Proceedings of the Annual Meeting
of the
American College of Veterinary Pathologists
and
American Society for Veterinary Clinical Pathology
- Tucson, Arizona 2006 -

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Acute Phase Proteins as Biomarkers of Disease in Production Animals

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Introduction

The acute phase proteins (APP) are blood proteins the measurement of which provides a means to assess the innate immune system’s response to disease.\textsuperscript{1-3} By definition, the APP serum concentration increases or decreases by \textgreater{} 25\% in response to inflammation, infection and trauma. They can be used as quantitative markers for prognosis and monitoring responses to therapy, for general health screening as well as for diagnosis of disease. The APP are highly sensitive for the presence of pathological lesions although they have a low specificity for a particular disease as they are elevated in numerous conditions. Their use has been likened to provision of a molecular thermometer.

However, there are major differences between species in the APP response in disease (Table 1). In any one species positive APP have been found that have either major, moderate or minor responses. A major APP has a low concentration in the serum of healthy animals, but with the concentration increasing over 100- or 1000-fold on stimulation, reaching a peak 24-48 hours after the insult and falling rapidly during recovery. A moderate APP is present in the blood of healthy animals but on stimulation the concentration will increase 5-10 fold, reach a peak concentration 2-3 days after stimulation and decrease more slowly than the major APP. A minor APP shows a gradual increase of 50-100\% of the resting level. Negative APP have also been identified, which fall in concentration during the response, though apart from the hypoalbuminemia of infection and inflammation the measurement of these proteins has not yet been exploited by clinical pathology laboratories.

Acute Phase Proteins in Ruminant Medicine

Perhaps the most significant species difference in the acute phase response in relation to veterinary clinical pathology is that in ruminants haptoglobin (Hp) is a major APP. In healthy cattle the serum concentration is below 20 mg/liter but it can increase in concentration to over 2 g/liter within a couple of days of infection. In cattle, Hp is an effective marker (Table 2) for the presence, severity and recovery of animals with mastitis, enteritis, peritonitis, pneumonia endocarditis, endometritis and for monitoring processes such as tail docking and surgical castration.\textsuperscript{2, 3} Elevations have also been reported in cows with fatty liver syndrome, at parturition, during starvation and following the stress of road transport.\textsuperscript{4-6}

In cattle SAA has been identified as a marker of inflammation being elevated more in acute rather than chronic conditions.\textsuperscript{7} It was raised also by experimental infection with \textit{Mannheimia haemolytica}, with bovine respiratory syncytial virus and in experimental and natural cases of mastitis.\textsuperscript{8-11}

The mammary isoform of SAA (M-SAA3) is secreted in milk from mammary glands of dairy cows with mastitis\textsuperscript{11-14} is also found in milk from ewes with this condition.\textsuperscript{14} The discovery that this isoform of SAA along with Hp is syn-

\begin{table}[h]
\centering
\caption{Acute Phase Protein: Major and Moderate Responders in Various Animal Species}
\begin{tabular}{|l|l|l|}
\hline
Species & Major APP & Moderate APP \\
\hline
Cat & SAA & AGP, Hp \\
Dog & CRP, SAA & Hp, AGP, Hp \\
Horse & SAA & Hp, \\
Cow & Hp, SAA & AGP \\
Pig & CRP, MAP, SAA & Hp, \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Bovine Diseases where an Acute Phase Response has been Described.\textsuperscript{3}}
\begin{tabular}{|l|l|}
\hline
Acute Phase Protein & Disease/Condition \\
\hline
Haptoglobin & \textit{Mannheimia haemolytica} \\
& Pasteurella multocida \\
& Bovine viral diarrhea virus \\
& Bovine respiratory syncytial virus \\
& Foot and mouth disease virus \\
& Mastitis \\
& Clinical respiratory tract disease \\
& Castration \\
& Metritis \\
& Uterine bacterial contamination \\
& Hepatic lipidosis \\
\hline
SAA & Mastitis \\
& \textit{Mannheimia haemolytica} \\
& Bovine viral diarrhea virus \\
& Bovine respiratory syncytial virus \\
\hline
AGP & Hepatic abcesses \\
& Metritis \\
& Mastitis \\
& Respiratory tract disease \\
\hline
\end{tabular}
\end{table}

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thesised in the mammary epithelia during mastitis suggests a potential role as a biomarker for this condition.

As the APP are raised in a variety of infectious diseases the suggestion has arisen that they could be employed at ante or post-mortem inspection in assessment of animal health and welfare and as an aid to meat inspection. With their low specificity for a particular disease, the APP would not be used as a front line test for specific infection. However, as a screening tool for monitoring the general health and welfare of animals at slaughter the APP could be valuable and have potential advantages in being able to be adapted to assays of the required accuracy, precision and robustness. Initial studies of the APP at slaughter have given encouraging results. Six-fold increases were found in Hp concentration comparing dairy cows with infectious, metabolic or traumatic disease at slaughter to those with only minor lesions. A more recent study showed a 40-fold increase in Hp and a 7-fold increase in SAA concentration between healthy beef cattle and dairy cattle culled with acute pathological lesions. The APP in other ruminants have not been studied in as much detail as cattle, but it appears that the acute phase response is similar. In sheep a recent study has shown that although a pathogen may cause a chronic rather than an acute reaction the APP can still be stimulated. In an experimental model of ovine caseous lymphadenitis, an initial rise in Hp and SAA concentration was found which peaked within one week and had returned close to normal within 14 days. This was followed by a lower and more lasting increase in AGP which was still evident 4 weeks after infection.

**Acute Phase Proteins in Porcine Medicine**

In the pig, as in the dog CRP is a major APP. Serum CRP concentration increased following aseptic inflammation and with experimental infection with *Actinobacillus pleuropneumoniae*. In this experimental model plasma levels of CRP correlated with clinical findings and were reduced following antibiotic treatment. Porcine CRP has also been found to rise in experimental models of *Mycoplasma hyorhinis*, *Toxoplasma gondii*, *Streptococcus suis* and porcine reproductive and respiratory syndrome virus infection. Raised Hp concentrations are also found during the porcine acute phase response. Increases in Hp were found associated with clinical signs of lameness, respiratory disease, diarrhea, tail bite and ear necrosis. At slaughter, increased Hp has been found to be related to the presence of lesions and chronic abnormalities. Experimental or natural infection with *Actinobacillus pleuropneumoniae*, *Mycoplasma hyorhinis*, *Toxoplasma gondii*, *Bordetella bronchiseptica*, *Pasteurella multocida* and Porcine Reproductive and Respiratory Syndrome virus lead to increased Hp concentration in serum.

During the acute phase response in pigs a major acute phase protein (pig MAP) can be detected and has been identified as porcine inter-alpha-trypsin inhibitor heavy chain 4. Increases in pig MAP have been shown during infection with *Actinobacillus pleuropneumoniae*, in post weaning multisystemic wasting disorder and following transport. This APP was also increased in experimental models of *Mycoplasma hyorhinis*, *Toxoplasma gondii*, *Bordetella bronchiseptica*, *Pasteurella multocida* and Porcine Reproductive and Respiratory Syndrome virus.

In the pig AGP has been the subject of contrasting experience. AGP concentration was shown to be raised in pigs with naturally occurring pneumonia and meningitis but in studies where aseptic inflammation caused an acute phase reaction, the AGP concentration was not significantly affected. Furthermore, an experimental model of porcine reproductive and respiratory syndrome virus showed no increase in serum concentration of AGP while Hp was increased. However AGP was elevated and negatively correlated to weight in a study of the effects of stress and immune function.

In the new-born pig, AGP is present at 40 times the adult level with the concentration falling more rapidly in specific pathogen free animals than in animals exposed to the normal pathogens encountered in production. It is important to interpret AGP levels in the pig with regard to age as the elevated levels found at birth take about 20 weeks to fall to adult levels.

**Acute Phase Proteins in Animal Production**

Measurement of the APP can detect or confirm the presence of infection or pathological lesion but a major role for these analytes could be in monitoring the health status of animals in production. The APP can detect the presence of sub-clinical disease which is the cause of reduced growth rate and lost production. The pro-inflammatory cytokines that stimulate the production of the APP also cause the anorexia/cachexia of associated with infectious and inflammatory conditions and identification of the presence of sub-clinical disease is a pre-requisite for taking corrective measures. Use of an acute phase index, by combining the results of both positive and negative APP has been suggested as a means to increase the sensitivity of detection of sub-clinical disease.

**Acknowledgements**

Research has been supported by BBSRC and EU funding. Many colleagues have contributed to the research of the Acute Phase Laboratory of the Faculty of Veterinary Medicine, University of Glasgow: www.gla.ac.uk/vet/research/apph/genesandproteins/acutephase1/9. The assistance of Garscube Diagnostics is appreciated: www.gla.ac.uk/garscubediagnsinosc/
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