Acute phase proteins: how they are useful for practitioners

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discuss acute phase proteins, their effect on the immune system and how they change in response to injury before looking at their use in diagnosis

ACUTE phase proteins (APPs) are proteins that circulate in the blood and collectively modulate the innate immune system's response to tissue injury. The individual APPs also have numerous, more specific functions, listed in Table 1. In many instances, the range of these individual functions is not completely understood.

APPs are largely produced by hepatocytes, although other cells can also produce these proteins. Production of APPs is initiated by tissue injury prior to inflammation, as part of the acute phase response (APR). The APR occurs before the onset of a specific immune response and can also occur before the onset of clinical signs. In this way it is one of the first indicators that a pathological process is occurring. The other characteristics of the APR are fever and leukocytosis.

In general, APPs are much more sensitive than a leukocytosis as a marker of a pathologic process.

Circulating concentrations of APPs either increase or decrease in response to tissue injury. The so-called positive APPs have an increase in circulating concentration, while the concentration of negative APPs decreases in response to tissue injury (Figure 1).

Positive APPs

The majority of APPs are positive APPs, the concentration of which increase in response to tissue injury. The magnitude of the increase in production of positive APPs in response to an inflammatory stimulus varies between APPs and, based on the size of this increase, positive APPs have been classified as major, moderate or minor. The classification of individual APPs as major, moderate or minor is species specific.

Major APPs

Major APPs increase by 10 to 50-fold on recognition of an inflammatory stimulus, with a peak concentration occurring 24 to 48 hours after stimulation. The concentration of the major APPs remains elevated for as long as the inflammatory stimulus persists; however, once the stimulus is removed their circulating concentration falls rapidly over 24 to 48 hours. The major APPs in dogs are C-reactive protein (CRP) and serum amyloid A (SAA) while SAA and alpha- 1-acid glycoprotein (AGP) are the major APPs in cats.

Moderate APPs

Moderate APPs only increase by two to 10-fold upon tissue damage, with levels peaking four to seven days post-inflammatory stimulus. They undergo an equally gradual (relative to major APPs) return to normal values once the stimulus is removed. The most commonly measured moderate APP in both cats and dogs is haptoglobin (Hp).

Minor APPs

Minor APPs, as the name implies, have relatively small changes in circulating concentrations in response to tissue injury and so are not commonly measured.

Negative APPs

Negative APPs are so called because their concentration falls in response to an inflammatory stimulus. The negative APPs mainly include large proteins and transport proteins. This aids the APR because when the concentration of transport proteins in the circulation decreases, the unbound, biologically active portion of the molecules that they are transporting correspondingly increases. The unbound, or free, fraction of these molecules is then readily available for the organism to use.

Other molecules produced during the APR, such as cortisol and inflammatory cytokines, have an adverse effect on transcription of RNA from the genes responsible for the manufacture of albumin. This decreased formation of albumin allows more amino acids to be available for use for the

formation of positive APPs.

Assay techniques and reference ranges

The techniques used to measure the various APPs are listed in Table 2, along with their advantages and disadvantages. It is important to note that as new assay kits are developed, the technique most commonly employed to measure specific APP may vary.

It may be more helpful to measure a profile of APPs rather than a single protein as the various proteins vary in their response to inflammation and tissue damage. A profile could include one major, moderate and negative APP, to give more information about the evolution and temporal course of the disease.

Non-inflammatory variables

Some breed-specific variations exist, at least in dogs. Miniature schnauzers, for example, appear to have slightly higher CRP concentrations when compared to other healthy dogs. Greyhounds also appear to have lower concentrations of Hp and AGP compared to other breeds. Although the variations in APP concentrations due to breed and physiological factors may be slight, they make it difficult to apply a reference range for any APP that is applicable to the entire population.

Circulating concentrations of some APPs are lower in puppies less then three months of age relative to adult dogs, and the degree of elevation of circulating APP concentrations in response to inflammation may also be blunted in very young puppies. Although neither advancing age nor gender appears to affect APP concentrations in dogs, a study in cats showed concentrations of SAA, AGP and Hp were higher in older cats and in female compared to male cats.

Hp concentrations in dogs are particularly sensitive to glucocorticoid concentration and elevated levels of Hp are found after treatment with glucocorticoids and naturally occurring hyperadrenocorticism. Unfortunately, this may interfere with the ability of Hp to be used as a marker of inflammation in the presence of glucocorticoids.

Further work is investigating this trait of Hp, including its interaction with endogenous cortisol, which may be elevated naturally due to illness and other conditions causing a stress response. This may lead to further applications of measurements of this APP in the future.

It has been found SAA and CRP concentrations do not vary in bitches during the oestrous cycle; however, concentrations of Hp, ceruloplasmin and fibrinogen were found to increase in pregnant bitches in comparison to non-pregnant controls, independent of the stage of pregnancy. The role these APPs may have in the diagnosis of pregnancy and monitoring the health status of pregnant dogs is worth further investigation.

It has been well established how concentrations of APP vary widely in individual animals with otherwise very similar disease states and it may be physiological and genetic factors account for at least some of this inter-individual variation. For this reason, the change in circulating concentrations of APP in response to treatment can be considered more important rather than the discrete values.

Uses of APPs in veterinary medicine

APPs have been extensively used as diagnostic and prognostic indicators in human medicine for decades; however, their role in veterinary medicine is less well-established.

More recently, increasing numbers of studies have been published evaluating the utility of APPs in dogs and cats.

General principles

APPs can be used for early identification of inflammation, possibly at a subclinical stage. Positive APPs increase and negative APPs decrease in response to an inflammatory stimulus. A change in APP concentrations does not provide the information necessary to specifically localise an inflammatory stimulus, but indicates further diagnostic tests are required. It is important to be aware that although a rise in positive APP concentrations is a sensitive indicator of inflammation, they are very non-specific, as any type of inflammatory stimulus can cause an increase in circulating concentrations

The APPs have a higher diagnostic sensitivity for detecting inflammation and a wider dynamic range than white blood cells or neutrophils. Increases of circulating concentrations of APPs have been found to be up to six times more sensitive than leukocytes in detecting inflammation.

Following an inflammatory insult, circulating concentrations of major APPs increase more rapidly than white blood cell numbers, so give an earlier indication of the presence of inflammation. The APPs are not subject to fluctuation caused by extravasation, and therefore are more stable in the circulation than leukocytes.

APPs are a more stable, responsive and more accurate biomarker for the detection of inflammation compared to measuring haematology alone. Measurement of APPs may also have a role in detecting inflammatory events to which the bone marrow cannot respond normally. This is useful in myelosuppressed animals, for example those that have been undergoing chemotherapy treatment or are suffering from leukaemia.

APPs are such sensitive markers of inflammation that mild and potentially non-clinically significant inflammatory stimuli can be enough to induce small (1.5 times to two times) increases in major APP. It is also worth considering the total measured increase in APP can be derived from more than one inflammatory focus, and these foci may not be aetiologically linked. For example, a dog

with both prostatitis and periodontitis can have an increase in APP due to both of these conditions. If the prostatitis is treated the levels of APP would decrease, but possibly not normalise. In this setting the ongoing mild increase in APP could be due to either subclinical prostatitis and/or periodontitis. It is, therefore, extremely important that APP profiles must always be interpreted in light of a thorough clinical examination.

Monitoring and prognostication

Measurement of APPs allows an animal's response to treatment to be monitored. Once the inflammatory stimulus has been eliminated, APP concentrations decrease. If the inflammatory stimulus persists in the body APP concentrations remain elevated; therefore, suggesting further diagnostic tests are required or the treatment protocol needs to be changed.

In people with a variety of critical illnesses, failure of APP (usually CRP) concentrations to decline shortly following initiation of treatment is a negative prognostic indicator. This has been demonstrated in a number of studies and one recent meta-analysis demonstrated CRP concentrations measured 48 hours following admission had the greatest prognostic significance, with survivors having a reduction in CRP concentrations relative to admission concentrations, and non-survivors having no, or minimal, reductions in CRP concentrations.

A similar phenomenon has been demonstrated in dogs with a variety of illnesses, such as systemic inflammatory response syndrome (SIRS), acute abdominal problems, acute pancreatitis and parvovirus. It has been found many dogs with these conditions that died had no significant change or increase in APP levels over time, whereas dogs with these conditions that survived had a greater decline in APP levels as treatment progressed.

Diseases in which APPs have been measured

Table 3 lists conditions in which APP levels have been measured. Further evaluation of specific disease states where APP concentrations have been evaluated can provide clinical illustrations of the guidelines outlined in Table 3, as well as providing insights into the current utilities and possible future developments of APP testing in companion animal medicine.

FIP and retro-viral infections

Feline infectious peritonitis (FIP) is thought to be caused by the accumulation of a mutated form of coronavirus, is normally lethal, and can be extremely hard to diagnose by conventional approaches. The presence of the disease can be confirmed by histopathology on postmortem examination.

Measurement of circulating concentrations of AGP in conjunction with measurement of circulating concentrations of feline coronavirus antibody titres can assist in diagnosing FIP.

Non-symptomatic shedders of feline coronavirus (FCoV) have cyclical fluctuations of serum AGP, probably due to continuous reinfection, and care needs to be taken when interpreting AGP levels among groups of cats where the FCoV disease is endemic.

It has been found increases in AGP concentrations in FCoV-positive cats in catteries can occur a few days before FIP becomes clinically apparent.

It has been demonstrated how when there is a high clinical suspicion of FIP based on history and physical examination excluding other causes of inflammation, a moderate (1.5mg/ml to 2mg/ml) increase in AGP supports the presence of FIP, while a serum level of greater than 3mg/ml AGP in cats is extremely suggestive of a diagnosis of FIP, even in cats where there is an otherwise low index of suspicion for the disease.

We need to remember increases in AGP are not pathognomonic for FIP, as raised concentrations of AGP can also be produced by cats affected by other inflammatory conditions; hence the importance of a history and thorough clinical examination to detect or exclude these confounding variables.

The APR has also been evaluated in cats infected with feline immunodeficiency virus (FIV), which were experimentally infected with *Mycoplasma haemofelis* and *Candidatus Mycoplasma haemominutum*. The APR was shown to vary between FIV-positive and FIV-negative cats and, perhaps unsurprisingly, it is likely APP concentrations in cats should be interpreted in light of FIV status.

Neoplasia

APP levels can be used to monitor response to chemotherapy in dogs with lymphoma. Concentrations of CRP, AGP, SAA and Hp have been found to increase before treatment and decrease once a patient goes into remission. There is, however, much inter-individual variation and further work needs to be carried out before we can apply specific APP concentrations to indicate remission of neoplasia or predict a relapse. However, when looking at individual dogs, APP levels can be seen to decline as the neoplastic condition is treated.

In cases of canine lymphoma treated with doxorubicin, the concentration of AGP has been found to decrease as the animal goes into complete remission and also, interestingly, to rise again three weeks before lymphoma relapse.

In dogs with lymphoma, while a decline in APP concentrations appears to accompany a response to therapy, it is difficult to apply cut-off values in terms of absolute concentrations of APPs that allow us to determine remission status of any individual dog. In an effort to address this, a blood test (canine lymphoma blood test; cLBT) incorporating patient CRP and Hp concentrations into an algorithm containing other variables, such as age, sex and presence of lymphadenopathy, has

been launched. This test shows a good correlation with patient remission status as assessed via clinical examination, with lower values recorded for patients in complete remission versus those in other categories (out of remission or in partial remission).

It is possible this test may serve as a prognostic indicator, and provide an early indicator of relapse, as well as an aid to monitoring patients' responses to chemotherapy.

In variance to the situation in dogs, concentrations of APPs, specifically AGP, did not alter in response to chemotherapy in a cohort of cats with lymphoma in one study.

Steroid-responsive meningitis-arteritis

Measurement of APPs is useful to monitor progression and identify relapses of the inflammatory disease steroid-responsive meningitis-arteritis (SRMA).

Analysis of cerebrospinal fluid (CSF) and identification of a neutrophilic pleocytosis is the routine diagnostic test for SRMA and is also used to monitor response to therapy.

Concentrations of APPs, specifically CRP, SAA and Hp have been shown to increase in both CSF and peripheral circulation in dogs with SRMA. Following successful treatment of SRMA with prednisolone, circulating concentrations of CRP and SAA both return to normal in concert with a decline in CSF cell counts. A decline in circulating concentrations of these APPs may, therefore, act as an objective method of monitoring response to treatment. Due to the effect that glucocorticoids have in Hp concentrations, concentrations of Hp would not be expected to decline during prednisolone therapy.

Serum CRP and SAA have been found to increase during relapses of SRMA and may be a useful indicator to monitor for relapse of the disease post-diagnosis. As mentioned previously, APPs are non-specific diagnostic tests, and it is vital to ensure, via a thorough clinical examination, no other inflammatory focus exists other than SRMA that could engender a similar elevation in APP concentrations.

Amyloidosis

The APP SAA is thought to be the precursor of amyloid protein A and may be involved in the pathogenesis of amyloidosis and other chronic inflammatory conditions such as rheumatoid arthritis.

Amyloidosis can be inherited or acquired. Certain breeds of dogs and cats, such as the Shar Pei dog and Somali, Abyssinian or Oriental cat, are predisposed to amyloidosis.

The disease can develop as SAA – production of which is increased in animals suffering mild

inflammatory conditions and cannot be completely proteolysed in these breeds – following extravasation into tissues from the circulation. Following partial proteolysis, the SAA fibrils that are produced accumulate in tissues as amyloid, particularly in the liver and kidneys.

These particular breeds of dogs and cats have been shown to suffer from a familial inheritance of amyloidosis. In one study it was found the mean SAA concentrations in healthy Abyssinian cats was significantly higher than in healthy cats with no clinical evidence of amyloidosis or hospitalised non-Abyssinian cats, which may predispose to the development of amyloidosis.

Alternatively, mutations in the genes coding for the production of SAA have been identified in the dog, which lead to the production of subtypes of SAA with different amino acid sequences. Amyloid protein in Siamese and Abyssinian cats also differs from that of other feline breeds in terms of amino acid sequences, and it is possible mutations in the genes coding for SAA production influence the development on amyloidosis in predisposed breeds.

Amyloidosis can also occur sporadically and, in these cases, an underlying chronic inflammatory problem, such as chronic gingivitis, is thought to be the driving force for production of SAA.

Probably due to the fact the inciting inflammatory focus is often no longer in evidence by the time sufficient, amyloid protein has been deposited to result in clinical signs due to amyloidosis, SAA concentrations are not uniformly elevated in animals that develop clinical signs due to amyloid deposition.

Surgical trauma

CRP increases after the occurrence of surgical procedures in dogs. The magnitude of the increase is associated with the intensity of the surgical trauma. It seems when surgical trauma is more severe, such as following orthopaedic surgery, circulating concentrations of CRP post-surgery are greater than in dogs subject to less traumatic surgery, possibly due to the increased inflammatory stimulus.

In one study, all dogs involved underwent surgery without postoperative complications. CRP concentrations were increased one to two days following surgery, but concentrations had markedly decreased by the time of suture removal and this paralleled clinical recovery.

Conversely, a separate study showed monitoring postoperative levels of CRP and SAA following pyometra surgery in dogs allowed prompt detection of postoperative wound infections, as evidenced by a rise in APP concentrations following an initial decline post-surgery. Increased levels of these APPs preceded a rise in white blood cell parameters and served as an early marker for postoperative infections.

Advantages and disadvantages of APPs’ diagnostic tools

Advantages:

• Sensitive markers of acute and chronic inflammation.

• Prognostic monitoring.

• Diagnosis of FIP.

• Ease of testing.

Disadvantages:

• Low specificity for most specific disease processes.

• Little data available for cats.

Conclusion

Measurement of APPs is becoming an extremely useful tool. Information about their levels or the change in their values over time can be useful both as a prognostic indicator and in the diagnosis of disease.

Much research is being carried out to provide more information about the use of APP in diagnosing and monitoring specific diseases, as well as to enlarge knowledge about APP in feline medicine. As our knowledge grows, so the utility of these proteins is likely to increase, and measurement of APPs likely to become a much more routine test for general practitioners.

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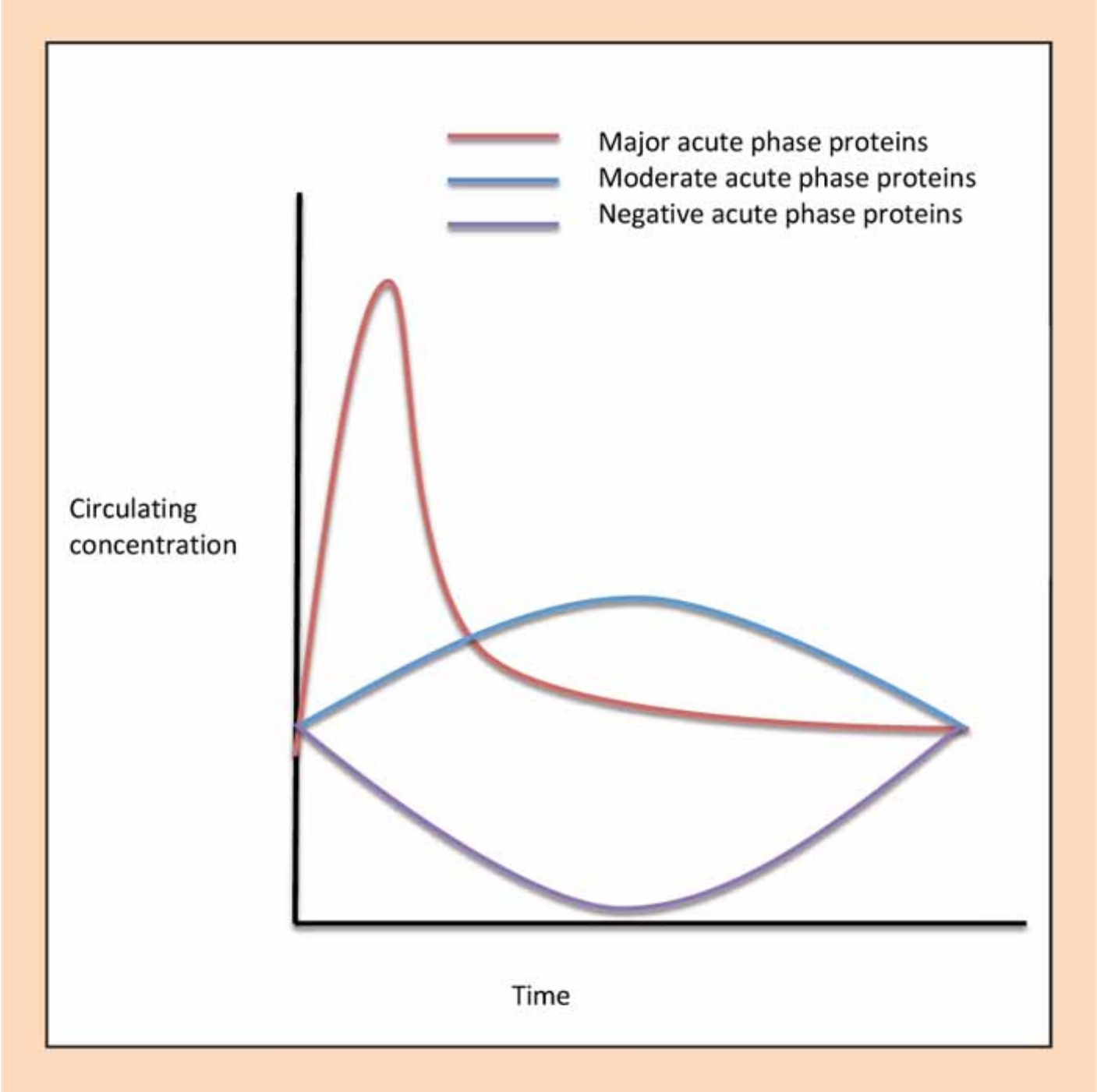

Figure 1. Relative changes in circulating concentrations of the main classes of acute phase proteins in response to an inflammatory stimulus.

Name	Positive or negative	Companion animal most important	Major or moderate	Speed of production following stimulus	Time of maximum peak concentration	Function
C-reactive protein (CRP)	Positive	Dog	Major	4 hours	24-48 hours	Modulates the efficiency of the immune system during inflammation by modulating the efficiency of some inflammatory cells.
Serum amyloid A (SAA)	Positive	Dog and cat	Major	5 days	7 days	Scavenger of potentially dangerous oxidised cholesterol, also has immunomodulatory activities.
Haptoglobin (Hp)	Positive	Dog and cat	Moderate	24 hours	3-4 days	Binding of free haemoglobin (a toxic and pro-inflammatory product of haemolysis). Has a bactericidal effect in infected wounds by binding haemoglobin and limiting the availability of haemoglobin iron for bacterial growth.
Alpha-1-acid glycopeotein	Positive	Dog and cat	Dog: moderate. Cat: major	5 days	3-7 days	Anti-inflammatory and immunomodulatory agent with anti-neutrophil and anti-complement activity. High levels diagnostically sensitive for cats with FIP.
Ceruloplasmin	Positive	Dog	Dog: moderate	24 hours	5 days	Transports copper needed for wound healing, collagen formation and wound maturation.
Albumin	Negative	Dog and cat	Main negative APP		5 days	Decreased albumin production ensures more amino acids are available to synthesise positive APPs and active forms of transported molecules are present in the circulation.

Table 1. Summary of the properties and function of the most important APPs of dog and cats

	Benefits	Disadvantages
Serum protein electrophoresis	Multiple samples can be run simultaneously. Only takes a few hours to run. Accurate albumin quantification. Overall, non-specific changes in APR can be quantitated. Most widely used test in humans.	Needs to be sent to an external laboratory. Only gives quantification of groups of inflammatory proteins. May not detect changes in proteins with low concentrations. Care needs to be taken to evaluate current reference intervals as variation in normal values is unknown. Lipoproteins or transport proteins with alpha or beta globulin motility may interfere with the specificity of the trace.
ELISA	Commercial test kits are available to evaluate a multitude of acute phase proteins. Best suited for batch analysis.	Lack automation. Expensive. Run at an external laboratory.
Cage-side snap ELISA test	Can be carried out in the clinic. Becoming more affordable. Currently available for canine CRP. More tests expected to be released in the future.	More expensive than laboratory batch testing. Some kits semi-quantitative only.
Immunoturbimetric assay	Recently validated assays for a variety of acute phase proteins. Commonly used to measure CRP..	Needs to be sent to an external laboratory.
Radioimmune assay	Several validated assays for measurement of a variety of APPs.	Needs to be sent to an external laboratory.

Table 2. Assay techniques and reference ranges.

Conditions in which APPs have been measured	Disease categories
Gastrointestinal disease	Inflammatory bowel disease
	Bacterial enteritis
	Intestinal obstruction
	Acute pancreatitis
Autoimmune disease	Rheumatoid arthritis
	Immune-mediated haemolytic anaemia
	Polyarthritis
	Steroid-responsive-meningitis-arteritis (SRMA)
	Amyloidosis
Endocrine disease	Hyperadrenocorticism
	Iatrogenic corticosteroid treatment (haptoglobin only)
	Diabetes mellitus
Neoplasia	Lymphoma
	Various carcinomas and sarcomas
Hepatic function	Terminal liver cirrhosis
	Acute and chronic hepatitis
Infectious disease	Parvovirus
	Pyometra
	Escherichia coli endotoxaemia
	Babesiosis
	Leishmaniosis
	Leptospirosis
	Ehrlichia canis
	Bordetella bronchiseptica
	Pneumonia
	Feline infectious peritonitis
Amyloidosis	Heritable and acquired
Surgical trauma	

Table 3. Conditions in which APP levels have been measured and may be useful in the future