

Québec/2004 Canada



23^e Congrès mondial de buiatrie • Québec, Canada, 11-16 juillet 2004
23 Congreso Mundial de Buiatria • Québec, Canada, 11-16 de Julio 2004

23rd World Buiatrics Congress • Québec, Canada, July 11-16, 2004
23. Welt-Kongress für Buiatrik • Québec, Canada, 11.-16. Juli 2004

ACUTE MASTITIS: REVISITING THE GOALS OF THERAPY

Dawn E. Morin, DVM, MS, DACVIM
University of Illinois, Urbana, IL 61802

Acute clinical mastitis affects dairy cows throughout the world and has a substantial impact on farm economics, milk quality, and cow welfare. Dairy producers and veterinarians must make clinical mastitis treatment decisions or recommendations on a frequent basis. Despite more than a century of research and a tremendous amount of field experience, clinical mastitis remains a frustrating disease to treat. Some cows die, become agalactic, or fail to return to profitable milk production despite aggressive and expensive treatment. Other cows experience recurrences of clinical mastitis after treatment or have persistently high somatic cell counts in their milk. Some producers avoid antibiotic therapy in cows with acute clinical mastitis because they believe it is ineffective and increases milk discard time and residue risk. Producers that use antibiotics often administer a short course of treatment or are quick to change drugs when immediate improvement is not observed. Non-approved drugs and even illegal drugs are used when labeled treatments are deemed unsatisfactory. It is time to critically evaluate clinical mastitis treatment practices on dairy farms, identify reasons for treatment failures, and make biologically-plausible, evidence-based treatment recommendations.

The outcome of clinical mastitis is influenced by a variety of factors, including the effectiveness of the cow's immune response, the severity of mastitis at the onset of treatment, the duration of infection at the onset of treatment, the causative pathogen, and the drug regimens and ancillary measures used. Treatment failures are usually attributed to poor drug efficacy, when in fact, cow or pathogen factors, or how we use the drugs, may be responsible. For a successful mastitis treatment program, we must manage cows to promote good immune function, know the pathogens responsible for clinical mastitis in a herd, and carefully choose which cows to treat. Once a decision is made to treat, we must avoid drugs and practices that are ineffective or potentially detrimental (*first do no harm*). Drugs must be used in appropriate doses, by appropriate routes, at an appropriate frequency, and for an adequate duration to achieve the desired outcome.

In my opinion, the desired outcome for most clinical mastitis episodes should be clinical and bacteriologic cure and return to profitable milk production. Clinical cure without bacteriologic cure can result in recurrence of clinical mastitis, transmission of infection to other quarters and other cows, and persistence of high somatic cell counts, even when infections are caused by environmental pathogens.^{1,3,9} Clinical cure alone might be acceptable if the intent is to recover a sick cow for salvage or temporarily reap profit (milk, calf) from a cow with a non-curable infection, as long as measures are taken to limit transmission risk. Because assessment of

bacteriologic cure requires multiple milk cultures, it is not practical to assess bacteriologic cure for all clinical mastitis episodes. Alternatives are to use published treatment regimens with high bacteriologic cure rates for the mastitis pathogens of concern (if available), or to determine bacteriologic cure rates for a representative subset of cows after initiating a treatment protocol. Return to low somatic cell count and profitable milk production are other desired outcomes of mastitis treatment, but milk yield may not return to normal even if clinical and bacteriologic cures are achieved. Some investigators consider return to $\geq 75\%$ of pre-infection milk production to be a satisfactory outcome for severe clinical mastitis episodes.¹⁰

Antibiotics are necessary for successful outcome of certain clinical mastitis episodes. However, antibiotic use has been discouraged because of concerns about cost, efficacy, drug residues, and potential development of antibiotic resistance. Complete avoidance of antibiotic use can result in increased severity, duration, or recurrence of mastitis and adverse effects on milk quality.^{1,9} Our goal should not be to avoid antibiotics, but to avoid unjustified, unnecessary, or inappropriate antibiotic use. The remainder of this manuscript is devoted to judicious antibiotic use.

Know the pathogens responsible for clinical mastitis in the herd. Even experienced veterinarians cannot accurately predict the organism responsible for an episode of clinical mastitis on the basis of clinical signs. A cow with a swollen mammary gland and clots in the milk might be infected with *Streptococcus uberis*, *Escherichia coli*, *Staphylococcus aureus*, *Mycoplasma bovis*, *Prototheca zopfii*, or a number of other pathogens; the effectiveness of antibiotic treatment would vary markedly depending on the causative pathogen. In some herds, it is feasible to culture milk from all cows with clinical mastitis before initiating treatment; for mild episodes of clinical mastitis, waiting up to 24 hours for culture results before beginning treatment is unlikely to be detrimental to the outcome.⁷ In herds in which culturing each cow is not practical, it is still important to determine the pathogens most frequently responsible for clinical mastitis so that appropriate treatment and prevention recommendations can be made.

Carefully select cows for antibiotic treatment. Some cows with clinical mastitis will recover spontaneously and are not likely to benefit from antibiotic treatment. Others will die, fail to return to profitable milk production, or have chronic mastitis despite treatment. The cows most likely to be helped by intervention are the ones we should focus our treatment efforts on.

Certain mastitis-causing pathogens, such as *Mycoplasma*, *Prototheca*, *Nocardia*, *Pseudomonas*, and yeast are non-responsive or poorly responsive to antibiotics. Antibiotic therapy would be expected to fail and should be avoided in these cases (hence the importance of knowing the pathogens causing clinical mastitis in the herd). Mildly affected cows with no bacterial growth or a low concentration of *E. coli* in milk also are unlikely to benefit from antibiotic therapy.⁷ On the other hand, resolution of mastitis caused by *Streptococcus* species is enhanced when intramammary antibiotics are used, and antibiotic therapy should not be avoided in such cases.^{8,15} Schemes to predict the outcome of severe clinical mastitis can assist producers and veterinarians in determining which cows to treat and which to euthanize (or stabilize and cull).¹³

A small number of cows in a herd are often responsible for a relatively large proportion of clinical mastitis episodes. Cows with repeated episodes of clinical mastitis during a lactation are poor treatment candidates and alternatives should be considered (such as culling, early dry off, or cessation of lactation in the affected gland). A number of cow-level factors have been identified that influence the response of *Staphylococcus aureus* mastitis to antibiotic treatment; these include parity, stage of lactation, quarter (hind vs front), somatic cell count, and duration of infection.^{11,12} Consideration of these factors can assist producers and veterinarians with antibiotic treatment decisions.

Initiate treatment promptly. Antibiotic treatment is most likely to be effective if initiated early in the course of clinical mastitis. Delaying treatment for several days can allow potentially susceptible pathogens, such as *Streptococcus uberis* and *Staphylococcus aureus*, to become well established and evade treatment and host defenses. Failure to examine milk before each milking may allow mild clinical mastitis episodes to go undetected until they are well established.

Choose appropriate antibiotics. Banned drugs (such as fluoroquinolones or potentiated sulfonamides in the US) must not be used for treatment of mastitis, even if they have been shown to be effective in other countries. Antibiotics labeled for treatment of mastitis should be used whenever appropriate (eg, in treatment of *Streptococcus agalactiae* mastitis). However, extra-label use may be indicated when no drugs are labeled for a particular type of mastitis, or labeled drugs are ineffective when used according to label instructions. Extra-label drug use requirements must be met, including avoidance of violative residues in milk and meat.

The spectrum of activity must be considered when selecting an antibiotic; for example, erythromycin, pirlimycin, and penicillin, all labeled for treatment of mastitis in the US, are not expected to be effective in cows with coliform mastitis because of resistance of coliform bacteria to these drugs. Antimicrobial susceptibility test results should not be relied upon for drug selection, as the cut-points used for most antibiotics are based on serum or interstitial fluid concentrations in humans after oral or intravenous dosing and cannot be assumed to be relevant to the treatment of mastitis.² There is no substitute for assessment of antibiotic efficacy in vivo.

Use pharmacokinetic/pharmacodynamic principles when designing antibiotic treatment regimens. The targeted compartment (milk, mammary tissue, blood) should be considered when choosing an antibiotic treatment regimen. In streptococcal mastitis, organisms reside mainly in the milk compartment and intramammary antibiotic therapy is appropriate; there is little benefit to using parenteral antibiotics.⁸ On the other hand, cows with severe coliform mastitis are often bacteremic, and parenteral antibiotic administration may improve the outcome.^{5,14} If MIC values are available, the likelihood of exceeding MIC₅₀ or MIC₉₀ values in the targeted compartment with different treatment regimens can be estimated; this can help avoid regimens that are not likely to be effective.⁵ However, regimens that are predicted to be effective can fail for a variety of reasons. For example, intracellular or walled-off organisms, such as *Staphylococcus aureus*, may not be effectively reached even though MIC values are exceeded in the milk compartment.

For most antibiotics, time above MIC is a critical determinant of efficacy.⁵ Intramammary antibiotics are typically labeled for 2 or 3 treatments 12 or 24 hours apart, which may not allow drug concentrations in milk to exceed MIC for a sufficient length of time in some infections. Improved clinical and bacteriologic cure rates have been observed for *Streptococcus uberis* and *Staphylococcus aureus* mastitis when intramammary antibiotics were administered at increased frequency or for longer duration;^{6,8} this requires extra-label drug use, but is more prudent than using a sub-therapeutic regimen.

In summary, judicious antibiotic use is necessary for successful mastitis treatment programs. Case selection is critically important in order to avoid unnecessary antibiotic use, which is costly to the producer and of concern to the public. Appropriate drug selection and the timing, dosage, frequency, and duration of treatment can have substantial impacts on the outcome. Antibiotic treatment regimens should be designed with veterinary input and monitored for efficacy. The aim is to know when to treat and to treat for success.

Abstract

En dépit d'une expérience étendue de recherches et de champ, la mastite clinique reste une maladie de frustration à traiter. La mort, le manque de retourner à la production laitière profitable, la mastite clinique persistante ou récurrente, ou le compte constamment élevé de cellules somatiques peuvent se produire chez les vaches traitées. Ces conséquences sont habituellement blâmées sur l'efficacité faible de drogue, quand les facteurs de vache ou de microbe pathogène ou comment nous employons les drogues peuvent être la cause. Ce manuscrit se concentre sur l'utilisation judicieuse des antibiotiques dans le traitement clinique de mastite. L'utilisation antibiotique judicieuse exige la connaissance des microbes pathogènes faisant éviter la mastite clinique et le choix rigoureux des points de droit pour le traitement afin de l'utilisation antibiotique inutile ou inadéquate quand des antibiotiques sont indiqués, la drogue utilisée et la synchronisation, dosage, la fréquence, durée de traitement doit être appropriée ; ceci peut rendre nécessaire supplémentaire-marquent l'utilisation de drogue dans certains cas. On ne devrait pas compter au moment l'essai antibiotique de susceptibilité pour le choix de drogue. L'efficacité des régimes de traitement doit être surveillée pour déterminer si les résultats désirés sont réalisés. Les résultats désirés sont dans la plupart des cas traitement clinique et bactériologique rapide et retour à la production laitière profitable.

Selected references

1. Cattell MB. An outbreak of *Streptococcus uberis* as a consequence of adopting a protocol of no antibiotic therapy for clinical mastitis. In: Proceeding. Natl Mastitis Counc 1996;35:123-127.
2. Constable PD, Morin DE. Treatment of clinical mastitis: Using antimicrobial susceptibility profiles for treatment decisions. *Vet Clin N Amer Food Anim Pract* 2003;19:139-155.
3. Dopfer D, Barkema HW, Lam TJGM, et al. Recurrent clinical mastitis caused by *Escherichia coli* in dairy cows. *J Dairy Sci* 1999;82:80-85.
4. Erskine RJ, Bartlett PC, VanLente JL, et al. Efficacy of systemic ceftiofur as a therapy for severe clinical mastitis in dairy cattle. *J Dairy Sci* 2002;85:2571-2575.

5. Erskine RJ, Wagner SA, DeGraves FJ. Mastitis therapy and pharmacology. *Vet Clin N Amer Food Anim Pract* 2003;19:109-138.
6. Gillespie BE, Moorehead H, Lunn P, et al. Efficacy of extended pirlimycin hydrochloride therapy for treatment of environmental *Streptococcus* spp and *Staphylococcus aureus* intramammary infections in lactating dairy cows. *Vet Ther* 2002;3:373-380.
7. Hess JL, Neuder LM, Sears PM. Rethinking clinical mastitis therapy. In: *Proceedings Natl Mastitis Counc* 2003;42:372-373.
8. Hillerton JE, Kliem KE. Effective treatment of *Streptococcus uberis* clinical mastitis to minimize the use of antibiotics. *J Dairy Sci* 2002;85:1009-1014.
9. Morin DE, Shanks RD, McCoy GC. Comparison of antibiotic administration in conjunction with supportive measures versus supportive measures alone for treatment of dairy cows with clinical mastitis. *J Am Vet Med Assoc* 1998;213:676-684.
10. Shpigel NY, Chen R, Winkler M, et al. Anti-inflammatory ketoprofen in the treatment of field cases of bovine mastitis. *Res Vet Sci* 1994;56:62-68.
11. Sol J, Sampimon OC, Snoep JJ, et al. Factors associated with bacteriologic cure during lactation after therapy for subclinical mastitis caused by *Staphylococcus aureus*. *J Dairy Sci* 1997;80:2803-2808.
12. Sol J, Sampimon OC, Barkema HW, et al. Factors associated with cure after therapy of clinical mastitis caused by *Staphylococcus aureus*. *J Dairy Sci* 2000;83:278-284.
13. Wenz JR, Barrington GM, Garry FB, et al. Use of systemic disease signs to assess disease severity in dairy cows with acute coliform mastitis. *J Am Vet Med Assoc* 2001;218:567-572.
14. Wenz JR, Barrington GM, Garry FB, et al. Bacteremia associated with naturally occurring acute coliform mastitis in dairy cows. *J Am Vet Med Assoc* 2001;219:976-981.
15. Yamagata M, Goodger WJ, Weaver VMD, et al. The economic benefit of treating subclinical *Streptococcus agalactiae* mastitis in lactating cows. *J Am Vet Med Assoc* 1987;191:1556-1561.