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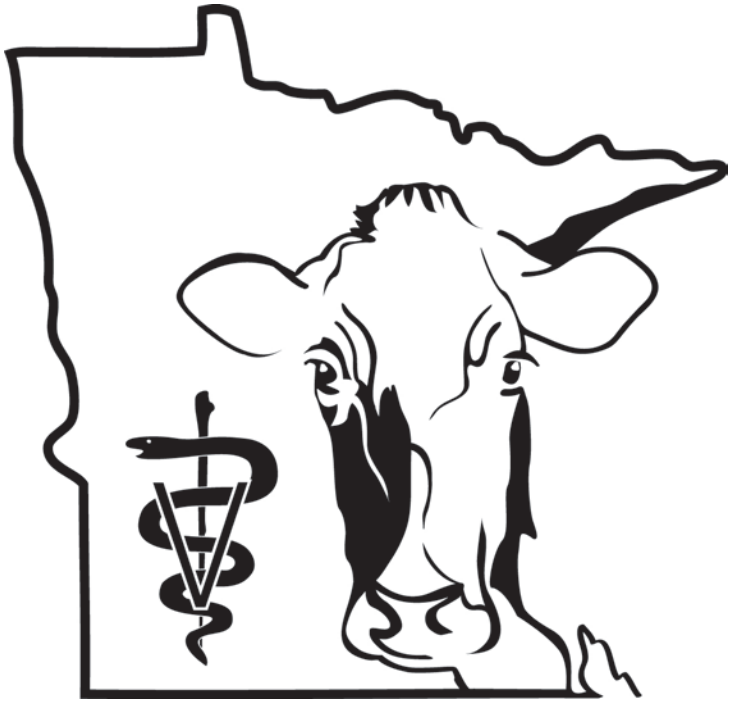

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Classification of Clinical Mastitis Severity: Focus on *E.Coli*

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In a clinical setting mild vs. severe mastitis is typically based on the extent and degree of systemic disease signs the cow is expressing. Upon evaluation a cow with flakes and clots in the milk that is otherwise normal is considered to have mild clinical mastitis. This is in contrast to the cow that simply "looks sick"; dehydrated, showing signs of depression and has little rumen activity, that is classified as having severe clinical mastitis. It is clear that the later cow requires more supportive care in an attempt to correct physiologic abnormalities. However, appropriate antimicrobial therapy is less clear. Should the 'severe' cow receive intramammary antibiotics or parenteral antibiotics, both or none? The importance of local inflammatory changes of the mammary gland in determining treatment and prognosticating outcomes is also unclear. For some, a firm quarter with a serum-like secretion (watery) is considered a 'severe' sign carrying a grave prognosis, even if the cow appears otherwise normal. However, there is little information in the scientific literature correlating local clinical signs with important outcomes of a clinical mastitis episode. Furthermore, it is important to keep in mind what outcomes are being considered. Outcomes important to the dairy producer are:

1. Will the cow survive the clinical mastitis episode?
2. Will the cow return to milk production or be culled?
3. Will the cow lose the affected quarter?
4. Will the cow need to be re-treated?

In the absence of any 'scientific information' we generally use our clinical experience to evaluate these outcomes and determine therapy. In the absence of 'better information' this is the best we can do, however, it is important to realize that our perception is often bias by the last "catastrophic treatment failure" and/or "miraculous treatment success".

To complicate matters further clinical mastitis research has often failed to identify severity by any measure, or classified severity but gave no clear indication of how it was assigned. Furthermore severity was often defined based on physiologic parameters such as neutrophil chemiluminescence or oxidative burst activity. While these parameters may be important in the pathophysiology of disease it is unclear how they relate to the clinical signs easily evaluated in the field. This has especially been true with research of coliform mastitis. This presentation will present recent work we have done at CSU to better classify clinical disease severity, with a focus on coliform mastitis.

Severity and Coliform Mastitis

Acute coliform mastitis (ACM) manifests as clinical disease ranging from mild, short duration cases to severe, peracute, life-threatening episodes. The severity of systemic signs in cows with a coliform mastitis episode is strongly associated with the degree of production loss and outcome of a clinical case.[1] Therefore, evaluation of the severity of a clinical coliform mastitis episode is important in determining appropriate therapy and making sound management decisions. Unfortunately in the realm of mastitis research and among 'the experts' there are many measures of the severity of clinical mastitis including; milk production changes, inflammatory changes in the gland, changes in milk composition and appearance, the extent and degree of systemic disease signs and hematological changes in the affected cow. Various scoring systems have been described to evaluate the severity of clinical mastitis.[2-5] In most of these studies severity classification was typically based on

normal versus abnormal scoring of physical characteristics of the mammary gland, the milk and the presence or absence of systemic disease signs based on definitions recommended by the International Dairy Federation.[6] The highest severity score was typically given to cows exhibiting any systemic disease signs. However, such systems do little to evaluate the extent and degree of systemic disease involvement, although systemic disease severity has a significant impact on milk production losses and adverse outcomes. Furthermore, none of these studies have shown important differences in the outcomes of a clinical mastitis event in cows based on such severity scoring. Therefore we have been working to develop a clinical mastitis scoring system that is simple yet effective in grouping cows according to their likely treatment needs and outcomes.

Experimental coliform mastitis

Much of our understanding of coliform mastitis is based on the experimental disease model which involves inoculation of a 'healthy' mammary gland with either purified endotoxin or a pure culture of *E. coli*. However, our recent studies have identified important areas in which experimentally induced disease fails to accurately model the naturally occurring disease. A major disparity, which may explain the important differences we have observed, is the diverse, multifactorial nature of innate host defense mechanisms. Use of the experimental disease model selects for cows that have shown resistance to ACM. Cows chosen for inclusion in studies incorporating the experimental disease model have a low somatic cell count (SCC), typically have not had clinical mastitis during the current lactation and have no evidence of IMI (negative serial milk cultures). It can be argued these cows have superior, intact host defenses compared with cows that succumb to the disease, presumably due to a failure of the same innate host defenses. Based on the experimental disease model it was determined that bacteria are typically cleared from the gland by the time clinical signs occur and bacteremia does not occur.

Recently we have reported on a rapid, simple severity classification scheme for ACM based on systemic disease signs (SSS) (Table 1).[7] For cows grouped according to this classification scheme, significant differences in hematological findings, number of bacteria in secretions from the affected mammary gland, death and culling outcomes, and occurrence of bacteremia were identified among severity groups. More than half of the cows classified as severe died during the mastitis episode or were culled within 30 days, compared with only 9% of those classified as mild (Table 2). While the SSS appears to be complicated, in practice cows with three or more abnormal systemic signs (scoring moderate or severe) clearly require more attention than those that are systemically 'mild'. In herds that use a core antigen vaccine (e.g. J-5) we typically find ~90% of cows with clinical mastitis are systemically mild. The distribution of cows by severity group in Table 2 is not representative of the expression of clinical mastitis in a herd since more cows with moderate and severe disease were enrolled to increase numbers in those less frequent categories.

Table 1. Scheme for classifying severity of acute coliform mastitis in dairy cows based on systemic disease signs (SSS)*

Variable	Criteria	Score
Rectal temperature (C [F])		
	37.8 (100) – 39.27 (102.7)	0
	39.33 (102.8) – 39.8 (103.7)	1
	> 39.8 (103.7) or < 37.8 (100)	2
Hydration status (degree of enophthalmos)		
	None	0
	Mild	1
	Moderate	2
	Marked	3
Rumen contraction rate (contractions/min)		
	≥ 2	0
	1	1
	0	2
Attitude (signs of depression)		
	None	0
	Mild	1
	Marked	2

Total Score- 0-2=Mild, 3-5=Moderate, 6-9=Severe

Table 2. Outcome following a coliform mastitis episode of cows in mild, moderate and severe groups. Cows remaining in the herd 30 days after the mastitis episode were considered retained.

Severity (n)	Survival			Retention			% Died or Culled
	Status	No.	%	Status	No.	%	
Mild (69)	Died	0	0^{a}	Culled	6	9^{a}	9^{a}
	Lived	69	100	Retained	63	91	
Moderate (44)	Died	1	2^{a}	Culled	9	$21^{a,b}$	23^{b}
	Lived	43	98	Retained	34	79	
Severe (31)	Died	6	19^{b}	Culled	10	40^{b}	52^{c}
	Lived	25	81	Retained	15	60	

Values within a column with different superscripts are significantly different ($p<0.05$).

In contrast to the experimental disease model we identified significant numbers of bacteria present in the milk of affected quarters at initial assessment *and* 48 hrs later. Furthermore, cows with more severe systemic signs had significantly more bacteria (Table 3). Almost a third of systemically mild and 75% of severe cows had >100,000 cfu/ml. These finding suggest intramammary treatment with an antibiotic effective against gram negative bacteria may be indicated.

Table 3 Bacterial numbers by systemic severity score at initial assessment (0hr) and 48hrs

	0hr				48hr		
	1	2	3	NG	1	2	3
Mild	58.0[a]	14.5[a]	27.5[a]	33.3[a]	39.1[a]	14.5	13.1[a]
Moderate	18.6[b]	30.2[b]	51.2[b]	14.0[b]	32.5[a]	27.9	25.6[a]
Severe	13.3[b]	10[a]	76.7[c]	7.7[b]	11.5[b]	19.3	61.5[b]

1 = <10,000 cfu/ml, 2 = 10,000-100,000 cfu/ml, 3 = >100,000 cfu/ml, NG = no growth. Values within a column with different superscripts are significantly different ($p<0.05$).

We also found significant differences in the percentage of cows with a positive blood culture (bacteremia) when evaluated based on systemic disease severity (Table 4).[8] Group 1 isolates are important pathogenic bacteria such as *E. coli, Klebsiella pneumoniae, Pasteurella (Manheimia)hemolytica,* and *Pasteurella multocida.* None of these organisms were identified in control cows compared to 42% of cows with severe systemic disease signs. It was interesting to find significantly more cows with ACM of any severity with blood cultures positive for environmental streps, coagulase negative staphs and bacillus compared with control cows.

Table 4 Bacteremia in cows with coliform mastitis

Severity (n)	All Isolates		Group 1 Isolates		Group 2 Isolates		Bacillus spp.	
	No.	%	No.	%	No.	%	No.	%
Control (156)	11	7.1[a]	0	0[a]	9	5.8[a]	3	1.9[a]
Mild (69)	21	30[b]	3	4.3[b]	10	15[b,c]	11	16[b]
Moderate (44)	10	23[b]	4	9.1[b]	3	6.8[a,c]	5	11[b]
Severe (31)	15	48[c]	13	42[c]	1	3.2[a,c]	5	16[b]

Group 1 isolates – *E. coli, Pasteurella multocida, Pasteurella hemolytica, Klebsiella pneumoniae, Enterobacter agglomerans, Salmonella typhimurium.* Group 2 isolates – environmental streptococci, coagulase negative staphylococci and *Acinetobacter* spp.. Values within a column with different superscripts are significantly different ($p<0.05$).

These results suggest parenteral antibiotics may be indicated in cows with more severe systemic disease signs. In fact a recent study found treatment of cows with more severe systemic disease signs associated with clinical mastitis benefited from systemic ceftiofur treatment.[5] For cows with coliform mastitis, death and culling was significantly lower when treated IM with ceftiofur (14%) vs. those not treated (37%).

Systemic disease severity scoring has shown poor outcomes are more common in cows with more extensive (severe) systemic disease signs. However, the majority of cows in herds using a core antigen vaccine have mild systemic disease and varying degrees of local

inflammatory changes in the udder. What is the importance of the presence and 'severity' of local disease signs?

Local signs associated with clinical mastitis

Local clinical signs associated with inflammatory changes of the mammary gland include: quarter firmness and swelling and secretion viscosity. Treatment and prognosis of clinical mastitis is often decided based on these signs, however, there have been no studies evaluating their association with important outcomes of clinical mastitis. In a recent study of 240 cows with systemically mild clinical mastitis we examined the association between local clinical signs and important clinical outcomes. [9] Cows were examined for firmness and swelling of the affected mammary gland and character of the secretion (thin, thick or serum). Outcomes assessed were re-treatment, recurrent clinical mastitis episode in the same quarter 15-60 later, dried quarter, death or culling and sick pen days. Re-treatment was necessary in 27% and recurrence occurred in 25% of clinical mastitis episodes. Dried quarter and culling occurred in ~5% of CM episodes and no deaths occurred.

When evaluated by culture result, re-treatment was necessary in about 30% of all clinical episodes except those with a No Growth (NG) result in which only 14% required re-treatment. NG clinical mastitis was not treated with intramammary antibiotics in this study, however, if there was no improvement after 3 days they were treated with cephapirin. Recurrence was about 20% for Gram neg and Gram positive infections vs. 31% for those with a NG culture result.

Many consider a clinical episode with a NG culture result to be a Gram neg (coliform) infection with low numbers of bacteria present at the time a sample for culture is taken.[10] While a clinical cure is more easily achieved in these NG clinical episodes (even without intramammary antibiotics), the high recurrence rate (31%) suggests a bacteriologic cure is often not achieved. In fact recurrence was about 3 times more likely in a cow with NG culture result vs. a cow with a Gram pos culture result. These data suggest treatment of NG clinical mastitis episodes with an intramammary antibiotic effective against Gram neg bacteria may reduce the incidence of recurrence if a bacteriologic cure can be achieved.

A serum-like secretion is often considered a grave local clinical sign. Many producers and practitioners associate a serum-like secretion with loss of the quarter. Accounting for culture result we found re-treatment was about 3 times more likely in cows with serum-like secretion which contributed to those cows having significantly longer days in sick pen compared to cows without a serum-like secretion. However, there was no association between a serum-like secretion and loss of quarter, death or culling.

Re-treatment and recurrence was about 4 times more likely in cows with swelling of the quarter. This finding may be due to poor distribution of intramammary treatment in quarters with significant swelling. Swelling, however, was present in ~70% of cows and therefore would have little discriminating ability. The odds of recurrence was ~4 and 2.8 times greater in cows with a mixed Gram pos./Gram neg. infection and No growth culture result respectively. Those cows without firmness were 4 times more likely to recur than those with firmness of the quarter. Presently, the significance of firmness of the gland vs. swelling of the gland is unclear, however, it likely relates to the underlying inflammatory process occurring in the gland. It is possible that the gland without firmness had a less vigorous inflammatory response that did not clear the bacteria as effectively. Thus that quarter has

greater odds of a recurrent clinical episode due to failure to achieve a bacteriologic cure. This is just wild speculation at this point.

In this dataset there was no association between more catastrophic outcomes such as death, culling or loss of quarter and these outcomes did not occur very frequently in cows with systemically mild clinical mastitis. A serum-like secretion from the quarter and swelling were associated with a higher re-treatment rate controlling for initial treatment and culture result. Lack of quarter firmness and swelling were associated with a higher clinical mastitis recurrence rate in the same quarter.

Presently it appears as though a two-stage severity classification scheme may be in order. First classify the cow based on systemic disease signs as described above (Table 1). For those in the moderate and severe groups, the local inflammatory changes of the udder are less important than addressing the systemic derangement of the cow. The quarter may be lost, but the primary focus is not to lose the cow.

Second classify those in the mild group based on local signs (secretion, and the presence of firmness and swelling). At present, however, we have very little information on how to approach therapy of these cows to reduce the re-treatment and recurrence rate. Perhaps, if swelling of the mammary gland precludes adequate distribution of an effective antibiotic, systemic therapy may be indicated. We recently reported on a study evaluating the effect of intramuscular (i.m.) ceftiofur (2.2 mg/kg) on important outcomes of systemically mild clinical mastitis episodes including re-treatment and recurrence.[11] The results of the study suggested that i.m. ceftiofur treatment had no beneficial effects on the outcome of systemically mild clinical mastitis. Obviously ceftiofur does not enter the milk to a significant degree; however, there were anecdotal reports in our area of significant reduction of recurrence associated with coliform mastitis in cows treated in this manner.

Many of you have probably approached clinical mastitis severity scoring by the two stage approach described above. It will be important that mastitis researchers adopt a similar approach to effectively classifies severity that will allow the results of treatment trials to be evaluated on the basis of systemic and local disease severity factors which we have shown are important to consider.

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