In the United States, only two antimicrobial classes are represented among commercially available IMM products that are approved by the U.S. Food and Drug Administration (FDA). Those classes include 6 or 7 commercially available IMM products that contain β -lactams (amoxicillin, ceftiofur, cephapirin, cloxicillin, hetacillin, and penicillin) and 1 product that contains a lincosamide (pirlimycin). While several products have been withdrawn from the U.S. market, no new antimicrobials have been approved for mastitis therapy since 2006.

In the U.S., there are no antimicrobials that are labeled for systemic treatment of mastitis, however extra label usage of some compounds is allowed under veterinary supervision. Of 589 cows treated for mastitis on 51 Wisconsin dairy farms in 2012, 66% received solely IMM therapy, 1% received solely systemic therapy, 16% received IMM and systemic therapy, 14% received secondary treatments via either IMM or systemic routes and 18% received supportive therapy (Oliveira and Ruegg, 2014). The majority of systemic treatments were for cases of severe mastitis and most of the antimicrobials used would not be expected to reach therapeutic concentrations in mammary gland tissue. As most treatments are administered simply based on observation of inflammation without determination of etiology, many treatments are difficult to justify both medically and to consumers. Of 585 cases that had a microbiological diagnosis, the most common treatment was use of IMM ceftiofur for treatment of microbiologically negative cases (23% of all treatments) (Oliveira and Ruegg, 2014). Based on the etiologies, case severity and available treatments, only about 35% of the antimicrobial usage can be justified based on the availability of scientific data that demonstrates a benefit of using an IMM antimicrobial (Table 2).

Table 2. Distribution of etiologies, availability of data that demonstrates benefit of use of IMM antimicrobials and proposed antimicrobial treatments for 690 cases of clinical mastitis occurring on 51 Wisconsin dairy herds.

Etiology of Case	Severity of Case	Cases (n)	(%)	Data demonstrating benefit of IMM antimicrobials	Proposed antimicrobial Treatment
<i>E coli</i>	Severe	76	11%	No	Systemic
<i>E coli</i>	Mild & mod.	114	17%	No	None ^a
<i>Klebsiella sp</i>	All	36	5%	No	IMM (mild/mod) & systemic (severe)
<i>Enterobacter sp</i>	All	19	3%	No	None (mild/mod) or systemic (severe)
<i>Strep spp.</i>	All	91	13%	Yes	Extended duration IMM
<i>Enterococci spp</i>	Mild & mod.	15	2%	No	unknown
CNS	Mild & mod.	43	6%	Yes	Short duration IMM
No Growth	Mild & mod.	203	29%	No	None
Yeast	Mild & mod.	23	3%	No	None
<i>Staph aureus</i>	All	23	3%	In some cases	Cull cow or dry quarter
				Yes	
<i>Truperella pyo.</i>	Mild & mod.	15	2%	No	Cull cow or dry quarter
					quarter
Other Gr. Neg.	All	32	5%	No	None (mild/mod) or systemic (severe)

^athe medical history of the cow must also be considered before making a decision to withhold antimicrobial therapy

Risks Associated With Mastitis Therapy

The use of antimicrobials to treat food animals has the potential to affect human health through 2 mechanisms: 1) increasing the risk of antimicrobial residues, and 2) influencing the generation or selection of antimicrobial resistant foodborne pathogens. In well regulated markets, the risk of antimicrobial residues in meat and milk is well known and is effectively controlled through intensive regulatory processes. However, there is increasing public concern about the impact of antimicrobial usage in food animals on the development of antimicrobial resistance. The use of antimicrobials for treatment of mastitis is naturally a focus of concern because most antimicrobial usage in adult dairy cows is for treatment or prevention of mastitis. While there is no compelling evidence that the use of IMM antimicrobials results in increased prevalence of resistant pathogens on U.S. dairy farms (Erskine et al., 2004, Pol and Ruegg, 2007) appropriate use of antimicrobials is a public health priority and ensuring judicious usage of antimicrobials in animal agriculture is a societal obligation that must be met.

Responsibilities Associated with Mastitis Treatment

Much antibiotic usage associated with treatment of clinical mastitis is difficult to justify because the infective bacteria is often gone before the inflammation is detected or the mastitis is caused by a type of bacteria that is not likely to respond to the types of drugs that are available. Mastitis is detected based on observation of inflammation, thus detection may occur after the successful clearance of pathogens by the immune system of the cow and these cases may not benefit from IMM antimicrobial therapy (Smith et al., 1985). However, microbiologically negative cases may also occur when the animal remains infected but the quantity of colonies that is shed is less than the detection limit of the microbiological method used in the laboratory. In some of these instances, antimicrobial therapy may be beneficial. Likewise, it is difficult to justify the use of antimicrobial for most cases of non-severe mastitis caused by *E. coli*. The majority of mild and moderate cases of mastitis caused by *E. coli* are spontaneously cured and it is difficult to justify the use of antimicrobials for these cases (Suojala et al., 2010, Suojala, et al., 2013). Some researchers have reported no difference in bacteriological cure rates for untreated cows compared to cows treated for mastitis caused by Gram-negative pathogens, and the majority of antimicrobials labeled to treat mastitis have limited activity against these organisms (Pyorala, 1988, Pyorala et al., 1994, Suojala et al., 2013). A multi-herd clinical trial compared outcomes of a treatment protocol based on on-farm culture (cases caused by Gram-negative pathogens or no pathogen recovered were not treated) to outcomes of cows in a positive control group where all cases were treated with cephapirin (regardless of etiology) (Lago et al., 2011a,b). In some instances, greater bacteriological cure have been reported for clinical mastitis caused by a variety of Gram-negative pathogens treated using IMM ceftiofur (compared to non-treated control cows), however treatment did not significantly influence SCC or milk yield in the remainder of the lactation (Schukken et al., 2011). Knowledge of the type of bacteria that is causing the infection is important because the likely outcome of the infection and need for treatment are influenced by important characteristics that vary among pathogens. Increased use of rapid diagnostic methods (such as culture on-farm or in local veterinary clinics) to guide treatment decisions for non-severe cases of CM has the potential to improve judicious usage of IMM therapies and reduce antimicrobial usage on dairy farms.

Recommendations for Responsible Use of Antimicrobials For Treatment of Mastitis

- 1) Milking technicians should be trained to detect cases early and aseptically collect milk samples. These samples should be used to rapidly arrive at a basic level of diagnosis (no growth, Gram positive or Gram negative) to guide therapy. Culturing using selective medias can occur either on-farm (large herds) or in local veterinary clinics (smaller herds). Cows affected with mild or moderate cases of clinical mastitis should be isolated and milk discarded for 24 hours until culture results are known. If the farmer wishes to immediately initiate treatment, the treatment can be stopped or the duration can be modified after culture results are known.
- 2) Treatments should be administered only after a well-trained animal health manager has reviewed the medical history of the cow and evaluated prognostic factors for the case. Cows that are $>3^{\text{rd}}$ lactation, have a history of previous clinical cases, or have a history of chronically elevated SCC are often poor candidates for routine therapy. Treatment decisions for these cows should be based on culture results and review of treatment outcomes from similar cases on each farm. In many instances, “watchful waiting” (isolation of the cow and discard of the milk from the affected quarter) will be an appropriate therapy. In other instances, culling, cessation of lactation in an individual quarter or extended duration therapy may be preferred.
- 3) Extended duration therapy is appropriate for some cases of mastitis but should be reserved for cases in which data indicates that it will improve case outcomes.
- 4) Unless contraindicated by the medical history of the cow, no antimicrobial treatment should be administered to cows affected with pathogens for which no antimicrobials can be expected to be successful or for most cases that are culture negative at detection. Watchful waiting is the appropriate strategy for these cases.
- 5) The use of antimicrobial treatment for mild cases of *E coli* mastitis should be considered when review of cow-level risk factors suggests that a chronic strain is involved. In the absence of other data, a thumb-rule is to initiate therapy if the cow has had increased SCC for ≥ 2 months or if the cow has risk factors that indicate her immune response may be compromised (first weeks of lactation, severe heat stress, very high production etc.).
- 6) Outcomes of treatments should be routinely monitored. At a minimum the rate of recurrence (within 60-90 days) and SCC reduction (by 60 days) should be routinely evaluated.

Conclusion

Mastitis is detected based on observation of the cow immune response to infection. Many cases are bacteriologically negative when detected and will not benefit from antibiotic therapy. Other cases are caused by bacteria that cannot be expected to benefit from antibiotic therapy. Antibiotic treatments should be reserved for cases that will benefit. Veterinarians should be involved in developing and implementing mastitis treatment protocols and should work with farm personnel and other professionals to actively monitor outcomes of treatments that farm personnel administer. Research evidence is available to help guide mastitis treatment decisions and to better select animals that will benefit from specific treatments.

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