Therapeutic Strategies for Contagious and Non-contagious Mastitis

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Abstract

In recent years veterinarians and dairymen have re-evaluated the advisability of treating clinical mastitis with antibiotics in herds where most of the clinical mastitis is caused by environmental pathogens. Most of the commercial antibiotic products available in the United States were tested against subclinical infections with contagious pathogens. A review of the current literature shows that antibiotics generally make no difference in the outcome of gram-negative intramammary infections. In gram-positive infections, the benefit of antibiotics depends on the pathogen. *Streptococcus agalactiae* infections respond well to therapy with any of the intramammary preparations available in the US. *Staphylococcus aureus* infections are generally refractory to antibiotic therapy according to the labels of the commercial tubes. The success of treatment may be increased by using antibiotics in conjunction with parenteral antibiotics or for longer durations than on the label. Coagulase-negative staphylococci generally cause mild mastitis in which antibiotic therapy makes little difference. The environmental streptococci are emerging as important and tough pathogens. Antibiotic therapy increases the success rate of treatment and may help prevent relapses and chronicity, but more research is needed in this area.

No one protocol for treatment of clinical mastitis can be applied to all farms. Recommendations should be based on analysis of bulk tank and clinical samples and of the milking and management practices on the farm. Since clinical judgment and extralabel use of drugs is generally involved, the knowledge and advice of the veterinarian are essential in developing and evaluating treatment protocols. A suggested protocol for use in large herds that have little or no contagious mastitis will be presented.

How should clinical mastitis be treated on farms?

Mastitis is the most common cause of antibiotic use in adult dairy cows. In surveys of well-managed herds with somatic cell counts (SCC) under 150,000/ml and virtually no mastitis due to coagulase-positive *Staphylococcus aureus (Staph.)* or *Streptococcus agalactiae (Strep. ag.)*, 35-55% of lactations had one or more incidents of clinical mastitis.[2,4,7,8,9] In such herds, 15-40% of the clinical cases had no bacteria isolated from the milk, 21-43% had coliforms, and 9-32% had environmental streptococci. [1,2,4,7] This contrasts with high SCC herds with a significant prevalence of *Staph.* and *Strep. ag.*, where most of the clinical mastitis is caused by those organisms.[4] As more herds respond to quality incentives and stricter SCC standards by controlling the contagious pathogens, we can expect the relative importance of the environmental pathogens to continue to increase.

The decision whether and how to treat clinical mastitis is an economic one, perhaps influenced by sentiment for a given cow. The future economic value of the cow in the milking herd, which depends upon her age, conformation, past performance, and present reproductive status, must be considered. So must the costs and benefits of treatment, the value of discarded milk, the probability that treatment will fail, the likelihood of a relapse, the cow's present value as a cull, the availability of replacement animals, and the risk of errors causing antibiotic contamination of milk or the carcass. The likelihood of a treatment failure or a relapse is higher for a cow that has had previous unsuccessful mastitis treatments. Almost all studies of clinical mastitis treatment focus on bacteriological cure.

Some dairymen and veterinarians have already decided that the risks of antibiotic use in most clinical mastitis cases exceed the benefits and have stopped treating clinical mastitis cows with antibiotics in herds with a low prevalence of the contagious organisms. They emphasize protocols of frequent milkout aided by oxytocin (OT) injections and anti-inflammatory drugs, along with heightened attention to management of housing, bedding, and premilking hygiene to prevent infection with environmental pathogens.

Since 1993, several studies have compared antibiotic to non-antibiotic therapy. While the results are not conclusive, more information is now available than in the past to help dairymen and their veterinarians to make these decisions. In general, it appears that antibiotic therapy of gram-negative udder infections makes no difference to the outcome. In gram-positive infections, responds on the organisms involved. *Streptococcus agalactiae (Strep. ag.)* infections are very

responsive to intramammary antibiotics.

Staphylococcus aureus resists conventional on-label antibiotics. Extended therapies or combinations with systemic treatment may increase the cure rate, but the definition of a cure is difficult. A true cure must be evaluated by culture weeks or months after treatment. If the cow is infected at that point it is difficult to say whether the infection is a new one or the same old one. Environmental streptococci are increasing in importance as the use of bacterins against gram-negative infection reduces the severity of gram-negative mastitis. Cure rates for these infections are only in the 50-60% range at best; extended or combination therapies need to be developed and proven for these organisms. The coagulase-negative staphylococci generally cause relatively mild mastitis that is self-limiting or easily cured with commercial mastitis tubes used according to the label.

It is absolutely clear that decisions about therapy of clinical mastitis cannot be made on the basis of general rules or protocols that will fit all herds. A veterinarian's or producer's impression of whether antibiotic therapy is worth while will depend on the mix of pathogens in the herd and the chronicity of the infections. These decisions require veterinary input to determine the pattern of infection in each herd and the ability and desire of management to execute treatment protocols. Whether the advantage of antibiotic treatment is worth the risk of antibiotic residues and the loss of ability to cull the cow until the withdrawal period has elapsed is an economic decision that will vary from owner to owner and even from cow to cow.

All of the approved intramammary mastitis preparations on the market in the United States as of May, 1996, with the exception of pirlimycin, were tested against subclinical infections with gram-positive organisms. Only one has a label claim for mastitis caused by *E. coli*, which is the most frequently isolated udder pathogen in many herds with low SCC.

The pharmacology of mastitis therapy has recently been reviewed.[6,13,14] Reasons why antibiotic therapy might fail are summarized in Table 1. Most treatment studies focus on bacteriological cures. Yet subclinical infections with environmental and contagious pathogens probably exist in every herd.[4] Clinical mastitis may be due to the flareup of subclinical infection in a stressed cow, and often signs of clinical mastitis persist after bacteria can no longer be isolated from the affected quarter. In the short run, the economically important clinical outcome in the treatment of clinical mastitis is not the absence of bacteria, but rather the return of milk and udder to their normal state, so that the cow's milk can once again be sold.

All mastitis treatment studies have to define an endpoint, usually 10 to 28 days after diagnosis. Infections occurring in the same cow or quarter after this endpoint are assumed to be new infections. Absence of the original pathogen at the endpoint is assumed to be a cure. Few, if any, mastitis treatment studies focus on relapse or recurrence rate. Perusal of on-farm treatment records shows that on many farms many of the clinical cows are cows that have had bouts of clinical mastitis before. In the future, treatment studies should focus on relapse rates and should use DNA fingerprinting technology to distinguish between new and chronic infections.

Table 1. Reasons for Failure of Antibiotic Therapy of Clinical Mastitis

A. Drug cannot reach all sites of infection
1. Microabscess formation (Staph.)
2. Blockage of ducts with clots of denatured milk.
3. Poor distribution of drug in udder, due to swelling, edema, or intrinsic properties of drug.
4. Abscessation.
5. Fibrosis.
6. Intracellular bacteria (Staph.)
B. Bacteria already killed by cow's immune system before therapy begins.
C. Inadequate concentration of drug to effect killing.
1. Poor dsistribution of drug in udder.
2. Absorption of drug from milk into systemic circulation.
3. Failure of drug to be absorbed by affected tissues.
4. Drug milked out at subsequent milking.
5. Failure of parenteral drug to cross blood-milk barrier.
6. Failure of client or veterinarian to repeat treatments in time to maintain MIC in tissue long enough to effect killing.
D. Bacteria refractory to killing by drug.
1. Bacteria not in rapid growth phase required for drug to act.
2. Organism is resistant to usable antibiotics (e.g., *Pseudomonas, Mycoplasma*, yeasts, etc.)
3. Drug with gram-positive spectrum used on gram-negative infection.
4. Acquired resistance by organism.
5. Emergence of L-forms, "naked" acapsular forms that resist beta-lactam antibiotics.
E. Reinfection of affected quarter.

Controlled Field Studies of Antibiotic Therapy of Clinical Mastitis

In evaluating the results of clinical mastitis trials, practitioners should remember the effect of sample

size. A large study may show a statistically significant difference of 10% (40% vs 50%) in a cure rate, but this difference may be inapparent in the 30 or so cases of clinical mastitis that can be expected in a 100-cow herd in a year. In small studies, each pathogen is often represented by only a few cows, so that a clinically significant difference may not be statistically significant. It is also important to distinguish studies of artificially infected cows in a challenge model from those of field cases where some chronic cases would be included. In studies where the people choosing the treatment are not blinded or the allocation is not random, there is a natural tendency to use antibiotics on the more severe cases and non-antibiotic therapy on milder cases, which may bias the results toward the non-antibiotic therapy.

An Ohio study of intramammary antibiotic treatment of mastitis under field conditions that includes untreated controls[25] reported results of three treatments. Treatments occurred over an eight year period. Treatment A was 100,000 IU penicillin and 150 mg novobiocin used twice. Treatment B was the same medication used three times. Treatment C was 200 mg of cephapirin used twice. Treatments A and B were used from 1979-1985 and treatment C from 1985-87. Group D were untreated controls, which were split into two groups contemporaneous with the antibiotic-treated groups. No contagious pathogens were reported. The abstract does not state whether the treated quarters were clinically abnormal, and only bacterial cure rates are reported. For environmental staphylococci, cure rates were 62.9%, 70.4%, 67.3%, and 0-7.3% for A, B, C, and D. For environmental streptococci, cure rates were 50.21%, 58.3%, 48.7%, and 1.9-7.7%. For all coliforms cure rates were 23.2%, 13.0%, and 7.9-13.4% for B, C, and D. For *Klebsiella* sp., cure reates were 20.4%, 6.5%, and 6.3-7.7% for B, C, and D. For *E. coli* alone, cure rates were 40.9%, 25.9%, and 20-47.7% for B, C, and D. Statistical tests of results were not reported but group numbers ranged from 20 to 413. It would appear that these antibiotics were of benefit in the staphylococcal and streptococcal infections, and of marginal or no benefit in the coliform infections.

Wilson[32] reported on the results of therapy of gram-positive mastitis in a large set of data collected by the Quality Milk Promotion Services at Cornell University, where therapy and bacteriological outcome were known. Quarters were recultured within two months of the first (clinical) sample. All intramammary treatments approved in the US were represented, except for pirilimycin. Cure rates were: *Strep. ag.*: 15% untreated, 75% with antibiotics; *S. aureus*: 20% spontaneous, 26% with antibiotics; *Strep.* sp.: 19% spontaneous, 36-78% with antibiotics; *Staph.* sp.: 76% spontaneous, 72% with antibiotics; all cases: 50% spontaneous, 72% with antibiotics; all cases without the *Strep. ag.* cases: 54% spontaneous, 67% with antibiotics. It is clear from this study that the perceived efficacy of commercial intramammary tubes in a given herd will be a function of the organisms causing mastitis. Lower efficacy will be perceived in a herd with no *Strep. ag.* cases. There is some advantage to treating the non-*ag.* streptococci with antibiotics, but hardly any to treating *Staph.* Cows that were culled because of mastitis would not be represented in this data, because they would not have had a second sample. Clinical outcomes were not given.

Robertson[30] reported preliminary results of a study of therapy of clinical mastitis comparing untreated controls, frequent milkout, an unspecified intramammary antibiotic, and the antibiotic plus frequent milkout. Isolates in the first 50 cases of the study were 18% negative, 20% environmental streptococci, 24% *E. coli*, 22% *Klebsiella*, 8% *Serratia*, 4% yeast, 2% *Staph. aureus*, and 2% coagulase-negative staphylococci. When all pathogens were pooled, the antibiotic and combination therapies showed higher cure rates than the untreated controls or the frequent milkout group. There were too few cases with coliform infections to draw any conclusions. Statistical tests were not applied to the data. Veterinarians should watch further progress on this study, which directly compares frequent milkout with antibiotics.

Intramammary infusion of pirlimycin, a lincosamide antibiotic, has been found to be effective against clinical mastitis caused by gram-positive organisms in research sponsored by its developer.[26,31] These studies used both bacteriological cure and return of milk to normal as endpoints and included untreated controls. Hallberg, *et al.*[31] summarized results from 1417 cases in 118 herds; in two of the three studies there was an untreated control group. There were pathogens isolated in 79% of the cases in the two controlled studies. Statistical analysis was not provided. Success was evaluated at the 23rd milking after onset. Pirlimycin treatment increased clinical cure rate by 10-17% and bacteriological cure rate by 20-23% for all pathogens. When only gram-positive pathogens were analyzed, the bacteriological cure rate was 50.6% for the treated cows and 3.3% for the untreated controls. Clinical cure rates for the gram-positives were not reported. The clear trend in the data is that the pirlimycin-treated quarters had a higher bacteriological and clinical cure rate, especially in gram-positive infections. In an earlier study, 50 mg of pirlimycin, the dose in the commercially available intramammary product, was found to cure 66.7% (16/24) of cases of experimentally-induced *Staph.* mastitis. This cure rate was significantly different for that of untreated controls. Cure was defined as absence of *Staph.* bacteria at 11, 14, 21, and 28 d post-treatment. Cows had both subclinical and clinical mastitis in this trial.

Chamings[3] reported an 87% clinical cure rate in cows that were not treated with antibiotics for mild clini-

cal mastitis caused by *Staph.* and *Streptococcus uberis*. The bacteriological cure rate for both organisms was 19-20%. This study did not have a positive control group for comparison.

California Study of Efficacy of Intramammary Antibiotics.

A controlled study of intramammary treatment for mild clinical mastitis caused by environmental bacteria was carried out at the Veterinary Medicine Teaching and Research Center of the University of California, Davis.[24] We compared the efficacy of cephapirin and amoxicillin mastitis tubes to that of OT alone in the treatment of mild clinical environmental mastitis in 254 quarters. Both tubes were used according to label instructions. Oxytocin cows received 100 units of OT intramuscularly just before milking. No other treatments were used on cows in the study. No contagious pathogens were isolated from any of the clinical cases. Cows treated in the study had mild mastitis, that is, abnormal milk with or without udder swelling, and no signs of systemic illness, and were randomly assigned to one of the three treatments. Cows that did not improve or got worse during the observation period were called treatment failures and withdrawn from the trial. A clinical cure was the return of the affected quarter and milk to normal at the eighth milking after initial diagnosis and treatment. A bacteriologic cure was the failure to isolate the primary pathogen present at the first milking, at the eighth milking and at 20 days after initial treatment. Results are shown in Tables 2, 3, and 4. There were no significant differences in overall clinical cure rates by milking 9 days after diagnosis or in bacterial cure rate by day 21 between antibiotic- and OT-treated quarters, although there was a significant effect of antibiotics on clinical cure in the category of "other bacteria," which were pathogens other than coliforms and streptococci.

Table 2. Pretreatment bacterial isolates of 3 treatment groups in randomized field trails of therapies for mild clinical mastitis, California, 1991-1992 (%)+.

Variable	Treatment			P value
	Oxytocin	Amoxi-mast	Cefa-lak	
Coliform	33.3	41.9	37.3	0.93
Streptococcus sp.	26.7	23.0	26.7	
Other	15.2	10.8	13.3	
Negative	24.8	24.3	22.7	
Number of cows	105	74	75	

+ Of the 94 coliforms, 81 (86%) were *E. coli*. Of the 65 *Streptococcus sp.*, 27 (42%) were *S. uberis*, 19 (29%) were *S. dysgalactiae*, and 14 (22%) were *S. viridans*. Of the 34 "Other" bacteria, 14 (41%) were *Staphylococcus* sp. (primarily S. hyicus). 9 (26%) were mixed infections, 3 (9%) were *Bacillus* sp., and 3 (9%) were *Corynebacterium* sp.

Table 3. Bacterial and clinical cure (%) by treatment group and herd in randomized field trail of therapies for mild clinical mastitis, California, 1991-1992.

Herd	Treatment			P value
	Oxytocin	Amoxi-mast	Cefa-lak	
Bacterial cure %*				
Herd 1 (n=64)	10/26 (38.5)	9/20 (45.0)	11/18 (61.1)	0.33
Herd 2 (n=31)	6/10 (60.0)	6/10 (60.0)	6/11 (54.5)	0.96
Herd 3 (n=43)	12/21 (57.1)	3/11 (27.3)	5/11 (45.5)	0.27
Total (n=138)	28/57 (49.1)	18/41 (43.9)	22/40 (55.0)	0.61
Clinical cure %				
Herd 1 (n=82)	23/33 (69.7)	20/24 (83.3)	17/25 (68.0)	0.41
Herd 2 (n=86)	19/36 (52.8)	12/25 (48.0)	16/25 (64.0)	0.50
Herd 3 (n=86)	28/36 (77.8)	18/25 (72.0)	17/25 (68.0)	0.69
Total (n=254)	70/105 (66.7)	50/74 (67.6)	50/75 (66.7)	0.99

* Of 254 cases, 61 were culture negative prior to the 1st treatment, 43 were given additional treatment prior to 9th milking, 2 were treated between 9th milking and 21 days, 2 were dried prior to 21 days, 4 were culled before 9th milking, and 4 were culled before 21-day sample.

Table 4. Bacterial and clinical cure (%) by treatment group and bacterium isolated at pretreatment sampling in randomized field trail of therapies for mild clinical mastitis, California, 1991-1992.

Herd	Treatment			P value
	Oxytocin	Amoxi-mast	Cefa-lak	
Bacterial cure %*				
Coliforms (n=63)	15/26 (57.7)	8/21 (38.1)	8/16 (50.0)	0.41
Streptococcus sp. (n=49)	10/21 (47.6)	6/13 (46.2)	11/15 (73.3)	0.23
Other bacteria (n=26)	3/10 (30.0)	4/7 (57.1)	3/9 (33.3)	0.48
Positive cultures (n=138)	28/57 (49.1)	18/41 (43.9)	22/40 (55.0)	0.61
Clinical cure %*				
Coliforms (n=94)	22/35 (62.9)	21/31 (67.7)	14/28 (50.0)	0.36
Streptococcus sp. (n=65)	17/28 (60.7)	9/17 (52.9)	14/20 (70.0)	0.56
Other bacteria (n=26)	7/16 (43.7)	7/8 (87.5)	9/10 (90.0)	0.02
Positive cultures (n=138)	24/26 (92.3)	13/18 (72.2)	13/17 (76.5)	0.18
Total cultures (n=254)	70/105 (66.7)	50/74 (67.6)	50/75 (67.7)	0.99

* Of 254 cases, 61 were culture negative prior to the 1st treatment, 43 were given additional treatment prior to 9th milking, 2 were treated between 9th milking and 21 days, 2 were dried prior to 21 days, 4 were culled before 9th milking, and 4 were culled before 21-day sample. There were no contagious pathogens cultured.

In this study tubes were used strictly according to label (two doses of cephapirin and three of amoxicillin) and OT was given at three consecutive milkings. The protocol may not correspond with the way in which OT and antibiotic tubes are actually used on most dairy farms.

Further analysis of the data from two of the three herds involved in this trial by Van Eenennaam, *et al.*[29] shows that there was no economic advantage to the oxytocin treatments, despite the lower cost of treatment, because of the higher relapse rate and greater number of additional mastitis infections incurred by the oxyto-

cin group. There was no difference in the number of days of nonsalable milk over the lactations of the cows in the study between the oxytocin and the antibiotic treatments. Many of the relapses and reoccurrences in the oxytocin group occurred when the mastitic event was associated with an environmental *Streptococcus* species. It may be that in herds with a higher rate of CM infection caused by gram-negative organisms, the oxytocin-treated cows would not have experienced more reoccurrences and relapses. It should also be remembered that in this trial the antibiotics were used strictly according to the label. On commercial dairies, where antibiotics may be used for more than two or three milkings, the economic impact of oxytocin and antibiotics might be different.

It would appear, then, that the primary reason to use oxytocin as a treatment for CM rather than antibiotics, at least in herds where environmental streptococci are the predominant cause of CM, would be to allow earlier culling of treated cows and greater peace of mind to the dairyman regarding antibiotic residues in the bulk tank. While the short term outcomes are the same among antibiotic- and oxytocin-treated cows, there may be long-term benefits to using antibiotics in cows with gram-positive environmental mastitis.

Van Eenennaam, *et al.* also found that overall lactation milk production was not affected by CM, when monthly test day data was compared. These data may have masked short term milk losses that would have been obvious from daily milk yield records. Also, higher-yielding cows are more likely to develop CM, which may mask any milk yield loss caused by CM. However, cows with CM were 2.1 times more likely to be culled than herd mates.

Antibiotic Therapy of Specific Mastitis Pathogens.

Only one common pathogen, *Strep. ag.*, is highly sensitive to and easily cured by approved intramammary antibiotics used according to the label. In most herds with low SCC the prevalence of *Strep. ag.* is low or zero. Many such herds have no *Strep. ag.* isolated from bulk tank samples or clinical cows for years. In herds with *Strep. ag.* infected cows, use of intramammary antibiotics is easily justified on medical, if not economic grounds because it stops the shedding of bacteria by the cow with clinical mastitis and because *Strep. ag.* is very sensitive to all of the antibiotic tubes on the market. Treatment of clinical mastitis in lactating cows is not effective, however, in reducing prevalence in the herd unless it is part of a total control program.[11] Only an integrated program of teat dipping, milking machine maintenance, milking hygiene, and dry cow treatment can bring about a long-term reduction in prevalence.

While all mastitis tubes carry a label claim for *Staph. aureus*, the cure rate is so low when they are used according to label that dairymen are best advised to consider it negligible.[10,11,12] The cure rate in *Staph.* cows is low because the organism forms microabscesses in the udder tissue outside the ducts, where intramammary drugs cannot reach it. It also can survive inside white blood cells, makes L-forms, and can acquire resistance to commonly used antibiotics.[10] The best hope for successful antibiotic treatment of *Staph.*-infected cows is in young cows with recent infections. Concurrent parenteral treatment, repeated intramammary treatment, and use of pirlimycin may increase the chance of a cure.[10,28] In herds with a high prevalence of *Staph.* infections, the emphasis should be on teat dipping, culling, milking machine maintenance, milking hygiene, and segregation of infected cows to gradually reduce the prevalence of the infection. Antibiotic treatment may reduce shedding of *Staph.* by clinical mastitis cows and thus help reduce the spread, but it will not reduce overall prevalence in the herd significantly.[11]

A sequential therapy protocol using pirlimycin has shown some preliminary success[33,34] in increasing the dismal cure rates of *Staph. aureus* infections. The protocol involves giving two infusions 24h apart (according to the label), waiting 36h, then repeating the two infusions 24h apart, waiting 36h again, and then repeating the two infusions again. This is a total of 6 infusions designed to maintain a minimum inhibitory concentration for 10d, which is longer than the estimated life of a neutrophil in the udder (7d). The repeated infusions, especially if given in all 4 quarters rather than just the infected one, result in higher concentrations of the drug in udder tissue than are obtained with just one course of treatment according to the label. Bacteriological cure rates using this protocol have ranged from 41.5 to 62.9% (111 cases), compared to 4.2-12% in chronically infected cows in field studies.

Daley, *et al.*[36] studied the effect of intramammary recombinant interleukin 2 (RBIL-2) on artificially infected cows with *Staph. aureus*. The study excluded cows that resisted three rounds of therapy. Cure was established by 14 consecutive days of sampling of the affected quarters. RBIL-2 alone cured 31% of the quarters. Sodium cephapirin alone cured 42%. Both together cured 85%. Using the commercial cephapirin tube (Cefalak®) and RBIL-2 in combination increased the efficacy of the tube by about 20% in four trials. The range of efficacy for the combination was 38% to 85%. This experiment should be repeated with field cases and longer-term follow up.

In herds with low SCC and low prevalence of contagious pathogens, clinical experience and published surveys[1,2,4,7] show that about 15-40% of pretreatment milk samples from cows with clinical mastitis are nega-

tive for bacterial growth on blood agar. We presume that these samples containing too few organisms for a positive culture result reflect the ability of the cow's immune system to rid the affected quarter of pathogens. Antibiotic treatment of these cows is difficult to justify; the problem is that we cannot know which cows they are until after treatment has to be initiated. The aim of treatment should be to return the quarter and the milk to normal, not to prevent the spread of infection. Anti-inflammatory drugs or immune modulators would seem indicated, rather than antibiotics.

A fairly large group of so-called "minor" pathogens--minor in prevalence in the industry, not to the infected cow or her owner--are refractory to all antibiotic treatment. This group includes the genera *Mycoplasma, Pseudomonas, Pasteurella, Serratia, Prototheca, Mycobacterium, Nocardia, Bacillus*, the yeasts and fungi, and *Actinomyces pyogenes*.

In surveys of clinical mastitis in herds with low SCCs, coliform organisms account for about one-third of isolates from clinical cows. Coliform organisms can cause mastitis of severity ranging from subclinical to peracute. Erskine[5,6] has shown that clinical signs appear in experimental coliform mastitis after bacterial numbers in milk have peaked, and that treatment of these cows with intramammary gentamicin did not affect clinical outcome. Pyörälä *et al.*[35] found antibiotics to be of no benefit in experimentally induced *E. coli* mastitis. Toxic mastitis can be reproduced by infusing endotoxin without living organisms into the udder; most of the clinical signs of coliform mastitis are thought to be due to the effects of endotoxin.[5] Treatment should therefore aim primarily at removing endotoxin from the udder with frequent and complete milkout and at counteracting the effects of endotoxin with appropriate anti-inflammatory and supportive treatments, such as fluids and calcium.[28] The most important part of a treatment protocol for coliform cows is to milk the quarter out completely and often, possibly with the help of OT injections. Unfortunately, treatment must begin before the organisms involved can be identified, and the appearance of the abnormal secretions alone is not a reliable basis for an etiologic diagnosis, except perhaps in the most severe cases. No studies have established the efficacy of antibiotic treatment of chronic or mild clinical coliform mastitis. The author has observed that in herds that use bacterins for gram-negative mastitis pathogens, most gram-negative clinical mastitis cases are mild and self-limiting.

The environmental streptococci and the coliforms account for the majority of environmental clinical mastitis cases where a diagnosis is obtained. Philpot[11] cited a cure rate for clinical mastitis caused by environmental streptococci of 36%. Erskine[6] states that acceptable cure rates (>75%) are attainable with a combination of intramammary antibiotics and intramuscular procaine penicillin. G. Tyler[13] states that response of clinical *Strep. uberis* infections to antibiotic therapy during lactation is poor, although a combination of parenteral and intramammary erythromycin appears to be the most efficacious treatment. Intramammary pirlimycin appears to be a promising treatment for clinical mastitis caused by environmental gram-positive organisms. More research is needed on therapy of the environmental streptococci, which are emerging as the most costly pathogens in herds with mostly environmental mastitis that use gram-negative bacterins that reduce the severity of gram-negative infections.

The challenges in treating clinical mastitis in a herd with low SCC are the impossibility of establishing an etiologic diagnosis at the time of first treatment, the fact that about a third of cows being treated have already cleared the infection, and the fact that in the case of coliforms at least, the primary aim of treatment has to be to counteract the effects of endotoxin rather than reducing bacterial numbers. This must be accomplished without incurring undue risk of antibiotic contamination of milk.

Efficacy and Safety of Oxytocin.

I have been unable to find controlled research studies in the literature that document the effectiveness of OT therapy in clinical mastitis. One study[15] showed that OT levels were higher in cows inoculated with 12.5 or 25 mcg of *E. coli* endotoxin in two quarters than in cows infused with saline. This suggests that lack of OT is not the reason for the often-observed failure of milk letdown in cows with clinical coliform mastitis.

The optimal dosage of OT and the optimal time of administration has not been established by research. Some clinicians have expressed the opinion that a small dose should be given at the end of milking, to aid in the expulsion of residual milk and to reduce strippings. The label dose for aid in milk letdown is 10-20 IU, while that for obstetrical use is 100 IU. One researcher recently confirmed that 20 IU would elicit milk letdown in 1.5-2 minutes and would also aid in ejection of strippings milk.[16]

Oxytocin is rapidly inactivated in the body and the potential for toxicity is low. Occasional anaphylactic reactions are reported in women given OT at parturition. No ill effects on health were found in a study in which cows received twice daily doses of 20 IU OT at milking throughout lactation.[16] Reproductive performance was the same in the treated and control groups in this study.

Oxytocin is part of the normal control mechanism of luteolysis in the estrous cycle in cattle. Oxytocin is secreted by the corpus luteum and acts on uterine receptors in the estrogen-primed uterus during late

diestrus.[17] The binding of OT to the uterine receptors in turn triggers the pulsatile secretion of prostaglandin F2α (PGF) by the uterus. This positive feedback mechanism causes luteolysis and allows estrus to occur. Injection of 230 IU of OT in cows on days 2-6 of the estrous cycle caused a significant increase in PGF concentration in the blood and shortened the cycle of two of six treated cows to 10-12 days.[18] However, in another study injection of about 230 IU (.33 IU/kg) at days 5, 10, and 15 of the cycle had no effect on cycle length, estradiol, or progesterone concentrations.[19] On the other hand, continuous infusion of OT in open heifers caused lengthened estrus cycles.[17] The PGF response to OT injection is suppressed after day 6 of the cycle and restored at d 13-16.[20] Immunization of sheep against OT prolongs the luteal phase of the estrous cycle.[21] OT also has a direct inhibitory effect on gonadotrophin-stimulated steroid hormone (progesterone, in particular) in isolated luteal cells.[21] Exogenous OT does not induce parturition in late-gestation cattle.

Oxytocin also has a role in the effects of heat stress on reproduction. Chronically heat-stressed ewes have smaller lambs than unstressed ewes, partly in response to reduced uterine blood flow.[22] The decrease in uterine blood flow is accompanied by a 60% increase in serum OT. Uterine blood flow was also reduced by exogenous OT and antidiuretic hormone (ADH) injections. OT and ADH are similar in structure and are both secreted by the posterior pituitary. Heat stressed pregnant heifers tended to have a higher PGF response to the injection of 100 IU OT. Five of six heat stressed pregnant heifers, compared to 1/5 nonstressed heifers, were classified as responders to OT (PGF concentration >193 pg/ml).[23] It would appear from this study that heat stress antagonizes the suppressive effect of the embryo on uterine secretion of PGF in response to OT.

In summary, OT used at the low doses used for milk ejection has little toxic potential aside from rare anaphylactic reactions. However, at higher doses it has been reported to affect cyclicity of cows in the early and late parts of the cycle and the level of progesterone secreted by the corpus luteum. Heat-stressed animals may be slightly more likely to abort due to OT-induced PGF release from the uterus, and chronic OT administration may reduce uterine blood flow and fetal size and viability. One study reported no health or reproductive effects from twice-daily injections of 20 IU of OT.[16] Since endotoxin can cause prostaglandin release and luteolysis, it would be hard to determine whether altered cyclicity or abortion was due to mastitis itself or to OT used as an aid in mastitis therapy.

Supportive Therapy.

Many clinicians (including me) use and recommend anti-inflammatory medications in cases of severe mastitis, where there is significant swelling of the affected quarter or systemic signs of illness in the cow. There is an extensive literature on the therapy of acute toxic mastitis, and space does not permit a complete review here. There has also been some interest and research in ways to stimulate the immune response in the udder of the cow to help eliminate intramammary infections. So far, none of the immunostimulants that are available commercially have been shown to be effective, but some appear to be promising for future development.

Hogan,*et.al.*[37] tested an equine immunostimulant based on *Propionobacterium acnes* on artificially induced *E. coli* infections and found no effect in severity of clinical signs, milk bacteria counts, rectal temperature, feed intake, milk yield or milk SCC. A field study in Colorado had similar results.

Descanio, *et al.*[38] tested flunixin meglumine (1 gm IV), phenylbutazone (4 gm IV), and an IV saline control in 45 field cases of acute toxic mastitis in which *E. coli* and *Klebsiella* represented the majority of the isolates. Of the 45 cases, 35 returned to the herd, 9 were sold, and 1 died. Physical and udder variables were assessed at initial examination and at 24h. There was no significant difference among groups in need for further treatment or clinical outcome. All cows also received intramammary gentamicin (150 mg in 60 ml volume).

Shpigel, *et al.*[39] studied the effect of ketoprofen on field cases of mastitis. The article implies, but does not state, that the cows on the study had systemic signs of illness. Recovery was defined as recovering at least 75% of pre-mastitis production. The other categories were cows that lost the affected quarter for the rest of the lactation and cows that were culled, died, sold, or did not return to 75% of production. All cows received concurrent therapy with sulfadiazine and trimethoprim. In the placebo-blinded phase of the study, there was a statistically significant difference between the ketoprofen treated group and the controls. Recovery rate was 70.7% for the blind placebo controls and 92.3% for the ketoprofen cows. In a non-blinded phase of the study, the difference was not significant but there was a trend favoring ketoprofen therapy.

In three recent studies of endotoxin-induced mastitis, neither IV sodium salicylate,[40] ibuprofen[41] nor hypertonic saline therapy[42] result in significant differences from untreated controls. One can speculate that in field cases, where endotoxin may be present over longer periods than in these one-time challenges, supportive therapy may be more helpful. However, it is very difficult to do field research on acutely ill cows because of the sudden onset, low prevalence, and understandable reluctance of owners to have an untreated control group. In this area we will probably have to rely on clinical impressions for some time to

come, and the desire to do something to help the acutely ill cow will probably overcome scientific detachment anyway.

Protocols for Mastitis Treatment on Dairy Farms.

Interpretation of the literature on treatment of clinical mastitis is difficult on the farm. Farm cases represent a mixture of pathogens, and we usually do not know which pathogen we are dealing with when therapy must begin. In small herds, small differences in efficacy seen in large studies may be inapparent. In general, however, we can divide the mastitis pathogens into four groups: 1) those where antibiotics are very effective (*Strep. ag.*); 2) those where antibiotics are known to be ineffective (*Staph.* sp., coliforms, yeasts, fungi, *Mycoplasma, Pasteurella, Pseudomonas, Actinomyces,* etc.); 3) those where conventional mastitis tube therapy may help prevent relapses and chronicity (environmental streptococci); 4) those where intensive and expensive therapy may cure about half the cows (*Staph. aureus*).

In the past, the standard recommendation was to treat all cows with clinical mastitis with antibiotic tubes used according to the label. In herds with low SCC, where all clinical mastitis is caused by environmental bacteria, we can design better treatment protocols that minimize antibiotic use, reduce the risk of residues, and still allow flexibility to beef affected cows if treatment does not work. A responsible treatment protocol requires that permanent records of clinical mastitis be kept so that a cow's past history can be consulted before treatment is initiated. Since almost any rational treatment protocol for clinical mastitis will include clinical judgment and off-label treatments, the cooperation of a veterinarian is essential for its design and implementation.

Any treatment program should be monitored with bulk tank samples, milking time observation, and samples from clinically affected cows. This was dramatized in the case reported by Cattell[43] in which the adoption of a non-antibiotic treatment program for clinical mastitis was followed by a severe outbreak of *Strep. uberis* mastitis. Milkers had not been forestripping the cows before the outbreak.

Clinical mastitis should be classified before treatment as mild or severe. Mild mastitis would be characterized by abnormal milk and slight udder swelling, while severe mastitis would include abnormal milk, severe swelling, the risk of losing the quarter, and systemic illness (fever, off feed, diarrhea).

Before a protocol is put in place, the veterinarian should collect and analyze the results of sampling of clinical mastitis cows to determine the pathogens generally involved on the particular farm in different seasons. On a farm where clinical mastitis is caused by *Strep. ag.*, for example, antibiotic tubes should be used on all clinical cases. On a farm where a third of the clinical samples show no growth and a half yield *E. coli*, antibiotic use may be justified for very few cows. In a herd with a high incidence of environmental gram-positive infections, pirlimycin or some combination of intramammary and systemic antibiotics may be effective. The veterinarian should also consider the milking procedures used on the farm, the pre- and post-milking hygiene practices, and the management ability of those who will be doing the treatments in designing a protocol.

Dairy personnel should be trained to look at the cow's record before beginning a course of lactating cow treatment. The people making the treatment decisions, usually milkers or herdsmen, need to be trained and trusted to make these decisions properly. The veterinarian and the owner should develop a treatment protocol based on the known past history of pathogens in the herd, age of the cow, reproductive status, milk yield, relative value in the herd, past mastitis history, other unsoundnesses (locomotor problems, poor udder conformation, etc.), and the severity of clinical signs. For example, a cow that is below the herd average, open, and late in lactation will most likely be culled eventually anyway and might as well be culled now that she has mastitis. An average first-lactation cow that is late in gestation should be dried off early, since dry cow preparations are stronger, stay in the udder longer, are more likely to clear up the infection than lactating cow tubes, and present less risk of contaminating the bulk tank with antibiotics. Cows with persistent or recurring infections despite past treatment are unlikely to respond to a repetition of the same treatment protocol. The risky approach on these cows is to turn to extralabel use of parenteral antibiotics, with all of the risk of illegal residues it entails. A safer approach is to evaluate the cow's record and the severity of the infection and decide either to cull the cow, dry her off, treat her, or to let her recover on her own. A young, high-yielding cow in early lactation with mild mastitis might be treated aggressively.

Treatment protocols should be modified to fit the culling philosophy and goals of each producer. A producer who is trying to build up herd numbers, for example, may be more inclined to dry off a pregnant cow with clinical mastitis than one whose facility is overcrowded and is looking for room for a new heifer.

On large dairies an aid in the management of clinical mastitis is to have a designated mastitis string, which is milked last, just before the hospital or antibiotic string. The mastitis string is milked into the bulk tank. It contains all cows that have had clinical mastitis during the current lactation, chronic high SCC cows, and cows known to be infected with *Staph.* that the owner does

not want to cull. On some dairies it might include slow-milking cows and cows with poor udder shape that require extra attention at milking time. On others, the slow cows are in a separate group. Cows in the mastitis string are generally not to be treated with antibiotics when they get clinical mastitis again. They are either culled, or milked out with the aid of OT injections until their milk is normal. Since abnormal milk may not be put into the bulk tank, cows in this group with clinical mastitis must either be milked into a separate bucket or put in the hospital string until their milk is normal. Cows may leave the mastitis pen only to be dried-off or culled, or if their individual SCC remains below 200,000 for three consecutive test days and they are not known to be infected with a contagious pathogen.

On dairy farms where facilities permit, one small pen may be designated a non-antibiotic hospital. This pen can then be milked at twice the frequency of the other pens by bringing the cows to be milked in the middle of each shift. Since no antibiotics are used in this pen, the pipeline does not have to be washed after it is milked, and the milk can be diverted to calf milk or down the drain.

Here is a suggested treatment protocol for dairy farms with no clinical mastitis caused by contagious organisms. It is assumed that the cow in question is considered to be worth treating. Cows that have had more than three or four bouts of clinical mastitis in a lactation should be considered for the chronic pen, culling, or dying off. Very mild cases, where a few flakes of garget in the first squirts of milk give way to normal milk, would be recorded but milked into the bulk tank. In mild cases where milk remained abnormal but the cow was not off feed or depressed, the cow would be milked more frequently than normal with the aid of OT injections. A sample would be taken at initial diagnosis, frozen, and discarded if the cow responded to the frequent milkout treatment. If the quarter did not improve rapidly, the sample would be taken to the laboratory. If the bacteria isolated are susceptible to treatment, antibiotic treatment would be initiated. If not, the cow would continue on frequent milkout, or the quarter would be dried off or the cow sold. In cases of severe, acute mastitis in which the cow becomes depressed and goes off feed, treatment would emphasize frequent milkout, use of anti-inflammatory drugs, and supportive care. **With this treatment protocol antibiotic use is limited to the comparatively small group of mastitis cows that will benefit from it, and residue risk is greatly reduced.**

Treatment of clinical mastitis is the most common use of antibiotics on dairy farms and the most common cause of illegal antibiotic residues. On well-managed dairy farms, most mastitis is caused by the environmental pathogens. With the use of bacterins that reduce the severity of gram-negative infections, the environmental gram-positive pathogens are becoming more important clinically. Highly effective therapies for these pathogens have not yet been developed, although existing therapies seem to be better than non-antibiotic treatments. The knowledge and experience of the veterinarian are essential for developing treatment protocols that greatly reduce the use of antibiotics and decrease the risk of violative residues, while still minimizing chronic and recurrent infections and elevated bulk tank somatic cell counts. These protocols must be designed to fit the pathogen profile of each herd and the goals and preferences of the owner and manager.

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Abstract

Neonatal mortality in a pair of identical twin calves: clinical and post mortem observations

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Parturition was induced, on day 278 of pregnancy, of identical twin male Blonde d'Aquitaine calves; the parturition was assisted by gentle traction. The calves died approximately four minutes and eight hours after birth. Detailed post mortem examinations revealed soft tissue hemorrhage, fractured ribs and intrapulmonary amniotic material. The calf which lived for four minutes had persistent fetal atelectasis and a solitary cartilage embolus in a meningeal vein. Atrioventricular valvular telangiectases were incidental findings in both calves. The observations suggest first that parturient trauma may contribute to neonatal mortality, secondly that the need for intensive neonatal care may be greater than is usually considered appropriate, thirdly that a post mortem examination may reveal unexpected lesions whose effects may contribute to the calves' failure to thrive, and finally that a critical assessment of neonatal pathology is restricted by the lack of data on the perinatal physiological status of the bovine dam and fetus.