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Severity of Mastitis Symptoms as a Predictor of C-Reactive Protein in Milk and Blood During Lactation

CATHERINE M. FETHERSTON,[1] JIM I. WELLS,[2] and PETER E. HARTMANN[3]

ABSTRACT

***Objective*: To investigate the presence of C-reactive protein (CRP) in breast milk and any relationship between changes in CRP in breast milk and blood, and the severity of systemic and breast symptoms experienced during mastitis.**

***Methods*: Mothers ($n = 26$) were followed prospectively from day 5 postpartum to the end of their lactation. Milk from each breast, blood, 24-hour urine samples and data on breast and systemic pathologies were collected at reference intervals during the first 3 months postpartum, daily during the occurrence of any breast inflammation and at 7 days after resolution of symptoms.**

***Results*: CRP in blood was significantly increased during mastitis ($p < 0.001$, df:1,81; $F = 31$) and severity of systemic symptoms was a significant predictor for changes of CRP in blood ($p < 0.01$; df:3,42; $F = 9.6$). During mastitis both the symptomatic breast ($p < 0.001$; df:1,79; $F = 19$) and the contralateral asymptomatic breast ($p < 0.004$; df:1,75; $F = 8.7$) had a significantly higher milk CRP when compared with women with no mastitis.**

***Conclusions*: Although an increasing severity of breast and systemic symptoms in mastitis was predictive of an increasing CRP in milk and blood, respectively, the presence of CRP in similar concentrations in the mastitis and asymptomatic breast suggests it is of little use in making a differential diagnosis between infective verses noninfective forms of mastitis.**

INTRODUCTION

Effective treatment and prevention of mastitis in lactating women depends on accurate identification of the underlying cause(s). This can present dilemmas for treating clinicians when it is not always obvious whether symptoms of mastitis are related to either an infective process or an inflammatory response. Brodribb[1] has described the development of blocked duct(s), mastitis, and breast abscess as a continuum in which "the boundaries, especially between blocked duct(s), obstructive (inflammatory) mastitis and infective mastitis, are blurred."

Research by Osterman and Rahm[2] confirms the difficulties in establishing infective involvement using clinical signs alone. Their study found that nonpathogenic mastitis episodes, with breast milk cultures positive for skin flora only, can elicit equally as severe breast and systemic symptoms as do episodes

[1]Attadale Private Hospital, Perth, Western Australia, Australia.
[2]Western Diagnostic Pathology, Myaree, Western Australia, Australia.
[3]School of Biomedical, Biomolecular, and Chemical Sciences, The University of Western Australia, Crawley, Western Australia, Australia.

with breast milk positive for potential pathogenic bacteria. Serum C-reactive protein (CRP), although elevated, was also not significantly different in the two groups. Assuming that microbiologic cultivation of milk is representative of bacterial growth at the mastitis site, their findings indicate that neither serum CRP nor severity of symptoms experienced are accurate indicators as to whether an episode is either infective or only inflammatory.

Although there is one report of the presence of CRP in human colostrum,[3] the response of CRP in the breast milk of women during mastitis has not yet been reported. C-reactive protein in the milk of cows increased as much as tenfold as a result of mastitis and a decrease in the concentration of CRP in milk during antibiotic treatment was reflected in treatment success.[4] Another study[5] measured CRP in the milk of cows to evaluate its potential as an indicator of inflammatory changes in subclinical mastitis but found the application of CRP, as an alternative to using cell counts was not a useful diagnostic tool. They found, in particular, that the range detected in milk (50 to 170 μg/L) was very small, limiting its use as an inflammatory marker.

This study sought to investigate the presence of CRP in breast milk during mastitis and whether there is a relationship between changes in CRP in breast milk and blood and the severity of systemic and breast symptoms suffered.

METHODS

Sample collection, recruitment, and demographics of subjects have been reported in detail elsewhere;[6] however, briefly in addition to the study into CRP, the research undertaken also sought to describe changes in milk composition and breast permeability during lactation mastitis.[6] The study used a convenience sample of lactating women ($n = 26$), assessed to be at risk for developing mastitis, who were then followed prospectively from the fifth day postpartum to the end of their lactation. Criteria used to identify "at-risk" mothers were based on previous research[7,8] and included one or a combination of the following: a history of mastitis in previous lactations, nipple trauma, attachment difficulties, and either an uncomfortable oversupply or engorgement at lactogenesis II. Reference samples of milk and 24-hour urine were collected from women at days 5, 14, 30, 60, and 90 postpartum, and blood at days 5 and 14, to obtain data on the normal range of a set of potential biochemical markers for mastitis. These included sodium (Na), chloride (Cl), lactose, glucose, serum albumin, lactoferrin, and secretory immunoglobulin A (sIgA) in milk and lactose in blood and urine.[6] Also included in this range of markers, for the focus of this article, were CRP in milk and blood at days 5 and 14 postpartum.

Eighty-eight percent (88%, $n = 23$) of the sample were exclusively breastfeeding during reference sampling, three mothers were offering one to three complementary feeds/24 hours at day 90; and one mother who initially experienced low supply was offering supplementary feeds from day 5 to 21, but was thereafter exclusively breastfeeding. Women were interviewed at collection times to establish any coexisting breast (e.g., nipple trauma, low supply) or systemic pathologies. If women suffered with mastitis at any time during their lactation, further samples were collected daily during the course of their mastitis and at follow-up 7 days after resolution of symptoms. If the mother had not already commenced antibiotic treatment at the time of the researcher's first visit (day 1 of the episode), milk also was collected for culture and sensitivity of aerobic bacteria. Women with mastitis completed a symptom log to provide descriptive data on the characteristics and management surrounding the onset and duration of their mastitis.

The study was approved by The University of Western Australia, Human Research Ethics Committee.

Operational definitions

Breast inflammation. Breast inflammation was defined as a warm to hot, red, and tender or painful area of the breast. It was further categorized as localized, segmental, or total breast inflammation according to the area of inflammation present.

Systemic symptoms. Systemic symptoms were defined as *mild* (feels unwell, tires easily, afebrile [body temperature (T°) <37.5°C]); *acute* (unwell, T° >37.4°C and <38.5°C, myalgia, needs to go to bed); and *hyperacute* (T° >38.4°C, myalgia, headache or vomiting, rigors).

If overlap of symptoms between categories occurred, T° would be the primary defining factor. Any inflammation of the breast present for more than 24 hours and accompanied by any degree of systemic illness was categorized as mastitis.

Measurement of C-reactive protein in milk and serum

C-reactive protein in milk and serum was quantified at a commercial laboratory by Rate Nephelometer (Beckman-Immage®, Gladesville, New South Wales, Australia) using CRP reagent kits supplied by Beckman Instruments, Inc. The recovery of a known amount of serum CRP added to defatted milk samples was 90.5 ± 5.6% ($n = 10$). Interassay CV was determined using Dade Behring Immuno 1 (10 mg/L) and 3 (38 mg/L) and was 4.4% ($n = 41$) and 6.3% ($n = 41$), respectively. Sensitivity for serum and milk CRP determination was 1 mg/L.

Bacteriologic analysis of milk

The nipple and areola areas of each breast were cleaned with sterile water and allowed to dry. Using gloves, the first 5 mL (approximate) were expressed into a clean sample tube for biochemical analyses and a further midstream sample was then expressed into a sterile 5-mL polypropylene tube. The midstream sample was transported on ice and stored at 4°C for no longer than 6 hours, when 100 μL was then cultured on horse blood and chocolate agar, both formulations using oxoid agar bases. Each plate was air dried in 35°C for 45 minutes and dried before inoculating each agar plate with sample. Both plates were incubated at 35°C in an 8% CO_2 atmosphere for a total of 48 hours. Colony counts were performed at 24 hours incubation and again at 48 hours. The identification of the different species and their antibiotic sensitivity was carried out by a range of classical characterization tests.[9]

Statistical analysis

Descriptive statistics used means and standard deviations or medians and interquartile ranges, as appropriate, depending on normality. Hypothesis testing of all outcome measures was based on analysis of variance with repeated measures within a mixed model[10] (MIXED procedure). Models were used in which individual women were treated as random effects and comparison groups (e.g., mastitis/no mastitis) as fixed effects.

In the analysis of outcomes that occurred at various stages of lactation appropriate adjustment, using stage of lactation (day postpartum) as one of the covariates in analysis of variance models, were made. Estimate effects were presented as means and 95% confidence intervals (95% CI). Any p-values < 0.05 were considered significant. All data was analyzed using the mixed model module (MIXED) in SPSS 11.0 for Mac OSX (2002).

RESULTS

Mastitis incidence

The sample of 26 women yielded 14 women suffering a total of 22 episodes of mastitis. Two women experienced one episode each of bilateral mastitis. Range of occurrence was from day 5 to day 400 postpartum. Fifty-four percent (54%, $n = 12$) of episodes were experienced in the first 30 days.

C-reactive protein response in blood and milk postparturition

The concentration of CRP in the blood of women with asymptomatic breasts ranged from 9 to 45.5 mg/L on day 5 ($n = 12$) and 1 to 102 mg/L on day 14 ($n = 10$) postpartum. The concentration of CRP in milk from asymptomatic breasts ranged from below the level of detection to 1.91 mg/L in samples on day 5 ($n = 25$ breasts) and below the level of detection to 3.0 mg/L on day 14 ($n = 26$).

Blood and milk CRP were analyzed according to type of birth in women without mastitis. Results for days 5 and 14, respectively, are shown in Table 1.

Breast milk bacteriology during mastitis

Breast milk was collected for culture, sensitivity, and leucocyte and bacterial counts from both breasts of nine women experiencing 13 mastitis episodes (two bilateral episodes, n = 15 mastitis breasts). In the remaining episodes, samples for culture were not collected because women had already commenced antibiotics before the visit from the researcher. Only samples from two of the 13 episodes cultured positive for pathogens. *Staphylococcal aureus* was cultured in one single breast episode and penicillin-resistant *S. aureus* in one bilateral episode. Milk from the other bilateral episode contained scant to moderate leucocytes and $>10^3$ cfu/mL of *Streptococci (Strep) viridans* and coagulase-negative staphylococci (CNS). Milk from seven of the remaining nine single breast nonpathogenic episodes showed higher counts ($>10^3$) of CNS and/or *Streptococci viridans* in the affected breast than in the unaffected breast

C-reactive protein response during mastitis

C-reactive protein (CRP) was measured daily in both the milk and blood of women who consented to sampling during mastitis episodes and at follow-up (7 days after resolution of mastitis symptoms). The concentration of CRP in blood for mastitis samples (n = 36) ranged from 7 to 316 mg/L (mean = 65.5 ± 62.9). Mean serum CRP was highest (77 ± 58 mg/L) on day 2 of mastitis episodes. The concentration of CRP in blood, on the second mastitis day, for the infective episodes of mastitis (*S. aureus*, n = 2) was variable (55 and 145 mg/L) when compared with the mean serum CRP for the noninfective mastitis episodes (68 ± 51 mg/L). When adjusted for stage of lactation, the concentration of CRP in blood was significantly increased during mastitis ($p < 0.001$; df:1,81; F = 31); however, mixed model analysis did not find any particular day of the mastitis episodes (first, second third, fourth, or fifth day) to be a significant predictor for CRP concentration in blood ($p < 0.75$; df:3,28; F = 0.4; Fig. 1). When adjusting for coexisting pathologies and stage of lactation, the concentration of CRP in blood at follow-up was not significantly different from women without mastitis with asymptomatic breasts ($p < 0.55$; df:1,44; F = 0.4).

The mixed model analyses showed the concentration of CRP in blood increased according to both the severity of breast and systemic symptoms (Fig. 2). The model for severity of systemic symptoms was a significant predictor for change in the concentration of CRP in blood ($p < 0.01$; df:3,42; F = 9.6), whereas the severity of breast symptoms did not predict changes in blood CRP ($p < 0.37$; df:2,31; F = 1.0). The estimated means (95% CI) and significance values for type of symptoms from the mixed effects models are shown in Figure 2.

During mastitis, the concentration of CRP in milk from the mastitis breast ranged from below the level of detection to 5.2 mg/L and similarly the concentration in the contralateral asymptomatic breast ranged from below the level of detection to 4.8 mg/L. Both the symptomatic mastitis breast ($p < 0.001$; df:1,79; F = 19) and contralateral asymptomatic breast ($p < 0.004$; df:1,75; F = 8.7) had a significantly

Table 1. Median (25, 75 Quartile) C-Reactive Protein (mg/L) in Blood and Milk of Women Without Mastitis According to Type of Birth at Day 5 and Day 14 Postpartum

CRP (mg/L)	*Spontaneous vaginal birth*	*Vacuum birth*	*Nonelective Cesarean birth*	*Elective Cesarean birth*
Day 5 (blood)	18.9 (6.7, 25.9) n = 7 women	14.9 (11.5, 18.3) n = 3	30.3 (16.8, 67.5) n = 5	48 (12.4, 58.2) n = 9
Day 14 (blood)	2.2 (1.0, 38.5)	3.7 (2.0, 5.4)	6.8 (4.5, 57)	3.5 (1.7, 10.6)
Day 5 (milk)	0 (0, 1) n = 14 breasts	1.5 (0, 2.1) n = 6	1.0 (0, 1.6) n = 10	0 (0, 0) n = 18
Day 14 (milk)	0 (0, 1.2)	1.1 (0, 1.6)	0 (0, 0.3)	0 (0, 0)

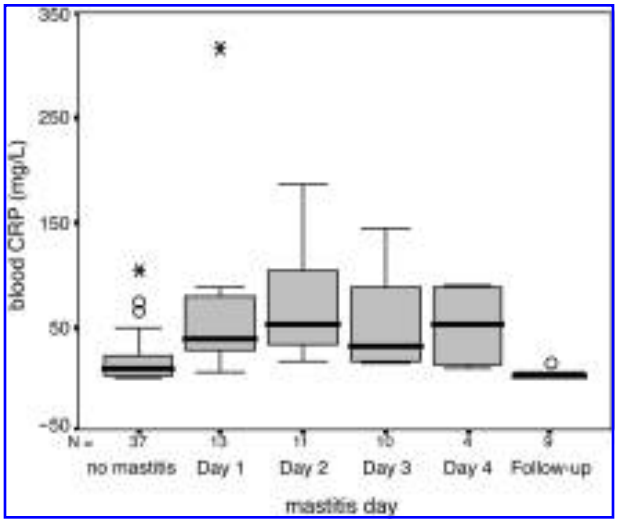

FIG. 1. Descriptive data (median, interquartile range) for C-reactive protein (CRP) (mg/L) in blood for each day of mastitis episodes (day 1 to day 4). Concentrations of CRP in blood for women with asymptomatic breasts (no mastitis) and at follow-up 7 days after resolution of mastitis are included for comparison. The no mastitis cases include reference measurements at day 5 and day 14 postpartum when CRP may have been elevated after trauma from birth. Outliers (>2 box lengths) are shown as ^{0} and extremes (>3 box lengths) as *.

higher milk CRP when compared with women who did not have mastitis. The estimated mean (95% CI) for concentration of CRP in milk from the mixed model was 2.0 mg/L (1.4, 2.6) in mastitis breasts ($n = 58$) and 1.76 mg/L (1.1, 2.4) in contralateral asymptomatic breasts ($n = 41$). This was not significantly different ($p < 0.221$; df:1,87; $F = 1.5$). The concentration of CRP in milk increased over the period of the mastitis episode to reach a peak on day 4 of the episode (2.3 mg/L); however, the statistical model was not significant ($p < 0.31$; df:4,41; $F = 1.2$) (Fig. 3). The mean for the two infective (*S. aureus*) episodes (2.9 mg/L) was higher than the mean milk CRP of noninfective mastitis breasts (2.0 mg/L). When adjusted for coexisting pathologies and stage of lactation the concentration of CRP in milk from mastitis breasts ($n = 12$) at follow-up (7 days after resolution of symptoms) was not significantly different ($p < 0.21$; df:1,57; $F = 1.6$) from the concentration of CRP in milk from women without mastitis with asymptomatic breasts ($n = 49$ breasts).

C-reactive protein response in breast milk during mastitis was observed to increase with severity of breast symptoms (Fig. 4). The concentration of CRP in milk was within a very narrow range compared with the concentration of CRP in blood, and the predictive model for severity of breast symptoms was not significant ($p < 0.82$; df:2,47; $F = 0.2$). Severity of systemic symptoms also was not a significant predictor for change in the

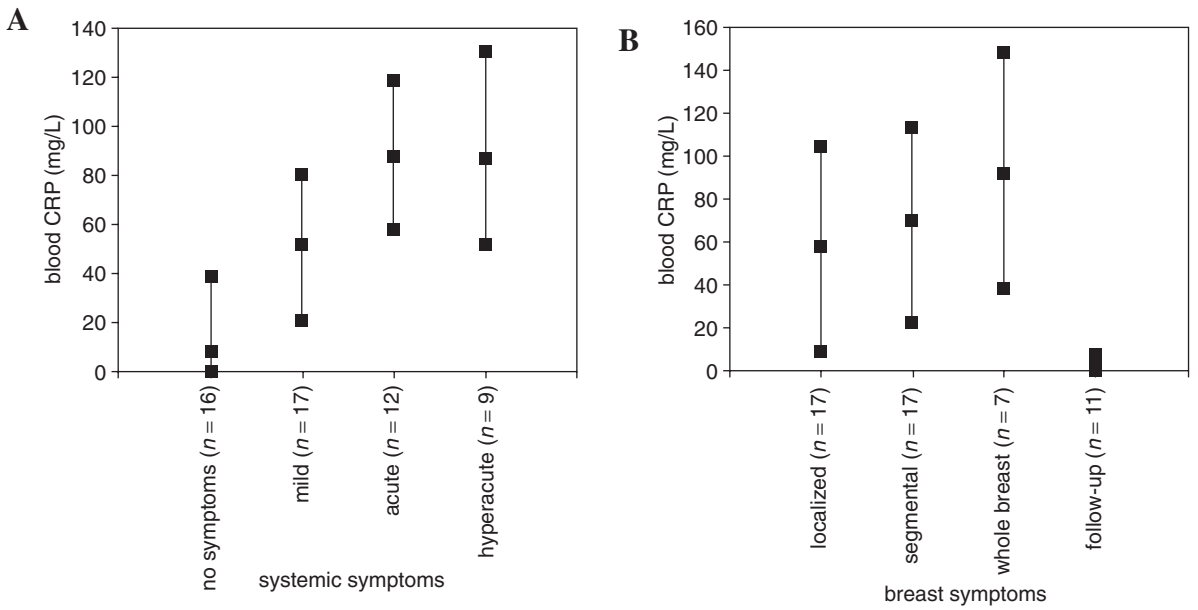

FIG. 2. Estimated means (95% CI) from the mixed model analysis for C-reactive protein (CRP) in blood according to the severity of systemic symptoms **(A)** and breast symptoms **(B)** experienced during mastitis. Follow-up data are included in **(B)**. The midpoint represents the estimated mean with upper and lower points, the 95% CI.

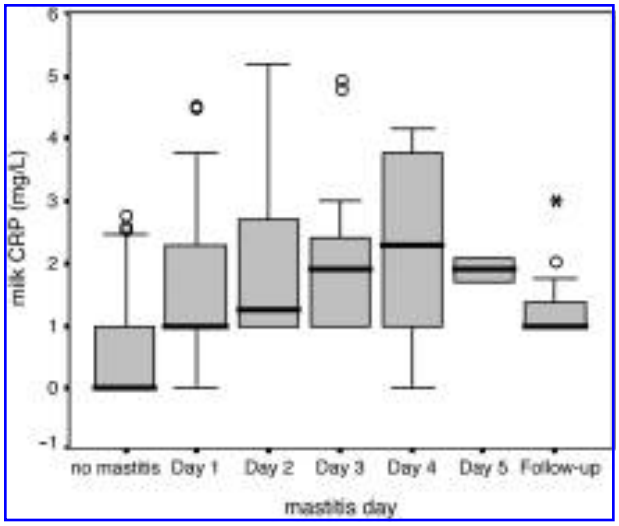

FIG. 3. Descriptive data for C-reactive protein (CRP) (mg/L) in milk on each day of mastitis episodes (day 1 to day 5). Concentrations of CRP in milk for women with asymptomatic breasts (no mastitis) and at follow-up after mastitis are included for comparison. The no mastitis cases include reference measurements at day 5 and day 14 postpartum when the mean CRP was below the level of detection.

concentration of CRP in milk ($p < 0.59$; df:3,45; $F = 0.63$). The estimated means (95% CI) from the mixed models are shown in Figure 4.

DISCUSSION

The concentration of CRP in breast milk at days 5 and 14 postpartum was generally below the level of detection in women without mastitis (<1 mg/L), despite significantly increased concentrations of CRP in blood. Previously reported concentrations of 8 to 12 mg/L in colostrum at 36 to 48 hours postpartum[3] were not accompanied by results of recoveries or coefficients of variance. However, assuming the validity of this report, these comparatively high concentrations may be explained by the increased paracellular pathway permeability present at this time. The dramatic drop to negligible concentrations at day 5 in this study is commensurate with closure of the tight junctions, which is largely complete by 72 hours.[11]

The increased CRP in blood in the postpartum period is likely to have resulted from tissue trauma associated with birth and birth interventions. Whereas previous studies[12,13] reported peak CRP concentrations in blood rapidly decreasing to baseline after the second or third day postpartum, the present study CRP concentrations remained increased at day 5 postpartum and a high variation above the

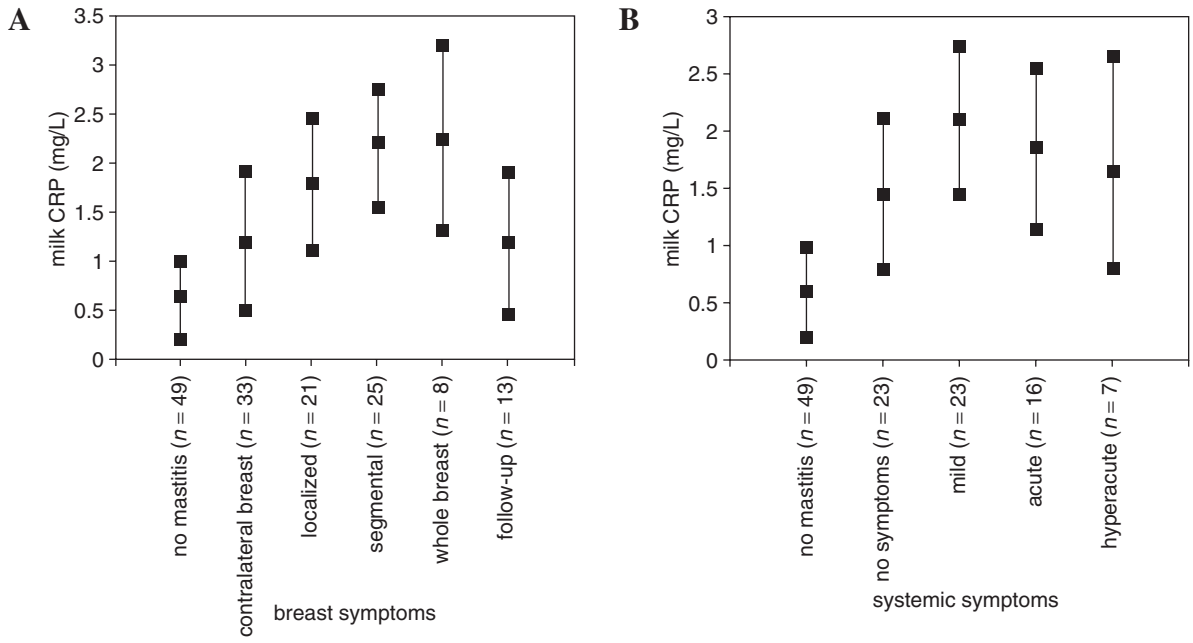

FIG. 4. Estimated means (95% CI) from the mixed model analysis for C-reactive protein (CRP) (mg/L) in milk according to the severity of breast symptoms **(A)** and systemic symptoms **(B)** experienced during mastitis. Data from women with asymptomatic breasts (no mastitis), the contralateral asymptomatic breast and the mastitis breast at follow-up is included in **(A)**.

mean was observed, particularly for spontaneous vaginal and nonelective Cesarean sections at day 14 postpartum.

Recruiting breastfeeding women with known risk factors for mastitis, in particular, a past history of mastitis and/or nipple trauma, and attachment difficulties, provided an efficient means of obtaining a high incidence of mastitis with a wide range of severity of symptoms appropriate for the observation of changes in CRP and other components in breast milk. However, because of the specific nature of the sample, these results should not be generalized to a normal population.

The concentrations of CRP in blood observed during mastitis were similar to those reported by Osterman and Rahm[2] who reported the highest observed CRP at 280 mg/L with a mean of 61.5 mg/L in 40 women presenting with mastitis. The slightly lower results obtained, compared with the authors' study (mean 77 mg/L, highest 316 mg/L), may result from the time of sampling. Although not stated, it is assumed samples were taken on the first day of mastitis presentation, whereas the peak mean CRP observed in the authors' study occurred on the second day of mastitis episodes. As the most acute symptoms were experienced during the first day of mastitis, the delay in peak observed CRP was expected, because the plasma level can double every 8 hours in the presence of continuing inflammatory stimulus.[14]

An increasing severity of systemic symptoms in mastitis was predictive of an increasing concentration of CRP in blood. Blood CRP also increased with escalating severity of breast symptoms; however, the differences among localized, segmental, and inflammation of the whole breast were not significantly predictive. Women who had recovered from systemic symptoms but breast symptoms had not yet resolved had a mean concentration of CRP in blood <10 mg/L, which is considered normal.[14] This rapid fall occurs because of the short half-life of CRP of 5 to 7 hours. This indicates that the presence of systemic symptoms in mastitis is a stronger predictor than breast inflammation for a raised concentration of CRP in blood.

The increase in the concentration of CRP in milk during mastitis did not reach the levels reported by Abdulla et al. in colostrum[3] despite elevated concentrations in blood. This may suggest the increase in paracellular pathway permeability in response to mastitis may be only localized resulting in less movement of CRP into the milk space compared with that occurring during the first 48 hours postpartum when there is believed to be uniform pathway permeability present. Although the source of CRP in milk cannot be positively determined, the association between breast symptoms and the concentration of CRP in milk indicates there is either some local production or transfer of CRP to the site in a dose-related response to the severity of local inflammation. The presence of an increased CRP in milk from the asymptomatic breast suggests an additional systemic source; however, there was no relationship observed between CRP in milk and the CRP in blood at day 5 or 14 that supports the latter proposal. An explanation for the observed rise in milk CRP in the contralateral asymptomatic breast is illusive, particularly because the other milk components measured in this breast were within normal range.[6]

Bacteriology

Only two (one bilateral) of the 13 tested episodes of mastitis had breast milk cultures from the mastitis breast(s) that were positive for the growth of pathogenic bacteria. Previously, when breast milk culture has been negative during mastitis, there has been some doubt as to whether milk obtained for culture was representative of the affected area. However, the changes observed in milk composition combined with the increased excretion of lactose in the urine[6] indicate that the milk expressed was representative of milk from the inflamed or infected area of the breast.

There was a high count (10^3 to 10^5 cfu) of *Strep. viridans* and/or CNS present in the milk from affected breasts (both pathogenic and nonpathogenic) compared with asymptomatic breasts. It cannot be discounted that the presence of either CNS or *Strep. viridans* within the breast, especially when present in high numbers, may be the causative mechanism for what is normally considered "noninfective" episodes of mastitis experienced by the women in this

study. *Strep. viridans* generally are considered a normal commensal, most abundant in the human mouth and pharynx. Some of these organisms can cause brief low-grade bacteremias when they pass into the circulation, via injury to the gums. However, generally they are cleared rapidly from the circulation as they do not possess protective devices against host defenses.[15] The source of *Strep. viridans* in the breast milk of these women could have been through hematogenous spread, but it is most likely to have been through the nipple from the infant's mouth. Matheson et al.[16] found *Strep. viridans* present in only 8% of milk samples from healthy women; a relatively low percentage compared with its presence in 7 of the 13 nonpathogenic mastitis breasts cultured from women with mastitis in this study.

Coagulase-negative staphylococci were isolated in all mastitis samples cultured in the present study in numbers ranging from 10^3 and 10^5 cfu/mL. The presence of CNS is generally disregarded as being either a contaminant from the skin or at least a normal occurrence in breast milk, with 86% of milk samples from healthy donors containing CNS.[17] However, these isolates were present in counts greater than 10^2 cfu/mL, despite being midstream samples. Abakada et al.[17] found that CNS appeared to have some pathogenicity in the breasts of women with mastitis, with *S. epidermidis* appearing to be the most virulent. Pathogenic strains of CNS have been described previously[18] and also considered as possible causative factors in the occurrence of mastitis.[19]

CONCLUSION

The concentration of CRP found in the milk from breasts of women with mastitis was much lower (1/60) than that observed in blood; however, it was still considerably higher than that detected in cows milk (1 to 5 mg/L compared with 50 to 170 μg/L, respectively). Because of the low concentrations of CRP observed in milk, an alternate assay method with a lower sensitivity level compared with the commercial rate nephelometry used in this study may be more discerning of the changes in CRP. As paracellular pathway permeability was found to be normal in the unaffected breast during mastitis,[6] the presence of CRP in the milk from both the mastitis and contralateral asymptomatic breast appear to indicate some active transport of CRP into the milk compartment, or *de novo* synthesis. There was no observed relationship between the concentrations of CRP in milk and blood either during mastitis or the immediate postpartum period, although increasing severity of breast symptoms did result in an increasing concentration of CRP in milk. However, the increase was not statistically predictive because the range in concentration of CRP observed in milk was very narrow. This, and its presence in the asymptomatic breast in similar concentrations to the mastitis breast, suggest it is of little use in making a differential diagnosis between infective and noninfective forms of mastitis.

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Address reprint requests to:
Catherine M. Fetherston, Ph.D.
Attadale Private Hospital
21 Hislop Road
Attadale 6156
Perth, Western Australia, Australia

E-mail: cfethers@gmail.com