

Treatment of Clinical Mastitis – What the Research Tells Us

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Introduction

While considerable progress has been made in controlling contagious mastitis, mastitis continues to be the most frequent and costly disease of dairy cows. In some countries *Staph aureus* remains a significant cause of mastitis (Unnerstad, et al., 2009) while in other areas, widespread implementation of effective control measures has significantly reduced its prevalence (Makovec and Ruegg, 2003). Control of mastitis caused by *Streptococcus agalactiae* and *Staphylococcus aureus* has resulted in reductions in bulk tank somatic cell count (SCC) but many herds continue to struggle with treatment of clinical mastitis caused by environmental pathogens. Common environmental mastitis pathogens include both Gram negative bacteria (such as *E. coli* and *Klebsiella* spp.) and Gram positive bacteria (such as *Streptococcus uberis* and *Streptococcus dysgalactiae*). Environmental pathogens tend to be less adapted to survival in the udder and often trigger an immune response that results in mild or moderate clinical symptoms. The duration of infection is associated with the degree of host adaptation of the pathogen. Some environmental pathogens (such as most *E. coli*), are truly opportunistic and the immune response successfully eliminates them after a brief period of mild clinical disease. Other environmental pathogens (such as *Streptococci* spp) have become more host adapted and may present as mild clinical cases that erroneously appear to resolve when the case has actually returned to a subclinical state. Both of these scenarios make it very difficult for the veterinary practitioner to discern success of mastitis treatments. While farmers often remember the most severe cases of mastitis, research demonstrates that the majority of clinical mastitis cases are mild to moderate in severity. On many farms, detection, diagnosis and administration of treatments for mild and moderate cases of clinical mastitis are the responsibility of farm personnel and veterinarians are often consulted only when a case becomes life-threatening. It is vitally important for veterinarians to be involved in developing and evaluating treatment protocols for clinical mastitis but the ability to assess the results of treatment is often limited because of inadequate records (Hoe and Ruegg, 2006). The purpose of this paper is to review research based principles that can help practitioners improve treatment of clinical mastitis.

Determining Relevant Outcomes of Mastitis Therapy

Veterinarians are often unaware of mastitis treatments and it may be difficult for them to determine if mastitis treatments are successful because there is no standard outcome that is used to determine success. For most farmers, the practical goal of treatment is to rapidly produce a reduction in clinical symptoms, eventually reduce SCC, prevent recurrence of additional clinical cases and maintain expected milk yield. Interpretation of treatment outcomes can be confusing because most cases of mastitis caused by mastitis pathogens present with mild or moderate clinical signs (Table 1). When cows present with mild cases of mastitis, clinical signs will normally abate within 4-6 days, regardless of treatment. However, disappearance of clinical signs does not always indicate that the infection has been successfully treated. While the milk may appear visually normal, many of these cases may have simply regressed to a subclinical state and maintain increased SCC. This occurrence is especially true for Gram positive pathogens.

Bacteriological cure rates are generally used in research studies as the primary indicator of treatment efficacy but few farmers or veterinarians evaluate bacterial clearance of pathogens from affected glands. The ability to achieve a bacteriological cure depends on the pathogen, case severity, variation in immune response among cows, efficacy of the treatment protocol and the promptness of initiating treatment (Hillerton and Berry, 2003). In one study, bacteriological cure

was 7 times more likely for first cases of mastitis as compared to recurrent cases (Pinzon-Sanchez et al., 2010). Laboratory issues can also influence the probability of recovering bacteria from milk samples. Issues such as the frequency of sampling, the volume of milk that is inoculated, the time period after therapy until sampling and time between collection of consecutive samples all contribute to the wide variation in bacteriological cure rates noted in the literature (Ruegg and Reinemann, 2002). Therefore, bacteriological cures should be reviewed critically in both research and clinical settings before therapeutic success can be confirmed.

Table 1. Distribution of pathogens causing clinical mastitis from recent studies

Study	Cases	Strep ag ¹ or Staph aureus	CNS	Env. Strep	Coliform	Other	No growth
Oliveira & Ruegg, 2011 ^a	788 cases in 51 herds	4%	7%	13%	30%	16%	31%
Bar et al 2007	5 herds	5%	3%	21%	40%	10%	21%
Hoe & Ruegg, 2005	217 cases in 4 herds	0%	14%	24%	25%	8%	29%
Pinzon & Ruegg, 2010	207 cases in 4 herds	2%	3%	18%	26%	9%	42%
Olde Riekerink, 2007 (Canada)	2850 in 106 herds	11%	6%	16%	14%	7%	46%
Kromker and other (Germany)	100 case in 1 herd	5%	3%	33%	18%	5%	36%
Tenhagen et al (Germany)	1261 cases in 10 herds	12%	24%	14%	12%	15%	23%
McDougall et al 2007 NZ	1359 quarters	19%	6%	44%		4%	26%
Lago et al., 2005	421 cases in 8 herds	6%	10%	16%	25%	10%	32%

^anot yet published

On a practical basis, farmers often determine clinical efficacy based on indicators such as recurrence of clinical mastitis, reduction in SCC, return of milk yield to normal, retention of the cow within the herd and number of days milk is discarded. Recurrence of another case of clinical mastitis is one of the least desirable outcomes after treatment and is much more likely for cases that are early in lactation as compared to cases that occur later (Figure 1; Pinzon-Sanchez, 2010). This may indicate the need for more aggressive treatment protocols (for example, longer duration therapy) for cows experiencing mastitis in early lactation as compared to treatments for cases that occur later.

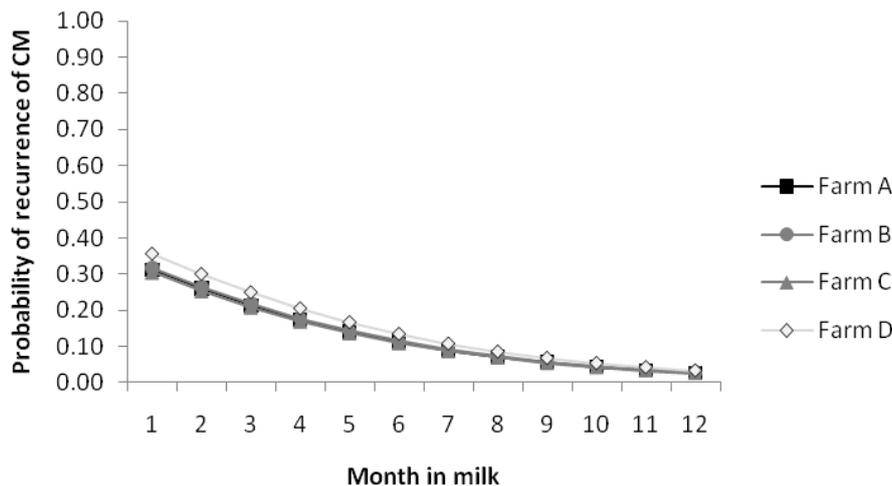


Figure 1. Probability of Recurrence of clinical mastitis (CM) by cow's month in milk

Somatic cell reduction below 200,000 cells / mL is another desired outcome after treating mild and moderate cases of clinical mastitis but occurs slowly and this outcome is highly influenced by pathogen. Pinzon-Sanchez (2010) reported that 63% of cases caused by Gram-negative pathogens or no growth resulted in somatic cell reductions to less than 200,000 cell/mL within 21-55 days after treatment in contrast to only 44% of cases caused by Gram-positive bacteria. While long-term SCC reductions should occur after successful therapy, short-term changes in SCC should not be used to determine when to stop therapy nor to determine if therapy has been effective.

Useful Research for Improving Mastitis Therapy

While there is very little research that compares specific intramammary (IMM) treatments there are quite a few research studies that contain information that practitioners can use to make better mastitis treatment decisions.

Cow Factors Influencing Treatment Outcomes. The relationship between incidence of intramammary infection caused by environmental pathogens and parity (or age) of cattle has been well known for at least 25 years (Smith et al., 1985). Older cattle have a greater risk of both subclinical and clinical mastitis and several studies have indicated that older cattle have poorer responses to treatment as compared to younger cattle. Deluyker et al., (1999) used a rigorous definition of clinical cure (normal milk by 5 d and no relapse within 3 weeks post-treatment) and reported a reduction in combined "clinical & bacteriological cure rates" from 39% (lactation 1) to 26-30% for older cattle. Sol et al., (2000), McDougall et al., (2007a&b) and Pyorala et al., (1998) all reported that bacteriological cure after mastitis therapy were less for older cows. Age has also been associated with reduced clinical responses to therapy. Hektoen et al., (2004) measured responses to treatment by comparing scores for both acute and chronic symptoms obtained before treatment and at various periods post-treatment. While parity was not associated with differences in acute symptoms, the reduction in chronic symptoms (changes in the milk, gland or inflammatory response) were markedly greater in first lactation as compared to older cattle. The effect of parity should be considered by practitioners before initiating mastitis treatments. For example, when IMM compounds are approved for extended duration therapy, veterinarians may want to consider using longer duration of treatment for cases occurring in older cows. Likewise, older cows (>3 lactation) may not be considered as good candidates for withholding -treatment if that option is used for managing some types of mastitis on particular farms.

Differences Among Pathogens. While it is difficult to incorporate microbiological examination of milk samples in all situations, it is well known that mastitis is caused by a diverse group of bacteria (Table 1) and the probability of cure is highly influenced by the characteristics of the pathogen. While some cases occasionally experience spontaneous cure, therapeutic cure rates for several mastitis pathogens (yeasts, pseudomonas, mycoplasma, prototheca etc.) are essentially zero, regardless of treatment. Combining data from 2 equally efficacious treatments, McDougall et al., (2007) noted the following typical differences among pathogens in bacteriological cure after treatment: *Strep uberis* (89%, n = 488 cases); *Strep dysgalactiae* (69%, n = 32 cases), *Staph aureus* (33%, n = 40 cases), and CNS (85%, n = 71). On farms that have controlled contagious mastitis, approximately 25-40% of clinical cases are microbiologically negative before treatment (Table 1). Clinical and spontaneous cure rates for these "no-growth" samples are often very high with or without treatment (Guterbock et al., 1993, Morin et al., 1998). For example, Hektoen et al., (2004) noted that both acute symptoms and long term responses were significantly improved for mastitis cases which were microbiologically negative as compared to cases from which *Staph aureus* or other bacteria were isolated. In contrast, mastitis caused by environmental Streptococci typically respond well to IMM antimicrobial therapy but have a low spontaneous cure rate and high rate of recurrence when antimicrobials are not administered (Morin et al., 1998). These differences

among pathogen demonstrate that identification of pathogen considerably improves mastitis treatment protocols. With current laboratory methods, it is not feasible for all farms to achieve a microbiological diagnosis before beginning therapy but guiding treatment by use of on-farm culture systems has been shown to be economically beneficial (Lago, et al., 2005, Lago et al., 2008). Even if a diagnosis is not immediately available, farmers can submit milk samples to laboratories for rapid provisional diagnosis and then readjust therapy when the pathogen is diagnosed 24-48 hours after beginning treatment. In the future, it is likely that rapid methods will become available to guide treatments and consistent and accurate identification of pathogens before initiating therapy should result in improved therapeutic responses.

Treatment of mastitis caused by Staphylococcus aureus. As compared to other mastitis pathogens, there is a much larger body of evidence upon which to base treatment decisions for Staph aureus. Expectations for spontaneous bacteriological cure of subclinical and clinical mastitis caused by Staph aureus are essentially zero (Oliver et al., 2004). Most of the evidence agrees that treatment of clinical mastitis caused by chronic infections with Staph aureus is not rewarding and many of these cows will have periodic episodes of mild or moderate clinical mastitis. It is not considered cost-effective to treat clinical mastitis in cows that are chronically infected with Staph aureus because cure rates are typically <35% and in most instances, when the clinical symptoms disappear, the infection has simply returned to a subclinical state. Somewhat effective cure of cows infected with Staph aureus have been shown to be strongly related to duration of subclinical infection. In one study, bacteriological cure rates for chronic (> 4-weeks duration) Staph aureus infections were only 35% compared to 70% for newly acquired (< 2-weeks duration) infections (Owens, et al., 1997) but it is important to note that these infections were induced using laboratory strains of bacteria. Treatment protocols designed for farms where Staph aureus infections are common should not prescribe the use of antimicrobial to treat mild clinical cases occurring in chronically infected cows. In these instances it is more cost effective to simply isolate the cow or affected quarter, discard the milk until it returns to normal and then make a decision about culling or retaining and isolating the cow. An excellent review of factors influencing therapeutic success of mastitis caused by Staphylococcus aureus notes that treatment outcomes can be influenced by cow factors (age, duration of infection, SCC, etc.), pathogen factors (different strains, inherent resistance to penicillin as indicated by presence of β -lactamase) and treatment factors (duration or therapy) (Barkema, et al., 2006). Cure rates for subclinical mastitis caused by Staph aureus have been shown to decrease with age (from 81 % for cows \leq 48 months of age to 55% for cows \geq 96 months), the number of infected quarters (from 73% for 1 infected quarter to 56% for 4 infected quarters) and increasing SCC (Sol et al., 1997). Similar results have been demonstrated for clinical mastitis and bacteriological cure rates have been shown to be significantly greater if the pathogen is β -lactamase negative as compared to positive. The use of extended duration therapy has been shown to increase cure of clinical mastitis caused by Staph aureus and at least 5 days of therapy is recommended (Pyorala et al., 1998, Sol et al., 2000). Extended duration IMM treatment of clinical cases of Staph aureus may be successful for young cows, in early lactation with recent single quarter infections but should not be attempted for chronically infected cows. It is also important to note, that in the best of circumstances, only about 30-50% of cows affected with Staph aureus will be expected to cure, thus expectations of the farmers should be appropriately lowered and preventive programs initiated to limit spread of the infection.

Duration of Therapy. Discarded milk is the greatest proportion of expense associated with treatment of clinical mastitis. In general, duration of antibiotic treatment is kept as short as possible to minimize the economic losses associated with milk discard. The appropriate duration of antibiotic treatment for clinical mastitis has not been well-defined and varies depending on the causative pathogen. There is considerable evidence that extended administration of antibiotics increases cure rates for pathogens that have the ability to invade secretory tissue (Staph aureus and some environmental Streps). For example, bacteriological cure for subclinical mastitis caused by

Staph aureus treated with IMM ceftiofur were 0 % (no treatment), 7% (2 days), 17% (5 days) and 36% (8 days) (Oliver et al., 2004). Cure rates reported for clinical mastitis caused by β -lactamase negative *Staph aureus* were significantly greater when extended duration therapy was used (50%) versus administration of 3 treatments over 36 hours (38%) (Sol et al. 2000). Likewise, bacteriological cure rates for experimentally induced *Strep uberis* infections increased from 58% (2-d treatment) to 69-80% for treatments of 5 or 8 days (Oliver et al., 2003). Therefore, for mastitis caused by potentially invasive pathogens, the duration of therapy should be 5 to 8 days. However, research to support the use of extended duration therapy to treat pathogens that infect superficial tissues (for example coagulase negative staphylococci or most *E. coli*) has not been published and the use of extended duration therapy to treat these pathogens increases costs without improving treatment outcomes (Pinzón-Sánchez, et al., in press).

Use of Oxytocin and Frequent Milking. Frequent milking (FM) with or without administration of oxytocin is commonly recommended as an ancillary or primary treatment for clinical mastitis. In recent years, several studies have been conducted to evaluate this practice either alone or in combination with antimicrobial therapy. One researcher experimentally induced *E coli* mastitis in 8 cows and compared responses to 8 cows enrolled as controls (Leininger et al., 2003). Cows were divided into 4 groups of 4 cows each: 1. induced *E coli* mastitis, treated with FM & oxytocin, 2. induced *E coli* mastitis but no treatment, 3. healthy cows with FM & Oxytocin, or 4. healthy cows with no treatment. In cows that developed *E coli* mastitis (n = 8) the use of FM and oxytocin did not significantly affect SCC response, time to bacteriological cure, time to systemic cure or time required for milk to return to normal appearance. In another small study, Roberson et al., (2004) compared outcomes after dividing cases into 4 groups: 1. use of FM & oxytocin (n = 19 cases), 2. FM and IMM amoxicillin (n = 22), 3. IMM amoxicillin (n = 22) or 4. no treatment (n = 19). Enrolled cases included mastitis caused by environmental streptococci, *E coli*, *Klebsiella* and “no growth.” Clinical cure was defined as recovery of normal milk without relapse by 36 days after treatment. Clinical cures were 64% (no treatment), 57% (IMM amoxicillin), 25% (FM), and 52% (FM plus IMM amoxicillin). Bacteriological cures were 55% (no treatment), 67% (IMM amoxicillin), 49% (FM), and 53% (FM plus IMM amoxicillin). While the study lacked statistical power, there was no indication that the use of FM improved neither bacteriological cures nor clinical cures. Recently, the addition of two extra daily milkings (4x/day) was compared to twice daily milking for cows that received IMM treatment for mild or moderate cases of clinical mastitis (Kromker et al., 2010). The researchers enrolled 93 cows from a commercial dairy herd. The addition of two extra milkings had no effect on clinical cure or milk yield after treatment. Of enrolled cows (n = 93), approximately 32% of both treatment groups had normal milk, SCC <100,000 cells/ml and bacteriological cures at the end of the observation period. The use of FM seems logical and many veterinarians have been taught to recommend this practice in veterinary school. However, while all 3 studies lack sufficient sample size, all have failed to identify positive outcomes associated with FM and therefore this practice is not supported by available evidence.

Parenteral Treatment of Acute Coliform Mastitis. Use of IMM antibiotics to treat animals experiencing coliform mastitis has been questioned because of the high rate of spontaneous cure and because many antimicrobials have limited activity against Gram-negative organisms (Pyörälä, et al. 1994, Roberson et al., 2004). However, the use of parenteral antimicrobial therapy for treatment of acute severe coliform mastitis is often recommended. Erskine et al., (2002) compared survival of cows with acute severe clinical mastitis that received supportive and IMM therapy to survival of cows that received supportive and IMM therapy combined with parenteral treatment using ceftiofur. While a general treatment effect was not noted, cows with mastitis caused by coliform organisms that did not receive systemic ceftiofur were more likely to be culled or die (37%) as compared to cows that received that treatment (14%). A similar study was conducted for cows experiencing mild and moderate cases of coliform mastitis (Wenz et al., 2005). Animals in this study received IMM treatment alone (one of two separate products) or IMM treatment

combined with systemic ceftiofur. No significant differences were noted in culling, loss of quarter, bacteriological cure or recurrence of mastitis. More recently, outcomes after administration of systemic danofloxacin were compared to outcomes experienced by a non-treated control group in cows that had acute induced mastitis caused by E coli (Poutrel et al., 2008). The use of systemic danofloxacin improved elimination of E coli and resulted in better clinical outcomes (reduced body temperature, improved appetite etc.). In summary, current research evidence appears to support the use of parenteral antimicrobial treatment to improve survival and clinical outcomes of cows experiencing severe coliform mastitis but the routine use of systemic therapy is not recommended for mild or moderate cases.

Research About Use of Alternative Treatments for Clinical Mastitis. In the U.S., cows used for production of organic milk may not receive any antimicrobials (Ruegg, 2009) and producers use a variety of herbal and homeopathic remedies for treatment of mastitis (Pol and Ruegg, 2007). Many alternative therapies have some theoretical basis for efficacy but there are almost no peer reviewed studies that demonstrate clinical efficacy. One recent review of veterinary usage of botanical and herbal remedies stated that “With few exceptions, controlled studies on the clinical effects of herbal or botanical preparations in veterinary medicine appear to be essentially nonexistent” (Ramey, 2007). One small, randomized, controlled clinical trial performed to evaluate treatment of subclinical IMM infections using several alternative therapies reported no significant effects of treatment on either bacteriological cure or SCC (Tikofsky and Zadoks, 2005). While theoretical basis for efficacy may exist no credible evidence has been published that demonstrates effectiveness of herbal compounds currently used as alternatives to antimicrobials.

Homeopathic remedies were first introduced in Germany in the era before microorganisms were identified and a few articles have specifically evaluated veterinary homeopathy. Of 3 published studies investigating the effect of homeopathic nosodes on mastitis outcomes, none have demonstrate efficacy (Egan, 1998; Hektoen et al., 2004; Holmes et al., 2005). Evidence that demonstrates efficacy of veterinary homeopathy is completely lacking and practitioners seeking to apply concepts of EBVM will not be able to support the use of these products.

Conclusion

Veterinarians should continue to increase their involvement in developing and implementing mastitis treatment protocols and should 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. There is sufficient research evidence to help practitioners develop mastitis treatment protocols that vary depending on animal characteristics and the history of subclinical disease. Research can also be used to guide decisions about duration of therapy, determine if cows affected with Staph aureus should be treated or culled and to make rational decisions about the use of alternative & ancillary treatments.

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