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Acute phase proteins as indicators of calf herd health

Charina Gånheim [a,b,*], Stefan Alenius [b], Karin Persson Waller [a,c]

[a] Department of Clinical Sciences, Division of Comparative Reproduction, Obstetrics and Udder Health, P.O. Box 7039, Swedish University of Agricultural Sciences, SE-750 07 Uppsala, Sweden
[b] Department of Clinical Sciences, Division of Ruminant Medicine and Veterinary Epidemiology, P.O. Box 7019, Swedish University of Agricultural Sciences, SE-750 07 Uppsala, Sweden
[c] Department of Pigs, Poultry and Ruminants, National Veterinary Institute, SE-751 89 Uppsala, Sweden

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Abstract

The potential for using acute phase proteins (APPs) in the assessment of herd health was studied by examining the levels of serum haptoglobin, serum amyloid A (SAA) and plasma fibrinogen in relation to clinical findings and leukocyte counts in calves. Two groups of calves from conventional dairy farms were studied. The animals were examined 10 times during the first six weeks after introduction into a new environment. Haptoglobin, SAA and fibrinogen were analysed and weight gain, disease symptoms and treatments were recorded. Analysis of antibodies against viral infections was performed. An acute phase reaction (APR) score was established at each sampling by combining the APP results and total leukocyte counts. The health status differed between the two groups, although no manipulation of health had been performed, except that the group with a higher incidence of disease had a concurrent experimental infection with lungworm as part of another study. In the group with a higher incidence of disease, the mean weight gain was significantly lower, and the number of sampling days with elevated serum concentrations of APPs, and the mean maximum concentrations of haptoglobin and fibrinogen were significantly higher compared to the healthier group. The APR score was significantly higher at days 4 and 8 of the study in the group with a higher incidence of disease. The results indicate that measurement of APPs could be a useful tool for evaluation of health in calf herds.

Keywords: Acute phase proteins; Calf herd health; Haptoglobin; Serum amyloid A; Fibrinogen

1. Introduction

An important contributor to beef production is the specialised rearing of dairy calves for slaughter. This production system comprises transportation of young calves from their birth farms to specialised units, and mixing of individuals from several different breeders. Stress due to transportation and mixing, in combination with exposure to a variety of microorganisms often leads to outbreaks of infection such as respiratory disease (Dyer, 1982). Important microorganisms include bovine respiratory syncytial virus (BRSV), bovine corona virus (BCV), bovine virus diarrhoea virus (BVDV), bovine parainfluenza virus type 3 (PIV-3), bovine adenovirus (BAV), and certain bacteria, e.g., *Mannheimia haemolytica* and *Pasteurella multocida* (Ames, 1997; Bengtsson and Viring, 2000; Tråvén et al., 2001).

Disease outbreaks can cause substantial costs for the farmer and result in serious animal welfare problems – an important consideration given the rising concern about animal welfare and food safety. Tools for surveillance of herd health status could be a useful component of a quality assurance programme and there is a need to identify new indicators of health and disease.

The acute phase response (APR) is a non-specific reaction by an individual to different kinds of tissue damage such as infection, neoplasia or trauma (Gruys

* Corresponding author. Tel.: +46 18 671927; fax: +46 18 673545.
E-mail address: Charina.Ganheim@kv.slu.se (G. Charina).

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et al., 1994). The tissue damage induces a cascade of events that leads to the production of acute phase proteins (APP) in the liver. Haptoglobin and serum amyloid A (SAA) are important bovine APPs, which increase in serum for example during viral and bacterial diseases (Murata et al., 2004; Petersen et al., 2004), but are absent, or present in very low levels, in healthy animals (Godson et al., 1996; Heegaard et al., 2000; Gånheim et al., 2003). Moreover, sub-clinical inflammatory disorders can induce increase in APP concentrations (Karreman et al., 2000). The concentration of fibrinogen, another APP, is increased in the plasma of animals with inflammatory disorders (McSherry et al., 1970) and has been used for many years to evaluate inflammatory disease in cattle (Eckersall and Conner, 1988). Lungworm infection (Gånheim et al., 2004), and stress due to poor housing (Alsemgeest et al., 1995), weaning, transportation and mixing (Arthington et al., 2003), can also result in increased APP concentrations in cattle.

APPs have been considered both as potential indicators of disease and well-being in individual animals and as indicators of herd health (Alsemgeest et al., 1994; Murata et al., 2004; Petersen et al., 2004). Studies show that SAA (Karreman et al., 2000) and haptoglobin (Saini et al., 1998) have been found useful in herd screenings to identify cows with inflammatory diseases. APPs may also be an important tool at the slaughterhouse to improve food safety (Saini et al., 1998).

The aim of this study was to further evaluate the potential of using serum APPs in the assessment of overall calf herd health by examining the levels of haptoglobin, SAA and fibrinogen in relation to clinical findings and leukocyte counts in calves in farms specialised for beef production. Two groups of calves differing in clinical health status were studied. The hypothesis was that analysis of one or several APP may be used as an objective tool to evaluate animal health and management on this type of farm.

2. Materials and methods

2.1. Animals and housing

Two groups of male calves were used, groups A and B. All calves were of the dairy breeds Swedish Red and White, or Swedish Holstein, or of crosses between these two breeds. The calves were obtained from 16 different conventional dairy farms, mediated through the Swedish Meats Organization for purchase of live animals. Group A consisted of 35 calves from eight different farms. The age of the calves at the start of the study ranged from 4 to 13 weeks (mean 8 weeks, SD 1.7). At a private commercial farm specialising in beef production, the calves were housed in a stable that had been cleaned and empty for more than two months before their arrival. The calves, weighing 50–99 kg, were kept in large boxes on straw bedding. Milk replacer was offered via an automated feeder for the first two weeks after arrival. Hay and concentrates were fed according to Swedish recommendations during the study period of six weeks.

Group B consisted of 11 calves from eight farms, different from those from which group A calves were selected. The age of the calves at the start of the study varied between 9 and 13 weeks (mean 11 weeks, SD 1.1) and their weight ranged from 65 to 110 kg. The animals were weaned either before or on arrival at the Division of Ruminant Medicine, Department of Clinical Sciences, Swedish University of Agricultural Sciences. The calves were housed in large boxes on straw bedding in a stable that had been cleaned and empty for more than four weeks before the experiment started. The animals were fed hay and concentrate according to Swedish recommendations during the study period of six weeks. These animals were also part of another study, in which they were inoculated orally with lungworm (*Dictyocaulus viviparus*) (250 L3) on days 1 and 2. However, the infection did not induce a patent infection with larvae present in faeces, probably because the larvae were not sufficiently viable.

The study protocol was approved by the Swedish National Board for Laboratory Animals, Uppsala, Sweden.

2.2. Samplings and clinical observations

Jugular blood samples were taken twice weekly from each calf, during the first four weeks following arrival and once weekly for the following two weeks. Venoject tubes with EDTA and without additive (Terumo Europe N.V.) were used. Clinical observations of the calves were performed at the same time, including recordings of any coughing and/or diarrhoea.

The farm personnel decided which individuals were to be examined by the herd veterinarian for possible treatment during the observation period. The weight of the calves in both groups was recorded on arrival and again at the end of the study using heart girth measurement in group A, and a scale in group B.

2.3. Analyses

Within a few hours of sampling, EDTA-blood was analysed for total and differential leukocyte counts and fibrinogen at the Division of Diagnostic Imaging and Clinical Pathology, Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences. The leukocyte counts were performed using Cell-Dyn 3500 (Abbot Diagnostic Division), and fibrinogen was analysed according to Becker et al. (1984) using an automated analyser (Konelab 30, Konelab Corporation).

Samples without additive were centrifuged (1600*g*, 40 min) and the serum was frozen at −20°C until analysed for haptoglobin, SAA, and viral antibodies. Analysis of serum haptoglobin and SAA was performed using the Tridelta Phase Range Haptoglobin Assay and SAA Assay (Tridelta Development Limited), respectively; the working range for the haptoglobin assay was 0.05–6 g/L, and the intra- and inter-assay coefficients of variation were 5% at the concentration 1.3 g/L . The SAA assay had been slightly modified by adding extra standard points. The working range was 1.4–750 mg/L with samples diluted 1:500. In this range, the intra- and inter-assay coefficients of variation were <10%. Serum antibody titres against bovine respiratory syncytial virus (BRSV), bovine corona virus (BCV), parainfluenza virus type 3 (PIV-3), bovine virus diarrhoea virus (BVDV) and bovine adenovirus type 3 (BAV-3) were analysed on three occasions per group, i.e. days 1, 18 and 39, using ELISAs (Svanova Biotech AB for BRSV, BCV, PIV-3 and BVDV, BIO-X Diagnostics for BAV-3) and all analyses were performed according to the manufacturer's instructions. Seroconversion was defined as a negative optical density value in the first or second sample, converting to a positive value in either the second or the third sample in paired sera.

2.4. APR scoring

A total scoring of the results from the different APR parameters was calculated. Where above normal values of SAA, haptoglobin, fibrinogen or total leukocyte count occurred, one point was allocated for each. The sum of the points was calculated for each individual and sampling occasion as well as the mean (SD) value for each group. Previously established (Gånheim et al., 2003) basal APP threshold levels differing between healthy and diseased animals were used, namely, 0.13 g/L for haptoglobin, 25.6 mg/L for SAA, and 6.45 g/L for fibrinogen. A total leukocyte count $>13.8 \times 10^9$/L was considered above normal (Jain, 1986).

2.5. Statistical analyses

Leukocyte counts, APP concentrations, numbers of sampling days with above normal APP values and APR scores in groups A and B, were compared using Student's *t* tests. The Bonferroni correction was used to avoid mass significances. A P value <0.05 was considered significant.

3. Results

3.1. Clinical observations and treatments

In group A, 22.9% and 14.3% of the calves had signs of respiratory disease and diarrhoea, respectively, on at least one of the observation points (Table 1). Some calves had both respiratory symptoms and diarrhoea, but not on the same occasion. During the study period, three calves with respiratory disease were treated with antibiotics (benzylpenicillin procaine, Ethacilin Vet, Intervet), based on evaluation of the farm veterinarian (Table 1).

In group B, all calves showed signs of respiratory disease on at least one of the sampling days, and 27% of the calves also had diarrhoea at the same time as respiratory symptoms (Table 1). Almost half of the calves were treated with antibiotics for respiratory disease as described for group A (Table 1). The proportions of calves in the two groups having respiratory symptoms or diarrhoea, at each sampling occasion, are given in Fig. 1. The proportion was very low in group A, while a higher proportion of sick calves, especially with respiratory symptoms, was obvious in group B during the first two to three weeks after arrival.

The average (SD) daily weight gain of the calves in group A was 0.88 (0.25) kg during the study period. In group B, the average (SD) daily weight gain for the calves (0.76 [0.15] kg) was significantly lower.

3.2. Viral antibodies

None of the 35 calves in group A seroconverted against BRSV, BCV, BVDV, or PIV-3, during the study period, but 17% of the animals seroconverted against BAV-3 (Table 1). All calves had elevated antibody titres against one or several viruses at the beginning of the study.

Table 1
Numbers (%) of calves with respiratory symptoms (Resp), or diarrhoea (Diar), or being treated for respiratory disease (Treat), or seroconverting against BRSV, BCV, BVDV, PIV-3, BAV-3, in two groups A ($n = 35$) and B ($n = 11$) of calves over a period of six weeks after housing

Group	Resp	Diar	Treat	Seroconversion[a]				
				BRSV	BCV	BVDV	PIV-3	BAV-3
A	8 (22.9)	5 (14.3)	3 (8.6)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17)
B	11 (100)	3 (27)	5 (45.4)	0 (0)	4 (27.5)	0 (0)	0 (0)	8 (73)

[a] See text for key.

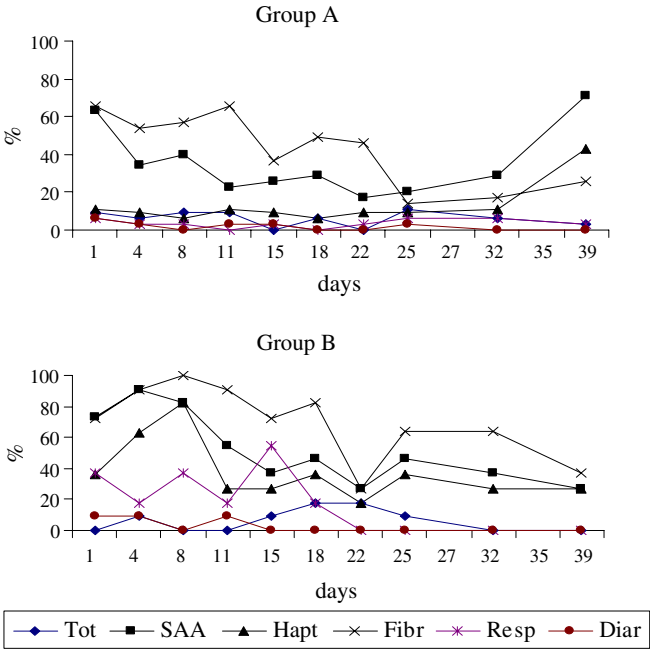

Fig. 1. Proportions (%) of calves in group A ($n = 35$) and B ($n = 11$) with above normal values of total leukocyte numbers (Tot), or concentrations of serum amyloid A (SAA), haptoglobin (Hapt) and fibrinogen (Fibr) at each sampling occasion during the six weeks after arrival in a new environment. The proportions of calves with respiratory symptoms (Resp) or diarrhoea (Diar) are also shown.

In group B, one-quarter of the calves had seroconverted against BCV between the first and second sampling, while the remainder of the calves already had high antibody titres against BCV at the start of the study (Table 1). A majority of the calves also seroconverted against BAV-3, while the rest of the group had such antibodies from the beginning of the study (Table 1). There were no seroconversions against BRSV, BVDV and PIV-3 during the study, but most calves had antibodies against one or several of these viruses on arrival.

3.3. Leukocyte counts

The total leukocyte counts, and the numbers of neutrophils, lymphocytes and eosinophils for groups A and B are given in Fig. 2. The mean number of monocytes was constantly close to 1.5×10^9/L in both groups throughout the study (data not shown). The proportions of animals with above normal total leukocyte counts were low in both groups (Fig. 1). No significant differences between the groups were observed in total leukocyte counts, or in numbers of lymphocytes and neutrophils. However, the eosinophil numbers were significantly higher in group B than in group A on days 18, 22 and 25.

3.4. Haptoglobin, SAA and fibrinogen

Out of 35 calves in group A, 32 (91%), 20 (57%) and 32 (91%) calves had above normal values of SAA, haptoglobin and fibrinogen, respectively, at least once during the study period. In group B, all 11 calves had

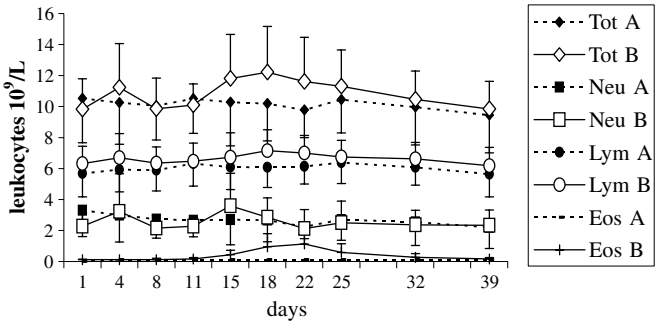

Fig. 2. Mean (SD) total numbers of leukocytes (Tot), and numbers of neutrophils (Neu), lymphocytes (Lym) and eosinophils (Eos) in the blood of calves in two different groups, A ($n = 35$) and B ($n = 11$), sampled during the six week period after arrival in a new environment. Significant differences between groups were observed for eosinophils at days 18, 22 and 25.

above normal values of all three APP on at least one occasion. The proportions of calves having above normal concentrations of SAA, haptoglobin and fibrinogen were numerically higher in group B than in group A at most sampling occasions (Fig. 1).

In group A, the mean maximum concentration per calf was 0.32 g/L (SD 0.29, range 0.06–1.23 g/L), 62.8 mg/L (SD 34.2, range 21.1–177.9 mg/L) and 8.3 g/L (SD 1.7, range 6.0–12.2 g/L) for haptoglobin, SAA and fibrinogen, respectively. In group B, the mean maximum concentrations of haptoglobin (0.76 g/L [SD 0.44, range 0.15–1.62 g/L]), and fibrinogen (11.6 g/L [SD 2.7], range 8.8–18.3 g/L) were significantly higher than in group A. The mean maximum concentration of SAA (115.6 mg/L [SD 106.5], range 36.1–429.4 mg/L) was numerically higher, but not significantly different, from in group A.

The mean numbers of sampling days per calf with above normal SAA, haptoglobin and fibrinogen concentrations in groups A and B are presented in Table 2. The numbers were significantly higher in group B than in group A for all three APP.

3.5. APR scoring

The mean APR scores for the two groups are given in Fig. 3. The scores were significantly higher in group B than in group A on days 4 and 8 after arrival.

Table 2
Mean (SD) number of sampling days per calf with levels of serum haptoglobin, serum amyloid A (SAA) and plasma fibrinogen values above basal levels[A] in two groups (A and B) of calves sampled on ten occasions during the six week period after housing

	Haptoglobin[B]	SAA [B]	Fibrinogen [B]
Group A	0.9[a] (1.0)	3.5[c] (2.6)	4.0[a] (2.4)
Group B	3.6[b] (2.1)	5.4[d] (2.7)	7.3[b] (1.9)

[A] Basal levels used were 0.13 g/L, 25.6 mg/L and 6.45 g/L for haptoglobin, SAA and fibrinogen, respectively.
[B] Values in the same column with the letters a and b differ at $P < 0.001$, while letters c and d indicate a difference at $P < 0.05$.

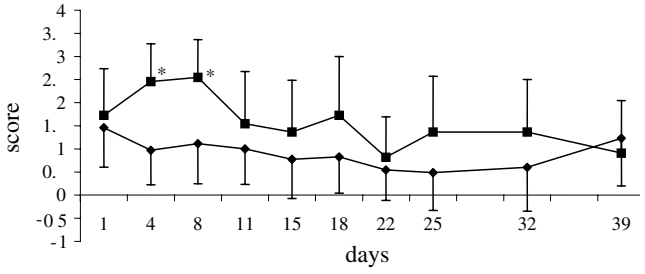

Fig. 3. Mean (SD) APR scores for two groups of calves (A (◆) $n = 35$ and B (■) $n = 11$) sampled during the six week period after housing. Significant differences between the groups were observed at days 4 and 8. *The groups differ significantly ($P < 0.05$) at that time point.

4. Discussion

A large proportion of calves in both groups had elevated concentrations of one or more APPs at one or several occasions during the study. This is consistent with the expectation that many animals would experience infection after transportation and mixing with animals from other farms. Some also had elevated antibody levels against the viruses of interest.

The disease and treatment incidences were considerably higher in group B than in group A, as was the proportion of animals with above normal values of APPs, and the APR score. However, also in group A, where the health status was considered to be good, many calves had elevated APP-values, indicating sub-clinical disease. The mean number of sampling days per calf with above normal APP-values was well correlated with the clinical findings in the groups. The difference between the groups was most obvious for haptoglobin, indicating that this may be the most useful predictive APP and is in agreement with Carter et al. (2002) who concluded that analysis of serum haptoglobin was a better tool for discrimination between calves that became ill and those that did not, compared to other APPs. SAA is reported to be more sensitive to stimulation (Horadagoda et al., 1999; Heegaard et al., 2000), and as an increase can be induced also by other factors than disease, such as stress (Alsemgeest et al., 1995) it may be less suitable as an indicator of health problems.

The treatment incidence also differed between the two groups. In group B, almost half of the calves were treated with antibiotics, while only 1/10 calves was treated in group A. The difference may not only reflect the health status in the groups, but could also be due to different evaluations by the persons handling the animals. However, no deaths occurred in group A, suggesting that all animals in need of treatment received it. The mean weight gain differed significantly between the groups, with the healthier group A having the greatest weight gain. Different methods were used in the groups for evaluating weight, indicating these results must be interpreted with care. However, Heinrich et al. (1992) demonstrated that, among the different body measures, heart girth is the best estimate for body weight, and Sørensen and Foldager (1991) and Andersson (1996) showed a good correlation between the heart girth and body weight.

The total leukocyte counts exceeded normal values for calves of this age (Jain, 1986) only on a few occasions and in a few individuals. The results did not differ between groups indicating that an above normal leukocyte count alone is not a good indicator of disease. The significantly higher number of eosinophils in group B was probably due to the experimental inoculation with lungworm, as eosinophilia is a rather consistent finding during lungworm infection (Radostits, 2000). This result was

surprising as none of the animals had a patent infection with the presence of larvae in faeces. However, the eosinophilia indicates that the immune system of the calves had responded to the parasites. Thus, the lungworm infection may be one factor responsible for the elevated APP levels observed in group B, as lungworm infection can induce production of APP (Gånheim et al., 2004).

The seroconversion against BCV and BAV-3 in group B indicates that these infections were probably the main reason for the disease symptoms in this group. It is likely that some calves brought the infection from the farm of origin and spread it in the new group. The four calves that seroconverted against BCV reacted with increases in haptoglobin and fibrinogen and three of them also reacted with an increase in SAA. However, as indicated above, the lungworm infection may also have affected the clinical outcome; mixed infections are likely to result in more severe symptoms as was shown when combining viral and bacterial infections (Gånheim et al., 2003). There may also have been other infectious agents circulating in the group, such as other serotypes of adenovirus or secondary bacterial infections, e.g., with *M. haemolytica*, or other opportunistic invaders, but other viral or bacteriological examinations were not performed in this study.

The APR score, combining the results of the three APPs and the total leukocyte counts, was created to give a better overview of the reactions in the groups. Other researchers have reported that measurement of a single APP is not reliable for health evaluation and recommend a combined analysis of several parameters (Toussaint et al., 1995; Young et al., 1996). In our study, differences in clinical health status between groups A and B, were consistent with the differences in the APR score. However, the results need to be interpreted with care, as the experimental infection with lungworm may have been partly responsible for the APP elevation.

The results of the present study support the usefulness of APP measurement in monitoring animal health, and supports the proposals made by other authors (Alsemgeest et al., 1994; Murata et al., 2004; Petersen et al., 2004). At present, routine use of APP analyses at the herd level is not realistic because of the high costs involved. However, pooling of serum from several animals in a herd may offer a way to minimize the costs. If less expensive analytical methods become available, the calculation of mean APR scores could be a useful tool for the evaluation of herd health. However, to provide the best evaluation of health status in a herd, or in a group of animals, frequent samplings during the whole rearing period should be made and again this is probably not a realistic approach as it would be too expensive. Sampling during the first weeks after arrival in the herd would give an indication of the pressure of infections and/or stress during transportation and mixing and so may not give a fair picture of the management conditions of the actual farm. In our opinion, samplings at, for example, monthly intervals during the middle and later stages of the rearing period may be more relevant if the main interest is to evaluate the animal health conditions of a specific farm. The establishment of suitable APP or APR score thresholds for herd health would require analysis of a much larger number of herds.

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