Antibiotic treatments for bovine mastitis: Who, what, when, how and why?

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Abstract

Mastitis is the most common disease of dairy cattle, and control of this disease is responsible for the majority of antimicrobials administered to adult dairy cows. Mastitis is detected subsequent to initiation of the immune response based on recognition of inflammation. Thus, most cases present with mild or moderate symptoms, and many cases are culture-negative. Most mastitis is treated by milking technicians without diagnosis of the etiology or review of the medical history of the cow. Obtaining a microbiological diagnosis is essential because some cases may spontaneously cure or respond to short-duration therapy, some cases may require longer-duration therapy, some cases are culture-negative, and some cases are caused by pathogens for which there are no effective approved antimicrobials. Practitioners have an opportunity to reduce antimicrobial usage and improve mastitis treatment protocols by targeting treatments based on etiology and cow characteristics. Veterinarians should monitor selected outcomes after treatment and design treatment protocols based on etiological agents specific to individual cases or farms. Milking personnel should be trained to detect abnormal milk and aseptically collect milk samples, but treatment protocols should be performed by animal health managers based on etiology and review of the animal health history. The ability to achieve bacteriological cure is strongly associated with etiology and history of previous cases occurring in the affected cow. The need for antimicrobial therapy and the duration of treatment depend primarily on characteristics of the agent and the ability of the cow to initiate a strong immune response. Bacteria that have the ability to invade secretory tissue, such as *Staphylococcus aureus*, many environmental streptococci, and many strains of *Klebsiella* spp typically respond better to extended-duration therapy. In contrast, pathogens that infect superficial mucosal surfaces, such as coagulase-negative staph, *Streptococcus agalactiae*, and most strains of *Escherichia coli*) are typically cured with short-duration therapy. Producers should be trained to review the somatic cell count history of the cow and use that data to direct treatment decisions. Cows with a longer duration of subclinical infection prior to the clinical case are more likely to require antimicrobial therapy. The decision to administer antimicrobials should be based on determination of etiology by use of rapid-culture systems used either on-farm or in veterinary clinics. Many mild and moderate clinical cases that are culture-negative and detected in otherwise healthy cows can be successfully managed using a strategy of watchful waiting. Cows that are chronically affected and have frequent recurrences should not be repeatedly dosed with antimicrobials, but should either be culled or have the affected glands therapeutically dried off.

Key words: dairy, mastitis, antibiotic, treatment

Résumé

La mammite est la maladie la plus commune chez les bovins laitiers et son contrôle monopolise la grande majorité des antimicrobiens administrés aux vaches laitières adultes. On reconnait la mammite à l'initiation d'une réponse immunitaire basée sur l'observation d'une inflammation. Par conséquent, la plupart des cas impliquent des symptômes légers ou modérés et plusieurs cas sont négatifs à la culture. La plupart des cas de mammite sont traités par des techniciens laitiers sans l'établissement d'un diagnostic pour l'étiologie ou une consultation de l'histoire médicale de la vache. Il est impératif d'obtenir un diagnostic microbiologique parce que certains cas peuvent guérir par eux-mêmes ou bien réagir à un traitement de courte durée, d'autres peuvent exiger un plus long traitement ou sont négatifs à la culture alors que d'autres sont causés par des pathogènes pour lesquels il n'existe pas de traitement antimicrobien approuvé et effectif. Les praticiens ont une chance de réduire l'utilisation des antimicrobiens et d'améliorer les protocoles de traitement de la mammite en ciblant des traitements sur la base de l'étiologie et des caractéristiques de la vache. Les vétérinaires devraient surveiller certains résultats du traitement et planifier les protocoles en fonction des agents étiologiques particuliers aux cas ou aux fermes. Le personnel alloué à la traite devrait être formé pour pouvoir détecter le lait anormal et recueillir aseptiquement des échantillons de lait. Néanmoins, les protocoles de traitement devraient être administrés par les professionnels de la santé des animaux sur la base de l'étiologie et de l'histoire de santé des animaux. La guérison bactériologique sera fortement associée à l'étiologie et l'histoire des cas précédents d'une vache atteinte. L'utilité d'un traitement antimicrobien et la durée dépendent en grande partie des caractéris-

tiques de l'agent et de l'aptitude de la vache à initier une forte réaction immunitaire. Les bactéries qui peuvent envahir les tissus sécréteurs, comme *Staphylococcus aureus*, plusieurs streptocoques environnementaux et plusieurs souches de *Klebsiella* spp., répondent mieux à des traitements de longue durée. Au contraire, les pathogènes qui infectent superficiellement la surface des muqueuses (comme les staphylocoques à coagulase négative, *Steptococcus agalactiae* et plusieurs souches de *Escherichia coli*) se guérissent assez souvent avec des traitements de courte durée. Les producteurs devraient être à même de suivre l'historique des comptages de cellules somatiques d'une vache et d'utiliser ces données afin d'informer le choix de la thérapie. Les vaches dans un état d'infection asymptomatique de longue durée avant l'apparition des signes cliniques ont plus souvent besoin d'une thérapie antimicrobienne. La décision d'administrer des antimicrobiens devrait se faire en fonction de l'étiologie déterminée par des systèmes de culture rapide à la ferme ou à la clinique. Plusieurs cas cliniques légers ou modérés qui sont négatifs à la culture et détectés chez des vaches qui sont autrement en santé peuvent être gérés avec succès en adoptant une stratégie d'attente surveillée. Les vaches affectées de façon chronique qui ont des rechutes fréquentes ne devraient pas recevoir des doses à répétition d'antimicrobiens mais devraient plutôt être réformées ou subir un tarissement thérapeutique des glandes affectées.

Introduction

Structural shifts in the US dairy industry have resulted in dramatic changes in the management of dairy cows, and more than 60% of milk is produced from herds that contain more than 500 cows.[39] As herds have modernized, the prevalence of pathogens such as *Streptococcus agalactiae* and *Staphylococcus aureus* has greatly diminished.[16,22,23] On many US dairy farms, clinical mastitis is caused by a variety of environmental pathogens. The need for antimicrobial treatment to resolve infections caused by these opportunistic organisms depends on virulence characteristics of the pathogen, severity of clinical signs, duration of infection, and the ability of the cow to mount a successful immune response. No pathogens are recovered from milk samples obtained from about 25-30% of clinical cases of mastitis,[22-24] and it is difficult to justify use of antimicrobials to treat many of these cases. Some gram-negative environmental pathogens (most *E. coli*), are successfully eliminated by the cow's immune response after a brief period of mild clinical disease. Other environmental pathogens (such as *Streptococcus* spp or *Klebsiella* spp) appear to be more host-adapted, and often present as mild clinical cases that erroneously appear to resolve when the case has actually returned to a subclinical state.

As farms have expanded, detection, diagnosis, and administration of treatments for clinical mastitis have become the responsibility of farm workers. Treatment of mastitis accounts for the majority of antimicrobials administered to dairy cows,[26,32] but there is scant evidence that treatments have evolved to match the changes in etiology. Most cases of clinical mastitis present with mildly abnormal milk, and few cases are examined or treated by veterinarians.[29] Intramammary (IMM) antimicrobial therapy is the usual treatment for mild and moderate cases of bovine mastitis, and most cases are treated without knowledge of etiology.[23] In the US, almost all approved IMM antimicrobials have label indications solely against streptococci and staphylcocci. No approved IMM products are labeled for treatment of mastitis caused by *Klebsiella* spp nor for the other etiologies that account for most cases of clinical mastitis. Cephalosporins are the most commonly used IMM drugs and were administered to 65% of cases of clinical mastitis occurring on 51 large Wisconsin dairy herds.[23] Approximately 35% of these treatments were given to cases which were culture-negative at the time of detection. There is a large opportunity for veterinarians to work with dairy producers to improve mastitis therapies and ensure judicious usage of antimicrobials. The purpose of this paper is to discuss research-based principles that can help improve treatment of mild and moderate cases of clinical mastitis.

Determining the Desired Outcomes of Mastitis Therapy

A variety of outcomes have been used to assess efficacy of mastitis treatments: 1) clinical cure (return to normal appearance of milk, duration of milk discard or days in hospital pen); 2) bacteriological cure (absence of causative pathogen in follow-up milk samples); 3) somatic cell count (SCC) reduction within a defined time period; 4) recurrence of clinical mastitis case within a defined time period; 5) retention of the animal within the herd; and 6) milk production in the remainder of the lactation.[8,12-14,17,18,24,34,36] Suggested key performance indicators for clinical mastitis outcomes can be found online: http://milkquality.wisc.edu/milking-management/recordkeeping/.

It seems intuitive to evaluate mastitis outcomes based on monitoring the appearance of milk or the number of days that milk is discarded. However, this outcome has little variation and is usually greatly influenced by other factors, such as etiology, space in hospital pen, defined treatment protocols, case definition and cow factors. On most farms, mild and moderate clinical signs will resolve within 4 to 6 days, regardless of treatment. Detection of both subclinical and clinical mastitis is based on recognition of inflammation (the immune

response) resulting from the infection. Thus, return to normal milk is expected because immunologically competent cows will often successfully reduce the number of bacteria infecting the gland. Disappearance of clinical signs does not always indicate that infection has been successfully eliminated. As inflammation lessens, the milk may return to normal appearance, however, some of these cases have simply regressed to a subclinical state and maintain increased SCC.

Somatic cell reduction below 200,000 cells /mL is another desired outcome, but occurs slowly and this outcome is highly influenced by pathogen. Sixty-three percent of cases that were culture-negative or caused by gram-negative pathogens resulted in somatic cell reductions to < 200,000 cell/mL within 21 to 55 days after treatment, in contrast to only 44% of cases caused by gram-positive bacteria.[24] While long-term reductions in SCC should occur after successful therapy, short-term changes in SCC should not be used to determine when to stop therapy nor to determine if therapy has been effective. Likewise, the use of cowside tests like the California Mastitis Test should not be used to determine when to stop treatment.

Return to normal milk yield and retention within the herd are important longer-term indicators of mastitis outcomes, but these variables are highly correlated and strongly influenced by other factors. Etiology, severity, stage of lactation at occurrence of the case, parity, and number of previous clinical cases are all associated with milk production after clinical mastitis.[3,9,10,15,33] Involuntary culling is also a potential outcome that can be monitored, but the decision to remove a lactating cow is strongly influenced by milk production. In one Wisconsin study, about 13% of 143 cows with mild and moderate clinical mastitis were culled within 60 days of occurrence; however, milk yield after the case was predictive of the chance to remain in the herd.[24]

Recurrence of another case of clinical mastitis is 1 of the least desirable outcomes after treatment, and should be monitored as an indicator of mastitis outcomes. Depending on the time period that is monitored, less than 20 to 30% of cows experiencing mild and moderate clinical mastitis should have a recurrence within the next 60 to 90 days. Recurrence can result from new infections or due to a failure to eliminate infection as a result of insufficient treatment or treatment failure. Recurrence can be defined at the quarter or cow (regardless of quarter) level, and may be monitored for defined time periods ranging from 30 days[8] to the remainder of the lactation.[12,13] Like other outcomes, it is important to recognize that a number of factors influence this outcome. Recurrence is more likely for cases that occur early in lactation as compared to cases that occur later, is more common for older cows, occurs more frequently for cows that have a history of previous cases, and is more common for quarters that do not successfully result in bacteriological cure.

Bacteriological cure (BC) is assessed by comparing the presence of bacteria in milk samples collected before and after treatment, and is the standard outcome evaluated in drug trials. However, interpretation of BC is not straightforward. Issues such as the frequency of sampling, the volume of milk that is inoculated, the time period between therapy and sampling, and time between collection of consecutive samples all contribute to the wide variation in BC noted in the literature.[31] There are relatively few negatively controlled clinical trials that have been performed to evaluate BC after mastitis therapy, and interpretation of these trials is confusing because most include a variety of mastitis pathogens.[4,10,14,19,27,30,34,41] Expectations for spontaneous cure range from less than 20% for mastitis caused by *Staph aureus*[2,41] to 100% for induced *E. coli* infections.[1,10,14,27] Cases that achieve BC typically have better clinical outcomes, such as fewer recurrences and faster return to normal SCC. However, failure to achieve BC doesn't result in negative outcomes for all cases. In crude analysis of mild and moderate cases of clinical mastitis occurring on 51 Wisconsin dairy herds, the difference between pre- and post-case milk yield was strongly associated with pathogen group: -13.4 lb (-6.1 kg) (gram-negative; n = 86), -9.9 lb (-4.5 kg) (no growth; n = 83), and -8.1 lb (-3.7 kg) (gram-positive; n = 89) and was not influenced by BC.

Bacteriological cure is defined based on microbiological results and depends on etiology, severity of the case, ability of a cow to achieve a successful immune response, efficacy of the treatment protocol (when needed), and the promptness of initiating treatment.[6] Many factors other than treatment are well known to influence bacteriological cure. For example, bacteriological cure was 7 times more likely for first cases of mastitis as compared to recurrent cases.[24] Bacteriological cures are almost always greater for gram-negative, as compared to gram-positive pathogens (Figure 1).[23] While a number of outcomes can be monitored, it is important to recognize that the greatest influence on these outcomes is generally related to differences among cows and pathogens.

Selecting Cows for Antibiotic Therapy

Host factors are well known to influence the probability of success responses to mastitis infections.[1] Older cattle have a greater risk of both subclinical and clinical mastitis, and several studies have indicated that they have poorer responses to treatment as compared to younger cattle.[6] Deluyker et al used a rigorous definition of clinical cure (normal milk by 5 days and no relapse within 3 weeks post-treatment) and reported a reduction in combined "clinical and bacteriological cure

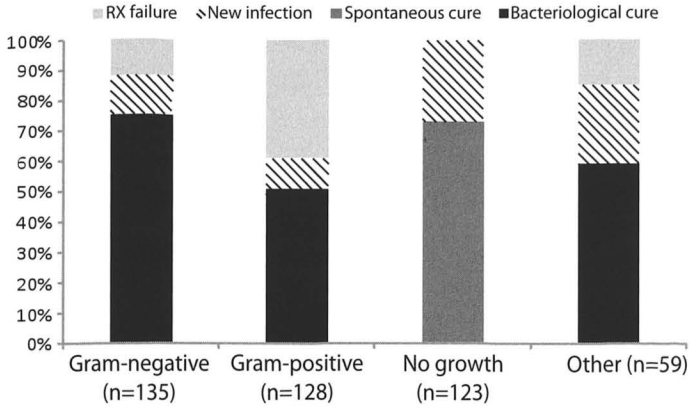

Figure 1. Microbiological outcomes based on comparison of milk samples collected at detection of clinical case and follow-up samples collected 3 weeks later.[23]

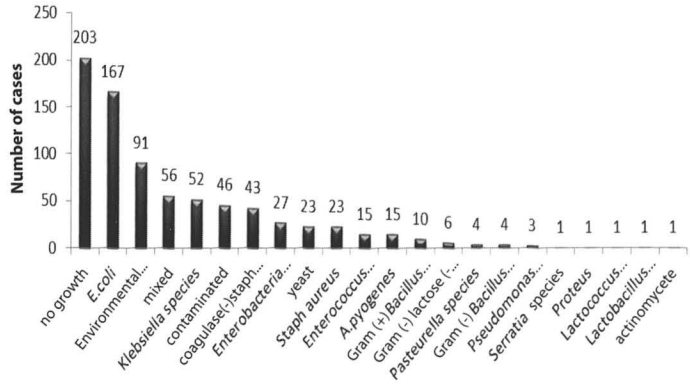

Figure 2. Results of milk samples submitted from 793 cases of clinical mastitis occurring on 51 large Wisconsin dairy farms in 2010.[23]

rates" from 39% (lactation 1) to 26-30% for older cattle.[2] Numerous other researchers have reported that bacteriological cures after mastitis therapy were less for older cows.[17,18,28,36] Age has also been associated with reduced clinical responses to therapy. Hektoen et al measured responses to treatment by comparing scores for both acute and chronic signs obtained before treatment and at various periods post-treatment.[5] While parity was not associated with differences in acute clinical signs, the reduction in chronic signs (changes in the milk, gland or inflammatory response) were markedly greater in first lactation as compared to older cattle. The effect of parity should be considered by practitioners before initiating mastitis treatments. For example, when IMM compounds are approved for extended-duration therapy, veterinarians may want to consider using longer duration of treatment for cases occurring in older cows. Likewise, older cows (greater than 3 lactations) may not be good candidates for withholding treatment if that option is used for managing some cases of mastitis on particular farms.

Differences Among Pathogens

On many modern dairy farms, mastitis is caused by an increasingly diverse group of opportunistic pathogens (Figure 2), and this change in distribution of pathogens should be considered by practitioners as they develop treatment protocols. Administration of 1 standard antimicrobial for all cows that present with abnormal milk is difficult to justify when approximately 25% of cases are culture-negative and an additional 17% are caused by pathogens for which there are no known effective antimicrobials. Common environmental mastitis pathogens include both gram-negative and -positive bacteria, and the distribution of predominant microbial populations varies among farms (Figure 3). For example, in 38 Wisconsin dairy herds, for 38% of herds greater than 40% of cases were caused by gram-negative pathogens, while for another 16% of herds greater than 40% of cases were caused by gram-positive pathogens (Figure 3). Without understanding the microbial populations, it is impossible to prescribe appropriate antimicrobial therapies.

It is well known that mastitis is caused by a diverse group of bacteria, and the probability of BC is highly influenced by the characteristics of the pathogen. The pathogenesis, virulence, and prognosis of clinical mastitis are influenced by important characteristics that vary among pathogens. Depending on specific virulence factors, organisms infect different locations in the mammary gland, have differing abilities to cause systemic signs, vary in the expected duration of subclinical phases of infection, and differ in the expected rate of spontaneous bacteriological cure. Understanding these differences is fundamental to development of effective control programs. For example, expectations for spontaneous bacteriological cure of subclinical and clinical mastitis caused by *Staph aureus* are essentially zero,[21] while the expectation for spontaneous cure of mastitis caused by *E coli* is quite high.[38] In contrast, therapeutic cure rates for several mastitis pathogens (yeasts, *Pseudomonas*, *Mycoplasma*, and *Prototheca*) are essentially zero, regardless of treatment. Even among gram-positive pathogens, outcomes vary. After equivalent treatment, the following differences in BC among pathogens have been noted: *Strep uberis* (89%, n = 488 cases); *Strep dysgalactiae* (69%, n = 32 cases), *Staph aureus* (33%, n = 40 cases), and CNS (85%, n = 71).[17] On farms that have controlled contagious mastitis, approximately 25 to 40% of clinical cases are microbiologically negative before treatment. Clinical and spontaneous cure rates for these "no-growth" samples are often very high, with or without treatment.[4,19]

Many practitioners assume that all coliform bacteria behave in a similar fashion, but there is great

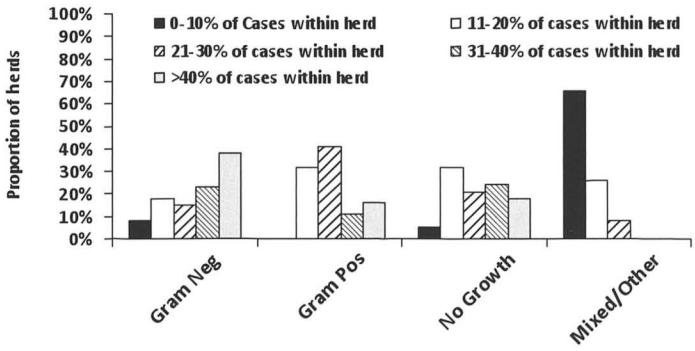

Figure 3. Distribution of common etiologies within herds for 38 large Wisconsin dairy farms.

diversity in how these pathogens behave. Most cases of clinical mastitis caused by *E coli* are detected well after the immune response of the cow has been initiated, and that response is usually successful in eliminating the infection However, the duration of intramammary infection (IMI) caused by other coliforms (such as *Klebsiella, Enterobacter*, and *Serratia*) is much longer.[37] After *E. coli* infect the mammary gland they multiply rapidly, but most do not adhere to or invade the epithelial cells.[1] If the immune response is rapid and efficient, infection will be quickly eliminated and there will be little long-term impact on cow health or productivity. The outcome of clinical mastitis caused by coliform bacteria depends on the severity of the case, which is usually dependent on the balance between the dose (relative degree of exposure to bacteria) and the ability of the cow to respond immunologically. Severe cases of mastitis occur most frequently in the periparturient period and early lactation, and are primarily associated with characteristics of the cow that influence her ability to respond to IMI.[1,17,35,40] When influx of neutrophils is delayed, or phagocytosis or intracellular killing mechanisms of neutrophils is impaired, bacterial multiplication continues, resulting in greater concentrations of inflammatory mediators and more severe clinical disease.

In contrast, mastitis caused by environmental *Streptococcus* spp typically responds well to IMM antimicrobial therapy, but has a low spontaneous cure rate and high rate of recurrence when antimicrobials are not administered.[19] These differences among pathogens demonstrate that identification of etiology is necessary in order to apply effective mastitis treatments. With current laboratory methods, it is not feasible for all farms to achieve a microbiological diagnosis before beginning therapy, but guiding treatment by use of on-farm culture systems (OFC) has been shown to be economically beneficial.[12,13] The use of OFC to direct treatment of clinical mastitis gives farmers the opportunity to make better treatment decisions and reduce costs associated with milk discard and treatment of microbiologically negative cases. A positively controlled clinical trial evaluating OFC demonstrated that there were no significant differences in either long-term or short-term outcomes for cases of mastitis that received treatment based on results of OFC, as compared to cases treated immediately without regard to diagnosis.[12,13] In this study, antimicrobials were not administered to cases that were culture-negative or gram-negative thus the use of intramammary antimicrobials was reduced by approximately 50% as compared to cases which were treated without prior diagnosis. Most smaller herds cannot adopt OFC, and an alternative is to encourage veterinary clinics to offer in-veterinary clinic culturing (IVCC). In these instances, farmers initiate treatment immediately but may modify treatment duration or drug after receiving a preliminary microbiological diagnosis within 24 hours. Development and oversight of a culture program (either OFC or IVCC) is an ideal way for veterinarians to increase involvement in mastitis control programs. The use of veterinary technicians to supervise these programs may also increase veterinary involvement and oversight of mastitis treatments. Veterinary technicians can visit farms to restock supplies, train farm personnel, and provide oversight and quality control.

Determining Appropriate Duration of Therapy

In general, duration of antibiotic treatment should be kept as short as possible to minimize the economic losses associated with milk discard while maximizing the probability of achieving BC. The appropriate duration of antibiotic treatment for clinical mastitis has not been well defined, and varies depending on the etiology. There is considerable evidence that extended administration of antibiotics increases cure rates for pathogens that have the ability to invade secretory tissue (*Staph aureus* and some environmental streps). For example, BC for subclinical mastitis caused by *Staph aureus* treated with IMM ceftiofur were 0 % (no treatment), 7% (2 days), 17% (5 days), and 36% (8 days).[21] Bacteriological cure rates reported for clinical mastitis caused by β-lactamase-negative *Staph aureus* were significantly greater when extended-duration therapy was used (50%) versus administration of 3 treatments over 36 hours (38%).[36] Likewise, BC for experimentally induced *Strep uberis* infections increased from 58% (2-day treatment) to 69-80% for treatments of 5 or 8 days.[20] Thus, for mastitis caused by potentially invasive pathogens, the duration of therapy should be 5 to 8 days. Research to support use of extended-duration therapy to treat pathogens that infect superficial tissues (for example CNS or most *E. coli*) has not been published, and the use of extended-duration therapy to treat these pathogens significantly increases costs without improving clinical outcomes.[25,34]

It is especially difficult to justify the use of extended-duration therapy to treat culture-negative cases. The difference in expected monetary value (EMV, sum of costs of positive and negative effects of treatment multiplied by the expected probabilities of those outcomes) between a 2- and 5-day treatment is approximately $50 per case.[25] For a typical 1,000-cow dairy farm, with about 400 cases per year, the decision to use standard 5-day IMM therapy reduces EMV by $16,200 per year as compared to 2-day therapy. Extended-duration therapy is not without risks. When it is considered, veterinarians should assess the ability of the farm personnel to perform aseptic infusions, as extended intramammary treatment is associated with an increased risk of infection from opportunistic pathogens, and herds with poor infusion techniques are not good candidates for multiple doses of intramammary tubes.

Recommendations for Treatment of Mild and Moderate Cases of Clinical Mastitis

While there is limited evidence regarding clinical outcomes of mastitis caused by many opportunistic pathogens, current research indicates that there is a tremendous opportunity for veterinarians to help dairy producers improve mastitis treatment protocols. These improvements can result in reduced antimicrobial usage without negatively impacting dairy animal well-being. When developing treatment protocols, the following guidelines should be considered:

1. Milking technicians should be trained to detect cases early, and aseptically collect milk samples. These samples should be used to rapidly arrive at a provisional diagnosis to guide therapy. Culturing can occur either on-farm (large herds) or in-veterinary clinics (smaller herds). Cows affected with mild or moderate cases of clinical mastitis should be isolated, and milk discarded for 24 hours, until culture results are known. If the farmer wishes to immediately initiate treatment, the treatment can be stopped or the duration can be modified after culture results are known.
2. Treatments should be administered only after a qualified animal health manager has reviewed the medical history of the cow and evaluated prognostic factors for the case.
   a. Cows that are in greater than third lactation, have a history of previous clinical cases, or have a history of chronically elevated SCC are often poor candidates for routine therapy. Treatment decisions for these cows should be based on culture results and review of treatment outcomes from similar cases on each farm. In many instances, "watchful waiting" (isolation of the cow and discard of the milk from the affected quarter) will be an appropriate therapy. In other instances, culling, cessation of lactation in an individual quarter or extended-duration therapy may be preferred.
3. Extended-duration therapy is appropriate for some cases of mastitis, but should not be the default therapy for all cases.
4. No antimicrobial treatment should be considered for cows affected with pathogens for which no antimicrobials can be expected to be successful, or for most cases that are culture-negative at detection. Watchful waiting is the appropriate strategy for these cases.
5. The use of antimicrobial treatment for mild cases of *E. coli* mastitis should be considered when review of cow-level risk factors suggests that a chronic strain is involved. In the absence of other data, a thumb-rule is to initiate therapy if the cow has had increased SCC for 2 months or more, or if the cow has risk factors that indicate her immune response may be compromised (first weeks of lactation, severe heat stress, or very high production).
6. Outcomes of treatments should be routinely monitored. At a minimum, the rate of recurrence (within 60-90 days) and SCC reduction (by 60 days) should be routinely evaluated.

Conclusions

Veterinarians should be involved in developing and implementing mastitis treatment protocols, and should work with farm personnel and other professionals to actively monitor outcomes of treatments that farm personnel administer. Research evidence is available to help guide mastitis treatment decisions and to better select animals that will benefit from specific treatments. There is sufficient research evidence to help develop mastitis treatment protocols that vary depending on animal characteristics and the history of subclinical disease. The use of OFC or IVCC is an ideal way for veterinarians to become more involved in helping farmers make rational decisions about antimicrobial therapy used for treatment of mastitis.

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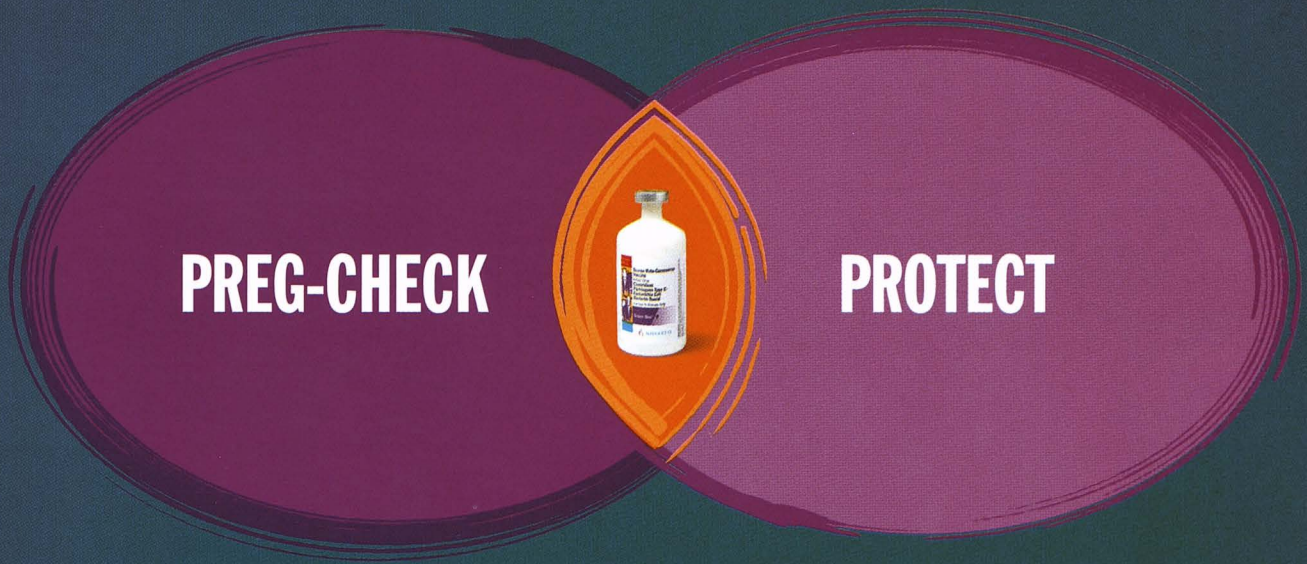

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