

Myth: Better to treat too many than not enough

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Abstract

Use of antimicrobials in animal agriculture is increasingly scrutinized, and it is important that veterinarians are engaged with farmers to ensure that they are used in a manner that meets evolving societal expectations while maintaining animal well-being and farm profitability. On most North American dairy farms, mastitis is the most common bacterial disease of cows, and is usually treated by farm workers without veterinary supervision. On most farms, treatment of mastitis accounts for the majority of antimicrobial treatments and many cases are treated symptomatically without knowledge of etiology. However, as farmers have adopted modern management practices, the distribution of mastitis pathogens has shifted and varies among farms based on differences in housing and management. On many farms, a large proportion of cases are microbiologically negative when detected, or are caused by pathogens that have high rates of spontaneous cure. Other cases are often caused by bacteria that are intrinsically resistant to available antimicrobials or occur in cows with characteristics that greatly reduce the probability that antimicrobial therapy can result in successful bacterial clearance. When antimicrobials are routinely used to treat mastitis without determining the etiology, approximately 35 to 60% of antimicrobial treatments will be of no-benefit to the cow. In an era when use of antimicrobials on farms is increasingly controversial, this is difficult to justify. To develop appropriate treatment protocols, veterinarians should review the spectrum of action of approved drugs and implement protocols that include options for managing cases that will not benefit from antimicrobial use. When possible, veterinarians should encourage farmers to use culture-based treatment protocols and review the medical history of the cow before administration of antimicrobial treatments. When culture-based protocols are not feasible, veterinarians should recommend use of approved narrow-spectrum intramammary antibiotics for short durations. There is considerable opportunity for veterinarians to promote responsible use of antimicrobials by increasing engagement with farmers in development of mastitis treatment protocols.

Key words: dairy, mastitis, treatment, culture-based

Résumé

L'utilisation d'antimicrobiens en production animale est de plus en plus scrutée à la loupe. Il est important que les vétérinaires s'impliquent avec les producteurs pour s'assurer que leur utilisation réponde aux nouvelles attentes de la société

tout en préservant le bien-être animal et le rendement de la ferme. Pour la plupart des fermes laitières nord-américaines, la mammite est la maladie bactérienne la plus courante chez les vaches et elle est traitée par les employés de la ferme sans surveillance vétérinaire. Pour la plupart des fermes, le traitement de la mammite représente le traitement antimicrobien le plus fréquent et elle est traitée symptomatiquement sans égard à l'étiologie. Avec l'adoption par les producteurs de pratiques de gestion modernes, la distribution des pathogènes de la mammite a évolué et varie d'une ferme à l'autre selon le type d'enclos et la régie. Dans plusieurs fermes, la plupart des cas détectés sont négatifs en culture microbiologique ou sont causés par des pathogènes qui ont de fort taux de guérison spontanée. D'autres cas sont souvent causés par des bactéries qui sont essentiellement résistantes aux antimicrobiens disponibles ou impliquent des vaches dont les caractéristiques réduisent grandement les chances que la thérapie antimicrobienne parvienne à éliminer les bactéries. Lorsque les antimicrobiens sont utilisés couramment pour traiter la mammite sans égard à l'étiologie, près de 35 à 65% des traitements antimicrobiens ne seront pas bénéfiques à la vache. À une époque où l'utilisation des antimicrobiens à la ferme est de plus en plus controversée, cet état de chose est difficile à justifier. Afin de développer des protocoles de traitement appropriés, les vétérinaires devraient bien connaître le spectre d'action des drogues approuvées et mettre en œuvre des protocoles qui offrent des options pour la gestion des cas qui ne bénéficieront pas de l'utilisation d'antimicrobiens. Lorsqu'il est possible de le faire, les vétérinaires devraient encourager les producteurs à utiliser des protocoles de traitement à base de culture et bien connaître les antécédents médicaux de la vache avant l'administration de traitements antimicrobiens. Si l'utilisation de protocoles à base de culture n'est pas possible, les vétérinaires devraient recommander l'utilisation d'antibiotiques intramammaires à spectre étroit approuvés pendant une courte période de temps. Les vétérinaires ont beaucoup d'occasion de promouvoir l'utilisation responsable des antimicrobiens en favorisant l'implication des producteurs dans le développement de protocoles de traitement de la mammite.

Introduction

Mastitis is a disease of the mammary gland that is detected based on observation of inflammation that is usually caused by intramammary infection (IMI) by bacteria. Depending on characteristics of the pathogen and the cow, IMI may result in subclinical and/or clinical disease. When inflammation causes visible abnormalities of milk, the mam-

mary gland or the cow, the infection is usually defined as a clinical case of mastitis (CM) and the milk must be discarded. About 10 to 15% of CM cases result in severe clinical signs with systemic effects,¹² but most clinical signs are restricted to abnormalities of milk or udder and most cannot be detected unless foremilk is observed during the milking process. While severe cases of CM are medical emergencies and treatment is usually guided by protocols developed with veterinary input, most treatments of non-severe CM are performed by farmers without veterinary supervision, and treatment of mastitis is the most common reason that antibiotics³ are used on North American dairy farms.^{17,24}

Use of antimicrobials in agricultural settings is increasingly scrutinized and must be justified as necessary to maintain animal well-being.²² Appropriate use of antibiotics for treatment of non-severe mastitis is based on assessment of etiology, review of the cow's medical history, and application of sound therapeutic principles to select among approved antibiotics.^{19,23} Some use of antimicrobials on dairy farms is necessary, but appropriate usage infers that treatment will improve the well-being of the cow. Guidelines for treatment of non-severe CM should include options indicating when use of antibiotics is not recommended and alternative strategies for managing those cases. The purpose of this paper is to review use of antimicrobials for treatment of non-severe CM to help veterinarians develop protocols that ensure responsible and justifiable usage.

Pathogen and Cow factors that Influence Responses to Therapy

Until about 30 years ago, the vast majority of bovine mastitis was caused by *Streptococcus agalactiae* and *Staphylococcus aureus*, and most treatment protocols were originally developed with those pathogens in mind.²¹ While antibiotic therapy played an important role in control of *Str. agalactiae*, antibiotics are much less effective for achieving bacterial clearance of cows with IMI caused by *Sta. aureus*.² Use of treatment protocols based on historical incidences of *Str. agalactiae* and *Sta. aureus* does not meet the needs of modern dairy farmers, as *Str. agalactiae* is almost eradicated and treatment of CM plays a minor role in control of *Sta. aureus*.¹⁵ Improvements in herd management have greatly reduced the prevalence of subclinical mastitis caused by these pathogens and is reflected in bulk tank SCC data for the US dairy herds. Between 1995 and 2015, average bulk-tank SCC in the US dropped from 304,000 to 204,000 cells/mL²⁰ partially as a consequence of decreased prevalence of subclinical IMI caused by these pathogens. During the same period, national survey data indicates that the incidence of CM approximately doubled from 13 to 26% of lactating cows.^{28,29} These trends reflect tremendous changes in herd management as the dairy industry has restructured and herd sizes have grown.

As dairy farmers have adopted intensive management strategies, the distribution of pathogens recovered from

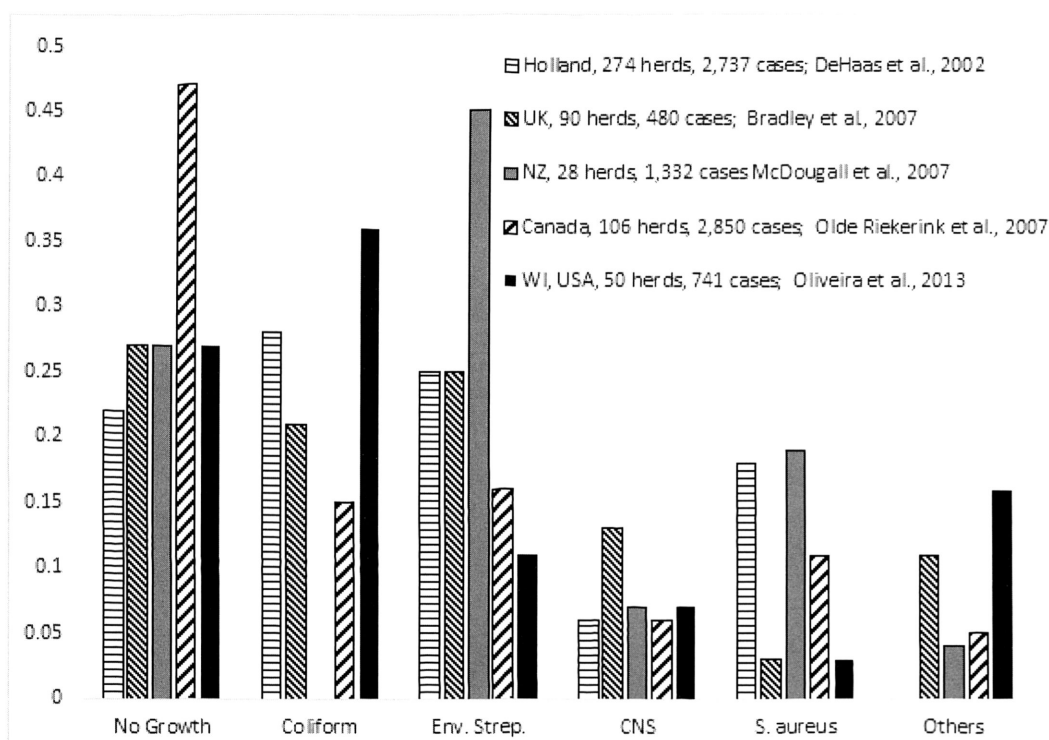


Figure 1. Results of selected studies that describe the distribution of bacteria recovered from milk of cows with clinical mastitis in modern dairy herds in developed countries.

cases of CM has become more diverse, and on most farms is dominated by opportunistic environmental organisms (Figure 1). Based on surveys that included >28 farms located in developed dairy regions,^{3,4,10,12,18} the most common outcome of culturing milk collected from cases of CM is usually no microbial growth (about 30%), followed by either coliforms (about 30% in intensively managed cows) or environmental *Streptococci* (up to 45% in extensively managed cows in New Zealand). The proportion of cases caused by *Sta. aureus* is highly variable, ranging from 3% in large herds in Wisconsin,¹² 11% in a Canadian national survey,¹⁸ and 19% in New Zealand,¹⁰ but in general is more prevalent in studies that include smaller herds or extensive management systems. Overall, about 5% and 7% of cases of CM were caused by “other pathogens” or CNS, respectively. When data from these studies (Figure 1) is combined, the weighted average proportion of etiologies across surveys are: no growth (32%), environmental streptococci (24%), coliform bacteria (19%), *Sta. aureus* (13%), and other pathogens (5%). On individual farms, the usefulness of antimicrobial therapy for treatment of non-severe CM is highly dependent on using antimicrobials that can effectively target the predominant etiological agents.

Guidelines for appropriate use of antibiotics recommend that narrow-spectrum drugs are used when possible,³⁰ with the goal of reducing the likelihood that broader-spectrum drugs will acquire resistance. No class of antimicrobials is equally efficacious for all pathogens, and treatment protocols that do not account for the underlying distribution of etiologies are very difficult to justify. The purpose of antibiotic treatment is to enhance clearance of bacterial pathogens, and efficacy is usually initially evaluated based on estimates of the rate of bacteriological cure. Bacteriological cure is assessed by comparison of recovery of bacteria from milk samples collected at detection of the cases and subsequently at various intervals after treatment is completed. However, bacteriological cure also occurs spontaneously, and expected rates of spontaneous bacteriological cure vary widely among pathogens (Table 1). The greatest contrast is between expectations of spontaneous bacteriological cure of IMI caused by *Sta. aureus* (close to zero) and CM caused by *Escherichia coli* (about 90%).²⁵ Additionally, limited efficacy of antibiotic therapy is well documented for IMI caused by *Sta. aureus*² and some pathogens (such as yeast, *Prototheca zophii*, *Mycoplasma*

Table 1. Estimated rate of spontaneous bacteriological cure by pathogen from selected studies.

Etiology	Spontaneous bacteriological cure (%)		Sources
<i>Sta. aureus</i>	0-11%		Deluyker et al, 1999; Gillespie et al, 2002; Oliver et al, 2004
Env. <i>Streptococci</i> spp	28-30%		Deluyker et al, 1999; Hoe and Ruegg, 2005; Morin et al, 1998
CNS	44-66%		Apparao, et al, 2009; Deluyker et al, 1999; Oliver et al, 2004
<i>E. coli</i>	80-95%		Fuenzalida and Ruegg-personal communication; Lago et al, 2011; Suojala et al, 2010
<i>Klebsiella</i> spp	25 - 60%		Lago et al, 2010; Fuenzalida and Ruegg-personal communication
No growth	75-85%		Fuenzalida and Ruegg-personal communication

Table 2. Proportion of non-severe cases of clinical mastitis that would be expected to achieve bacteriological cure from routine IMM antibiotic therapy used without knowledge of etiology.

Actual etiology	A. Proportion of cases ^a	B. Assumed rate of spontaneous bact. cure	Assumed efficacy of IMM treatment ^b		Proportion of total cases benefiting from antibiotic usage ^d	
			C. Scenario 1 Some benefit of antibiotic	D. Scenario 2 Highly efficacious antibiotic ^c		
					A x (1-B) x C Scenario 1	A x (1-B) x D Scenario 2
No growth	32%	85%	15%	50%	0.7%	2.4%
Coliforms	19%	75%	25%	50%	1.2%	2.4%
Env. Strep.	24%	20%	80%	95%	15.4%	18.2%
CNS	7%	60%	40%	80%	1.1%	2.2%
<i>Sta. aureus</i>	13%	10%	25%	60%	2.9%	7.0%
Others	5%	50%	5%	20%	0.2%	0.5%
Proportion of cases benefiting from antibiotic usage:					21.5%	32.7%
Proportion of treated cases receiving no benefit from antibiotics:					78.5%	67.3%

^aweighted average of studies included in Figure 1

^bproportion of cases in excess of spontaneous cures that would result in bacteriological cure due to antibiotic therapy

^cassumes reduced rate of spontaneous cure and increased efficacy of antibiotic

^dcalculated as proportion of cases x (1-Spon. Cure) x assumed efficacy of IMM treatment

spp, and others) are intrinsically resistant to all approved antimicrobial drugs.

Based on the typical distribution of pathogens that cause CM (Figure 1), when antibiotics are administered without knowledge of etiology, the economic and welfare benefits of their use is diminished. Using reported values for the rate of spontaneous cure (Table 1) and a range of assumed efficacies for treatment of various pathogens (Table 2), the overall proportion of cases that can be expected to benefit from non-specific antibiotic therapy ranges from about 22 to 33% (Table 2). Thus, approximately two-thirds of antibiotic treatments given by farmers treating mastitis without any knowledge of etiology are of no benefit to the cow. This use is difficult to reconcile with evolving societal expectations to limit use of antimicrobials to those necessary to preserve animal well-being.

Before administration of an antibiotic, it is also important to consider cow factors that are known to influence treatment outcomes. It is well known that efficacy of antibiotic therapy is not equal for all cows, and the medical history of the cow should be reviewed before antibiotic therapy is administered. Cows that have a previous diagnosis of mastitis caused by refractory mastitis pathogens (such as *St. aureus*, *Mycoplasma bovis*, *Prototheca* spp, *Serratia* spp, or yeast) will usually not benefit from use of antibiotics. Likewise, cows that have a history of repeated treatments for CM (≥ 3 treatments in the current lactation) or have a long history of chronically high SCC may not benefit from additional use of antibiotics. Additionally, the use of IMM antibiotics for cows that are concurrently affected with other chronic diseases may not be beneficial. When use of antibiotics is not considered to be beneficial, other options for managing non-severe CM should be considered.²³

Evaluating Therapeutic Options for Treating Non-Severe Clinical Mastitis

Clinical mastitis is detected based on observation of non-specific clinical signs and is usually treated without knowledge of etiology,^{8,13} thus many antibiotic treatments do not enhance animal welfare nor productivity. In the US, first or third-generation cephalosporins are the most commonly used IMM drugs and were administered to 78% of cases of clinical mastitis occurring on 51 large WI dairy herds.¹³ About 35% of these treatments were given to cases which were culture-negative at the time of detection, and a further 17% were administered to cases for which approved antimicrobials cannot be expected to be effective due to intrinsic resistance. In both of these instances, the use of antibiotics is difficult to justify. However, it is important to note that evaluation of efficacy of mastitis treatments is very difficult for both farmers and veterinarians.

Dutch researchers have demonstrated that farmers are insecure about appropriateness of mastitis treatments and will often extend antibiotic therapy simply based on

meeting perceived social norms of being a “good farmer.”²⁷ Occurrence of abnormal milk is the most obvious symptom of mastitis, and it seems logical to evaluate treatments based on improved appearance of milk or by reducing the number of days that milk is discarded. However, this outcome has little variation¹³ and is greatly influenced by factors other than treatment, such as etiology, case definition, and cow factors. Detection of both subclinical and clinical mastitis is based on recognition of inflammation (the immune response) resulting from IMI. Thus, with or without treatment or bacteriological clearance, return to normal milk is expected to occur within 4 to 6 days 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 will return to normal appearance, however some of these cases have simply regressed to a subclinical state and maintain increased SCC. Thus other longer-term indicators, such as recurrence of clinical signs and eventual SCC reduction, are better suited to monitor treatment outcomes.

Anecdotally, on some dairy farms the duration of treatment or choice of drug is based on the appearance of abnormal milk. Abnormal appearance of milk is a non-specific sign of inflammation that is not always associated with continued IMI, and is not predictive of the etiology. Most approved IMM drugs are active against organisms that are rapidly dividing, and there is no evidence that changing among drugs with similar spectrums of action or extending duration based on continued appearance of abnormal milk will result in improved clinical or bacteriological outcomes. Neither duration of treatment nor choice of drug should be based solely on appearance of milk or on indirect indicators such as CMT or quarter-level SCC values. With or without treatment or bacterial clearance, milk will return to normal appearance by day 7 for about 85% of non-severe cases of CM. After treatment, if milk remains abnormal for more than 6 or 7 days, before administration of another antibiotic, every attempt should be made to determine the etiology of the infection as it is unlikely that switching among drugs with similar spectrums will improve clinical outcomes.

In North America, when antibiotic therapy is indicated for treatment of non-severe CM, approved IMM antibiotics should be used as the first choice. Veterinarians in the US, have access to 7 IMM antibiotics and Canadian veterinarians also have access to an approved product that contains a combination of 4 antimicrobials and 2 steroids (Table 3). In the US, no antibiotics are approved for systemic administration to cows affected by mastitis, and few have the ability to reach a therapeutic concentration in the udder. Based on the absence of clinical trials that demonstrate efficacy, this route should only be used when there is a compelling reason to give an extra-label treatment, such as a severe case. Approved IMM antibiotics have pharmacological characteristics that ensure a sufficient concentration of the drug or active metabolite

Table 3. All drugs approved for intramammary use in the US and selected drugs approved in Canada.

Product name active compound	Label dosing instructions no. and interval	Label claims for efficacy	Additional comments from labels or www.AAVPT.org/ resources
Amoxi-Mast 62.5 mg amoxicillin	3 tubes @ 12 h	<i>Str. agalactiae</i> <i>Sta. aureus</i>	<i>Aminopenicillin</i> . From label... "Most strains of <i>Pseudomonas</i> , <i>Klebsiella</i> , and <i>Enterobacter</i> are resistant."
DariClox 200 mg cloxacillin	3 tubes @ 12 h	<i>Str. agalactiae</i> <i>Sta. aureus</i>	..active against most gram-positive organisms associated with mastitis. It is effective against <i>Streptococcus agalactiae</i> and non-penicillinase-producing <i>Staphylococcus aureus</i> , and there is laboratory evidence that indicates cloxacillin is resistant to destruction by penicillinase-producing organisms.
Polymast 62.5 mg ampicillin	3 tubes @ 24 h	<i>Str. agalactiae</i> , <i>Str. dysgalactiae</i> <i>Sta. aureus</i> <i>E. coli</i>	<i>Aminopenicillin</i> . Aminopenicillins are susceptible to destruction by beta-lactamases and therefore are not effective against bacteria that produce these enzymes. Most strains of <i>Klebsiella</i> , <i>Proteus</i> , <i>Pseudomonas</i> , and <i>Staphylococcus</i> are resistant.
Masti-Clear 100,000 IU penicillinG	3 tubes @ 12 h	<i>Str. agalactiae</i> , <i>Str. dysgalactiae</i> <i>Str. uberis</i> .	..highly susceptible to beta-lactamases and has little activity against organisms that can produce these enzymes. Penicillin G is ineffective against bacteria that are resistant by certain other mechanisms, such as having a relatively impermeable cell wall. Therefore, penicillin G has little activity against many staphylococci and most gram-negative bacteria.
Pirsue 50 mg pirlimycin	2-8 tubes @ 24 h	<i>Sta. aureus</i> , <i>Str. dysgalactiae</i> <i>Str. uberis</i> .	<i>From Canadian label:</i> Coliform bacteria such as <i>E. coli</i> and <i>Klebsiella</i> spp are intrinsically resistant. Resistance to pirlimycin is detected frequently in some gram-positive pathogens, particularly streptococci, in some Canadian herds.
SpectramastLC 125 mg ceftiofur	2-8 tubes @ 24 h	<i>CNS</i> <i>Str. dysgalactiae</i> <i>E. coli</i>	Ceftiofur has demonstrated in vitro activity against coagulase-negative staphylococci, <i>Streptococcus dysgalactiae</i> , and <i>Escherichia coli</i> .
Special Formula 17900 (Canada)	1 tube, repeat once @ 24 hours "if necessary"	susceptible strains of <i>Staphylococci</i> , <i>Streptococci</i> , <i>coliforms</i> or <i>Pseudomonads</i>	<i>Contains:</i> Penicillin G Procaine , Dihydrostreptomycin, Novobiocin, Polymyxin B, Hydrocortisone acetate, Hydrocortisone Sodium Succinate
Today CefaLak (Canada) 200 mg cephapirin	2 tubes @ 12 h	<i>Str. agalactiae</i> <i>Sta. aureus</i>	..wide spectrum of activity against gram+ and gram – organisms. Cephapirin is more resistant to beta-lactamases than are the penicillins and so is effective against staphylococci, with the exception of methicillin-resistant staphylococci.

will be present in the udder during the approved dosing interval to kill or restrict growth of the organisms listed on the product label. Almost all approved IMM antibiotics are labeled for treatment of *Streptococci* and *Staphylococci*, and some include label claims for *E. coli* (Table 3). No products have explicit label claims for treatment of mastitis caused by *Klebsiella* spp and this organism is considered to be intrinsically resistant to several available products. Little to no research exists to support efficacy claims for other organisms, and the lack of efficacy data makes it very difficult to justify use of antibiotics for treatment of mastitis caused by many opportunistic pathogens.

Success or failure of antimicrobial therapy is dependent on characteristics of the case, the pathogen, and the chosen therapy. For example, *Sta. aureus* deeply infiltrates mammary tissue and even if the antibiotic is effective *in vitro*, it likely has little chance to result in bacteriological clearance of a chronically infected cow. Similarly, there is little benefit to using antibiotics on CM cases caused by pathogens that have high rates of spontaneous cure or present as culture-negative cases (often as a result of spontaneous cure before recognition of clinical signs). The benefit of antibiotics can be estimated using a metric called the "number needed to treat" (NNT). This metric accounts for spontaneous cure and

Table 4. “Number needed to treat” based on improvement in bacteriological cure versus spontaneous cure when using antibiotic therapy that results in apparent 80% bacteriological cure.

Spontaneous cure (%) ^a	70%	65%	60%	55%	50%	45%
Improvement based on treatment (%) ^b	10%	15%	20%	25%	30%	35%
Number needed to treat ^c	10	7	5	4	4	3
95% CI ^d	7.3-16.1	5.3-9.0	4.2-6.2	3.5-4.8	2.9-3.8	2.6-3.2

^aProportion of cases achieving spontaneous bacteriological cure without use of antibiotics

^bProportion of cases in excess of spontaneous cure that result in bacteriological cure due to efficacious antibiotic therapy

^cDefined as the number of treated cases that will result in 1 additional bacteriological cure

^dConfidence interval is based on 1000 control and 1000 treated cases

intractable cases and estimates the number of cases that need to receive treatment to prevent 1 treatment failure. Assuming use of a highly efficacious antimicrobial with an expected 80% bacteriological cure, if the pathogen has an expected rate of spontaneous cure of 45 to 50% (such as CNS) the farmer must treat 3 to 4 cases to prevent 1 failure of bacteriological cure (Table 4). In contrast, when treating mastitis caused by *E. coli* (with a high rate of spontaneous cure), the farmer must treat about 10 cases to prevent 1 failure of bacteriological cure (Table 4). For dairy cows, the economic impact of these decisions is magnified when long duration treatment is used as the standard therapy, as it extends the period that milk must be discarded without improving outcomes of most cases. The cumulative economic impact of these probabilities has been modeled previously using Decision Tree Analysis.¹⁶ As compared to non-selective treatment, use of culture-based selective treatments is the most economically efficient decision and practitioners should make every effort to encourage farmers to determine etiology of clinical cases.¹⁶

When culture-based therapy is simply not an option, non-specific IMM antibiotic treatments are usually recommended. In this instance, based on the typical distribution of culture results from modern dairy farms (Figure 1), more than 50% of treated cases (the culture-negative, most gram-negative, and non-susceptible pathogens) are unlikely to benefit from use of antibiotics. Because only some cows will benefit from antibiotics and even fewer will benefit from extended duration therapy, the best economic decision is to treat for a short duration using an IMM antibiotic.¹⁶ When this decision is made, it is important to recognize that therapy will usually be completed before milk returns to normal appearance. Unless previous culture data or the medical history of the cow are supportive of using a broad-spectrum drug for an extended duration, use of a narrow-spectrum IMM drug for short duration is recommended. Longer-duration therapy may be considered for cows with a history of several months of increased SCC (indicative of failed chronic inflammation) or a previous short-duration treatment in the same quarter.

Conclusions

Appropriate use of antimicrobials on dairy farms contributes to improving animal well-being and dairy farm sustainability. However, it is important for veterinarians to

recognize that many cases of non-severe clinical mastitis will not benefit from antimicrobial therapy. Mastitis is caused by a diverse group of bacterial pathogens with differing distributions among farms. In intensively managed herds, many cases of clinical mastitis are culture-negative when detected or are caused by pathogens with high rates of spontaneous cure. In such herds, if treatments are administered without determination of etiology, the majority of antimicrobial treatments may be unnecessary. There is considerable opportunity for veterinarians to improve antimicrobial usage on dairy farms by encouraging farmers to adopt culture-based treatment protocols that limit antimicrobial usage to cases that will benefit. When this option is not feasible, farmers should be encouraged to review the medical history of the cow before treatment, and when antimicrobial use is warranted initiate therapy using a narrow-spectrum drug for short duration.

Endnotes

^aThe terms antimicrobial and antibiotic are used interchangeably in this paper but are not synonymous. In technical terms, “antibiotics” refer only to substances of microbial origin (such as penicillin) that are active against other microbes while “antimicrobial” refers to any substance (including synthetic compounds) which destroy microbes.

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