Mastitis Therapeutics

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Mastitis remains the most frequent cause of antibacterial use on dairy farms and is one of the most costly diseases for the dairy industry. The objective of therapeutic interventions are 2 fold, first to mitigate losses associated with clinical disease and secondly to prevent new infections and recurrent disease episodes by hindering the establishment of new infections and by eliminating bacteria from infected quarters. The therapeutic susceptibility of bovine mastitis pathogens varies among the different pathogens hence a herd mastitis pathogen profile is useful for formulating a general herd level mastitis therapeutic plan. On those properties that regularly culture milk from cows with mastitis therapeutic interventions may, when necessary, be tailored for the individual cow.

Establishing a Diagnosis

Mastitis is usually diagnosed on the basis of clinical signs plus or minus bacterial culture of milk samples to identify the infecting organism. Approximately 30 – 35% of bacteriologic cultures of milk samples collected from cows with clinical mastitis will not yield any microorganism. Inflammation within the gland may eliminate the pathogen or the number of organisms present may be below the limit of detection. The isolation of multiple pathogens from a single milk sample is suggestive of sample contamination and should be verified by repeated sampling. Sample contamination usually reflects poor asepsis during sample collection.

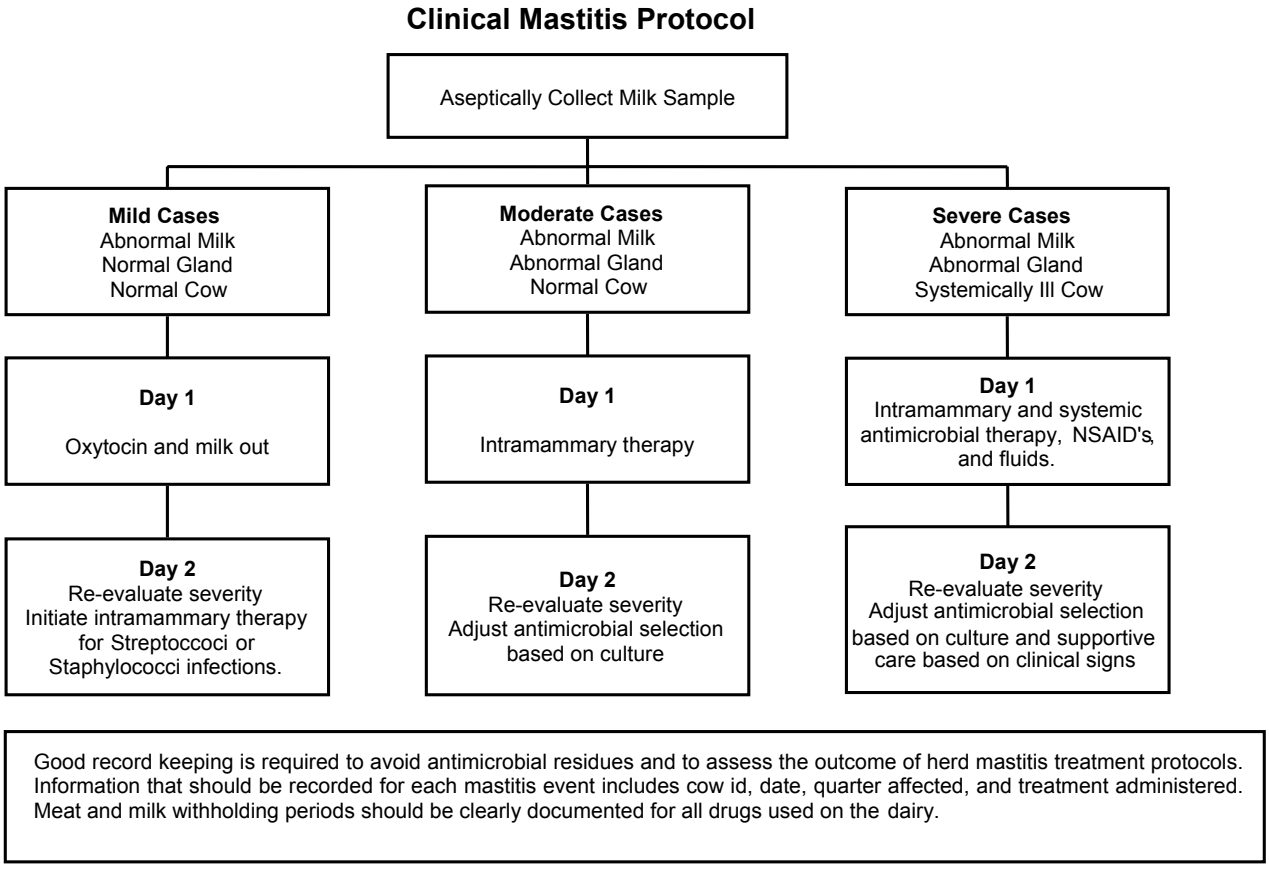
Milk cultures are normally performed using blood agar, with the identity of bacterial isolates verified using a series of simple tests. The process of isolating and identifying bovine mastitis pathogens may be enhanced by plating milk on selective agar in addition to blood agar. Modified Edwards media facilitates identification of *streptococci* and MacConkey agar is useful for identification of coliforms. Tri-plates containing one third blood agar, one third modified Edwards media, and the last third MacConkey agar provide a relatively inexpensive primary isolation medium. The only limitation of this system is that it will not identify the presence of *Mycoplasma spp*. When mycoplasma is suspected, milk needs to be plated on a mycoplasma selective media and incubated in a CO_2 incubator or under micro-aerophillic conditions.

When assessing the efficacy of antimicrobial therapy it is important to recognize the distinction between clinical resolution and bacteriological cure as clinical resolution is frequently observed in the absence of bacteriological cure. Therapeutic cures are usually based on culture results. The sensitivity and specificity of milk cultures varies according to the methodology employed. Variables that may impact the results of milk cultures used to assess therapeutic outcome include the number of times a quarter is sampled, the volume of milk inoculated for culture, and the time period after therapy when sampling occurs. Apparent bacteriological cures may reflect false negative cultures. This is particularly true for invasive pathogens such as *Staph. aureus* and *Strep. uberis*, *Pseudomonas*, and *Klebsiella*. Bacteria exposed to antimicrobials may be injured and fail to grow when cultured. A 30 day refractory period of decreased probability to isolate bacteria in milk has been demonstrated for *Staph. aureus* intra-mammary infections. Chronic intramammary infections are often associated with intermittent shedding of bacteria in milk. Collection of multiple samples following treatment reduces the risk of incorrectly classifying an infection as cured.

Clinical Case Definition

The severity of clinical mastitis represents a continuum from mild to life threatening. From a therapeutic perspective this continuum is important as the implications and needs of patients at different ends of the clinical spectrum are very different. A number of clinical parameters have been evaluated as predictors of severity. These variables include rectal temperature, rumen motility, hydration, characteristics of the secretion, respiratory rate, heart rate, and characteristics of the gland. Considering most mastitis therapies are administered by farmers or employed labour, algorithms for therapeutic interventions need to be based on easily recognized parameters. Simple classification of mastitis as mild, moderate or severe based on the characteristics of the milk, mammary gland and cow health, provides a clear case definition. Mild clinical mastitis is characterized by abnormal secretion associated with a normal gland and no systemic signs of disease. Moderate severity is reflected by abnormal secretion and gland without evidence of systemic disease, and severe clinical mastitis is indicated by abnormal secretion, abnormal gland and systemic signs of disease (depressed mentation, dehydration, anorexia, fever, paresis). A mastitis therapy algorithm for a progressive farm that routinely cultures milk samples from cows with clinical mastitis is presented in Figure 1.

Figure 1. Clinical mastitis treatment algorithm for a farm performing routine milk cultures.



This definition of severity is useful for outlining therapeutic protocols. The goal of antibacterial therapy is to attain effective drug concentrations at the site of infection. The classification of mastitis into mild, moderate, and severe according to the nature of the secretion and condition of the mammary gland and cow fits with the concept of three potential therapeutic targets, or pharmacologic compartments.

1. The milk and epithelial lining of the ducts and alveoli of the mammary gland.
2. The interstitial tissues of the mammary gland.
3. The cow

Non-invasive pathogens such as *Strep. agalactiae*, *Strep. dysgalactiae*, and coagulase negative *Staph. spp.* colonize the epithelial lining of the ducts and alveoli of the mammary gland. Intra-mammary therapy is generally effective for treatment of infections caused by these organisms as the drug is delivered to the site of infection. Intra-mammary treatment of the more invasive pathogens such as *Staph. aureus* and *Strep. uberis* is generally less effective in part reflecting the difficulty of delivering antimicrobials to the site of infection. Efficacy of therapy for invasive pathogens may be improved by combining intra-mammary and systemic antimicrobial therapy. Severe intra-mammary infections are often caused by coliforms. *Staph. aureus*, *Pseudomonas aeruginosa*, and *Bacillus cereus*. Bacteraemia is a common feature of severe coliform mastitis and improved clinical outcomes have been reported in cases treated systemically with oxytetracycline, ceftiofur, or trimethoprim sulfadiazine supporting the role of systemic antimicrobial therapy for these cases.

Antimicrobials in the Bovine Udder

Intra-mammary Lactating Cow Formulations: Most antimicrobials labeled for intra-mammary administration have been designed for use against gram-positive cocci and have little or no activity against gram-negative pathogens. While intra-mammary lactating cow therapy may be effective for eliminating acute infections caused by susceptible organisms the typical 24 – 36 hour duration of therapy for intra-mammary infusions limits the time period of effective concentration in the gland necessary to eliminate more chronic or invasive pathogens. Drug distribution within the gland is not necessarily uniform and the fibrosis associated with chronic infections may limit distribution of infused drugs to the site of infection. With the advent of three times a day milking the duration of effective drug concentrations may also be reduced.

***Parenteral Therapy*:** Factors that determine the penetration of antimicrobials across the blood – milk barrier include lipid solubility, extent of protein binding, and degree of ionization. Both non-polar lipid soluble compounds and polar substances that possess sufficient lipid solubility passively diffuse into milk. The rate of transfer is directly proportional to the concentration gradient between blood and milk and the lipid solubility of the drug. Since milk is acid relative to plasma the dissociation of antimicrobial compounds in milk differs from that in serum. Antimicrobials that are weak bases become more dissociated in milk and once dissociated (charged) are unable to diffuse back out. This phenomenon is referred to as ion trapping. Lipophilic basic drugs concentrate in milk. The significance of this favored distribution decreases with mastitis as mastitic milk has a higher pH than normal milk although it is still lower than the pH of serum.

Drug characteristics desirable for parenteral mastitis therapy are a low MIC for the target pathogen, high lipid solubility, and weakly basic or otherwise non-ionized in serum. Systemically administered acidic and or polar drugs (sulfonamides, penicillins, aminoglycosides, and early-generation cephalosporins) do not readily penetrate the mammary gland. Macrolides (erythromycin, tilmicosin), trimethoprim, tetracyclines, and fluoroquinolones distribute well to the mammary gland. Systemic use of antibacterials has been moderately successful for improving cure rates compared with intra-mammary infusions for chronic *Staph. aureus* infections in lactating and dry cows.

Antimicrobial Selection

Important considerations for antibiotic treatment of bovine mastitis are efficacy, economics, and potential for antimicrobial residues. Efficacy to a large degree is determined by the antimicrobial spectrum of the drug, the concentration of drug at the site of infection, and by the duration of treatment. Studies that have evaluated the efficacy of antimicrobial therapy to promote resolution of acute infections report variable effectiveness. Questions regarding efficacy of lactating cow therapy and concern regarding antimicrobial residues promoted some producers to employ a "no-antibiotic" approach to mild clinical mastitis. This "no-antibiotic" approach was associated with a higher rate of relapses and recurring cases and an increased incidence of clinical mastitis, prevalence of intra-mammary infection, and a subsequent increase

in herd somatic cell count. Despite the concern regarding the development of antimicrobial resistance associated with the use of antimicrobials to treat bovine mastitis there is evidence to indicate this is a problem. A seven year study evaluating antimicrobial susceptibility of bovine mastitis pathogens examined 2778 bacterial isolates. The proportion of bacterial isolates determined to be susceptible did not change during the 7-yr period for the majority of bacterial-antibacterial interactions tested. (Erskine et al, 2002)

Selection of antimicrobials for treatment of intra-mammary infections is often empirical based on a presumptive cause and prior historical efficacy. On those farms that routinely culture milk samples from cows with mastitis antimicrobial selection may be based on the herd's recent microbial history and results of prior antimicrobial susceptibility testing. Two methods commonly used to assess antimicrobial susceptibility are Kirby Bauer (disk diffusion) and broth dilution. With the Kirby Bauer method, radial zones of bacterial inhibition are measured and then cross-referenced to breakpoints for the particular organism. Broth dilution provides a more direct method of determining the minimal inhibitory concentration of antimicrobials for the bacterial isolate. Ideally antimicrobial susceptibility breakpoints should be derived from bacterial isolates originating from cows with clinical mastitis with consideration for the pharmacokinetics of antimicrobials in the bovine udder. The only drugs with validated veterinary breakpoints based on bovine mastitis data are pirlimycin (Thornsberry et al, 1993) and a penicillin-novobiocin (Thornsberry et al, 1997) combination used for dry-cow treatment. Unfortunately the breakpoints for classifying bacteria susceptible, intermediate, or resistant for other antimicrobials are derived from pharmacokinetic data originating from human studies. These breakpoints are not necessarily relevant to the concentration of antimicrobials in the milk of lactating dairy cows after intra-mammary, subcutaneous, intramuscular, or IV administration of antimicrobials.

Other potential limitations of antimicrobial susceptibility testing relate to the media in which the test is conducted and the use of specific antimicrobials as representative indicators to specific classes of drug. Antimicrobial susceptibility testing is usually performed on Mueller Hinton media. Relative to Mueller Hinton media, milk decreases the activity of many antimicrobials. Milk is therefore preferable to Mueller Hinton broth as a test medium for determining susceptibility of mastitis pathogens and for this reason some laboratories conduct antimicrobial broth dilution tests in milk. Extrapolation of class representative antimicrobial susceptibility to a related drug does not always accurately reflect the antimicrobial susceptibility to that drug. For example, cephapirin is a first generation cephalosporin. Cephalothin is used as a representative test antimicrobial for cephapirin yet there is a one dilution difference in MIC_{50} values for the two drugs.

There are a limited number of studies validating the capacity of antimicrobial susceptibility testing to predict clinical outcomes. The results of three field studies suggest that the MIC breakpoints for penicillin G administered parenterally for treatment of sub-clinical *Staph. aureus* infections, intra-mammary cephaprin for treatment of infections caused by gram positive organisms and parenteral trimethoprim-sulfadiazine for treatment of clinical *E. coli* infections may be valid although not necessarily optimal. In the study of sub-clinical *Staph. aureus* infections, parenteral treatment with procaine penicillin G (20,000 U/kg IM q24 hr) produced a higher cure rate in quarters infected with susceptible strains (MIC $\leq$ 0.1 ug/ml) verses quarters infected with resistant strains (MIC $\geq$ 1 ug/ml) (Ziv and Stroper, 1985). In the study examining the efficacy of cephapirin the outcome of 121 episodes of clinical mastitis were evaluated over a two year period. Overall, there was no difference in the bacteriologic cure rate at 14 or 28 days between susceptible and resistant mastitis episodes; however, clinical mastitis episodes caused by susceptible gram-positive bacteria treated with intra-mammary cephapirin had a higher bacteriologic cure rate at 28 days (85%) verses 20% for infections caused by resistant organisms (Constable and Morin, 2002). In the third study examining the outcome of systemic antimicrobial therapy for coliform mastitis a higher clinical cure rate (89%) was reported for infections caused by antimicrobial sensitive organism verses infections caused by antimicrobial resistant organisms (75%). In this study cows were administered trimethoprim sulfadiazine 48 mg/kg on the first day followed by 24 mg/kg daily (Shpigel et al, 1998).

The notion of assessing antimicrobial susceptibility to develop a "herd profile" for mastitis pathogens to facilitate future treatment decisions may be useful for detecting ß lactamase production by *Staph. aureus*

isolates and therefore for predicting treatment outcome in herds with contagious mastitis. However, the "herd profile" has little merit in herds with environmental mastitis because of the diverse source of pathogens. While in principal the use of antimicrobial susceptibility testing is desirable for guiding appropriate antimicrobial selection the methodology has not been validated for all bovine mastitis pathogens. Further research is required to define the sensitivity and specificity of antimicrobial susceptibility testing for predicting clinical and bacteriological outcomes following antimicrobial therapy.

Environmental Mastitis

Coliforms: Coliform mastitis ranges in severity from mild to severe. Treatment recommendations for mild and moderate cases of coliform mastitis are somewhat controversial. Therapeutic and spontaneous cure rates for mild clinical mastitis caused by coliforms are very similar. However improved bacteriological cure and a reduction in recurrence were reported in a comparative study of antimicrobial treatment verses supportive care.

Following experimental bacterial inoculation of the teat the number of bacteria present in milk increases rapidly with peak bacterial concentrations in milk usually observed within a few hours. The release of bacterial endotoxin stimulates influx of neutrophils which is followed by a rapid decline in bacterial numbers. Coliform infections usually clear spontaneously within 7-10 days. Inflammation and leukocytosis in the affected quarter may persist for several weeks or the quarter may become agalactic.

Many of the adverse effects observed with coliform mastitis are mediated by the release of endotoxin. Endotoxin (lipopolysaccharide) is a potent inflammatory mediator activating the cyclo-oxygenase and lipoxygenase pathways producing prostaglandins, leukotrienes, and thromboxanes. Endotoxin in conjunction with endotoxin binding protein also activates macrophages which promote the inflammatory cascade by producing the inflammatory cytokines IL1 and TNF- α. Empirical therapeutic management of severe clinical mastitis includes administration of supportive care (IV fluids for cows displaying signs of septic shock) and anti-inflammatory drugs to manage the endotoxic shock. Clinical recognition of coliform mastitis usually occurs after peak bacterial numbers have been attained. Thus by the time therapy is initiated bacterial numbers in the gland may be low and maximal release of endotoxin has already occurred. Favorable responses to anti-inflammatory therapy have been reported in experimental studies when treatment is initiated prior to or at the same time as induction of mastitis. The relevance of these experimental models to clinical practice has not been established. Glucocorticoids prevent arachidonic acid release by stabilizing cell membranes and inhibit production of adhesion molecules that facilitate migration of inflammatory cells into the mammary gland. In experimental trials with prednisolone (40 mg) and dexamethasone (30 mg) administered to cows immediately following introduction of *E. coli* into the mammary gland, treatment reduced mammary swelling and was associated with better subsequent milk production. There are no clinical studies reporting efficacy under field conditions.

Similar beneficial effects have been reported with non-steroidal anti-inflammatory drugs administered to cows prior to or at the time of intra-mammary inoculation of bacteria. Non steroidal anti-inflammatory drugs evaluated for efficacy in the management of severe coliform mastitis in the field include ketoprofen, phenylbutazone, dipyrone, and flunixin meglumide. Ketoprofen improved recovery of cows with acute clinical mastitis (Shpigel et al, 1994). In the field study evaluating phenylbutazone and dipyrone the recovery rates for the non-medicated controls, phenylbutazone medicated and dipyrone medicated cows were 81.1, 89.4 and 86.6%, respectively. The difference among groups was not statistically significant (Shpigel et al, 1996). Two field studies examining the efficacy of flunixin meglumine failed to demonstrate an increased rate of survival or milk production (Dascanio et al, 1995; Green et al, 1997). The number of cows included in these studies was 54 and 45 respectively and the dosage regimens for one study involved a single dose. Despite the lack of conclusive evidence demonstrating improved clinical outcomes non-steroidal anti-inflammatory drugs are often administered to cows with severe coliform mastitis.

Blood cultures collected from cows with coliform mastitis have demonstrated that a proportion of cows become bacteraemic. The likelihood of bacteraemia correlates with the severity of infection. Bacteraemia was detected in 4.3% of mild, 9.1% of moderate, and 42% of severe cases (Wenz et al, 2001). The results of studies evaluating the efficacy of systemic antimicrobial therapy are mixed. The discrepancy between the results of the different studies may in part be explained by the pharmacokinetic and pharmakodynamic properties of the antimicrobials utilized in the different studies. Three doses of parenterally administered trimethoprim sulfadiazine failed to achieve clinical improvement in experimental *E. coli* infections. In this study cows were administered 48 mg/kg intravenously followed by 24 mg/kg intramuscularly Q 12 hours for three treatments. Similarly systemic treatment with gentamycin also failed to improve clinical outcomes. In contrast cows in a field study of coliform mastitis infected with susceptible bacteria that were treated with trimethoprim sulfadiazine had a higher rate of recovery than cows treated with trimethoprim sulfadiazine that were infected with organisms resistant to this drug. In this study the same dose of drug was administered. Therapeutic benefit has been reported following systemic therapy with cefquinome (a fourth generation cephalosporin) 1 mg/kg by intramuscular injection Q 24 hours for two doses, intravenous oxytetracycline 16.5 mg/kg Q 24 hours, and ceftiofur 2.2 mg/kg Q 24 hours for five days. The reduction in mortality observed following administration of ceftiofur was attributed to management of bacteremia as mammary and milk concentrations of ceftiofur following systemic treatment remain below the MIC_{90} of *E. coli*.

Environmental Streptococci - Environmental streptococci are responsible for approximately 1/3 of all mastitis cases. A high rate of clinical cure is often observed for mild cases, however spontaneous bacteriologic cure may be no more than 20%. Bacteriologic cures following antimicrobial treatment range from 40 – 80%.

Controlled field studies suggest that equivalent clinical cure may be achieved with parenteral or intra-mammary therapy. However no advantage is reported using a combination of intra-mammary and parenteral treatment for environmental streptococci. Greater efficacy has also been shown following early initiation of treatment using conductivity meters to detect infected quarters. Treatment with oxytocin and frequent milking may provide clinical resolution of mild cases however it does not affect a bacteriological cure.

Coagulase-negative Staphylococci – The coagulase negative Staphylococci include *Staph. chromogenes*, *Staph. hyicus*, *Staph. simulans*, *Staph. epidermidis*, *Staph. hominis*, and *Staph. xylosus*. Intra-mammary infections are usually considered environmental in origin, however, when the prevalence of coagulase-negative staphylococcal infections in a herd increases one or two pathogen types are often isolated from most of the infected quarters implying cow to cow spread similar to contagious pathogens. The rate of spontaneous cures for coagulase negative *Staphylococcus* infections may be as high as 73% however in herds infected with *Staph. hyicus* and *Staph. chromogenes* spontaneous cure is less common (12%). Coagulase negative staphylococci infections are easier to treat than *S. aureus* infections. The efficacy of dry cow therapy is reported to be 80-100%. Antimicrobial resistance is common in coagulase-negative staphylococcal isolates, and about 88% of the isolates are resistant to at least one antibiotic. Most coagulase-negative staphylococci isolated from the bovine mammary gland are resistant to trimethoprim-sulfonamide, ampicillin, and erythromycin.

Coagulase negative staphylococci are the primary cause of intra-mammary infections in heifers at calving. Prophylactic prepartum administration of intra-mammary cloxacillin or parenteral administration of tylosin have been used to reduce the incidence of infections in herds experiencing a high rate of coagulase negative staphylococcal infections in post partum heifers.

Treatment of Sub-clinical Intra-mammary Infections

The contagious pathogens *Strep. agalactiae* and *Staph. aureus* are often the cause of sub-clinical intra-mammary infections. Therapy is administered on the premise that treatment costs will be out weighed by compensatory production gains or milk quality bonuses following elimination of infection. In the case of contagious pathogens elimination of an intra-mammary infection also removes a reservoir of infection. The efficacy of antimicrobial therapy is largely dependent on the target pathogen. The prevalence of *Strep. agalactiae* can be rapidly reduced in endemically infected herds by treating the whole herd or all the infected cows. Cure rates of 70 – 90% are reported. It is necessary to monitor treated herds using somatic cell count and bacteriology as a small percentage of cows may not respond to therapy and may need to be culled. Other streptococci causing intra-mammary infections are *Strep. dysgalactiae*, *Strep. bovis*, and *Strep. uberis*. As with *Strep. agalactiae*, most of these streptococci are very sensitive in vitro to penicillin. Despite this apparent sensitivity, these streptococcal infections are not as readily cured as those caused by *Strep. agalactiae*. Cure rates greater than 90% have been reported for infections caused by *Strep. uberis* and *Strep. dysgalactiae* strains with in-vitro susceptibility to a combination of penicillin and novobiocin, and 77% cure rates are reported for other *Streptococci*. Repeated treatment of chronic intra-mammary infections is not warranted. Drying off a chronically infected quarter is an alternative to culling the cow.

Therapeutic efficacy for *Staph. aureus* intra-mammary infection is in part dependent on the duration of the infection and duration of treatment (Sol et al, 2000). A cure rate of 70% following intra-mammary treatment with penicillin-novobiocin has been reported for intra-mammary infections of $\leq$ 4 days duration verses a cure rate of 35% in chronically infected quarters (Owens et al, 1997). Chronic *Staph. aureus* intra-mammary infections lead to fibrosis and abscessation of the gland. Therapeutic efficacy may be compromised by resistance to antimicrobials (particularly to ß lactams due to reversion to L forms) and by failure to deliver therapeutic concentrations of antimicrobial agents at the site of infection. Drug delivery is compromised by tissue fibrosis and the intracellular location of the organism. Combining intramuscular procaine penicillin G and intra-mammary amoxicillin achieved a better cure rate (18/35 infected quarters) than intra-mammary amoxicillin alone (10/40 infected quarters) in an experimental infection model in lactating cows (Owens et al, 1988). The results of other studies evaluating combinations of intra-mammary and systemic therapy for treatment of naturally occurring intra-mammary *Staph. aureus* infections have not demonstrated efficacy. Systemic oxytetracycline, in combination with intra-mammary dry cow treatment, did not improve the rate of cure for *Staph. aureus* mastitis compared to intramammary therapy alone. The rate of cure by 30 days post partum for systemic oxytetracycline (11 mg/kg daily for 4 days) in combination with intramammary cephapirin benzathine treatment was 29.4% compared with 27.5 for the cephapirin intra-mammary treatment only (Erskine et al, 1994). Systemic therapy with tilmicosin and florphenicol has also failed to improve the rate of bacteriological cure for *Staph. aureus* mastitis (Wilson et al, 1996; Owens et al, 1999). Cure rates for chronic intra-mammary infections with *Staph. aureus* are less than 20%.

Dry Cow Therapy

The dry period presents a number of challenges and benefits in regard to susceptibility to infection and opportunities for treatment. Involution of the mammary parenchyma begins 1 – 2 days after the end of lactation and continues for 10 – 14 days. During this time the gland is particularly vulnerable to new infections and in conjunction with the periparturient period constitutes the times of greatest risk for new intra-mammary infection. The rate of new intra-mammary infections is 6 times higher in the first 3 weeks of the dry period compared with the previous lactation. The rate of new intra-mammary infections in bacteriologically negative quarters that do not receive dry cow therapy is generally believed to be 8-12%. Ninety five percent of new infections acquired during the dry period are caused by environmental pathogens. Studies suggest 50% of clinical coliform mastitis cases in the first 100 days of lactation and 36% of streptococcal infections observed at calving originate in the dry period. Milk production losses in the next lactation of 35% have been reported following infections acquired during the dry period. The reduction of new intra-mammary infections during the dry period achieved by dry cow therapy has been estimated at 50-80%.

Antimicrobial residues are not an issue during the dry period, providing an opportunity to maintain therapeutic drug concentrations for longer. The objective of intra-mammary therapy is to facilitate clearance of existing intra-mammary infections and importantly to help prevent new intra-mammary infections. Sub-clinical and chronic intra-mammary infections are treated more effectively during the dry period than during lactation. Therapeutic efficacy for gram positive cocci other than *Staph. aureus* is reported to be as high as 80 – 90 %. The formulation of some products may limit efficacy for preventing gram negative infections and limited drug persistence may leave the udder unprotected in the pre-partum period. Products containing novobiocin have a short duration of persistence with only 12.5% of quarters testing positive 14 days into the dry period. Products with procaine penicillin G and novobiocin persist less than 28 days, and benzathine cloxacillin for 49 days.

A number of studies support the proposition that low-grade infections of the lactating gland by *Corynebacterium bovis* or coagulase-negative staphylococci may be protective against secondary infections by major pathogens. Other studies suggest that the rate of infection by environmental streptococci may be enhanced in quarters infected with either *C. bovis* or coagulase negative staphylococci. Dry cows infected with *C. bovis* were also reported to be more prone to environmental streptococci infections. The proposed mechanism was colonization of the teat duct rendering the gland more susceptible to bacterial invasion. This evidence suggests an additional value from dry-cow antibiotic treatment because it readily eliminates minor pathogen infections.

The practice of blanket dry cow therapy has been questioned on the basis of cost, emergence of antimicrobial resistance, and the risk of antimicrobial residues. Selective dry cow therapy is hard to justify on the basis of cost. In a study comparing selective and blanket dry cow therapy the benefits of blanket dry cow therapy included a lower rate of clinical mastitis, a marked reduction in somatic cell count, and an increased milk yield in the next lactation. There are however, reports that blanket dry cow therapy may not offer economic advantage in some herds. The difficulty in practicing selective dry cow therapy is the lack of predictive models for infection status and risk of new infections to elucidate the economic consequences of the practice.

An internal teat sealant of bismuth subnitrate applied at dry-off has been shown to be especially effective in preventing mastitis caused by *Strep. uberis* that originates in the dry period. Teat sealants however do not address existing infections.

Staphylococcus aureus –Mastitis cured by *Staph. aureus* is difficult to treat effectively and the presence of cows with chronic mastitis poses a threat to other cows in the herd. The success of treatment is influenced by the choice of drug, susceptibility of the organism, duration of treatment, immune status of the animal, and the duration of the infection. Chronic infections are more difficult to treat and the likelihood of curing a quarter is reduced 43% when a cow is infected with *Staph. aureus* in more than one quarter. Because treatment success is correlated with the duration of therapy the dry period is considered the most effective time to initiate treatment. The success of dry cow therapy is reported to be 20-70%. Elimination of *Staph. aureus* from the lactating cow is enhanced when treatment is extended over 6 – 8 days in order to maintain therapeutic levels of antibiotic. In studies in which extended therapy with commercial infusion products have been evaluated in naturally infected cows, cure rates have varied from less than 20% to over 60%, with a marked reduction in milk somatic cell count. Somatic cell count prior to treatment provides an indicator as to the likelihood of successful treatment. In cows with a somatic cell count $<$ 1 million, the cure rate can exceed 40% whereas in glands with a somatic cell count $>$ 1 million and in cows with multiple infected quarters, the cure rate is less than 20%.

Vaccination has been used in conjunction with antimicrobial treatment to enhance the clearance of *Staph. aureus* infections. In one study cows were vaccinated 2 weeks and 2 days prior to intra-mammary treatment with pirlimycin. *Staph. aureus* was eliminated from 78% of infected quarters and 79% of the cows compared with elimination of infection from 22% of quarters treated with antibiotics alone. An improvement in response to antimicrobial treatment was also reported in a second larger study in which infections from 54% of infected quarters were cleared in vaccinated cattle verses 17% cows treated with antimicrobials alone.

Occasionally a high prevalence of *Staph. aureus* infection is observed in heifers shortly after calving. Potential sources of infection include milk fed to calves and skin. Fly bite dermatitis of the teat end may be a contributing factor. Intra-mammary infusion of ß lactams 7 – 14 days before expected calving dates may reduce the rate of intra-mammary infection at calving.

Outcome Assessment

There are numerous parameters that may be utilized to assess the outcome of mastitis treatment protocols. These outcomes may include resolution of clinical signs, treatment failure rate, recurrence rate, individual somatic cell count response, and bacteriological cure. While follow up cultures are rarely performed on commercial dairies to assess infection status good record keeping and regular herd testing does allow for assessment of treatment failure rate, recurrence rate, and somatic cell response. Examples of a mastitis herd monitoring system is presented below in Figures 2-5.

Figure 2. Tracking the number of cases of mastitis and bulk tank somatic cell count helps to provide an indication of the herd mastitis control program performance.

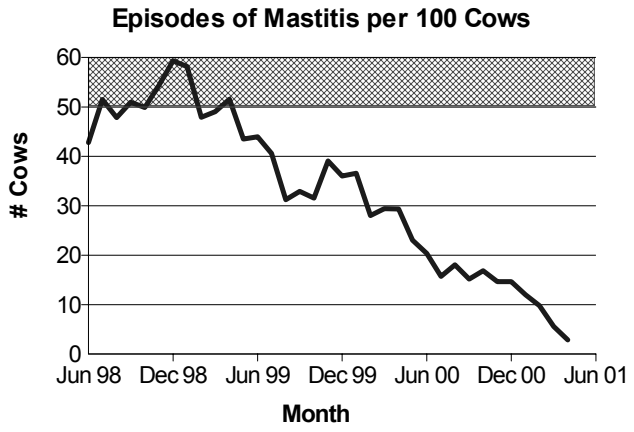


Figure 3. Monitoring the proportion of cases treated provides an indication as to the severity of the mastitis cases observed. It is also useful for providing a perspective when you monitor outcomes for medicated and non-medicated cows.

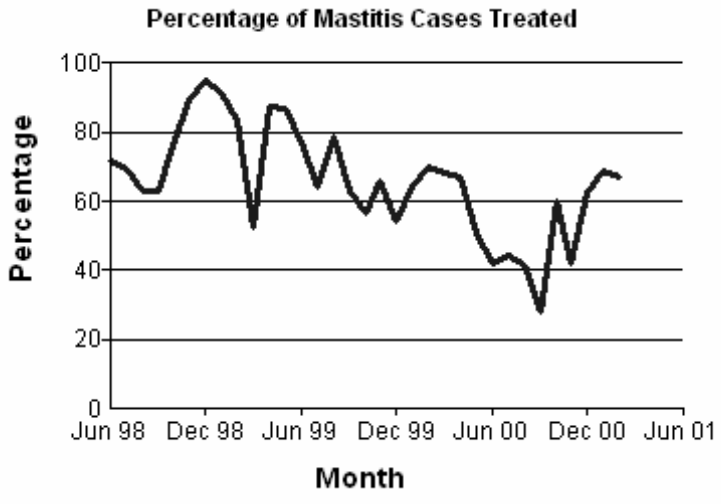


Figure 4. Monitoring the incidence of contagious pathogens provides an indication as to the adequacy of preventative and therapeutic interventions.

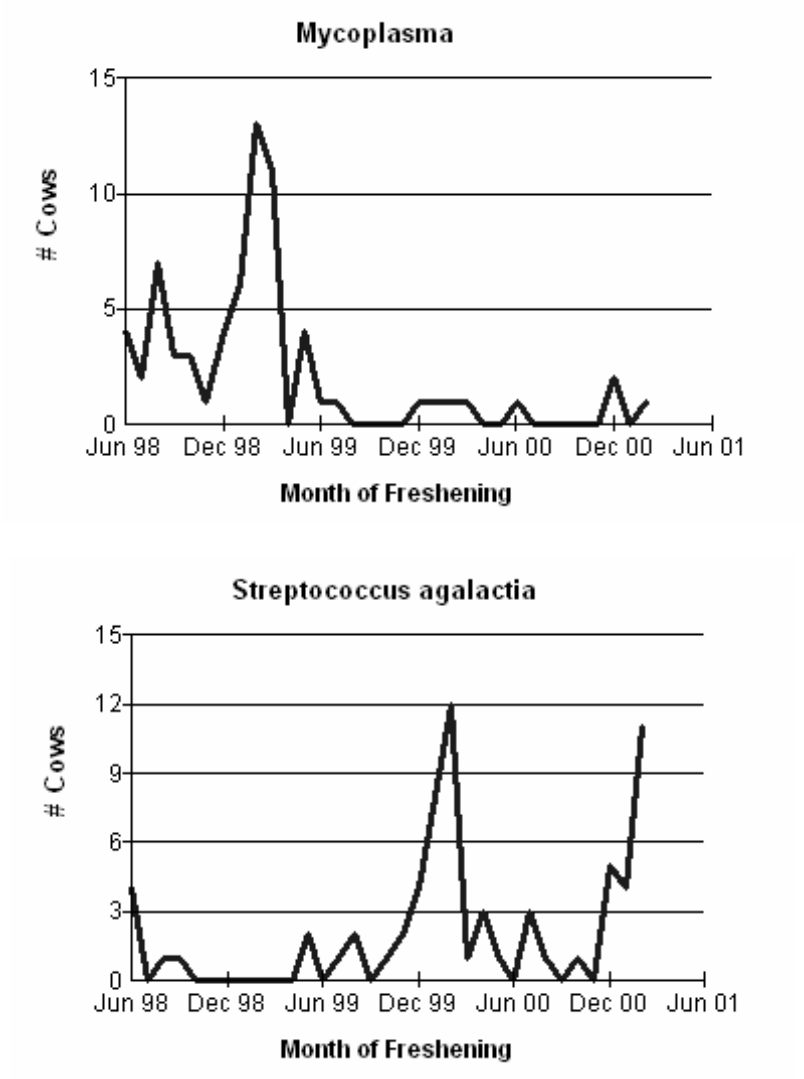


Figure 5. A relapse in clinical mastitis is regarded as a treatment failure. On the dairy on which this program was set up treatment failure was most often observed with Mycoplasma mastitis.

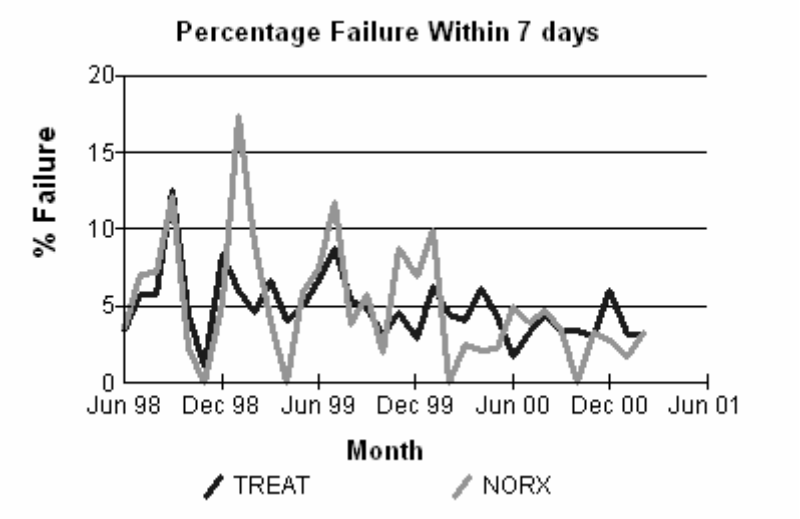
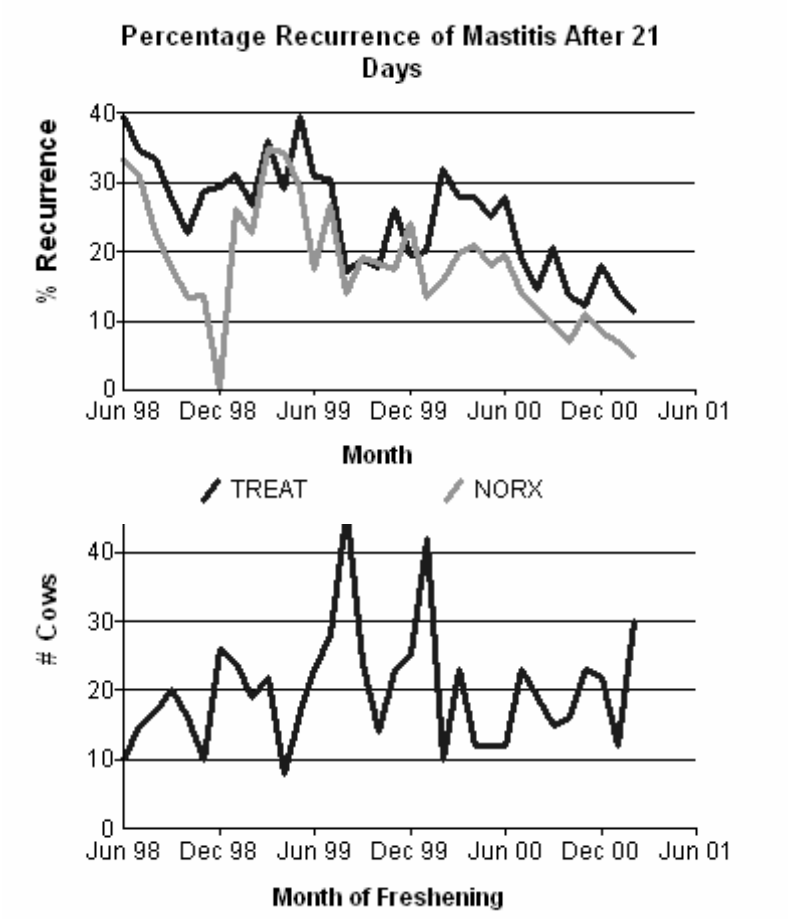


Figure 6. Reccurrent episodes of mastitis in the same quarter suggest clinical resolution was not associated with bacteriological cure. Tracking the recurrence rate is useful for monitoring the concequences associated with not initiating treatment.



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