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Review article

ACUTE PHASE PROTEINS AS MARKERS OF INFECTIOUS DISEASES IN SMALL ANIMALS

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During the acute phase response, there is an increased production and release of certain proteins known as acute phase proteins (APPs) which can be produced by hepatocytes and peripheral tissues such as C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin (Hp), alpha-1 acid glycoprotein (AGP). These proteins have been investigated as markers of various infectious diseases in small animals and the purpose of this review is to update the current knowledge about APPs in infectious diseases in dogs and cats.

Key words: acute phase proteins; Haptoglobin; C-reactive protein; Serum amyloid A; dogs

INTRODUCTION

The acute phase response is considered a part of the innate host defense system that precedes the acquired immune response [1,2]. During this response, there is an increased production and release of certain proteins known as acute phase proteins (APPs) which can be produced by hepatocytes and peripheral tissues. They are classified according to the change in concentration into two groups: positive APPs (e.g. C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin (Hp), and alpha-1 acid glycoprotein (AGP)) if they increase and negative APPs (e.g. albumin and paraoxonase-1) if they decrease when there is an acute phase response [3,4]. Production of APPs is controlled by proinflammatory cytokines interleukin-1, interleukin-6 and tumor necrosis factor alpha released from the inflammatory site in response to local tissue injury [4,5].

C-reactive protein is a major APP in the dog and its serum concentration can increase rapidly, peaking at 24-48 h, from 1 mg/L to > 100 mg/L in a number of infectious diseases (Figures 1 and 2) but has a low concentration in healthy animals (< 1μg/L). However, CRP is not a major responder in the cat [1,3]. CRP inhibits chemotaxis and modulates neutrophil function, binds to bacteria activating the complement pathway and induces anti-inflammatory cytokine production [3].

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SAA is a major positive APP in dogs and cats [3,6]. Recently, this protein has been investigated as a significant prognostic marker and as a useful predictive indicator of prognosis in various diseases [7-10]. An isoform of SAA (SAA-2) is involved in reactive amyloidosis and other chronic inflammatory diseases. Its main biological functions are related to binding of cholesterol, immunomodulation and opsonization [3,11].

Hp is a moderate APP in dogs and cats that will increase 2- to 10-fold during the response, peaking at 2 to 3 days after stimulation and decreasing more slowly than the major APP [4,5]. Inflammation in the dog promotes a moderate Hp response (Figures 1 and 2), and in this species is stimulated by cortisol, after treatment with glucocorticoids and during hyperadrenocorticism [12], but needs to be further investigated in cats. Hp inhibits granulocyte chemotaxis and phagocytosis and has also a direct bactericidal effect in inflammation by binding haemoglobin, limiting the availability of Hb iron for bacterial growth and by preventing oxidative damage mediated by heme iron [3,13].

Alpha-1 acid glycoprotein, previously known as orosomucoid, has anti-inflammatory and immunomodulatory activities during the acute phase response. It has a major acute phase response in cats (Figure 4) and has a moderate response in dogs [4,6]. Most studies on feline AGP have focused on feline infectious peritonitis (FIP) recognizing this APP as a biomarker of this disease [3,14,15]. Alpha-1 acid glycoprotein functions are related to drug-binding, as an immunomodulatory agent with protective effects in bacterial infections and acts as a plasma transport protein [3,11].

Paraoxonase-1 (PON 1) is an oxidase inhibitor that recently has been identified as a negative acute phase protein in dogs related to inflammation and oxidative status [16]. Albumin is also a negative acute phase protein biomarker as its concentration decreases by more than 25% during the inflammatory response [5].

Although many infectious diseases will produce a measurable increase in APPs concentrations they do not indicate the specific disease entity but are considered highly sensitive biomarkers of inflammation [1].

The purpose of this review is to update the current knowledge about APPs in infectious diseases in dogs and cats and present flow charts that could help to interpret changes in their concentration in the diagnosis, treatment monitoring and prognosis of these diseases in both species. Most information in this review will be related to dogs because APPs have been more thoroughly studied in this species then in cats.

Acute phase proteins in infectious diseases

Most naturally or experimentally induced infectious diseases produce an increase in positive APPs concentrations and the magnitude of increase is often related to the causative agent [3].

Dogs

C-Reactive protein concentrations in dogs with severe clinical signs of parvovirus enteritis that did not survive infection was higher at admission and at 12 and 24 hours

after admission when compared with dogs that survived [17]. In this study, increased CRP was also associated with a longer hospitalization time, and with the sensitivity and specificity to differentiate between survivors and non-survivors at 24 hours after admission (86.7 and 78.7%, respectively). A recent study suggested that a higher

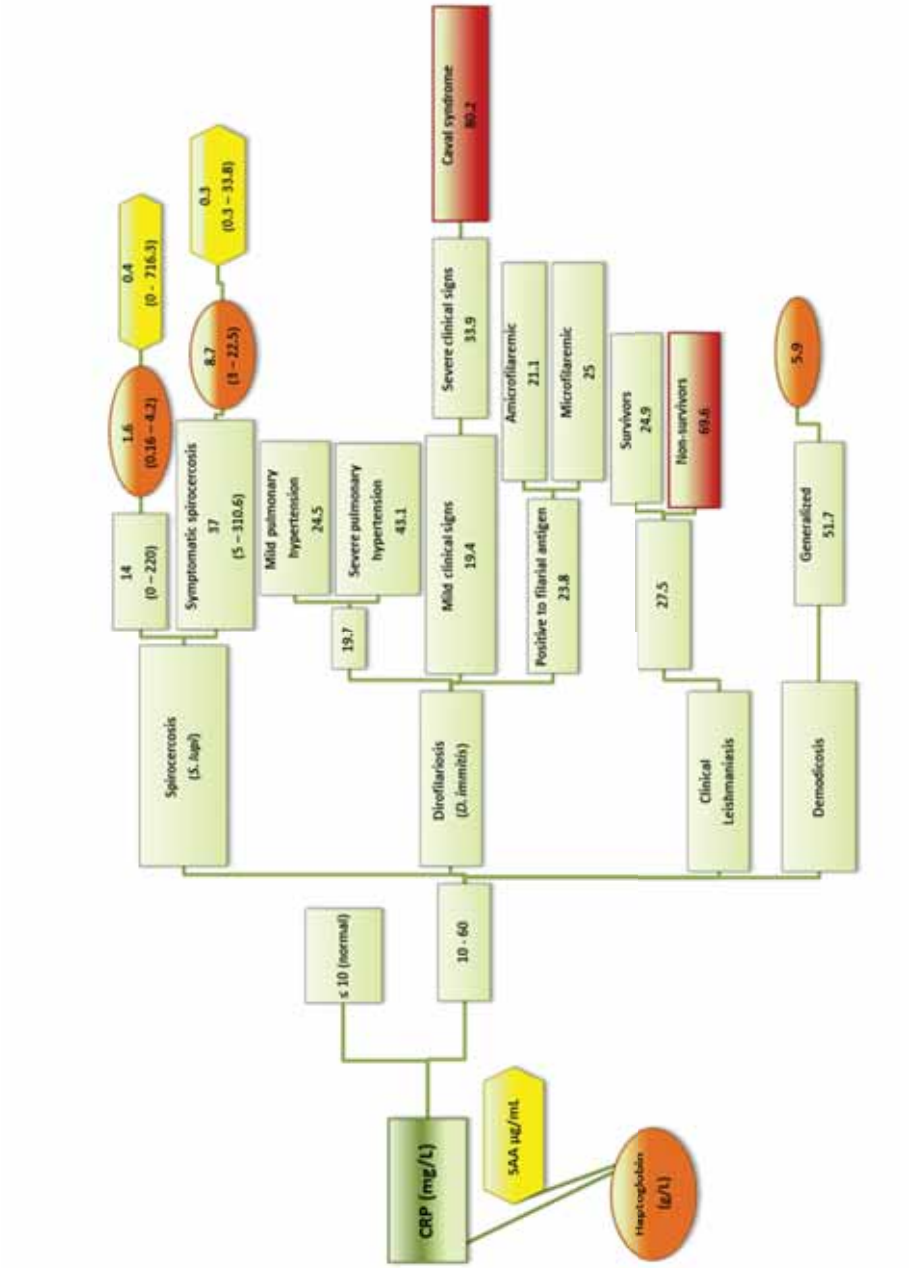

Figure 1. Approach to C-reactive protein, haptoglobin and serum amyloid A concentrations in infectious diseases in dogs [43-46,48,49,51]

magnitude increase in CRP values is related to the magnitude of secondary bacterial infection in this disease as a result of sepsis. Interestingly, severe parvovirus enteritis in dogs in the same study showed an elevated CRP concentration (> 180 mg/L) which was not accompanied by elevated Hp values (>4 g/L) , thus suggesting that along with severe sepsis, there could be a complication due to gastrointestinal haemorrhage

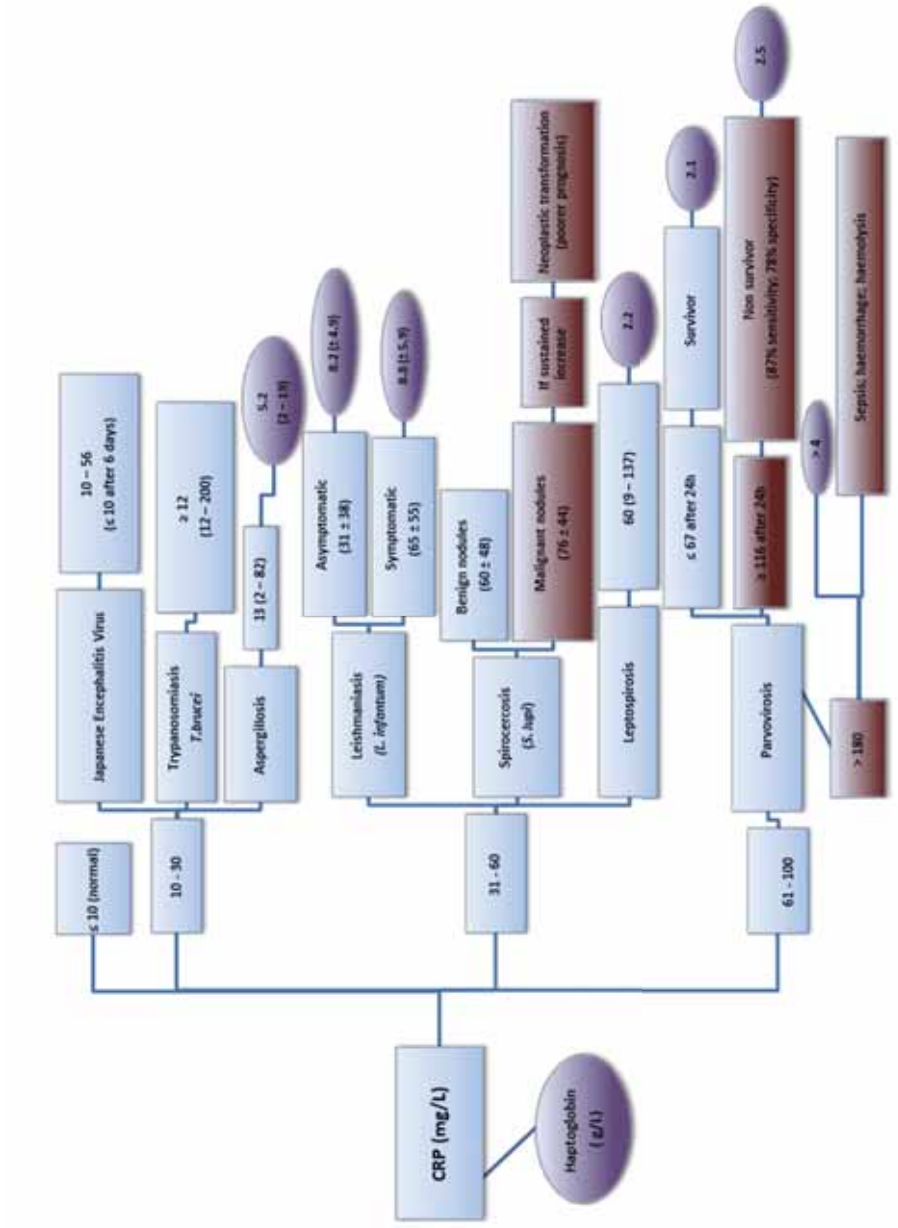

Figure 2. Approach to C-reactive protein and haptoglobin concentrations in infectious diseases in dogs [17,18,22,23,27,40,41,50]

or haemolysis present in all severe cases [18]. Diminished plasma concentrations of Hp were reported in patients with various haemolytic diseases [19] and haemorrahage or haemolysis associated with haemolytic anaemia [20] as Hp has been identified as the principal scavenger of free haemoglobin in the blood [21]. PON 1 activity was significantly decreased in dogs with parvovirus enteritis with a high correlation with albumin possibly caused by the effects of inflammatory cytokines in the liver [18]. In another study, dogs that did not survive parvovirus enteritis infection associated with severe clinical signs and leukopenia had a 72-fold increase in CRP and a 3.1-fold increase in haptoglobin concentrations. The sensitivity and specificity of CRP and haptoglobin predicted mortality in these dogs was 91% and 61%, and 52% and 63%, respectively [22].

In dogs experimentally inoculated with Japanese encephalitis virus the only altered parameter was CRP (10 to 56 mg/L). Dogs with clinical signs of nasal disease and positive serology for aspergillosis showed significantly higher CRP (2 to 82 mg/L) and Hp (2 to 19.2 g/L) concentrations when compared to healthy animals. However, no significant differences for SAA and AGP were found [23].

Regarding bacterial infections, CRP levels in beagles challenged with *Bordetella bronchiseptica* (canine infectious tracheobronchitis) peaked 24h after inoculation with a rapid decrease thereafter. The serum concentration of CRP was not affected in the experimentally inoculated group treated with prednisolone [24]. SAA values were significantly increased one day after *Bordetella bronchiseptica* inoculation in dogs [25]. After intraperitoneal inoculation of *Leptospira interrogans* serovar *canicola* in beagles, CRP concentration peaked between 2 to 4 days coinciding with a brief or mild pyrexia and increased alkaline phosphatase concentrations [26]. C-reactive protein and haptoglobin levels were increased in dogs with symptomatic leptospirosis [27].

Experimental endotoxaemia by *Escherichia coli* in dogs produced an acute phase response with CRP and haptoglobin peaking 24h and 48h after LPS injection, respectively. This response demonstrated a major (CRP) and moderate (Hp) type of response. In addition, the response to endotoxin in dogs showed decreased concentrations of adiponectin and insulin growth factor 1 (IGF-1), demonstrating their roles in systemic inflammation and behavior as negative acute phase proteins [28].

In pyometra (Figure 3), CRP, SAA and haptoglobin were valid indicators of the inflammatory state of the uterus and systemic inflammation mainly caused by *E. coli* endotoxins, making it possible to differentiate between open and closed cervix infections and to evaluate the severity of the inflammatory process especially with post-surgical complications [10,29,30]. A recent study demonstrated the clinical value of SAA determination in bitches with significant differences between septic (130.8 mg/L) and non-septic pyometra (88.5 mg/L) while CRP values did not show significant differences between both groups. Thus, apparently SAA and CRP levels have a different clinical diagnostic and prognostic value in pyometra when compared to the major acute phase response in other diseases [31]. In a further study, the same

authors demonstrated that IGF-1 and iron levels were significantly decreased in bitches with pyometra, indicating the possible value of these parameters as prognostic markers [32]. Elevated AGP levels were related to the severity of the disease and prolonged hospitalization [33]. Additionally, CRP concentration in combination with

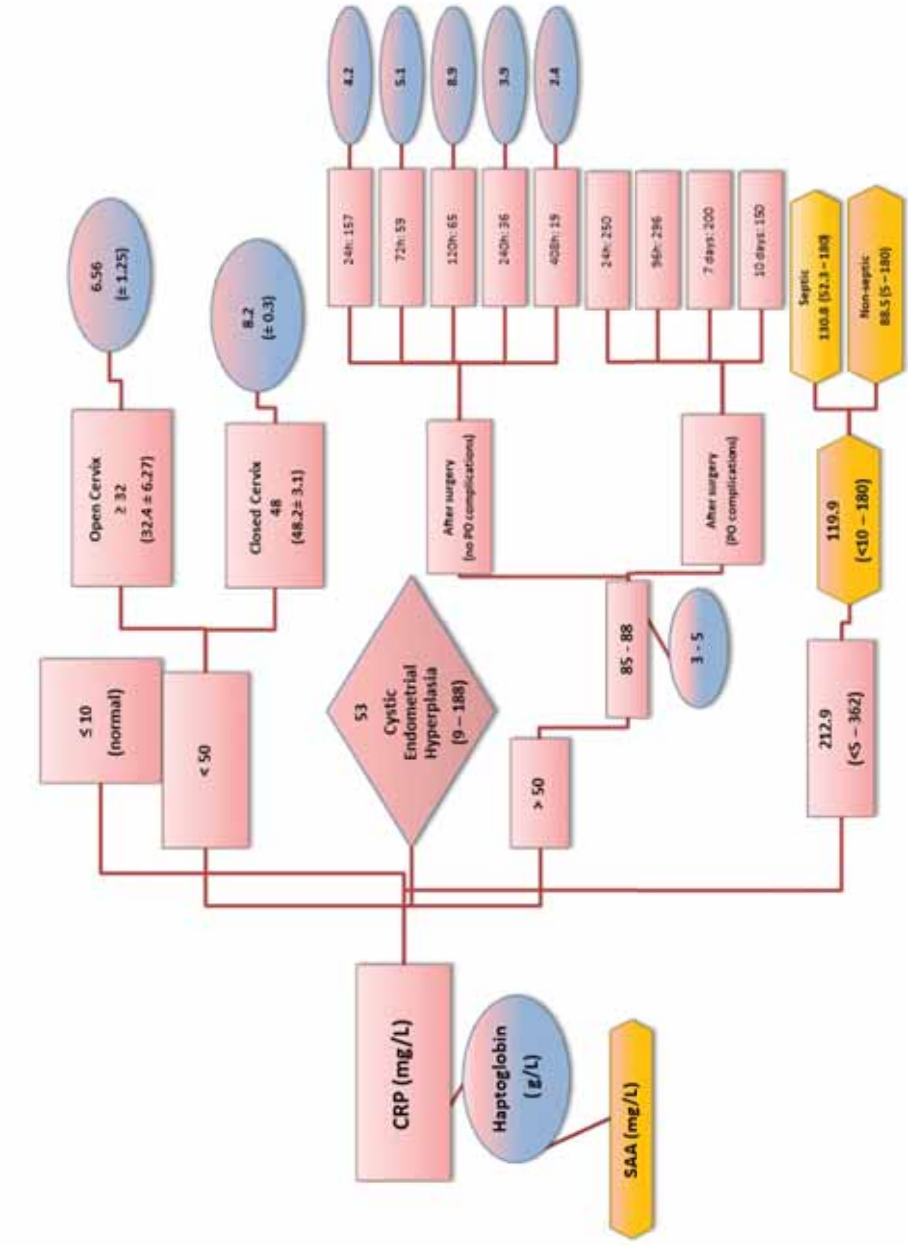

Figure 3. Overview of C-reactive protein, haptoglobin and serum amyloid A concentrations in pyometra in bitches [3,10,29,30,32,34]

the percentage of band neutrophils was useful to differentiate between pyometra and cystic endometrial hyperplasia. CRP showed 97.7% sensitivity and 75% specificity in predicting the presence of pyometra [34].

In naturally occurring canine monocytic ehrlichiosis while raised concentrations were found for CRP, SAA and Hp on admission, there was no predictive value for the clinical outcome from the levels found [35]. Nevertheless, CRP and Hp were higher in dogs with the myelosuppressive form (chronic), thus being useful indicators of the clinical phase of the disease. On the other hand, CRP and AGP concentrations were increased in dogs infected with *Ehrlichia canis* at the acute stage of infection [36,37].

Elevated serum levels of CRP have been found in naturally infected dogs with *Babesia rossi* showing clinical signs of acute babesiosis. Following treatment with imidocarbdipropionate CRP values decreased [38]. Furthermore, CRP was not associated with the outcome in *Babesia rossi* infection in dogs but none of the survivors had on the day of admission CRP levels lower than than 63.2 mg/L [39]. Dogs with *Babesia canis* clinical signs of infection had significantly higher CRP levels but significantly lower levels of Hp. This finding indicates that the systemic inflammation and haemolysis were caused by complicated babesiosis [20].

Elevated CRP levels were found after peaks of parasitemia in experimentally infected dogs with *Trypanosoma brucei*. CRP concentration demonstrated the presence of an active infection and the success of chemotherapy while Hp values remained elevated during the course of the disease but decreased gradually after treatment [40].

In natural *Leishmania infantum* infection in dogs, CRP showed 93% sensitivity for detecting symptomatic dogs and 82% sensitivity for detecting asymptomatic dogs [41]. C-Reactive protein, SAA and haptoglobin levels were higher before immunoglobulin G and immunoglobulin M increase and the appearance of clinical signs in experimental *Leishmania infantum* infection in dogs. Hp remained increased during the entire infection period and treatment significantly decreased all APPs [42]. A recent study demonstrated that dogs with leishmaniasis have lower serum iron and total iron-binding capacity and higher CRP concentrations suggesting that this combination is a risk factor for mortality in dogs diagnosed with the clinical disease [43].

At the time of diagnosis in naturally infected dogs with the heartworm nematode, *Dirofilaria immitis*, CRP concentration was significantly higher in positive animals to filarial antigen. Albumin and PON-1 concentrations were significantly decreased demonstrating that an acute phase response occurs in dogs with heartworm disease independent on the presence or absence of clinical signs. However, the authors found a significantly decreased Hp concentration in positive dogs showing a divergence in the behavior of this positive APP. This could be explained by the presence of haemolytic anaemia in the cases with caval syndrome (Class IV) due to the binding of hemoglobin from the erythrocytes (Hp-Hb complex) and its rapid removal by Kupfer cells in the liver (13,44). In a complementary investigation, CRP was significantly increased (higher than 6.8 mg/dL) in dogs with heartworm disease and associated pulmonary

hypertension [45]. In the same study, severe associated pulmonary hypertension was suspected if CRP values were >29.8 mg/dL. Vascular and pulmonary tissue damage caused significant CRP increase in dogs with Class III and IV heartworm disease, indicating the pathological processes associated with the presence of adult parasites, microfilariae and release of *Wolbachia* spp, a bacterial endosymbiont [46].

Discrimination between benign and neoplastic transformation of oesophageal nodules in *Spirocerca lupi* infections in dogs is challenging. An acute phase reaction and systemic inflammation has been characterized in infected dogs in investigations evaluating CRP, SAA, Hp and albumin concentrations [47-50]. Naturally infected dogs with *S.lupi* showed a sustained increase in CRP values associated with neoplastic transformation of the oesophageal nodules which means a poor outcome prognosis [50]. In dogs with *S. lupi* ova on faecal specimens and clinical signs, CRP and Hp concentrations were increased by 68 and 95%, respectively, but the number of nodules is not associated with the concentration of these proteins [49]. Dogs with endoscopic evidence of oesophageal neoplasia showed significantly higher CRP, SAA and Hp concentrations when compared with findings of benign nodules. However, these results had a limited use to discriminate between malignant and benign nodules and its clinical use to monitor response to treatment was non-satisfactory [48]. On the other hand, CRP values could be useful for monitoring treatment in benign spirocercosis [50].

In canine demodicosis, CRP and Hp were valid indicators of the generalized inflammatory skin disease process. It is likely that the release of inflammatory cytokines from the follicular epithelium is due to tissue damage induced by proliferation of the *Demodex* mites in hair follicles and skin surfaces [51]. It was also demonstrated that APP determination was useful to discriminate between generalized and localized demodicosis and that CRP and Hp levels decreased after treatment.

Cats

Although studies on APPs in small animals have advanced recently, investigations on APPs in feline infectious diseases deserves to be further explored.

Alpha-1 acid glycoprotein in cat serum or effusion samples is a recognized biomarker of FIP [14,15,52]. Serum AGP concentration higher than 1.5 g/L is the cut-off value in differentiating naturally occurring infection from cats with clinical signs similar to FIP but not suffering from this disease [14]. Additionally, serum AGP values ranged between 2.04 to 14 mg/mL in cats with FIP confirmed by immunohistochemistry, with a diagnostic concordance of 100% specificity and sensitivity [53].

The measurement of SAA concentration (29.4 – 88.3 mg/L) in FIP was clinically valuable to detect the inflammatory process in affected cats [54] and a 10-fold increase has been found, suggesting its potential as a biomarker of this disease [15]. Moreover, a study suggested that the median survival time of cats with elevated SAA levels (>0.82 mg/L) was significantly shorter in various diseases, including FIP [8].

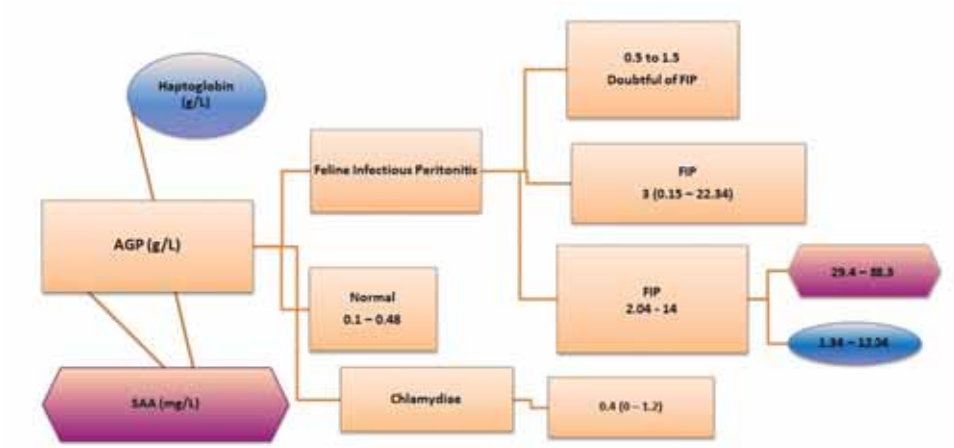

Figure 4. Approach to α 1 Acid glycoprotein, serum amyloid A and haptoglobin concentrations in infectious diseases in cats [14,52,53,56]

Cats experimentally infected with *Mycoplasma haemofelis* and "*Candidatus* Mycoplasma haemominutum" associated or not with FIV infection demonstrated a significant increase in APPs concentrations and variable concentrations of haptoglobin, SAA and AGP according to the stage of infection [55]. Interestingly, only AGP concentrations were significantly higher in *Mycoplasma haemofelis* infection of cats in the same study.

SAA concentration was elevated in cats with high antibody titers for Chlamydiae when the bacteria were detected in conjunctival swab samples [56]. A recent study demonstrated that AGP and SAA are good predictors of immunomodulation in FIV and FeLV positive cats undergoing recombinant interferon omega therapy [57].

Final considerations

In the last few years, assays for APPs, especially in the canine serum have become more available but only recently investigations are evaluating temporal changes of APPs in small animals while the use of APPs analysis in research as biomarkers of canine and feline diseases is expanding. Numerous investigations now have demonstrated the value of APPs as biomarkers of infection. However, the studies are currently restricted to a limited number of investigators across the world as the majority of veterinary laboratories do not have APPs assay kits available and to date there are no sufficient published results concerning the specificities, sensitivities and applications of these tests [58].

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PROTEINI AKUTNE FAZE KAO MARKERI INFEKTIVNIH BOLESTI MALIH ŽIVOTINJA

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Tokom odgovora akutne faze, postoji povećana proizvodnja i oslobađanje određenih proteina, poznatih kao proteini akutne faze (APP), koje mogu proizvesti hepatociti i periferna tkiva. Proteini akutne faze su C-reaktivni protein (CRP), serumski amiloid A (SAA), haptoglobin (Hp), alfa-1 kiseli glikoprotein (AGP). Ovi proteini su ispitivani kao markeri raznih infektivnih oboljenja pasa i mačaka. Svrha ovog rada je da se ažuriraju savremena saznanja o APP tokom zaraznih bolesti pasa i mačaka.