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Think Positive ToDAY: Research summary from the 2008 National Mastitis Council annual meeting

Mastitis remains the most costly disease and the most common reason antibiotics are used on U.S. dairy farms. Despite recent advances achieved by approaching mastitis control within a broader context of overall udder-health management, antibiotic therapy continues to be an important – if not indispensable – tool. In theory, these therapies could be selectively applied using on-farm culture systems.^{1, 2, 3, 4, 5} Culturing can, first, help identify which bacteria are the cause of clinical or subclinical infections and, second, help specifically design a treatment program specifically for those bacteria. Advantages of basing a treatment program on culture results include:

- Targeted treatment of Gram-positive bacteria, which often lowers individual and bulk-tank SCCs.
- Potential cures.
- Reduced shedding and potential disease spread.
- Fewer recurring flare-ups.
- More prudent antibiotic use by avoiding needless therapy for Gram-negative and no-growth samples.

Culturing causative agents also helps identify weaknesses in overall farm mastitis control programs by identifying the source of the infection. By working with their herd veterinarian to identify the source of the mastitis problem and by implementing specific prevention strategies, producers can lower the risks of this common disease. New research presented at the 47th Annual Meeting of the National Mastitis Council adds to this body of knowledge, demonstrating the employment of culture-based treatment systems to guide strategic treatment of intramammary infection (IMI).

*Subclinical Infection Prevalence and Etiology: Gram-negative vs. Gram-positive Bacteria*⁶

One study conducted by investigators from the Universities of Minnesota, Guelph and Wisconsin enrolled 1,028 U.S. and Canadian cows in their first three days postpartum. The 11 herds involved ranged from 60 to 2,500 cows. The results reported were preliminary results from an ongoing multi-site, multi-herd controlled field study. The objective of the three-year project is to validate the efficacy and quantify the cost-benefit of assessing treatments by culturing both clinical and subclinical mastitis cases at the farm.

After excluding cows showing signs of clinical mastitis at calving, cows with fewer than three functional teats and cows treated with antibiotics for any other condition, the research team ended up with a total of 4,044 study quarters. Frozen quarter samples were picked up

Table 1. Prevalence of IMI at calving

	Quarters	Animals
Heifers	43%	82%
Cows	30%	62%
Overall	37%	72%
No. of quarters infected (% of infected animals)		
One quarter	39%	
Two quarters	28%	
Three quarters	22%	
All quarters	11%	
Average infected	2 quarters	



by study technicians weekly for culture in the lab using standard methodologies. Quarters were considered infected if the lab identified one or two bacterial pathogen species, but contaminated if the sample yielded three or more. Any cow with one or more infected quarters was classified as an infected animal.

Results: The team reported a “remarkable” percentage of first lactation animals infected – at 82 percent – which was 20 percent higher than multi-parous cows. (See Table 1.) The pattern was present in nine of the 11 test herds. In agreement with other studies,⁷ the researchers also showed that fewer than 9 percent of the isolated pathogens were Gram-negative. (See Table 2.) Only 5 percent of all IMI were caused by *E. coli*.

Subclinical IMI Self-Cure Rate in Fresh Cows⁸

The same team reported preliminary results on a second aspect of its multi-site, multi-herd three-year project. They selected a random group of 175 fresh cows not given early lactation antibiotic therapy for additional analysis. The objective was to ascertain how frequently quarters that were subclinically infected at one to three days in milk self-cured. The 175 cows represented 366 quarters infected with 442 cultured bacteria. The team assessed whether quarters were considered cured bacteriologically by re-culturing all four quarters from each study cow at approximately 14±3 days and 21±3 days after enrollment. Quarters were considered cured when cultures showed one or two organisms in the enrollment milk sample that were then absent in the follow-up samples.

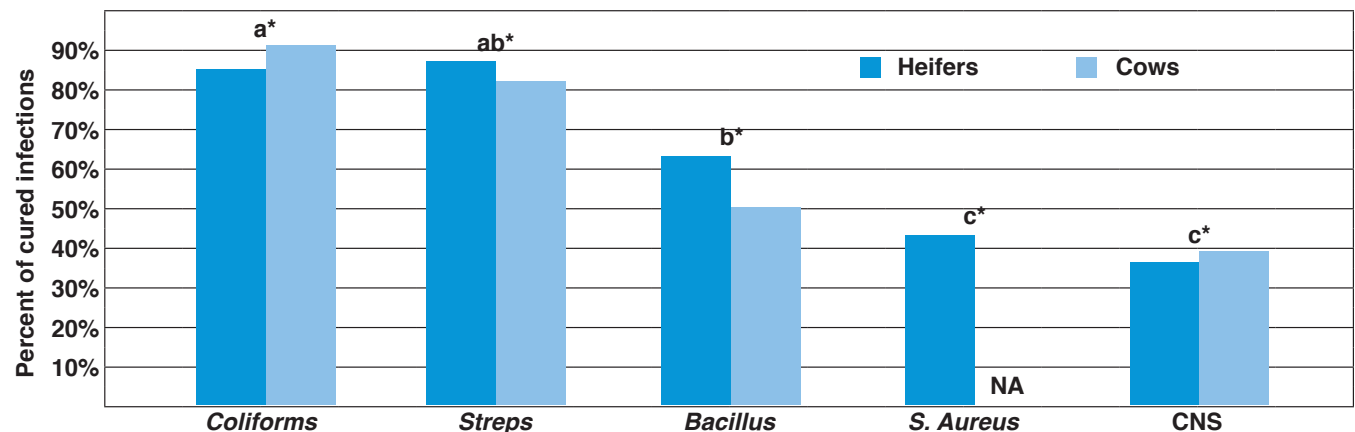
Results: Only 54 percent of the quarters self-cured, with no significant differences across parity. There were significant differences in cure rates for the different isolated pathogens. (See Figure 3):

- The authors considered cure rates for *Staphylococcus* spp. and *Staphylococcus aureus* infections to be “very poor.”
- More than 60 percent of *Staph.* spp. infections persisted until at least two to three weeks in milk (the point at which monitoring was ceased).
- *Bacillus* spp. infections showed an intermediate pattern, with 45 percent of those infections persisting until at least two to three weeks after calving.
- Environmental *Streptococci* and *coliform* infections showed a high propensity to self cure. Almost nine out of ten of them were eliminated by two to three weeks in milk.

Table 2. Pathogens isolated:

Gram-positive	Coagulase-negative <i>Staphylococcus</i> spp.	51%
	<i>Bacillus</i> spp.	16%
	<i>Streptococcus uberis</i>	8%
	<i>Enterococcus</i> spp.	7%
	<i>Aerococcus</i> spp.	5%
	<i>Staphylococcus aureus</i>	2%
	<i>Streptococcus dysgalactiae</i>	<1%
	<i>Corynebacterium bovis</i>	<1%
	<i>Arcanobacterium pyogenes</i>	<1%
	<i>Acinobacterium</i> spp.	<1%
	TOTAL	<93%
Gram-negative	<i>Escherichia coli</i>	5%
	<i>Enterobacter</i> spp.	2%
	<i>Klebsiella</i> spp.	1%
	<i>Citrobacterium</i> spp.	<1%
	TOTAL	<9%
	Yeast	1%

Figure 3. Proportion of fresh quarters with IMI that self-cured in early lactation for cows and heifers.



* P<0.05

The study authors cautioned the results of this aspect of their study, combined with results reported in the first section, demonstrate a significant need for improved mastitis management, as half of all cows could be subclinically infected with infections that persist at least two to three weeks into lactation. Their results echo previous studies suggesting subclinical IMI remains a critical industry problem.⁹

*Clinical Case Cure Rates and Antibiotic Use Guided by On-Farm Culturing*¹⁰

The previous results along with others suggest mastitis caused by Gram-negative or unidentified bacteria may not benefit from antibiotic therapy. Conversely, known Gram-positive infections do benefit from therapy. Within the context of those two factors, the research team presented a third study aspect, in which they tested whether using on-farm culturing of clinical cases to strategically apply therapy could affect either the number of treatments or the bacteriological cure rates.

They selected 452 mild or moderate mastitic quarters from eight of the test herds, ranging in size from 150 to 2,000 cows. They then divided them into one of two test groups:

- A positive control treated immediately with the labeled dosage of cephapirin (ToDAY[®]).
- A culture-based treatment, in which cows were treated the following day with the labeled doses of cephapirin (ToDAY) only if a Gram-positive bacteria was cultured.

Results: Using the same cure definition used in the previous report, they found that although limiting treatments to culture positives resulted in a significant reduction in antibiotic use, it made no statistically significant difference in cure rate between the two groups. (See Figure 4.)

*Usefulness of susceptibility testing of cultured pathogens to predict bacteriological outcome*¹¹

As part of the same investigation, the research team attempted to demonstrate improvements in clinical outcomes based on the susceptibility of identified causative Gram-positive pathogens. The study enrolled 136 subclinical and 51 clinical quarters with severity scores of less than three. In this study, only quarters infected with a single Gram-positive pathogens and treated with two intramammary infusions of 200 mg cephapirin sodium 12 hours apart were included. Bacteriological cures and failures were determined similarly to the previously reported studies. The researchers determined the minimum inhibitory concentration of Gram-positive pathogens using an extended dilution panel containing 12 antimicrobials, which were captured on the Trek Sensititre system. Because cure rates for the clinical and subclinical cases were not different, those two data sets were combined, and any isolates not inhibited at the highest concentration were censored.

Results: Of enrolled clinical quarters, 84 percent (43 of 51) were cured. Of enrolled subclinical quarters, 82 percent (110 of 136) were cured. Similar to other studies, the percent of resistant isolates in the cured and failed groups were 5 percent and 9 percent, respectively.¹² Because both cured and non-cured quarters demonstrated

Figure 4. Clinical mastitis treatment: Proportion of quarters treated and cured for two programs

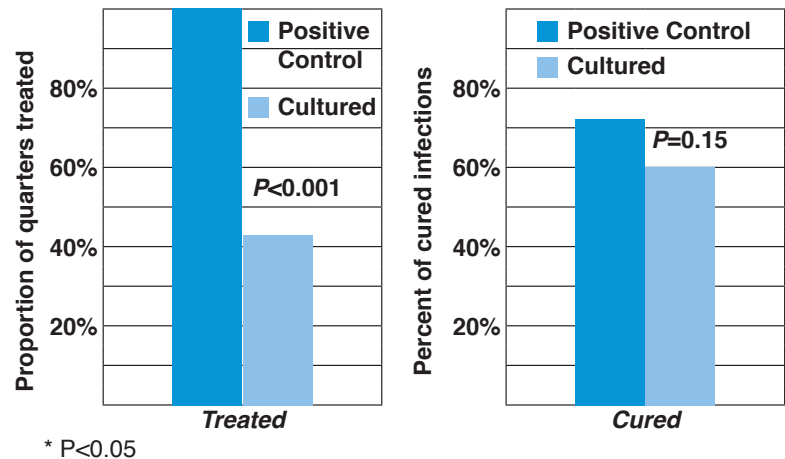
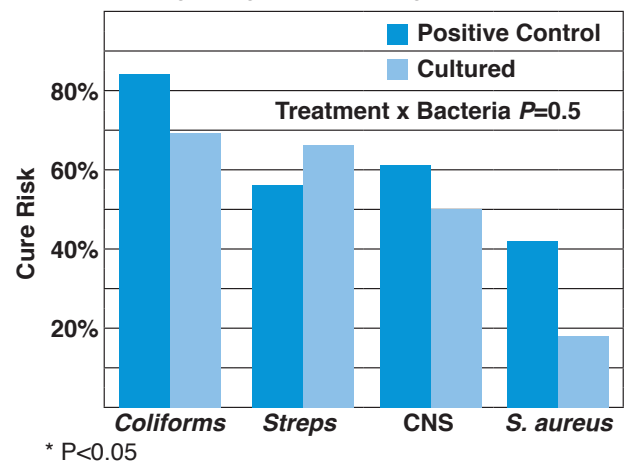


Figure 5. Clinical mastitis treatment: Cure risk by etiological agent for two programs

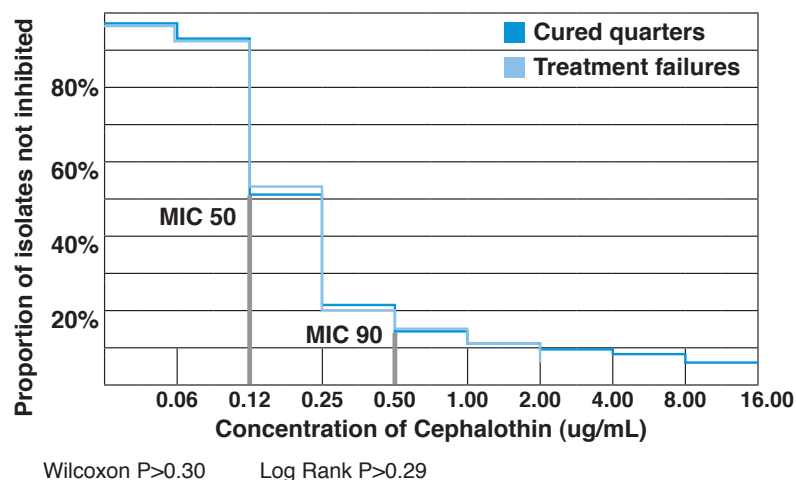


similar MIC curves (see Figure 6), the resulting lack of significant association between MIC and bacteriological cure rate illustrates the reality that numerous confounding factors can render in-vitro susceptibility testing an unreliable predictor of in-field therapeutic failure or success.

Summary

- Gram-positive bacteria were confirmed as a significantly more frequent cause of subclinical mastitis than Gram-negative pathogens.
- Gram-negative bacteria appear to be much more likely to self-cure than Gram-positive. More than 90 percent of *E. coli* IMI in multi-parous cows, for instance, were found to cure without therapy. Few previously published reports have shown any advantage of IMI therapy against Gram-negative pathogens.^{13, 14}
- Withholding IMI treatment for Gram-positive bacteria pending on-farm culture did not make a significant difference in treatment outcome. Although on-farm culturing can save on antibiotic costs by directing therapy specifically against Gram-positive organisms, if you don't employ culturing, select antibiotics known to be highly effective against Gram-positive pathogens.
- In choosing an antibiotic, it's important to remember first-generation cephalosporins like the cephalosporin in ToDAY[®] continue to maintain high effectiveness against those Gram-positive organisms, while third-generation cephalosporins appear to trade their increased activity against Gram-negative bacteria for reduced activity against the Gram-positive pathogens.^{15, 16} See the product labeling for complete directions for use.

Figure 6. Kaplan-Meier curves of MIC by outcome



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