

Clinical mastitis treatment decisions

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Introduction

Mastitis is the most common bacterial disease of lactating cows^{1,2} and throughout the world accounts for the majority of antibiotic doses given on dairy farms.³⁻⁸ Many of these antibiotic doses are unnecessary because of high spontaneous cure rates for many intramammary infections (IMI) affecting otherwise healthy cows. Mastitis is recognized based on the extent of the inflammatory response after IMI is established. It is considered “subclinical” when the immune response causes increased somatic cell count (SCC), but the cow remains healthy with no visible changes in the milk or udder. Milk from cows with subclinical mastitis can be comingled with milk from healthy cows and sold, thus treatment during lactation is not usually cost effective and most of these cases are treated with antibiotics at dry off. Clinical mastitis occurs when the immune response to IMI results in visually abnormal milk with or without secondary signs. Fortunately, few cases of clinical mastitis cause systemic signs that require immediate therapy, but abnormal milk may not be sold for human consumption, so farmers emphasize interventions (such as antibiotic therapy) that are perceived to hasten the return to normal milk. Non-severe cases of mastitis that present with abnormal milk, or abnormal milk accompanied by localized swelling of the udder account for about 85% of all CM cases.⁹⁻¹¹ Mastitis caused by many opportunistic bacterial pathogens often have high rates of spontaneous bacteriological clearance, so on many farms, most cases of clinical mastitis occurring in otherwise healthy cows do not benefit from antibiotic therapy. Treatment protocols for non-severe clinical mastitis should include an assessment of the immune capabilities of the cow, the likely etiology of the case, a review of the medical history of the cow and an assessment of the probability that she will remain productive long enough to recoup the costs (including discarded milk) associated with treatment. The purpose of this paper is to review treatment decisions for non-severe clinical mastitis, emphasizing evidence-based criteria that indicate when antibiotic therapy is beneficial to the cow.

Selecting cows that may benefit from antibiotic treatment

Clearance of bacterial infections occurs when the immune system recognizes the bacterial challenge and can mount a rapid and successful response. Antibiotics are given to aid the immune response by reducing or slowing the bacterial challenge but are not necessary nor indicated to achieve bacterial clearance for all IMI.^{12,13} A clinical judgement of the ability of the cow to successfully respond to infection is key to understanding when antimicrobial therapy is necessary.¹⁴ The ability to successfully eliminate pathogens has been associated with age, stage of lactation, negative energy balance (Hammon et al., 2006), history of previous treatments and environmental factors (such as heat-stress).¹⁵ Cow level risk factors such as parity, mastitis severity and subclinical mastitis history are associated with the likelihood of bacteriological clearance (Table 1)^{16,17} (Pinzón-Sánchez and Ruegg,

2011). While there are differences among etiological agents, in general, younger cows and cows without a long history of subclinical IMI have fewer cases of clinical mastitis, greater odds of BC and fewer recurrences. Veterinarians should create treatment protocols that encourage producers to review SCC history, case severity, parity and history of prior cases before prescribing antibiotic treatment and use those characteristics to select cows that may truly benefit from therapy.

Understanding differences among pathogens

The value of antimicrobial therapy is based on the marginal difference between spontaneous and therapeutic cure rates. Expectations for spontaneous and therapeutic cure vary among bacterial agents, so knowledge of etiology is essential to know when antimicrobial therapy is indicated. Depending on location and enrollment criteria, bacterial etiologies of cases of clinical mastitis that were enrolled in clinical trials in Europe and the Americas since 2000, were distributed roughly as 12-50% no growth when detected, 3-26% *Staph aureus*, 18-30% *Streptococci* (about 30-40% combined Gram-positive), 9-40% Gram-negative bacteria, and 10% other pathogens.¹⁸ In general, researchers have documented that antimicrobials provide little to no benefit for treatment of non-severe cases of mastitis caused by *E. coli*^{16,19} or cases that are microbiologically negative when detected,¹⁷ because of high rates of spontaneous cure. Based on low expectations for efficacy of IMM antibiotics, treatment of clinical mastitis cause by *Staph aureus*²⁰ or mastitis caused by refractory or resistant pathogens such as *Serratia* spp., *Pseudomonas* spp., or yeasts is not indicated. Antimicrobial treatment is considered beneficial for cases of clinical mastitis caused by *Streptococci* spp., and occasionally for some cases caused by *Klebsiella pneumoniae*. Based on the distribution of etiologies on most North American dairy farms, antibiotic treatment is usually indicated for < 30% of non-severe cases of clinical mastitis. Use of selective treatment protocols provides a tremendous opportunity to reduce antimicrobial usage on while maintaining health, welfare and productivity of affected cows. If culture-guided selective therapy is not feasible, it is important to recognize that most cases of CM will not benefit from antimicrobial therapy so when etiology is not known, the minimum duration of IMM antibiotic treatment should be routinely recommended.

Differentiating among intramammary antibiotics

There are no injectable antibiotics approved for treatment of bovine mastitis in North America and almost all antibiotic treatments for clinical mastitis are administered using IMM infusion. Among 7 approved IMM antimicrobials in the U.S., all are β -lactams, only 5 are currently marketed, and most treatments are either a first- or third-generation cephalosporin (Table 2). In Canada, only 2 IMM products are currently marketed. Of 5 IMM antibiotics available in the U.S., 3 products are labeled for 3 infusions at 12-hour intervals (1.5 d therapy), 1 product is labeled for 2 treatments at 12-hour intervals (1 d

Table 1: Influence of selected characteristics on bacteriological cure and recurrence of clinical mastitis from 4 selected studies (unadjusted, univariate values)

	Incidence of Cl. Mastitis % of cases	Bacteriological cure overall %	Recurrence overall %
⁹n = 143 cases on 4 WI farms; All cases received intramammary treatment			
Parity 1	15%	83%	6%
Parity 2	85% ^a	81%	18%
Parity 3	-----	90%	21%
Parity 3+	-----	61%	37%
Prev. Clinical Case YES	30%	52%	---
Prev. Clinical Case NO	70%	81%	---
Gram +	28%	63%	---
Gram -	30%	75%	---
No Growth	42%	86%	---
¹⁶n = 168 cases from 2 WI farms; only Gram-negative cases were enrolled; Compared 2 & 8 d of intramammary treatment with ceftiofur to non-treated controls			
Parity 1	16%	90%	16%
Parity 1+	84%	60%	46%
Mild	80%	66%	41%
Moderate	20%	66%	39%
Prev. Clinical Case YES	35%	69%	35%
Prev. Clinical Case NO	65%	60%	65%
¹⁷n = 121 cases from 1 WI farm; only culture negative cases were enrolled; Compared 5 d of intramammary treatment with ceftiofur to non-treated controls			
Parity 1 & 2	34%	92% ^b	5%
Parity 3 & 4	37%	68%	18%
Parity >=5	28%	84% ^b	14%
Mild	55%	79% ^b	13%
Moderate	45%	74%	10%
Prev. Clinical Case YES	19%	61% ^b	11%
Prev. Clinical Case NO	81%	80%	12%
Kolar, Erskine, Godden and Ruegg, unpublished; 240 cases enrolled from 4 farms; Only Gram-positive cases were enrolled; Compared 3 d IMM treatment with ceftiofur or hetacillin to non-treated controls			
Parity 1	18%	94%	17%
Parity 1+	82%	74%	12%
Mild	82%	89%	14%
Moderate	18%	80%	5%
^a Parity 2+			
^b remained culture negative at subsequent samplings			

Table 2: All antibiotics^a approved for treatment of bovine mastitis in the U.S. and Canada.

	Amoxi-Mast®	Polymast®	Today®/ CefaLak®	Masti-Clear®	Spectramast® LC
U.S. purchase status	Prescription	Prescription	OTC ^b	OTC ^b	Prescription
Country	U.S.	U.S.	U.S., Canada	U.S.	U.S., Canada
Active ingredient	Amoxicillin	Ampicillin	Cephaparin (1 st gen.)	Penicillin G	Ceftiofur (3 rd gen.)
Gram Pos activity	Excellent	Excellent	Excellent	Some resistance	Excellent
Gram Neg activity	Limited	Limited	Limited	Negligible	Excellent
<i>Strep ag</i>	YES	YES	YES	YES	
<i>Staph aureus</i>	YES	YES	YES		
<i>Strep dysg.</i>			YES	YES	YES
<i>Strep ub.</i>				YES	
Other			<i>E. coli</i>		CNS & <i>E. coli</i>
Label dosing & duration	3 tubes and 12 h	3 tubes and 24 h	2 tubes and 12 h	3 tubes and 12 h	2-8 tubes and 24 h
Company	Merck	BI	BI	Hanford	Zoetis

^a intramammary formulations of cloxacillin (DairyClox®) and pirlimycin (Pirsue®) are approved in the U.S. but not currently marketed.

^b all antibiotics are prescription only in CA and all OTC antibiotic sales will be transitioned to prescription as of June 2023.

treatment), 1 product is labeled for 3 treatments at 24-hour intervals and 1 product has a flexible label that allows 2-8 days of treatment at 24-hour intervals (Table 2). It is important to recognize that the efficacy data for these products was approved using the labeled durations and there is very limited research to support routine recommendations for longer duration therapy. Of the 5 approved products, 4 have label indications for treatment of *Streptococci* and *Staphylococci*, and likely have similar efficacy against most Gram-positive pathogens. Only 2 products claim efficacy against *E. coli*, and none have explicit label claims for treatment of mastitis caused by *Klebsiella* spp. which is generally considered intrinsically resistant to aminopenicillins (ampicillin, amoxicillin and hetacillin). Antibiotic treatment is indicated for treatment of IMI caused by *Streptococci* spp., but there is very little research to support efficacy of IMM antibiotics against many non-traditional opportunistic Gram-positive pathogens. Fortunately, many of these organisms (such as *Lactococcus* spp.) have relatively high rates of spontaneous cure. Antibiotic treatment of non-bacterial causes of mastitis (such as yeast or *Prototheca*) cannot be recommended. In general, there are no studies that support superior efficacy of any current mastitis treatments used for treatment of CM caused by Gram-positive organisms and recommendations for antibiotic selection should be based on economic and use characteristics.

Economic realities of mastitis therapy

It is well known that mastitis is a very costly disease. Direct and indirect costs are attributable to mastitis and include expenses related to discarded milk, purchase of drugs, use of diagnostic testing, costs of increased labor, inputs purchased to facilitate prevention, reduced milk production and value of milk, as well as costs attributable to culling (Pinzón-Sánchez et al., 2011), and reduced fertility (Fuenzalida et al., 2015). Dairy producers are most aware of the cost of mastitis when they are required to discard (rather than sell) milk from cows affected with clinical mastitis, and when they pay for products used in

treatment protocols. Costs of milk discard are greater for older, higher producing cows and when milk price is greater. Leite de Campos²¹ (2022) recently used farm records and drug purchase data to estimate direct costs of treatment of clinical mastitis occurring on 37 WI dairy farms. Of > 20,000 cases, 64% received intramammary treatment only, while 30% received no treatments, 3% received IMM and injectable antibiotics and the rest received a variety of combinations including supportive treatments. Direct treatment cost per case was about \$200, but there was considerable variation among farms and most variation was explained by the duration of treatment. The least expensive cases were those that did not require or receive antibiotic treatment as > 85% of direct costs were related to milk discard. Spectramast® LC and Today® accounted for the majority of IMM treatments and for both products the average duration of milk discard (during treatment and withholding) was > 9 days. Using the labeled duration for Today (1 d) or the minimum duration for Spectramast® LC (2 d) would have resulted in saving > \$60 per case in discarded milk.

In a separate study using the same dataset, Goncalves et al. (2022) reported that a large proportion of older cows diagnosed with clinical mastitis were culled before they completed their lactation. Based on the cost of excess discarded milk, it may require up to 90 days of milking to recoup direct expenses related to mastitis treatment and longer duration therapy increases the time that cows need to remain milking to achieve break-even. Producers should be aware of costs associated with treatment of non-severe clinical mastitis, consider the potential productive life of cows before initiating treatment and recognize that few cows benefit from treatment durations that exceed minimum label recommendations. The decision to extend a treatment should be made only based on animal or pathogen characteristics that indicate longer-duration therapy will result in improved bacteriological clearance.

Summary

Most cases of non-severe clinical mastitis on many farms, are caused by opportunistic pathogens that have relatively high rates of spontaneous bacteriological clearance and do not benefit from antimicrobial therapy. Many older cows that have long histories of high SCC or previous cases of clinical mastitis have developed chronic IMI that may be refractory to antibiotic therapy. These chronic cows are not likely to respond to antibiotic therapy and are at high risk of premature culling. Farmers should be taught to review monthly SCC history as an indicator of prognosis relative to predicting efficacy of mastitis therapy. Antibiotics should not be routinely given to treat non-severe CM in cows with subclinical infections in multiple quarters, a history of repeated clinical episodes or previous diagnoses with refractory pathogens (*Staph aureus*, *Mycoplasma bovis*, *Pseudomonas*, *Serratia* spp., *Prototheca* spp., etc.). When antibiotics are not prescribed non-antibiotic interventions such as “watchful waiting” (cow is hospitalized but no antibiotics are administered, abnormal milk is discarded until it returns to normal), use of non-steroidal anti-inflammatories for moderate cases (to manage discomfort) and interventions to limit transmission (dry off of individual quarters or segregation) should be considered. When antibiotic therapy is indicated (for example, a first case of clinical mastitis caused by *Streptococcus* spp.) routine protocols should follow label instructions for minimum duration unless the etiology or case characteristics indicate that cows are likely to benefit from longer duration therapy.

Additional resources

<https://topmilk.msu.edu/Resources/Treatment-of-Mastitis>

Videos on Treatment and Use of Selective Therapy can be found at: <https://www.youtube.com/@TopMilkQuality/featured>

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