

MAKING MASTITIS TREATMENT DECISIONS

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SUMMARY

Therapeutic efficacy of mastitis can result in frustrating clinical outcomes, depending on the causative pathogen, the severity and duration of infection, and expectations of the dairy producer. In herds that have controlled contagious mastitis, costs incurred from clinical mastitis likely account for the largest proportion of total herd mastitis costs, and in some instances, a majority of these losses results from therapeutic costs, especially discarded milk following treatment. Additionally, mastitis remains the primary cause of antibiotic use on dairy farms and violative drug residues in marketed milk in the U.S.

Therefore, an approach to therapeutic decisions for mastitis must address the three fundamental "e"s : efficacy, economics, and evasion of drug residues. This paper will focus on mastitis treatment decision-making and promotes a perspective of treatment as an adjunct to immune function.

INTRODUCTION

Throughout the 1960s and 1970s a wide variety of antimicrobials became available as intramammary infusions for treatment of mastitis. Initial successes suggested 75% efficacy (cures) in both lactating and dry cow formulations. However, there has been growing skepticism that in some cases, we achieve far less than originally reported. Chronic intramammary infections caused by pathogens such as *Staphylococcus aureus* pose difficult therapeutic problems, and typical labelled dose regimens that provide antibacterial concentrations for 24 to 48 hours will not provide cures in many cases. Additionally, the major thrust of development of antimicrobials for treatment of mastitis has been directed against Gram-positive organisms, particularly staphylococci and streptococci. These continue to be important pathogens, however, many herds have seen the emergence of Gram-negative organisms as a substantial cause of mastitis losses, which are resistant to many current products.

Traditionally, the most significant economic losses of mastitis have been attributable to lost production resulting from inflammation. However, application of management practices that decrease the prevalence of contagious pathogens, has also altered the focus of mastitis control to environmental pathogens and economic losses that arise from clinical mastitis. Estimates on the cost of clinical mastitis are \$110/case and \$40 to \$50 per cow in herd per year (1,2). In a large Michigan herd using daily milk weight technology, discarded milk following treatment accounted for 70% of lost marketable milk (2), and in herds that do not have a judicious treatment program losses from discarded milk alone can exceed \$70 per cow in herd per year. Thus, there is increased awareness among producers of treatment-related costs, and the economic value of extensive antimicrobial therapy for mastitis.

In Michigan, mastitis remains the most frequent cause of antimicrobial use in dairy cows and accounts for 90% of occurrences when violative residues are detected in marketed milk. Considerable debate among the public and regulatory sector exists as to the dangers that antimicrobials and other drugs in milk pose as a health risk. Nonetheless, whether the dangers are real or perceived, frequency of milk

Proceedings of the British Mastitis Conference 1998, Axient/Institute for Animal Health, Milk Development Council/Novartis Animal Health, p9-14. testing and regulatory control of drug use on dairy farms is increasing and likely to increase in complexity as time continues. Thus, because of accountability to dairy producers and the consuming public, we must address two other key issues other than efficacy. Therapy must be economically viable and must not increase risk of drug residues in marketed milk.

Although these guidelines serve as a basis for therapeutic decisions, the practical realities faced by farmers and health advisors such as veterinarians still require that cows with mastitis will be treated. Although simplified, a mastitis therapy protocol can be designed from two "on-farm" perspectives; what to do with acute, systemic mastitis cases, and the other is the problems associated with chronic or relatively mild clinical cases. The key variables that influence the approach to formulating a treatment protocol are drug selection, causative agent, and cow immune status.

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS FOR MASTITIS TREATMENT DECISIONS

Antimicrobials have been the class of drugs most often advocated in clinical practice and research as a therapy for mastitis (3). This direction has seemingly offered the most potential because the purpose of these drugs is to inhibit the growth of, or kill infectious, pathogens. However, because of the limited therapeutic dosing of these drugs that is usually employed due to economic and residue avoidance concerns, we are often unable to maintain effective inhibitory concentrations. Our goal in selecting the best antimicrobial treatment regimen for an intramammary infection is simple, administer the drug at a dose and site that will allow accumulation in the mammary gland (pharmacokinetics), and identify the pathogen and minimal inhibitory concentration (susceptibility) so that we can maintain effective drug concentrations (pharmacodynamics). Although adequate for pathogens such as *Streptococcus agalactiae* and *dysgalactiae*, the minimal dose amount and frequency as suggested for many commercial intramammary preparations is inadequate from a pharmacokinetic and pharmacodynamic standpoint for more invasive pathogens such as *Streptococcus uberis* and *S. aureus*. Number of doses with intramammary preparations are usually maintained according to milking times of the cow. However, a more novel approach has been to apply parenteral (systemic) administration as an adjunct to intramammary therapy. Systemic use of antimicrobials has been successful for increasing cure rates for chronic *S. aureus* intramammary infections in dry cows and lactating cows in studies from Israel, Netherlands, and Louisiana, but not in dry cows in studies from Michigan and Louisiana (4,5,6,7). In these studies, antimicrobials such as fluorquinolones, macrolides, and tetracyclines were selected as good pharmacokinetic candidates because of good volume of distribution (lipophilic), relatively long half-life, and high bioavailability (low serum protein binding). Because of a high degree of resistance to antimicrobials in commercial intramammary products, systemic antimicrobial therapy for the treatment of acute Gram-negative mastitis has been attempted. Research from Alabama (8, intravenous ceftiofur, low bioavailability), Minnesota (9, intramuscular erythromycin, poor susceptibility; gentamicin, poor tissue distribution) and Finland (10, sulfatrimethoprim) have all realized poor therapeutic results with natural and experimental coliform infections. A recent Israeli study (11) with a fourth generation cephalosporin (cefquinome) with good tissue distribution and antibacterial activity reported better clinical outcomes. Thus, it is important to identify the pathogen and apply sound pharmacologic principles to promote the best probability for therapeutic efficacy.

MASTITIS THERAPY DECISIONS: COW'S POINT OF VIEW

It is well established that cows that have concurrent metabolic disease, inadequate nutrition, or that are subjugated to stress, including calving, are more likely to be affected by infectious agents. Mastitis is no exception to this principle, and numerous studies have demonstrated the direct correlation between *in vitro* phagocyte function and clinical outcome of experimentally challenged cows. Anti-oxidant supplementation of dietary rations improves *in vitro* anti-bacterial function of neutrophils collected from supplemented cows and decreases incidence and severity of clinical mastitis (12,13). Conversely, alteration of neutrophil migration into the gland occurs near calving and results in more severe coliform infections (14). Neutrophil function in clearance of pathogens from the mammary gland is critical, however the understanding of immunology has increased so that we now know that the neutrophil is part of a larger symphony of immune effectors that includes macrophages, lymphocytes, immune modulators such as cytokines, inflammatory mediators, and acute phase reactants (3). As a primer of humoral immunity, use of core-antigen vaccines improves the clinical outcome of cows with Gram-negative mastitis. Thus, preventive measures to establish optimum cow immunity are desirable. However, cow immune response to even the best of preventive programs is highly variable. At the time of clinical mastitis treatment, our ability to manipulate immune function is limited, and learning to assess immune function, even on a crude scale may offer some insight to therapeutic success. This is based on the premise that no antibiotic can clear an infection without a functional immune system and learning to read what a cow's defences are telling us may help in deciding our options or at least expectations. We need to support basic research that will allow us to gain recognition of cows with impaired immunity that pose a higher risk of unsuccessful therapy. Mammary quarters with infections of longer duration, that more consistently shed pathogens over time, and from cows that have multiple quarters with infections are a poorer therapeutic risk (5,15). These are somewhat crude predictors of therapeutic success, but suggest that we should explore genetic markers in dairy cattle that may allow us in the future to identify potentially immune impaired breeding lines as well as target our therapeutic efforts and expectations of treated animals.

A particularly attractive alternative would be to develop new strategies of dry cow therapeutics. This is an opportunity that could best realize the three fundamental criteria of therapy. Cost to the producer, particularly from discarded milk should be minimal, risks of residues in milk are certainly reduced, and as the involuted gland is a more hostile environment to bacterial survival than a lactating gland, improved efficacy gained through synergy with the immune system should be possible. Initial attempts to accelerate involution or potentiate immune activity at the end of lactation, or in lactating cows have not demonstrated practical clinical success (16,17,18,19), but are well targeted considering the high incidence of new intramammary infections during the early dry period.

DECISIONS FOR THERAPY OF ACUTE MASTITIS

Acute, or systemic, mastitis is most often caused by coliform and other Gram-negative organisms (20). However, numerous other pathogens including Gram-positive cocci and mycotic organisms can all result in severe mastitis. The case can be life threatening to the cow, and is often accompanied by marked production loss. If survival occurs, affected cows often perform poorly and may undergo premature culling. From a cowside appraisal, treatment of these cases is a forced decision, i.e. treatment is indicated, if only to relieve the cow of systemic signs. Supportive care is usually indicated, and in the case of coliform mastitis may be the most beneficial component of the therapeutic regimen (3). The obvious basis for antimicrobial therapy is knowledge of the causative pathogen. However, this is not attainable for some hours after initial onset of case recognition, and thus the practical problem remains of basing treatment on best clinical guess. Epidemiological information on the herd such as previous bacteriology, patterns of stage of lactation, season, age, etc suggest our best alternatives. Nonetheless, we remain in the situation of prescribing treatment to best cover all possibilities. Typically, intramammary therapy to inhibit Gram-positive growth in addition to parenteral (systemic) antimicrobials that have broad spectrums of activity are administered. Pharmacokinetic principles as previously discussed apply to severe mastitis cases. Although the drug may be available for distribution in the mammary gland, maintaining effective MIC can be more difficult due to increased resistance of many of these organisms. Caution should be employed in extending therapy for cows that have demonstrated marked clinical improvement, especially for cases of coliform mastitis, as recovering cows affected by these organisms have cleared the infection, and generally do not need antimicrobials to complete recovery. Unnecessary extension of therapy in these instances results in increased discarded milk expense for the dairy producer and risk of antimicrobials in marketed milk.

DECISIONS FOR THERAPY OF CHRONIC MASTITIS

Many intramammary infections that are chronic or are observed as mild clinical cases offer a more voluntary approach to therapy. Elimination of infections can result in increased production and, in the case of contagious pathogens, remove the reservoir of infection for non-infected cows. However, many of these infections are of long duration, frequently recur with mild clinical mastitis despite previous therapy, and can add substantial costs and risks associated with treatment. Treatment of subclinical IMI in lactating cows, especially caused by pathogens other than *Str. agalactiae* is usually uneconomical. The foundation for decisions should be based on bacteriology and sound pharmacology.

Given the slow onset of infection, identification of the pathogen should be performed before any extensive therapy is instituted. Drug distribution, although theoretically available in the mammary gland, may not be efficacious because of extensive fibrosis and micro-abscess formation in the gland. Finally, chronic cases offer us more leisure to determine the cow's immune status from a perspective of duration of infection, number quarters infected, and other variables as previously discussed.

CONCLUSION

Mastitis therapy has hit a critical impasse, dairy producers are demanding more accountability of economic consequences of mastitis therapy, consumers, and thus regulatory bodies, are elevating their perception of food safety. We must rethink our approach to mastitis therapy so that any new technologies will meet the criteria of efficacy, cost effectiveness, and decreased residue risks. Particularly in the case of more chronic infections, I propose that we maintain our interest in bacteriology and pharmacology, but increase our awareness of the cow's immune status as well. This may result in better realization of our therapeutic expectations.

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