PEER REVIEWED

Treatment of Candidal Mastitis in Two Holstein Cows: a Case Report and Review

Jerry R. Roberson, *DVM, PhD, DACVIM;* **Karen A. Kalck**, *DVM, DACVIM*
Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996
Corresponding author: Dr. Roberson, 2407 River Drive, University of Tennessee, Knoxville, TN, jrobers8@utk.edu

Abstract

Two Holstein show cows were presented for acute clinical mastitis in multiple quarters of five days and three weeks duration, respectively. The mastitis was classified as moderate to severe. Milk culture results revealed *Candida rugosa* and *Candida krusei* in pure culture, and California mastitis test (CMT) scores were a consistent 3 in all infected quarters. The cows were treated with intramammary miconazole (200 mg) every 12 hours for seven to eight total treatments. Milk cultures were collected and plated every 24 hours. A noticeable reduction in colony numbers during therapy was not evident. Miconazole was not an effective treatment for *Candida rugosa* or *Candida krusei*. An extensive review of the literature did not reveal any documented efficacious treatments for candida mastitis.

Key words: bovine, mastitis, yeast, candida, miconazole, treatment

Résumé

Deux vaches Holstein qui étaient à une exposition ont été admises en raison d'une mammite clinique aiguë dans de multiples quartiers persistant depuis cinq jours ou trois semaines, respectivement. La mammite était de type modéré à grave. La culture du lait a révélé la présence de *Candida rugosa* et de *Candida krusei* en culture pure et le score du *California mastitis test* (CMT) était de 3 dans tous les quartiers infectés. Les vaches ont été traitées avec une injection intramammaire de miconazole (200 mg) pendant 12 heures pour un total de sept à huit traitements. Des échantillons de lait étaient mis en culture sur gélose à toutes les 24 heures. Il n'y a pas eu de réduction évidente du nombre de colonies durant le traitement. Le miconazole n'a pas été un traitement efficace pour enrayer *Candida rugosa* ou *Candida krusei*. Une revue exhaustive de la littérature n'a pas mis en évidence des traitements efficaces pour les mammites provoquées par les levures du genre *Candida*.

Case Report

Two Holstein show cows, a two-year-old and a three-year-old, from a herd of 26 cows were evaluated for clinical mastitis that was unresponsive to treatment. Both cows were maintained on pasture at night and bedded on a shavings-straw mix during the day. The bulk tank average somatic cell count (SCC) was reportedly 270,000 cells/mL. Cows were milked twice daily.

The two-year-old was 42 days-in-milk, and clinical mastitis became apparent in multiple quarters five days prior to admittance. The owners were concerned that the mastitis was spreading to other quarters. The appearance of secretions from the affected quarters was described as mostly flakes, but milk production had decreased from 55-60 lb (25 to 27 kg)/day to 30 lb (13.6 kg)/day. The owners reported no signs of systemic illness in the cow, as she continued to eat well. One day prior to admittance to our clinic, the two-year-old cow was treated with pirlimycin,[a] ceftiofur hydrochloride,[b] flunixin meglumine,[c] long-acting oxytetracycline,[d] and aspirin. Physical examination revealed a slightly elevated rectal temperature of 103.1°F (39.5°C), an extra functional teat of the right rear quarter, and a California mastitis test (CMT) score of 3 on all five quarters. No other abnormalities were noted. Milk was collected aseptically from all functional quarters and submitted for culture. No treatment was initiated because the cow was in stable condition.

The three-year-old cow developed clinical mastitis in all four quarters and became a "downer" three weeks prior to admission. The cow responded positively to treatment with intravenous (IV) long-acting oxytetracycline,[d] calcium-magnesium-phosphorus-potassium solution, sugar, and oral amino acids. A CMT during that time revealed a score of 3 in all four quarters. The secretion was described as a clear liquid that became brownish at the time that the cow became a downer. Physical examination revealed no abnormalities other than clinical mastitis. Milk was collected aseptically from all quarters and submitted for culture. No treatment was initiated.

The following day, the condition of both cows was stable, CMT scores were still 3 in all quarters, and tiny pinpoint colonies were apparent on blood agar plates. A gram stain of the colonies revealed yeast-like organisms from all quarters except the right front of the three-year-old cow. Although there are no approved and/or known effective treatments for yeast mastitis, the owner wanted to attempt treatment because these were show cows. While a few proposed treatments for fungal mastitis could be found in the literature, no studies were found that reported treatment efficacy for yeast mastitis (success or failure). Because of local accessibility and being a suggested treatment for yeast mastitis, miconazole[e] was chosen.[34] Use of miconazole, or any other anti-fungal treatment specifically for yeast mastitis, is considered extra-label. The right rear quarter of the three-year-old cow was chosen to test the use of intramammary miconazole, and was treated with 200 mg via intramammary infusion. After treatment, no adverse reactions were noted other than a mild increase in the cow's rectal temperature (104.1°F; 40.1°C) the evening of treatment. The three-year-old cow was administered IV flunixin meglumine at 0.5 mg/lb (1.1 mg/kg) once, which appeared to reduce the cow's fever. The cow continued to eat, drink, and ruminate. Thereafter, each yeast-infected quarter of each cow was infused with miconazole at 200 mg BID after milking for four days (seven to eight treatments total). Following initiation of treatment in the two-year-old cow, she also developed an elevated temperature and was also treated with flunixin meglumine one time. Neither cow needed additional anti-inflammatory therapy throughout the rest of the treatment period.

Milk production of both cows increased slightly and the CMT scores decreased for some infected quarters over the next four days in the hospital. Milk samples from all affected quarters were cultured once a day for the duration of the cows' stay. There was no noticeable decrease in colony forming units for any of the eight infected quarters. Colony forming units were considered too numerous to count (Figure 1) while the cows were hospitalized. Both cows were discharged from the clinic seven days after admission without obtaining a microbial cure in any of the eight affected quarters.

Since published milk and slaughter withdrawal times for miconazole could not be found, extended milk and slaughter withdrawals of 30 and 60 days, respectively, were used. The question of withdrawal time was posed to the Food Animal Residue Avoidance Databank (FARAD) who offered the following response: "There are no identifiable published data available on the excretion of miconazole in milk in any species, thus it is not possible to make any predictions about a "safe" withdrawal interval for use of miconazole intramammary."

Using a biochemical typing system,[f] the yeast was determined to be *Candida rugosa* in all three infected quarters of the three-year-old cow, and *Candida krusei* in all five quarters of the two-year-old cow.

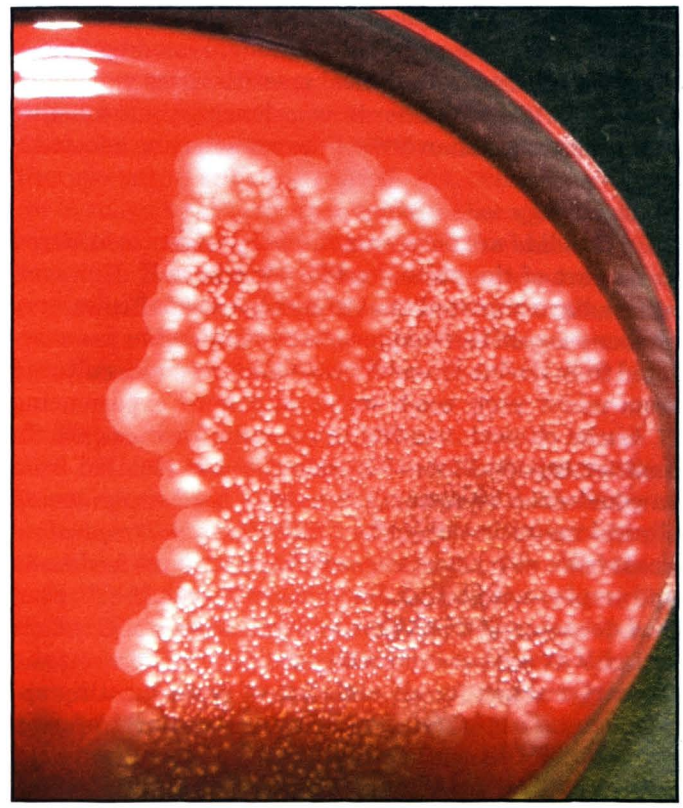

Figure 1. Growth of candida at 48 hour incubation on standard blood agar.

Both cows were subsequently treated at another university. After returning to the herd, the cows reportedly produced less milk than prior to developing mastitis. After a dry-off period and subsequent calving, both cows had ceased to lactate in one or two quarters. Two years after the initial visit, one cow remained in the herd, and the other was culled.

This case report was not designed to determine efficacy of miconazole as a treatment for candida intramammary infections. However, the outcome of these two cases suggests that miconazole is not an efficacious treatment for candida mastitis when used at the dose and frequency of administration in these two cows. Extra-label anti-fungal treatment for yeast mastitis does not appear to be justified.

Discussion

Etiology

The candida genus is reportedly the most commonly isolated yeast from cows with mastitis.[20,30] Yeast were isolated from 1-2% of milk samples submitted from mastitic cows to a laboratory.[15] In two other studies, the

prevalence of pathogenic yeast isolated from routine milk samples was 3.3% and 7%.[10,24] The prevalence of yeast mastitis isolated from clinical mastitis cases may range from 6.7%-12%.[1,29] In herds experiencing yeast mastitis outbreaks, more than 50% of the cows may be affected.[21]

Epidemiology

Candida are environmental organisms considered to be part of the normal udder skin flora.[19] However, others have reported that clinically normal cows may harbor yeast in their udders,[9] and candida has been isolated from bovine feces.[8,37] *Candida krusei* was cultured from udder prep wash water in a herd experiencing *C. krusei* clinical mastitis in recently fresh cows.[22] In another report, *C. pseudotropicalis* was isolated from sawdust used as bedding in a dairy herd experiencing clinical mastitis caused by *Candida pseudotropicalis*.[7] Yeast have also been isolated from ruminant feedstuffs and implicated in yeast mastitis outbreaks.[6,19,33] Elad *et al* determined that the most likely source of *Candida krusei* was contaminated wheat silage.[8] However, the primary method for an outbreak of yeast mastitis appears to be contamination of intramammary infusion products.[9,20] In some cases, the yeast contaminated product was prepared by a veterinarian in multiple-dose, large-volume vials designed to treat numerous cows by using a teat-end cannula.[21] When multiple cases of mastitis are treated with non-contaminated intramammary infusion products over a relatively short period of time, such as in clinical mastitis outbreaks or blitz therapy for *Streptococcus agalactiae*, clinical mastitis due to yeast may ensue. These outbreaks suggest improper preparation of the teat-ends for intramammary antibiotic infusion.[6,13] Sporadic yeast mastitis, without a history of intramammary infusion, occurs presumably because of the opportunistic nature of this environmental pathogen. The infective ability of yeast seems dependent on the number of organisms infused intramammarily; one challenge study did not result in long-term infection or clinical mastitis, whereas in another study mild clinical mastitis resulted from infusing between 10 and 20 thousand *C. krusei*, and severe clinical mastitis occurred when five million *C. krusei* were infused.[11,15]

Characteristics of yeast mastitis and clinical signs

Unless caused by contaminated intramammary products, affected cows tend to be infected in a single quarter.[8,28] In this case report, both cows had multiple quarters affected, suggesting that a contaminated intramammary product or unsanitary intramammary infusion technique was used. The owners reported, however, that the cows had not received intramammary therapy prior to developing clinical mastitis.

Yeast mastitis ranges in severity from toxic, as described by Moore, to subclinical as reported by Farnsworth and Sorensen.[10,25] In a Virginia Tech study, 10 of 16 cases of clinical mastitis caused by yeast or prototheca were moderate or severe, nine of 16 had a rectal temperature over 104°F (40°C) on day 1 of infection, and six of 14 had a hard swollen quarter.[29] In an outbreak of yeast mastitis in an Israeli dairy herd, the clinical mastitis was described as acute mastitis with a severe decrease in milk production and swollen mammary glands, indistinguishable from mastitis caused by coliforms and streptococci.[8] Crawshaw reported that cows affected by yeast mastitis had swollen glands, reduced milk production (20%), and some had clotted milk, but otherwise cows were healthy and had good appetites.[6] There does not appear to be any association between yeast mastitis and time of year, lactation number or days-in-milk.[29] Although Gonzalez reported that *Trichosporon beigelii* mastitis may be fatal, most reports on yeast mastitis do not mention fatalities.[13] Characteristics of yeast mastitis in other species may be considerably different. Singh *et al* reported that in experimentally-induced candidal mastitis in goats, the infection appeared to be self-resolving with time, but resulted in severe irreversible udder damage.[30]

Differentials

There are no unique signs of clinical mastitis caused by yeast, thus any of the numerous intramammary pathogens are considered differentials. Signs of yeast mastitis may range from subclinical infection to acute clinical mastitis, similar to *Escherichia coli*. Although the affected cow may show systemic signs of illness, such as an elevated temperature and a hard swollen quarter, rumen motility typically remains strong and appetite may be unaffected.[6,29] It has been suggested that yeast mastitis should be considered in cases with a history of unsuccessful antibiotic treatment.[19] While this may be true, unsuccessful treatment could indicate any number of mastitis pathogens.

Diagnosis

Yeast organisms grow well at 98.6°F (37°C) on standard blood agar media (Figure 1). The organisms are usually slow-growing, typically taking 48 hours until colonies are easily seen, but pinpoint colonies can be seen by 24 hours by tipping the blood agar plate back and forth. *Streptococci, Arcanobacterium pyogenes,* and *Corynebacterium* species are also small at 24 hours incubation, but a few simple tests help differentiate these microorganisms. A positive catalase test, conducted by placing a drop of hydrogen peroxide on a smear of the culture on a glass slide, indicates either yeast or corynebacteria, since both streptococci and *Arcanobacterium pyogenes* are negative. A positive catalase test is indicated by the production of bubbles. A gram stain should then be conducted on the catalase-positive suspect. Most

candida organisms appear as gram-positive, football-shaped microorganisms, whereas *Corynebacterium* species appear as small gram-positive rods. Most candida species are evident even under 10X microscope power, although 100X oil immersion is best to confirm the diagnosis. When species level identification is desired, bioMerieux's API 20 C AUX[f] has proven satisfactory. Kirk reported that a direct smear of stained milk may reveal the presence of large, oval yeast bodies with or without budding projections resembling baseball bats.[19]

Does a case of clinical yeast mastitis require treatment?

Several reports indicate that yeast mastitis may undergo self-cure within two to four weeks.[5,10,33] In a study of seven cows with clinical yeast mastitis that received no antimicrobial treatment, four of seven were negative for yeast by three weeks, and six of seven were negative for yeast by five weeks.[29] The remaining case had not achieved a microbial cure by 35 days, but decreased from more than 2,000 cfu/mL on day 1 to 80 cfu/mL on day 35, the last day of sampling. Likewise, Farnsworth reported that the majority of cows with candida and trichophyton infections return to normal in two weeks to a month with no residual effects.[9] Although most yeast mastitis clears within two to four weeks, some cows continue to shed yeast in non-clinical milk for up to eight months.[19] Results from a study where quarters were experimentally infected with *Candida krusei* indicated that yeast shedding was greatly reduced to absent, and quarter SCC was less than 100 cells/mL, by two to three weeks post-inoculation.[11] In contrast, the geometric means for obtaining a quarter SCC less than 500,000 cells/mL for naturally occurring clinical yeast cases was 25 days for the control group and 35 days for cases treated with intramammary antibiotics.[29] Only three of the 16 cows in the Virginia Tech study had a SCC less than 500,000 cells/mL by 21 days.[29]

Most dairy producers and veterinarians are interested in clinical cures. In the Virginia Tech study,[28] the geometric mean to clinical cure (normal milk and udder) of the control group was six days, and 10 days for the group treated with intramammary medication. In practically every case (14 of 16), clinical cure occurred prior to microbial cure. Although three of the 16 cows in the Virginia Tech study were considered to have severe clinical mastitis, no cows became downers or died. This is consistent with a report by Elad *et al*, who reported remission of clinical mastitis without treatment, with microbial cures by five weeks and SCC less than 150,000 cells/mL by two months.[8] Likewise, Kirk reported that most cases of candida regress spontaneously with only supportive therapy, although no specific treatment was reported.[19] In addition, Crawshaw and co-workers reported that cases were not treated, and all cows recovered fully over a two- to three-week period, although the decline in SCC took approximately two months.[6] Thus, one should consider whether treatment of clinical cases of yeast mastitis is warranted at all. The best method to manage clinical yeast mastitis cases may be to allow the disease to run its course, while providing symptomatic therapy only if truly warranted. Yet, there are no studies to suggest that any symptomatic therapies have any significant effect on the outcome of clinical cases of yeast mastitis. However, there may be times when the clinician may feel the need to attempt treatment; therefore, a review of the literature on anti-fungal treatments for yeast and fungal mastitis follows.

Antimicrobial treatments

In reference to yeast, Farnsworth stated that, "most species are resistant to common antibiotics, an exception is *Candida krusei*, which was reported to be sensitive to neomycin," citing Beck.[3,9] Yet, there is no mention of neomycin or *Candida krusei* in the article authored by Beck. Farnsworth and Sorensen reported that intramammary penicillin combined with dihydrostreptomycin and prednisolone had little or no observable effect upon the yeast population.[11] The number of yeast per mL of milk appeared to follow a similar pattern in both the treated and untreated quarters, suggesting the use of an intramammary antibiotic was neither effective against nor beneficial for the yeast. In general, antibiotic therapy is considered ineffective. In contrast to the findings of Farnsworth and Sorensen, yeast organisms may be able to utilize the nitrogen from antibiotics for growth.[23]

Anti-fungal treatments

A literature search was conducted to identify reports regarding efficacy of anti-fungal mastitis therapy. Although treatments for clinical fungal mastitis could be found in the literature, there are few known studies reporting efficacy of these various treatments. Clotrimazole was suggested as the drug of choice to treat yeast mastitis in cows.[26] Intramammary administration of 100-200 mg/quarter/day of 1% solution or cream, on one to four occasions as a single daily dose, reportedly gave positive clinical results when treating mycotic mastitis in cows, but no reference was given. VanDamme reported yeast cure rates over 78% among cows treated with either 100 or 50 mg of miconazole when infused intramammary for eight consecutive milkings, along with 45 g of thiabendazole *per os* daily for three days.[34] Cows were considered cured if culture results were negative for yeast at three and five weeks after therapy was completed. Non-treated cows were not used in the aforementioned study, making it difficult to discern the actual effect of the miconazole because untreated cows usually cure in the same time frame. One study reported successful treatment of *Aspergillus fumigatus*

mastitis when using intra-arterial and intramammary miconazole.[17] After milking, 100 mg of miconazole was injected into the external pudendal artery, and 100 mg of miconazole diluted in 50 mL of saline was infused into the affected quarter. This therapy was repeated for three successive days. Miconazole is a synthetic imidazole antifungal that acts by inhibiting the synthesis of ergosterol, which is a critical component of fungal cell membranes. Miconazole is primarily indicated for skin and mucous membrane fungal diseases such as ringworm, vaginal thrush, and athletes' foot. It is not recommended for systemic administration due to hepatic and cardiovascular side effects.[2]

A six-year Polish study reported that of 367 quarters of cows infected with mycotic pathogens, 77.6% of infected quarters were cured after a single course of clotrimazole therapy.[36] No controls were used in the aforementioned study, and the materials and methods were difficult to ascertain. Nystatin was used at 500,000 units/quarter/day for two to four treatments if clotrimazole failed to obtain a cure. The authors concluded that nystatin was more effective than clotrimazole. Intramammary infusion of clotrimazole at 100-200 mg/quarter/day once a day for one to four days has been suggested as the drug of choice for yeast mastitis in cows.[12] No reference was given for the aforementioned statement. Nystatin (800,000 units intramammary), intramuscular (IM) penicillin, IM oxytocin, and intramammary streptomycin had no apparent effect on a clinical case of *C. maltosa*.[18] Clinical mastitis caused by *Candida albicans* was treated with intramammary nystatin after being treated with various antibiotics for one month prior to culture and identification.[31] Six days after the beginning of nystatin treatment, milk returned to normal, inflammation subsided, and culture was negative. Although suggestive, it is impossible to determine if nystatin was actually efficacious or simply coincidental. Intramammary nystatin was not considered to speed recovery from *Candida pseudotropicalis* infection compared to cows receiving only symptomatic treatment.[7] Intramammary amphotericin B was reported to be ineffective (personal communication, Ruben Gonzalez). Intramammary natamycin was reported to be effective for treatment of cows with candida mastitis; 20 mL of a 2.5% solution or 10 mL of a 5% solution was infused intramammary once daily for three days.[15] The authors of that study noted that there was considerable irritation of the udder. Natamycin is available as an ophthalmic ointment approved for fungal keratitis. None of the treatments presented here are approved for treatment of clinical mastitis due to yeast, and most studies do not suggest withdrawal periods for meat or milk. However, authors of one study suggested a milk withdrawal period of 36 hours after intramammary infusion with natamycin.[15]

A 1987 study reported possible successful treatment of *Candida krusei* mastitis with sulphamethoxypyridazine.[22] An *in vitro* antifungal sensitivity test indicated sulphamethoxypyridazine was the only effective drug available for animal use. Eight cases were subsequently treated with sulphamethoxypyridazine at 10 mg/lb (22 mg/kg) for two to three days. Clinical cure was reported for four cases at the conclusion of therapy, whereas the other cases self-cured clinically by 10 days. No evidence of microbiological cure was given. Sulfonamides passively diffuse into milk following IV or oral administration, but concentrations achieved in milk are inadequate for treatment of mastitis.[4]

In an Italian study, 70% of nearly 1000 fungal mastitis cases appeared susceptible to undecylenic acid administered intramammary.[16] Undecylenic acid is a fatty acid found in sweat that has fungistatic properties. Undecylenic acid is listed as a less toxic antifungal agent that may provide more satisfactory therapy than other more toxic anti-fungal compounds when administered intramammary for yeast mastitis.[14] No other clinical trials using undecylenic acid to treat yeast mastitis were found.

Several varieties of iodine concoctions have been used, with variable success reported. Ten mL of povidone-iodine solution was used to treat fungal mastitis once a day for five days; milk was cultured weekly for six weeks.[32] Six of eight cows treated showed complete recovery and two showed no response, similar to a group of control cows. Materials, methods, actual time to recovery, and identity of the fungal organisms were not reported. A case of *Candida albicans* mastitis was treated with four treatments of IV sodium iodide (8%) every other day, and treatment was considered successful.[27] An intramammary preparation of two grams of iodine crystals dissolved in 30 mL of ether added to 150 mL mineral oil has been described, but success or failure of this preparation was not reported.[20] Spontaneous cures of untreated cows with candida mastitis also occur during the time frame of the aforementioned report. Excessive use of iodine at high concentrations for intramammary treatment may result in cessation of lactation of the treated quarter.

Intravenous gentian violet has been used to treat human cases of pulmonary candidiasis, but when used in cattle it caused shock, collapse, and seizure-like symptoms for 10-30 minutes prior to recovery.[3] Gentian violet is currently on the prohibited drug list for treatment of food animals, and is prohibited from use in food animal feeds.

Supportive therapy

As with any mastitis, there are various unproven methods to support and speed recovery from clinical mastitis. Suggestions include frequent milking, hydro-

therapy, massage, stripping, and oxytocin.[25,35] It is doubtful that any of these suggested supportive treatments are efficacious, but no efficacy studies have been conducted to date. Yet, many yeast mastitis cases will present as moderate to severe clinical mastitis with a hard, swollen quarter. Fluids, anti-inflammatory drugs, and systemic antibiotics should be considered in these cases, at least until the diagnosis of yeast mastitis is made.

Control

Complete elimination of yeast mastitis is unlikely to occur. However, outbreaks of yeast mastitis can be practically eliminated and overall incidence can be greatly reduced by 1) complete disinfection of the teat orifice prior to administration of an antibiotic; 2) avoiding multi-use bottles for intramammary treatment; 3) avoiding multi-use applicators for administration of intramammary treatment; 4) isolating or milking cows with mycotic mastitis last; and 5) utilizing proper milking-time hygiene to avoid spread from infected to non-infected cows. Culling should be considered for chronically infected cases, but most cows self-cure within one month.

Conclusion

Several preparations have been used to treat clinical mastitis caused by yeast. To date, there are no studies documenting true efficacy for any treatment. To provide substantial evidence of treatment efficacy, milk cultures should be conducted daily, or at least every other day, to demonstrate that the intramammary preparation is effective in reducing yeast colony numbers, and non-treated (control) cases should be used in the same study. Longer intervals between culturing are not helpful in demonstrating efficacy, as self-cures are known to occur within two weeks or less. Milk and slaughter withdrawal times are unknown for most of the reviewed treatments. Based on this literature review, the recommended method to manage clinical mastitis caused by yeast is supportive therapy alone.

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Endnotes

[a]Pirsue® Sterile Solution, Pfizer Animal Health, New York, NY

[b]Spectramast®, Pfizer Animal Health, New York, NY

[c]Banamine®, Intervet/Schering-Plough Animal Health, Summit, NJ

[d]Liquamycin® LA 200®, Pfizer Animal Health, New York, NY

[e]Monistat® 7 cream, Johnson & Johnson, New Brunswick, NJ

[f]API 20 C AUX, bioMerieux, Inc, Durham, NC

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or e-mail: nvap@aphis.usda.gov

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