

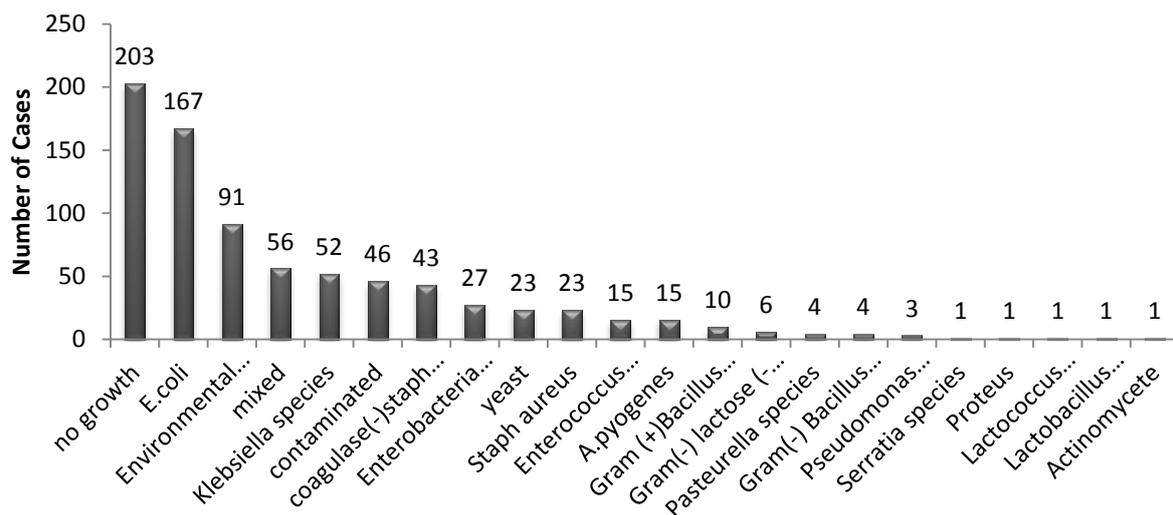
Improving Mastitis Treatments by Targeted Antimicrobial Therapy

Pamela L. Ruegg, DVM, MPVM, University of WI, Dept. of Dairy Science, Madison WI

Introduction

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. On many modern dairy farms, mastitis is caused by an increasingly diverse group of opportunistic pathogens (Figure 1). Common environmental mastitis pathogens include both Gram negative bacteria and Gram positive bacteria (Figure 1). The presentation of the symptoms and 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 to determine 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. The purpose of this presentation is to review research based principles that can help improve treatment of clinical mastitis.

Figure 1. Results of milk samples submitted from 793 cases of clinical mastitis occurring on 51 large Wisconsin dairy farms in 2010.¹



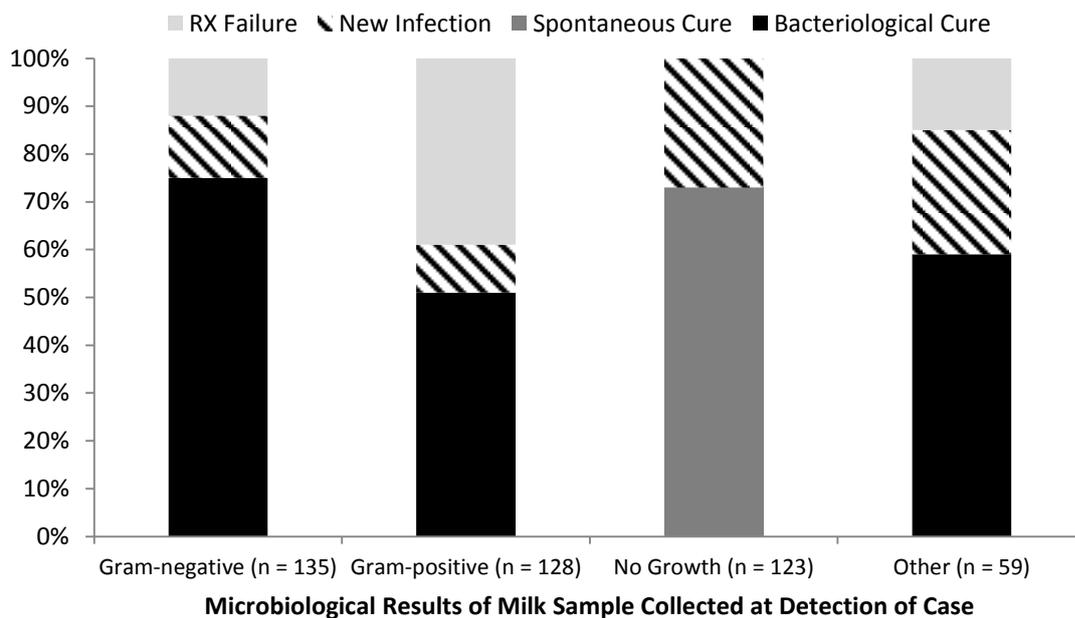
DETERMINING RELEVANT OUTCOMES OF MASTITIS THERAPY

It is often difficult to determine if mastitis treatments are successful because there is no standard outcome that is used to evaluate outcomes. The detection of mastitis is based on recognition of the immune response that is a result of the infection. Thus, interpretation of treatment outcomes can be confusing because, clinical signs will normally resolve within 4-6 days, regardless of treatment. This is expected, as the response of immunologically competent cows will often successfully reduce the number of bacteria infecting the gland. However, disappearance of clinical signs does not always indicate that the infection has been successfully eliminated. As the immune response lessens, the milk may return to normal

appearance, however 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.

The ability to achieve a bacteriological cure depends on the pathogen, case severity, variation in immune response among cows, efficacy of the treatment protocol (when needed) and the promptness of initiating treatment.² Even in the absence of mastitis caused by Staph aureus, bacteriological cures are almost always greater for Gram negative as compared to Gram positive pathogens (Figure 2).¹

Figure 2. Treatments outcomes based on comparison of microbiological results of Milk samples collected at detection of clinical case and follow-up samples collected 3 weeks later.¹



In one study, bacteriological cure was 7 times more likely for first cases of mastitis as compared to recurrent cases.³ Definition and interpretation of bacteriological cure also depends on laboratory procedures as differences in laboratory protocols can 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.⁴

On a practical basis, farmers often assess clinical efficacy based on the appearance of the milk or other indicators such as recurrence of another clinical case, reduction in SCC, return of milk yield to normal, retention of the cow within the herd and number of days milk is discarded (because of abnormal appearance or the presence of antibiotic residues). Recurrence of another case of clinical mastitis is one of the least desirable outcomes after treatment and may be more likely for cases that occur early in lactation as compared to cases that occur later (Figure 3).³ 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.

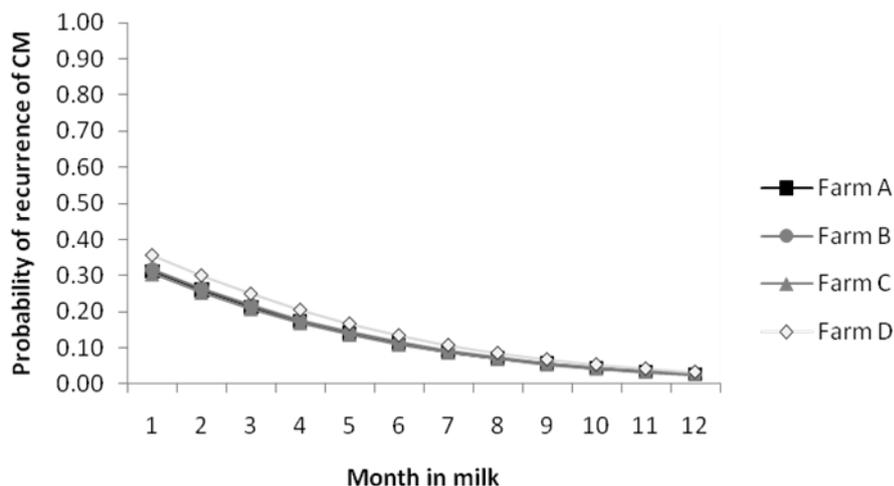


Figure 3. Recurrence of clinical mastitis (CM) by stage of lactation³

Somatic cell reduction below 200,000 cells /mL is another desired outcome but occurs slowly and this outcome is highly influenced by pathogen. Of cases caused by Gram-negative pathogens or no growth 63% 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.³ While long-term reductions in SCC 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. Likewise, the use of cow-side tests like the California Mastitis Test should not be used to determine when to stop treatment.

Cow Factors Influencing Treatment Outcomes.

Host factors are well known to influence the probability of success responses to mastitis infections.⁵ 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.⁶ Deluyker et al., 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.⁷ Other researchers have reported that bacteriological cure after mastitis therapy were less for older cows.⁸⁻¹¹ Age has also been associated with reduced clinical responses to therapy. Hektoen et al., measured responses to treatment by comparing scores for both acute and chronic symptoms obtained before treatment and at various periods post-treatment.¹² 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 good candidates for withholding treatment if that option is used for managing some cases of mastitis on particular farms.

Differences Among Pathogens

It is well known that mastitis is caused by a diverse group of bacteria and the probability of cure is highly influenced by the characteristics of the pathogen. The pathogenesis, virulence and prognosis of IMI is influenced by important characteristics that vary among pathogens. Depending on specific virulence factors, organisms infect different locations in 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. Understanding these differences is fundamental to development of effective control programs. For example, expectations for spontaneous bacteriological cure of subclinical and clinical mastitis caused by *Staph aureus* are essentially zero¹³ while the expectation for spontaneous cure of *E coli* is quite high.¹⁴ While a few cases may result in spontaneous cure, therapeutic cure rates for several mastitis pathogens (yeasts, *pseudomonas*, *mycoplasma*, *prototheca* etc.) are essentially zero, regardless of treatment. Even among Gram-positive pathogens, outcomes vary. The following typical differences among pathogens in bacteriological cure after treatment have been noted: *Strep uberis* (89%, n = 488 cases); *Strep dysgalactiae* (69%, n = 32 cases), *Staph aureus* (33%, n = 40 cases), and CNS (85%, n = 71).⁹ On farms that have controlled contagious mastitis, approximately 25-40% of clinical cases are microbiologically negative before treatment. Clinical and spontaneous cure rates for these “no-growth” samples are often very high with or without treatment.^{15,16}

Most cases of clinical mastitis caused by *E coli* are detected well after the immune response of the cow has been initiated and the immune response is usually successful in eliminating IMI caused by *E coli*. However, the duration of IMI caused by other coliforms (such as *Klebsiella* or *Enterobacter*) is much longer. After coliform bacteria infect the mammary gland, they multiply rapidly but most do not adhere to or invade the epithelial cells.⁵ If the cow's immune response is rapid and efficient, infection will be quickly eliminated and there will be little long-term impact on cow health or productivity. The outcome of clinical mastitis caused by coliform bacteria depends on the severity of the case, which is usually dependent on the balance between the dose (relative degree of exposure to bacteria) and the ability of the cow to respond immunologically. Severe cases of mastitis occur most frequently in the periparturient period and early lactation and are primarily associated with characteristics of the cow that influence her ability to respond to the infection.^{5,17-19} When influx of neutrophils is delayed or phagocytosis or intracellular killing mechanisms of neutrophils impaired, bacterial multiplication continues, resulting in greater concentrations of inflammatory mediators and more severe clinical disease

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.¹⁶ 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 (OFC) has been shown to be economically beneficial.^{20,21} The use of OFC to direct treatment of clinical mastitis gives farmers the opportunity to make better treatment decisions and reduce costs associated with milk discard and treatment of microbiologically negative cases. A positively controlled clinical trial evaluating OFC demonstrated that there were no significant differences in either long-term or short-term outcomes for cases of mastitis that received treatment based on results of OFC as compared to cases treated immediately without regard to diagnosis.^{20,21} In this study, antimicrobials were not administered to cases that were culture negative or Gram negative thus the use of intramammary antimicrobials was reduced by approximately 50% as compared to cases which were treated without prior diagnosis. Most smaller herds cannot adopt OFC and an alternative is to encourage veterinary clinics to offer in-veterinary clinic culturing (IVCC). In these instances, farmers initiate treatment immediately but may modify treatment duration or drug after receiving a preliminary microbiological diagnosis within 24 hours. Development and oversight of a culture program

(either OFC or IVCC) is an ideal way for veterinarians to increase involvement in mastitis control programs. The use of veterinary technicians to supervise these programs may also increase veterinary involvement and oversight of mastitis treatments. Veterinary technicians can visit farms to restock supplies, train farm personnel and provide oversight and quality control.

Duration of Therapy

In general, duration of antibiotic treatment should be kept as short as possible to minimize the economic losses associated with milk discard while maximizing the probability of achieving bacteriological cure. 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).¹³ 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%).⁸ 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.²² Therefore, for mastitis caused by potentially invasive pathogens, the duration of therapy should be 5 to 8 days. Research to support 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 significantly increases costs without improving treatment outcomes.²³ When extended therapy is considered, veterinarians should assess the ability of the herd personnel to perform aseptic infusions as extended intramammary treatment is associated with an increased risk of infection from opportunistic pathogens, and herds with poor infusion techniques are not good candidates for multiple doses of intramammary tubes.

Conclusion

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. There is sufficient research evidence to help develop mastitis treatment protocols that vary depending on animal characteristics and the history of subclinical disease. The use of OFC or IVCC is an ideal way for veterinarians to become more involved in helping farmers make rational decisions about antimicrobial therapy used for treatment of mastitis.

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