# Factors Influencing Therapy Decisions in Clinical Cases of Gram-Positive Mastitis

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## Abstract

**Therapy of clinical mastitis caused by gram-positive bacteria was reviewed, and a retrospective study was conducted. Reported cure rates for mastitis appear higher shortly after treatment. Apparent cure rates are markedly overestimated with only one follow-up culture by as much as 69%; these false cures can be attributed to antibiotic therapy. Spontaneous cure rates of mastitis are often not significantly different from those with antibiotic therapy. Most (93%) food animal veterinarians use steroidal and/or non-steroidal anti-inflammatory therapy. Clinical mastitis signs are considered responsive to this type of therapy, however, most studies of antiinflammatory drugs concern their effectiveness against coliform mastitis, rather than gram-positive clinical mastitis. Oxytocin therapy for clinical cases of *Strep* sp. mastitis was compared with amoxicillin or cephapirin therapy; cure rates were not statistically different. Clinical gram-positive mastitis was found in 1464 quarters in the current retrospective study. Treatments used were: amoxicillin (n=21), cephapirin (n=122), cloxacillin (n=89), erythromycin (n=109), penicillin (n=93), unknown treatment (n=574), untreated (n=456). Bacterial cure rates for treated and untreated cases, respectively for each gram-positive agent were: *Strep ag* 518/691 (75%), 6/41 (15%); *Strep* sp. 60/73 (82%), 101/171 (59%);*S aureus* 84/149 (56%), 51/149 (34%); *Staph* sp. 68/95 (72%), 72/95 (76%). Routine antibiotic treatment of these cases lost $123.50 for each case cured. Financial loss was worse for herds with no *Strep ag* present. Treatment of clinical mastitis caused by gram-positive organisms other than *Strep ag* with antibiotic therapy was not indicated by the results of this study.**

## Introduction

Mastitis remains the most costly disease in the dairy industry.[1,2] Relative importance of mastitis caused by *Streptococcus agalactiae* (*Strep ag*) and *Staphylococcus aureus* (*S aureus*) has been somewhat reduced by reduction of their prevalence within U.S. dairy herds, but other gram-positive mastitis bacterial infections caused by coagulase-negative staphylococci (*Staph* sp.) and non-agalactiae streptococci (*Strep* sp.) have increased in relative importance.[3,4] Clinical mastitis caused by these four gram-positive organisms presents a common therapeutic challenge for dairy producers and veterinarians. Returning cows affected by clinical mastitis to their previous level of milk production, and relieving clinical signs such as a hot, hard quarter, abnormal milk, or generalized illness in a cost-effective way is the goal.

Most of the cost of treatment of clinical mastitis results from milk discarded because of antibiotic therapy withdrawal times.[2,5] This report concerns the following questions: What is the rate of elimination of gram-positive bacterial infections following antibiotic therapy of clinical mastitis? What is the bacterial elimination rate associated with treatments other than antibiotics? What is it with no therapy at all? How many cases of clinical mastitis would need to be treated with antibiotic therapy in order to cure one more case than would be eliminated without antibiotic therapy? What are the financial effects?

## Materials and Methods

Milk culture results from approximately 500,000 milk samples from cows housed in approximately 3,000 dairy herds visited by the Eastern and Central Laboratories of the Quality Milk Promotion Services at Cornell University from 1985 to 1995 were retrospectively reviewed. These farms were in New York and northern Pennsylvania. For inclusion in this analysis the following criteria were necessary:

**Clinical mastitis** - An individual quarter had to be identified on the barnsheet used at the time of sample collection as clinically mastitic.

**Therapy** - Treatment of the clinical quarter immediately prior to the farm visit or following culture results had to be clearly identified as a particular antibiotic, or that the quarter was definitely treated but with an unknown medication, or that the quarter was definitely untreated. All cases with uncertain treatment status were excluded.

**Follow-up** - Reculture of milk within two months of the first culture.

Bacteriological cure was defined as no isolation of the same pathogen from the second culture sample that was isolated from the clinically mastitic sample. Failure was defined as isolation of the same pathogen on the second culture.

**Financial calculations** - Milk withholding cost following antibiotic therapy was calculated as 5.5 days x 55 pounds (25 kg) per day x $13.00/cwt = $39.39/case. Direct cost of antibiotic was calculated as 3 treatment tubes @ $1.20 = $3.60/case. Total cost of antibiotic therapy per case was therefore estimated at $43.00. No estimates for labor, veterinary expense, or other costs were included. The value of eliminating a clinical case of mastitis was estimated as $70.00 saved by avoiding lost milk production (that over and above milk discard), extra veterinary expense and labor, and culling costs associated with each case of clinical mastitis.[2,6]

This report also summarizes previous studies concerning therapy of clinical mastitis caused by gram-positive bacteria. Field cases treated with comparison to spontaneous elimination of untreated cases, or to treatment without antibiotics are emphasized.

*Microbiology*

Milk samples for bacteriological culture were plated by streaking 0.1 ml on to trypticase soy agar with 5% sheep blood and .1% esculin (TBA) (Crane Laboratories, Syracuse, NY). Plates were incubated at 37 C for 48 hours. All plates were read after 24 and 48 hours.

Preliminary microbiologic analysis used colony morphology and gram staining. Gram-negative organisms were further identified by colony morphology on MacConkey agar and biochemical reactions in MIL, Urea, V.P., Simmons Citrate, adonitol and raffinose tubed medias. Streptococci were identified by hemolytic patterns, presence or absence of esculin hydrolysis and the CAMP test. Staphylococci were further identified using hemolytic patterns on blood agar and the coagulase test.

*Statistical analysis*

Differences in overall cure rates, and for each gram-positive agent of mastitis among treatments were tested using Chi-square.

## Results

*Previous studies*

In an earlier trial, clinical mastitis cases were treated with an experimental antibiotic purported for treatment of mastitis, or with cloxacillin. Both treatments were administered for three consecutive milkings, with treatments assigned in a double-blind study. Ten commercial dairy farms in New York and Pennsylvania with 305 day mean actual milk production ranging from 11,000 to 23,600 pounds (5,000 to 10,715 kg), and mean bulk tank SCC for 6 months ranging from 130,000/ml to 815,000 participated.[7] Based on re-culture 14, 21, and 28 days post-treatment, cure rates for clinical mastitis were: *Strep ag* 5/8 (63%), *S aureus* 4/23 (17%), *Strep* sp. 7/25 (28%), *Staph* sp. 3/4 (75%). There was no difference among treatments.[7]

Another study of intramammary (IMM) treatment of *S aureus* for 6 consecutive milkings with amoxicillin reported cure rates of 25% of quarters and 30% of cows were reported.[8] IMM therapy for 6 milkings combined with intramuscular (IM) injection of penicillin once a day for 3 days resulted in cure rates of 51% of quarters and 48% of cows.[8]

Reported "cure rates" for *S aureus* are affected by how long following treatment the cases are followed for subsequent culture; cure rates appear higher shortly after treatment.[9]

Clinical cases caused by *Strep* sp. were reported to have a 60-65% cure rate following IMM therapy.[9]

Spontaneous cures of mastitis are accomplished by the cow's natural defenses without any therapy. This is especially important when only single milk samples are used before and after treatment. Because false positive cases are enrolled in studies and false negative results or naturally eliminated infections are judged as "cures", cure rates can appear to be as high as 69% when the true rate is zero; these false cures can be attributed to antibiotic therapy.[10]

Mastitis bacterial cure rates in untreated cows have been compared with cures following treatment with antibiotics including cloxacillin: *S aureus* 20% spontaneous, 26% with antibiotics; *Strep* sp. 19% spontaneous, 36-78% with antibiotics; *Staph* sp. 47% spontaneous, 50% with antibiotics.[11,12] Results are summarized in Table 1.

**Table 1.** Spontaneous vs. antibiotic treated cure rates for clinical mastitis.*

| Mastitis agent | Spontaneous Cures | Antibiotic Cures |
|---|---|---|
| *Staph aureus* | 20% | 25-26% |
| *Strep* sp.[a] | 19% | 36-78% |
| *Staph* sp.[b] | 47% | 50% |

* From Craven, 1987, Seymour, 1989
[a] Non-agalactiae streptococci
[b] coagulase-negative staphylococci

*Therapy of clinical mastitis other than with antibiotics*

A 1992 survey of food animal veterinarians revealed that 93% used anti-inflammatory therapy, with 81% using it at least once a week. Flunixin meglumine was used by 95% of veterinarians, while dipyrone, aspi-

rin, and phenylbutazone were each used by approximately two-thirds of those surveyed.[13] Clinical mastitis signs such as swelling, endotoxemia, depression and pain are considered responsive to this type of therapy.

Most studies of antiinflammatory drugs concern their effectiveness against coliform mastitis. Data comparing antibiotic therapy, antiinflammatory treatment, supportive therapy, and no treatment of gram-positive clinical mastitis is needed.

However, oxytocin therapy for clinical cases of *Strep* sp. mastitis was compared with amoxicillin or cephapirin therapy. Cure rates were 48% with oxytocin and 61% with antibiotics; this difference was not statistically significant.[14]

*Results of the current study*

Clinical gram-positive mastitis was found in 1464 quarters meeting the study criteria: *Strep ag* (n=732), *Strep* sp. (n=244), *S aureus* (n=298), *Staph* sp. (n=190). Cases treated with unknown therapy resulted when dairy producers routinely chose from among two or more different antibiotics or combination products for mastitis therapy, and did not specify at the time of farm visit which had been used. Treatments used were as follows: amoxicillin (n=21), cephapirin (n=122), cloxacillin (n=89), erythromycin (n=109), penicillin (n=93), unknown therapy (n=574), untreated (n=456). Results are summarized in Table 2.

**Table 2.** Cure rates for various treatments for gram-positive clinical mastitis.

| | *Strep ag* cure rate (%) | *Strep* sp. cure rate (%) | *S aureus* cure rate (%) | *Staph* sp. cure rate (%) | Total cure rate (%) | Non-*S. ag* cure rate§ (%) |
|---|---|---|---|---|---|---|
| Number cases | 732 | 244 | 298 | 190 | 1464 | 732 |
| Amoxicillin | 8/9 (89) | 4/4 (100) | 4/6 (67) | 2/2 (100) | 18/21 (86) | 10/12 (83) |
| Cephapirin | 58/87 (67) | 2/4 (50) | 8/17 (47) | 12/14 (86) | 80/122 (66) | 22/35 (63) |
| Cloxacillin | 51/62 (82) | 4/7 (57) | 4/6 (67) | 12/14 (86) | 71/89 (80) | 20/27 (74) |
| Erythromycin | 60/74 * (81) | 6/6 (100) | 8/21 (38) | 6/8 (75) | 80/109 (73) | 20/35 (57) |
| Penicillin | 55/68 (81) | 1/2 (50) | 7/16 (44) | 6/7 (86) | 69/93 (74) | 14/25 (56) |
| Unknown Rx | 286/391 (73) | 43/50 (86) | 53/83 (64) | 30/50 (60) | 412/574 (72) | 126/183 (69) |
| Treated | 518/691** (75) | 60/73 (82) | 84/149 (56) | 68/95 (62) | 730/1008** (72) | 212/317* (67) |
| Untreated | 6/41** (15) | 101/171 (59) | 51/149** (34) | 72/95 (76) | 230/456** (50) | 224/415 (54) |

§ All cases other than *S agalactiae*
** P < .001, chi-square
* P < .05, chi-square

Bacterial cure rates for treated and untreated cases, respectively for each gram-positive agent were: *Strep ag* 518/691 (75%), 6/41 (15%); *Strep* sp. 60/73 (82%), 101/171 (59%); *S aureus* 84/149 (56%), 51/149 (34%); *Staph* sp. 68/95 (72%), 72/95 (76%) [Table 2]. Treated *Strep ag* cure rates were significantly increased, and untreated *Strep ag* and untreated *S aureus* cure rates were low (P <.001, chi-square, Table 2).

Overall cure rate for all cases other than *Strep ag* was 212/317 (67%) for treated cases and 224/415 (54%) for untreated cases (P <.05, chi-square, Table 2). With *Strep ag* included, cure rates were 730/1008 (72%) for treated cases, and 230/456 (50%) for untreated cases (P <.001, chi-square). When all cases other than those caused by *Strep ag* were analyzed, overall cure rates ranged from 56% with penicillin to 83% with amoxicillin; with *Strep ag* included, cure rates ranged from 66% with cephapirin to 86% with amoxicillin, but differences among antibiotics were not significant.

When clinical mastitis cases caused by *Strep ag* were included, the increase over the spontaneous cure rate associated with antibiotic therapy for all cases was 22% (72-50). Therefore 4.5 cases would need to be treated with antibiotics to have a high probability of affecting one additional cure. Extra cost would be 4.5 x $43.00/case = $193.50, and money saved would be $70.00, for a loss of $123.50 per antibiotic-associated cure.

When *Strep ag* cases were not included, the overall cure rate increase was 13% (67-54). For herds with no *Strep ag*, 8 gram-positive clinical cases would need to be treated with antibiotics to cure one additional case. Cost would be 8 x $43.00 = $344.00 to save $70.00, for a loss of $274.00 per cure.

Among individual mastitis agents, the only significantly increased cure rate associated with antibiotic therapy was found for *Strep ag* (P <.001, cellular chi-square). Clinical *Strep ag* cure rate increase was 60% (75-15); 1.7 cases would need to be treated with antibiotics to cure one additional case. Cost would be 1.7 x $43.00 = $73.10 to save $70.00, for a loss of $3.10 per cure.

## Discussion

Cost effectiveness of antibiotic therapy for mastitis caused by gram-positive bacteria is a subject of great interest to dairy producers and their advisors. Most have never had an antibiotic residue violation in meat or milk; industry concerns about risk of antibiotic residues are therefore a secondary consideration but are important nonetheless.

**Many mastitis cases caused by gram-positive bacteria are eliminated whether antibiotics are administered or not. Previous investigations of antibiotic therapy versus no treatment or oxytocin therapy suggested that for cases not caused**

**by *Strep ag* there is little impact on cure rates. Apparent cure rates are affected by the follow-up sampling method used.**

In the current study reported here, when clinical mastitis cases caused by *Strep ag* were included, treatment of 4.5 cases with antibiotics was needed to produce one additional cure with a loss of approximately $123.00. For herds with no *Strep ag* present, the expected ratio is 8 cases to cure one additional case, for a loss of $274.00. Clinical cases of only *Strep ag* when treated with antibiotic resulted in a loss of $3.00 per cure.

Cost effectiveness of mastitis treatment is also affected by contagious spread: if curing *Strep ag* in particular, which has low spontaneous elimination rates and has a marked tendency to spread to herdmates, is economically important. Therapy of clinical cases of *Strep ag* mastitis appears to be less profitable than treating subclinical cases caused by that organism, but is important to controlling (and preferably eradicating) this bacteria in dairy herds.

However, *Staph* sp. and *Strep* sp. are increasing in relative importance as agents of clinical mastitis. Routine antibiotic treatment of these cases, as well as those caused by *S aureus* was not indicated by the results of this study. This analysis used conservative estimates of antibiotic-associated costs and assumed that all of the production effects of a clinical case could be recovered for cured cases. These assumptions may overestimate the savings from a cured case of mastitis. Nevertheless, antibiotic therapy did not appear to be cost effective. Information is needed regarding antiinflammatory and supportive therapy of gram-positive clinical mastitis. Perhaps clinical improvement and true bacterial elimination can be enhanced without the milk discard losses associated with antibiotic therapy.

## References


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