

Acute Phase Proteins

The last decade has seen growing interest in monitoring the acute phase response in horses for clinical and experimental purposes.

Investigations have shown that quantitative determination of acute phase proteins in plasma or serum can give useful diagnostic information in relation to establish prognoses and monitor disease.

The acute phase response is the organisms reaction to processes causing tissue damage, including:

Infections

- Bacterial (Heegaard 2000, Hultén et al 1999b, Pepys et al 1989)
- Viral (Hultén et al 1999b, Hultén et al 1999a, Pepys et al 1989)
- Parasitic (Heegaard 2000, Kent 1992)

Aseptic inflammation

- Arthritis (Hultén et al 1999b, Hultén et al 2002)
- Burns (Heegaard 2000)
- Chemical influence (Heegaard 2000)
- Trauma (Heegaard 2000)
- Surgery (Hultén et al 1999b, Pepys et al 1989)

Some types of neoplasia (Heegaard 2000)

Some types of immunologically mediated illnesses (Gabay & Kushner, 1999)

Processes, taking place locally and possibly hidden, causing no clinical symptoms and/or antibody development, may as well cause an acute phase response (Suffredini et al 1999).

It is important to know, that an acute phase response is not specific, but occur at any form of tissue damage (Heegård, 2000).

The acute phase response causes changes in the serum concentration of acute phase proteins plus physiological, biochemical and nutritional changes within the individual (Gabay & Kushner, 1999).

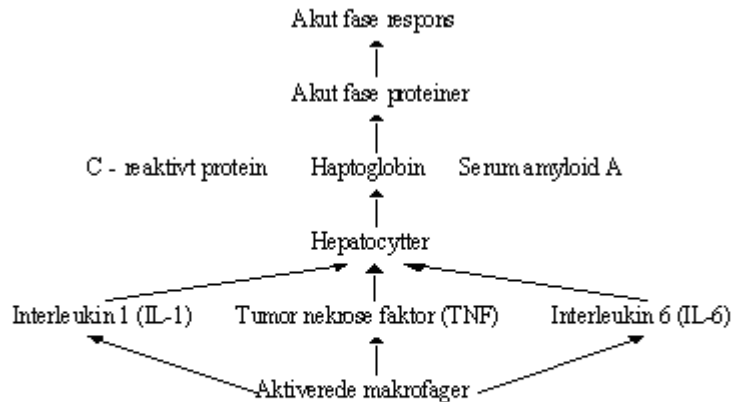
The acute phase response is induced by cytokines (especially Interleukin-1 (IL-1)), Tumor Necrose Factor alpha (TNF-alpha) and Interleukin-6 (IL-6), which act as messenger between the tissue damage and the acute phase protein producing hepatocytes (Petersen et al, 2004).

Cytokines are activated by tissue macrophages and monocytes at the inflammation spot (Gabay & Kushner, 1999).

In the veterinary area several acute phase proteins have been described including C-reactive protein (CRP), Serum Amyloid A (SAA), Haptoglobin (HP), a1-acid glycoprotein (AGP) and Fibrinogen (FB), but there is a large difference between their response and significance among different species.

During an acute phase response the serum concentration of acute phase proteins changes dramatically. The SAA- and CRP- (however not horse) response are markedly stronger than the HP- and FB-response (Gabay & Kushner, 1999). [See table 1.](#)

All acute phase proteins are normal serum proteins and characterized by a usually not measurable base-line level in serum in healthy individuals (Petersen et al. 2004).



Serum Amyloid A (SAA)

SAA reacts as the most powerful acute phase protein and is characterized by (Pepys and Baltz 1983):

1. A very low normal concentration in serum plasma (often not measurable).
2. An extreme fast and marked change in concentration (x 100/200-1000) as a response to tissue damage

By experiments it has been established that the SAA response develops from 6-8 hours after damaging stimuli and peaks after 24-48 hours, decreasing a little slower to its normal level, typically within 1 – 2 weeks unless new stimuli appear (Heegaard 2000).

In clinically healthy foals < 1-2 weeks, positive SAA concentrations can be measured just like mares have positive concentrations from day 3 post partum up to 1 month post partum (Nunokawa et al. 1993).

Haptoglobin (HP)

Primary function is to form stable complexes of free hemoglobin (in blood) and with that prevent the loss of iron to bacteria (bacteriostatic effect) (Petersen, 2004).

HP is a sensitive and efficient marker towards inflammation (Allen & Kold, 1988).

Fibrinogen (FB)

Up till now FB has been the most used acute phase protein in the veterinary horse practice. In clinically healthy horses FB is present in significant concentrations. Compared with the SAA response upon stimuli, the

FB response is smaller and delayed with maximum conc. 2-4 x normal concentration 4-6 days after stimuli (Hultén et al., 1999b).

Raised FB response is most often observed at inflammation (non specific) of chronic character. Low FB response is observed at DIC (Disseminated intravascular coagulation), liver insufficiency and extensive surgical operation (Eades & Bounous).

Table 1:

Acute phase proteins in horse and their response upon different tissue damages - an overview.

	Response (General)	Bacterial Infection	Viral Infect. Experiment	Trauma (Castration)	Aseptic arthritis*2 Experiment.
SAA	100-1000'er x NC < 2. day (Pepys et al 1989)	Response	Response Influenza A2 (Hultén et al 1999b). EHV1 (Pepys et al. 1989)	Response *1	Response (Hultén et al 2002)
Haptoglobin	1,5-9 x NC on 4.-5. day (Taira et al. 1992a)	Response (Taira et al. 1992a)	Response Influenza type 2 (Kent & Goodall, 1991)	Response (Taira et al. 1992a)	Response (Hultén et al 2002)
Fibrinogen	1,7-2 x NC on 4.-6.day (Allen and Kold 1988).	Response	Response	Response (Allen & Kold, 1988)	Response (Hultén et al 2002)

NC: Normal Concentration

*1:

Max concentration in SAA 2-3 days after operation.

Decrease to normal concentration after 7 to 14 days.

Anaesthesia alone, without operation, had no effect on SAA level.

Experiment with castration showed max. SAA max. concentration on day 2 in 6/7 horses. The seventh horse peaked on day 4 post op. The SAA concentration returned to normal within 8 day post op. (Pepys et al 1989).

*2:

Experimentally induced aseptic inflammation (amphetericin B carpalled):

SAA max conc.: 36-48 hours post injection

Gapt. Max. conc. 48-96 hours post injection

Fibrinogen max. conc. 36-72 hours post injection (Hultén et al 2002).

In addition to the above conditions, raised SAA concentrations can be observed at:

- Equin dysautonomia
- Colic
- Diarré
- Pyrexia (Pepys et al 1989)

Raised HP concentration can in addition be observed at:

- Equin dysautonomia
- Carbohydrate induced laminitis

Indicator of treatment effect

If the pathology, given the raised acute phase protein, is treated correctly or cleared the SAA concentration will decrease immediately and return to normal concentration.

If the state is chronic or the medical treatment have no effect, the SAA concentration stays high (Tridelta Equine Pages 2002).

A series of tests for acute phase proteins performed with regular intervals can indicate if the problem is solved due to treatment (medical) or by itself.

In addition a combined analysis for SAA, HP and FB offers an insight into the severity of a chronic state.

SAA can in that way be used as an indicator of treatment effect. Unpublished data (Pepys et al 1989) indicates, that an efficient antibiotic therapy (bacterial infection) involve a quick decrease in SAA concentration to normal concentration.

This can be used to confirm diagnose and the effect of the treatment. Cases where SAA don't decrease to it's normal level, indicate that:

- The primary diagnose is incorrect
- The treatment is insufficient or in other ways ineffective

A helpful tool for check of health

Acute phase serology combines the advantages of blood sampling with the level of details obtainable by clinical observations (body temperature, level of disease), offering the possibility of further differentiation based on determination of patterns from several different acute phase proteins over time (Heegård, 2000).

References

Allen BV, Kold SE (1988), Fibrinogen response to surgical tissue trauma in the horse, *Equine Vet.J.* 20: 441-443

Fagliari, J. J., D. McClenahn, O. A. Evanson, D. J. Weiss (1998). Changes in plasma protein concentrations in ponies with experimentally induced alimentary laminitis. *American veterinary Journal Research*, 59, 1234-1237.

Gabay, CEM & Irving Kushner (1999): Acute-Phase Proteins and other systemic responses to inflammation. *The New England Journal of Medicine*, february 11, 1999, pp. 448-454.

Heegaard, PMH (2000), Akut-fase responset og dets brug som klinisk parameter, *Dansk Veterinærtidsskrift* 19:

Hultén C, Gronlund U, Hirvonen J, Tulamo R-M, Suominen MM, Marhaug G, Forsberg M (2002), Dynamics in serum of the inflammatory markers serum amyloid A (SAA), haptoglobin, fibrinogen and alpha(2)-globulins during induced noninfectious arthritis in the horse, *Equine Vet.J.* 34: 699-704

Hultén C, Sandgren B, Skjöldebrand E, Klingeborn B, Marhaug G, Forsberg M (1999a), The Acute phase protein serum amyloid A (SAA) as an inflammatory marker in equine influenza virus infection, *Acta vet.scand.* 40: 323-333

Hultén C, Tulamo R-M, Suominen MM, Burvall K, Marhaug G, Forsberg M (1999b), A non-competitive chemiluminescence enzyme immunoassay for the equine acute phase protein serum amyloid A (SAA) - a clinically useful inflammatory marker in the horse, *Veterinary Immunology and Immunopathology* 68: 267-281

International Committee N (1988), Guidelines on selection of laboratory tests for monitoring the acute phase response, *J.Clin.Pathol.* 41: 1203-1212

Kent, JE. & J Goodall (1991): Assessment of an immunoturbidimetric method for measuring equine serum haptoglobin concentrations. *Equine Veterinary Journal*, 23, 59-66.

Kent J (1992), Acute Phase Proteins: Their use in veterinary diagnosis, *Br.Vet.J.* 148: 279-282

Nunokawa, Y, T Fujinaga, M Okumura, K Yamashita, N Tsunoda & M Hagio (1993): Evaluation of serum amyloid A protein as an acute-phase reactive protein in horses. *Journal of Veterinary Medicine Science*, 55, pp. 1011-1016.

Pepys MB, Baltz ML (1983), Acute phase proteins with special reference to C-reactive protein and related proteins (pentraxins) and serum amyloid A protein, *Adv.Immunol.* 34: 141-212

Pepys MB, Baltz ML, Tennent GA, Kent J, Ousey J, Rossdale PD (1989), Serum amyloid A protein (SAA) in horses: objective measurement of the acute phase response, *Equine Veterinary Journal* 21: 106-109

Petersen, HH., JP. Nielsen, PM Helweg & Heegård (2004): Application of acute phase protein measurements in veterinary clinical chemistry. *Veterinary Research*, 53, pp. 163-187.

Suffredini AF, Fantuzzi G, Badolato R, Oppenheim JJ, O'Grady NP (1999), New insights into the biology of the acute phase response, *J.Clin.Immunol.* 19: 203-214

Taira T, Fujinaga T, Okumura M, Yamashita K, Tsunoda N, Mizuno S (1992a), Equine Haptoglobin: Isolation, Characterization, and the Effects of Ageing, Delivery and Inflammation on Its Serum Concentration, *J.Vet.Med.Sci.* 54: 435-442

Taira T, Fujinaga T, Tamura K, Izumi M, Itoh H, Tunoda N, Yamashita K, Okumura M, Mizuno S (1992b), Isolation, characterization of alfa1-acid glycoprotein from horses, and its evaluation as an acute-phase reactive protein in horses, *Am.J.Vet.Res.* 53: 961-965

Tridelta Equine Pages. Acute phase proteins. www.trideltaltd.com (Tridelta Equine Pages) . 2002.

Ref Type: Internet Communication

Yamashita K, Fujinaga T, Okumura M, Takiguchi M, Tunoda N, Mizuno S (1991), Serum C-reactive protein in horses: the effect of aging, sex, delivery and inflammation on its serum concentration, *J.Vet.Med.Sci.* 53: 1019-1024