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Acute phase proteins in cats: Diagnostic and prognostic role, future directions, and analytical challenges

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Abstract

While clinical studies on acute phase proteins (APPs) have significantly increased in the last decade, and most commercial labs are now offering major APPs in their biochemical profiles, APP testing has not been widely adopted by veterinary clinical pathologists and veterinarians. Measurement of APP concentration is a useful marker for detecting the presence or absence of inflammation in cats with various diseases. APPs can also be reliably measured in different biological fluids (eg, effusions and urine) to improve their diagnostic utility. Measurement of APPs can be extremely beneficial in cats with feline infectious peritonitis (FIP) to discriminate between FIP and non-FIP cats with similar clinical presentations. Additional benefits come from multiple and sequential measurements of APPs, particularly in the assessment of therapeutic efficacy. APPs are more sensitive than WBC counts for early detection of inflammation and to demonstrate an early remission or recurrence of the diseases. Given the potential utility of APPs, more studies are warranted, with a particular focus on the applications of APPs to guide the length of antimicrobial therapies, as suggested by the antimicrobial stewardship policy. New inflammatory markers have been discovered in human medicine, with a higher specificity for distinguishing between septic versus nonseptic inflammatory diseases. It is desirable that these new markers be investigated in veterinary medicine, to further test the power of APPs in diagnostic setting.

KEYWORDS
haptoglobin, inflammation, sepsis, serum amyloid A (SAA), α-1-acid glycoprotein (AGP)

1 | INTRODUCTION

The use of acute phase proteins (APPs) in the clinical setting has significantly increased in the last decade, with most commercial labs now routinely including the measurement of APPs in their biochemical profiles. Thanks to intensive research, we now have a good understanding of the potential roles of APPs, from diagnosis to prognosis and treatment monitoring. Moreover, multiple species-specific assays are now available, including rapid point-of-care (POC) assays, which facilitate the measurement of APPs in any clinical setting. Nevertheless, APPs are still underused in veterinary medicine compared with human medicine.

2 | BIOLOGY AND KINETIC OF APPS

The APPs are blood proteins synthesized in the liver in response to the release of pro-inflammatory cytokines as part of the acute

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phase reaction (APR).[1–3] The APR is a series of pathophysiological events that occur in an animal exposed to infection, inflammation, trauma, or other stimuli. The APR begins when cells involved in the innate immune response (macrophages and, to a lesser extent, neutrophils) produce and release pro-inflammatory cytokines (mainly Interleukin (IL)-6, IL-1, and tumor necrosis factor α) at inflammatory sites.[4] These cytokines influence organs involved in homeostasis, such as the nervous system and endocrine glands, to establish a rapid and intense protective and reactive response. Cytokines also are responsible for the common clinical signs observed during systemic inflammation, such as fever, lethargy, and anorexia.[4] The APR includes changes in the concentrations of plasma APPs, some of which decrease in concentration (negative APPs, including albumin, transferrin, and PON-1 activity) while others increase in concentration (positive APPs, including serum amyloid A, alpha-1-acid glycoprotein, haptoglobin, and fibrinogen).[1–3,5] Thus, the APPs can be used to assess the innate immune system's systemic response and to differentiate local and systemic inflammatory diseases. APPs are also extremely useful in assessing response to therapy. Specifically, most clinical symptoms are mediated by prostaglandins, and several therapies work by interfering with phospholipase and COX pathways. For example, nonsteroidal anti-inflammatory drugs (NSAID) and low-dose corticosteroid administration reduce prostaglandin release only, without interfering with the inflammatory pathway.[6] However, higher steroid doses can also reduce cytokine release and consequently decrease APPs synthesis. Therefore, the improvement of clinical symptoms might not necessarily be related to the resolution of the inflammatory stimulus, making APPs an ideal marker to evaluate the real-time evolution of inflammation. In any given species, particular APPs demonstrate 'major,' 'moderate,' or 'minor' responses.

Major APPs have a low serum concentration in healthy animals but increase dramatically >1000-fold soon after stimulation. They peak at 24–48 hour, and then decline rapidly during the recovery phase.[2] Moderate responders increase 5- to 10-fold on activation, peak after 2–3 days, and decrease slower than major responders.[2] The major APP in cats is serum amyloid A (SAA), the moderate APPs are α-1-acid glycoprotein (AGP) and haptoglobin, and the minor APPs, C-reactive protein (CRP) and ceruloplasmin, have a maximum twofold increase from base values.[7,8]

Acute phase proteins have different functions, of which some are not clearly defined, but they share an overall role in modulation of the immune response. The biological function of SAA is not clearly defined; it acts as a scavenger of oxidized metabolites and protects tissues from excessive damage induced by inflammation.[9] SAA may also play a role in the down-regulation of the inflammatory process by inhibiting myeloperoxidase release and chemotaxis of phagocytes induced by the chemotactic N-formyl peptides.[10] The biological functions of AGP include the inhibition of lymphocyte proliferation, platelet aggregation, and neutrophilic function (phagocytosis, chemotaxis, and superoxide generation).[11–14] Because AGP is a heavily glycosylated protein, it has been hypothesized that desialylation has a pathologic role in the immunomodulatory function of AGP in cats with feline infectious peritonitis (FIP).[15] Haptoglobin plays a critical role in tissue protection and prevention of oxidative damage by binding highly toxic free hemoglobin.[16] Haptoglobin also has an inhibitory effect on granulocyte chemotaxis, phagocytosis, and bacterial activity.[17] Ceruloplasmin protects cells and tissues against oxidant compounds generated by leukocytes during phagocytosis of microorganisms or tissue debris.[1] CRP is involved in the activation of the complement pathway, the enhancement of phagocytosis, induction of cytokines, inhibition of chemotaxis, and modulation of neutrophil function.[18]

The most investigated APPs in cats are SAA and AGP. They are commonly used by clinicians and researchers because SAA is the major APP in cats, and multiple reliable species-specific assays are available. AGP is a moderate APP in cats, but due to its higher specificity for the diagnosis of FIP, it has been used and investigated extensively.

The kinetics of SAA and AGP have been investigated in cats subjected to two different experimental surgeries: ovariohysterectomy or gastrotomy.[19] Irrespective of the type of surgery, both AGP and SAA peaked 1–2 days after the surgery, but SAA returned to normal quicker (within 5 days), while AGP remained persistently above the reference interval for several weeks.[19] Another study demonstrated increases in SAA within 3–6 hours after ovariohysterectomy in cats, with the peak at 24 hour.[20]

As expected, the magnitude of increase is greater for SAA (major APP) than for AGP (moderate APP). SAA increased up to 27-fold above presurgery concentration, and the concentration was higher in cats after the more invasive surgery (gastrotomy) compared with ovariohysterectomy.[19] Thus, the increase in SAA concentration is proportional to the severity of the inflammation. AGP increased only up to fourfold the presurgery concentration in cats subjected to both surgeries. Haptoglobin is a moderate APP in cats, and its concentration decreases slowly in serum compared with other major and moderate proteins.[21]

3 | DIAGNOSTIC ROLE OF APPS

APPs are expected to increase in any pathologic condition characterized by the release of pro-inflammatory cytokines and systemic inflammation, such as infections, trauma and injury, congestive heart failure, tumors, metabolic diseases (such as diabetes mellitus and hyperthyroidism), and surgery (Table 1).[20,22–34] When the comparison is between healthy cats and cats with various pathologic conditions, SAA concentration is significantly higher in cats with inflammation than in healthy cats.[20,30] Specifically, SAA concentrations are higher in cats with confirmed diagnosis of inflammatory diseases such as upper respiratory tract infections, pneumonia, pyometra, and FIP than observed in healthy cats. Therefore, the measurement of SAA concentration is a useful marker for detecting the presence or absence of inflammation in diseased cats.[30] Unfortunately, unlike in human patients,[35] APPs are not able to discriminate between septic vs nonseptic inflammation.[28] Conflicting results have been observed

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TABLE 1 Positive acute phase proteins investigated in different diseases in cats.

Disease	Acute phase protein	Magnitude of increase	References
FIP	AGP	17×	Paltrinieri et al[29]
		10×	Duthie et al[22]
	Haptoglobin	2×	Duthie et al[22]
	SAA	144×	Yuki et al[30] Tecles et al[109]
Congestive heart failure	SAA	Not specified	Liu et al[31]
Upper respiratory tract infections	SAA	140×	Yuki et al[30]
Pneumonia		134×	
Pancreatitis		4×	
Sepsis	SAA	43×	Troia et al[28]
Pyometra	SAA	155×	Yuki et al[30]
		167×	Vilhena et al[32]
	Haptoglobin	2×	
Hyperthyroidism	SAA	Not specified	Glück et al[33]
	AGP	Not specified	
	Haptoglobin	Not specified	
CKD	SAA	2×	Javard et al[63]
Dirofilaria immitis and *Wolbachia* (with clinical signs)	SAA	100×	Silvestre-Ferreira et al[62]
	Haptoglobin	2×	
Hepatozoon felis	SAA	169×	Vilhena et al[23]
	Haptoglobin	8×	
Babesia vogeli	Haptoglobin	4×	
Gingivostomatitis	AGP	1-3×	Mestrinho et al[46]
	SAA	4×	Yuki et al[30]
Injury	SAA	102×	Sasaki et al[20]
Renal failure		52×	
Infectious diseases		78.7×	
FLUTD		47×	
Diabetes mellitus		13×	
Various tumors grouped in macro-categories: carcinoma, sarcoma, and discrete round cell tumors (lymphoma, mast cell tumor, and melanoma) in Sasaki et al study Nonspecified tumors in Selting et al study	SAA AGP	28× 2×	Sasaki et al[20] Selting et al[24]
Lymphoma	AGP	2×	Correa et al[25]
		3×	Winkel et al[34]
	SAA	10×	Winkel et al[34]
	Haptoglobin	2×	Love et al[26]
IBD	Haptoglobin	2×	Love et al[26]

Abbreviations: AGP, α1-Acid Glycoprotein; CKD, Chronic Kidney Disease; FIP, Feline Infectious Peritonitis; FLUTD, Feline Lower Urinary Tract Diseases; IBD, Intestinal Bowel Disease; SAA, Serum Amyloid A.

between studies for cats with cardiomyopathy, hyperthyroidism, and diabetes mellitus. Yuki and colleagues[30] did not find increased SAA in cats with any of those diseases, while other studies found increased SAA in cats with congestive heart failure,[31] diabetes mellitus,[20] and hyperthyroidism.[33] There are several explanations for the discrepancies between the studies. The number of cats enrolled in the study by Yuki et al was lower than in the other studies, and a type II error could have been present. The three studies used three different methodologies to quantify SAA; thus, there could have been different sensitivities across the methods that were responsible for the contrasting results. Also, the stage, severity, and chronicity of the three diseases may explain the conflicting results across studies. In cats with diabetes, SAA was only moderately increased, while the magnitude of the increase in hyperthyroidism and congestive

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heart failure was not reported (Table 1). In cats with hyperthyroidism, APPs other than SAA were increased (AGP and haptoglobin), supporting the presence of systemic inflammation.

Cats with inflammatory bowel disease (IBD) and small-cell gastrointestinal lymphoma had higher serum haptoglobin concentrations than healthy cats. Nevertheless, haptoglobin concentrations in cats with lymphoma were similar to cats with IBD, and the two diseases could not be differentiated.[26] Serum AGP concentrations were significantly higher in cats with tumors than in healthy cats, but no differences were found between different types of tumors (carcinoma, sarcoma, round cell tumors).[24]

3.1 | APPs and FIP: an exception to the rule

While APPs have high sensitivity and specificity for the detection of systemic inflammation, they are poorly specific for differentiation between different inflammatory conditions.[30] There is one exception: APPs play a crucial role in the diagnosis of FIP in cats. A definitive diagnosis of FIP is often challenging due to different clinical presentations (wet vs dry form). Most existing diagnostic tests cannot differentiate between feline enteric coronavirus and FIP virus, and in cats without body cavity effusions, it is often difficult to reach a definitive diagnosis ante mortem.[36] AGP (but not haptoglobin) concentration was higher in serum from cats diagnosed with FIP than in cats with clinical signs consistent with FIP (eg, peritoneal effusion) but were determined by histopathologic examination not to have FIP; AGP also was higher than in cats with other diseases characterized by systemic acute inflammation.[22] Specifically, a serum AGP concentration >1.5 g/L has 85% sensitivity and 100% specificity in differentiating cats with FIP and clinically similar conditions; the overall efficiency is 90%.[22] Similarly, another study demonstrated that high AGP concentrations might support the diagnosis of FIP in cats where the results of other clinicopathologic tests or histopathology were inconclusive.[29] That is, AGP can be used to support a clinical diagnosis of FIP according to the Bayesian approach; a higher cut-off is necessary when the pretest probability of FIP is low. Specifically, when the pretest probability of FIP is high, based on history and clinical signs, moderate serum AGP levels (1.5–2 mg/mL) can discriminate cats with FIP from others with FIP-like conditions, while only high serum AGP levels (>3 mg/mL) can support a diagnosis of FIP in cats with a low pretest probability of disease.[29]

APPs can be measured in biological fluids other than serum or plasma. The concentrations of SAA, AGP, and haptoglobin in abdominal effusions are significantly higher in cats with effusive (wet) FIP than in those without FIP but with a similar clinical presentation (eg, abdominal effusion).[37] AGP was the best APP to distinguish between cats with and without FIP in the effusion; a cut-off value of 1550 μg/mL had both a sensitivity and specificity of 93% for the diagnosis of FIP.[37]

Cats receiving treatment for FIP had three possible outcomes: death, total recovery, or remission. Remission is a source of concern because of the possibility of relapse. Relapse poses a risk for other cats sharing the same environment because infected cats can shed the virus.[38,39] APPs also play a role in the prognosis of FIP in cats treated with antivirals. A recent study demonstrated that a sustained return to normal AGP concentrations was the most rapid and consistent indicator for differentiating recovery from remission following treatment for FIP.[40] Because this was a retrospective study with different therapies used, interval from the time of presentation with FIP to the normalization of AGP could not be established. Normalization of AGP concentrations was faster with a novel antiviral nucleoside analog,[41] suggesting that a rapid decline might indicate superior virucidal activity. Similarly, a rapid and sustained decline in SAA concentration has been observed in cats with FIP treated with the same antiviral therapy.[42]

4 | ROLE OF APPS IN THE PROGNOSIS AND EVALUATION OF TREATMENT RESPONSES

Additional benefits from APPs could be gained from multiple, sequential measurements in sick animals as early markers for disease recurrence or objective markers to determine the duration of therapy. APPs are immediately secreted into the bloodstream after de novo synthesis in response to cytokines. Because APPs are not stored within hepatocytes or any other tissue, and major APPs have a short half-life, a rapid decline in serum concentration is expected as soon as the inflammatory stimulus ceases.

A good example of using sequential measurements is shown in cats with FIP (see above) and pancreatitis.

While SAA concentrations are significantly higher in cats with increased feline pancreatic lipase immunoreactivity (fPLI), SAA measurements alone cannot accurately predict the probability of increased fPLI in cats with clinical signs suggestive of pancreatitis.[43] Nevertheless, the kinetics of SAA were assessed in a cat with pancreatitis.[44] SAA concentrations were increased at the onset of the disease and then gradually decreased during treatment, paralleling the clinical signs. Similarly, the reoccurrence of pancreatitis was characterized by increased SAA together with clinical signs.

Given their immunomodulatory functions, an increase in APP concentrations might be expected if a therapy can stimulate the immune system. A possible clinical use of APPs is in monitoring immune responses to treatment in cats with retroviral infections, such as FIV or FeLV. SAA, AGP, and CRP significantly increased in cats undergoing interferon- ω therapy during and after treatment.[45]

In some cases, APPs can be used to evaluate the effectiveness of therapy. Feline chronic gingivostomatitis (FCGS) is a debilitating disease in cats that leads to anorexia and weight loss as well as triggers systemic inflammation. Systemic inflammation was confirmed by significantly increased AGP in cats with stomatitis, and there was a correlation between the severity of stomatitis and the magnitude of AGP increase.[46] AGP concentration did not decrease 1 and 2 months after dental extraction, demonstrating that systemic inflammation did not resolve with dental extraction alone, and a

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concurrent anti-inflammatory therapy may be needed.[46] A study on cats with various forms of lymphoma showed a gradual decrease in serum AGP and SAA concentrations after 4 weeks and 8 weeks of treatment, respectively; concentrations were comparable to those of healthy cats by 12 weeks of treatment, by which all cats achieved complete remission of the disease.[34]

Systemic inflammation has been demonstrated with obstructive feline lower urinary tract disease (FLUTD), with increased concentrations of positive APPs, including AGP, SAA, and fibrinogen, and decreased concentrations of albumin, a negative APP. Following the relief of urethral obstruction, SAA was increased at 12 hours (confirming the rapid kinetic response of SAA), peaked after 24 hours, and began declining by 48 hours. This trend suggested a resolution of systemic inflammation after treatment, but a longer follow-up was not provided. SAA may be a promising marker to assess the resolution of FLUTD objectively.[47]

Evidence for APPs as prognostic markers is variable. Congestive heart failure (CHF) is an inflammatory disorder, and SAA and ceruloplasmin have been shown to be higher in cats with CHF than in healthy cats and cats with preclinical cardiomyopathies.[31] While those APPs are not early markers and cannot distinguish between preclinical cardiomyopathy and CHF, serum AGP concentrations are independent and poor prognostic indicators in cats with CHF cats (hazard ratio = 40.2).[31] In other feline pathologic conditions, APPs did not demonstrate prognostic properties. In a study evaluating cats with different diseases, survival time at 180 days did not differ based on the SAA concentration at admission, suggesting that a single SAA measurement may not be useful as prognostic marker.[30] Similarly, in cats with lymphoma, serum AGP concentrations did not correlate with either duration of remission or survival time.[25] In cats with parvovirus infection, SAA and haptoglobin were significantly lower in cats that survived compared with nonsurviving cats; however, neither SAA nor haptoglobin concentration at admission was able to predict the probability of survival.[48] A combined measurement of multiple APPs (acute phase index) could improve the sensitivity of those markers for prognostication.[49–51]

5 | ANALYTICAL ASPECTS

The evolution of commercial assays for APPs quantification in animals has followed the increased popularity of those inflammatory markers in veterinary medicine (Table 2). Several species-specific assays have been developed for cats, and there is an active effort to provide clinicians with POC assays to have quick results for use in diagnosis and therapeutic planning. Any assay must be analytically validated prior to use in clinical or research studies, providing at least information on its precision and accuracy. If heterologous assays are used (ie, assays originally developed for humans or different animal species), cross-reactivity also should be demonstrated.

Traditionally, AGP has been quantified with a single radial immunodiffusion (SRID) test, and most studies on FIP have been done using this methodology.[29,52] Unfortunately, the SRID test has not been commercially available for > 10 years, and different assays have been proposed. An immunoturbidimetric assay for rapid quantitative measurement of feline AGP in serum and peritoneal fluid has been validated.[53] Other options available are ELISA and Spatial Proximity Analyte Reagent Capture Luminescence (SPARCL), (AGP Vetbio-1 assay, Veterinary Biomarker, Inc. West Chester, PA, USA) feline AGP assays. Luminescence immunoassays have the advantage of a shorter processing time, with results available in 30 minutes, compared with several hours required for ELISA. To the author's knowledge, no independent analytical validation has been performed for either the ELISA or immunofluorescence assay. Given the superior diagnostic power of AGP compared with other APPs in cats with FIP, independent validation of alternative methods to the SRID test is recommended.

In 2006, an automated turbidimetric assay based on a mixture of anti-human-SAA-specific monoclonal and polyclonal antibodies was validated in different species, including cats (LZ-SAA, Eiken Chemical Co., Tokyo, Japan). The human turbidimetric assay measured feline SAA with acceptable imprecision, and the investigation of linearity during dilution revealed no sign of significant inaccuracy.[54] Acceptable precision without significant inaccuracy was demonstrated in cats, and it has been used by numerous researchers,[23,28,44,55] and it became the reference method for validation of other assays.[56] Recently, the same manufacturer has developed an improved format of this assay targeting multiple veterinary species (VET-SAA, Eiken Chemical Co., Tokyo, Japan), which uses purely monoclonal antibodies (VET-SAA, Eiken), which should reduce variation between assay batches, and potentially increase specificity. Validation demonstrated that VET-SAA is a precise and accurate method for measurement of feline SAA and can clearly identify patients with inflammatory disease.[57]

In a recent study, an ELISA assay specific for the quantification of feline SAA used affinity-purified cat AGP antibodies for solid phase immobilization.[46] Despite promising analytical performances as demonstrated by the study, independent validation is still needed.

Two POC assays have been validated (for SAA): a sandwich immunoassay method using anti-mouse monoclonal antibody (FUJI DRI-CHEM IMMUNE AU CARTRIDGE vf-SAA, Fujifilm, Tokyo, Japan) and a latex agglutination test based on optical measurement of the change in turbidity caused by the agglutination of the latex particles with an antibody against SAA (SAA VET test kit, Eurolyser Diagnostica GmbH, Salzburg, Austria). Both POC demonstrated good precision but a significant bias when compared with the reference method.[56] The need for a specific reference range has been highlighted.

In cats, haptoglobin is often quantified using a commercially available multispecies-specific kit (Tridelta Development Ltd, County Kildare, Ireland) based on a colorimetric assay which can be adapted to any spectrophotometer.[23,26,32,33,37,43,58–64] It is important to highlight that haptoglobin colorimetric assay has been validated only in dogs. An alternative method, validated in cats, is a sandwich ELISA (TECO feline & canine haptoglobin ELISA, TECOmedical Group, Sissach, Switzerland) with affinity-purified

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TABLE 2 Methods used to quantify acute phase proteins in cats.

Acute phase protein	Method	Targeted species	Kit and manufacturer	References
SAA	Turbidimetric immunoassay	Human	LZ-SAA; Eiken Chemical, Tokyo, Japan	Savioli et al[128] Hazuchova et al[37] Vilhena et al[23] Hansen et al[54] Glück et al[33] Tamamoto et al[55] Krentz et al[42] Tamamoto et al[44] Troia et al[28] Glück et al[33] Silvestre-Ferreira et al[62] Vilhena et al[32] Tecles et al[109]
		Multispecies	VET-SAA; Eiken Chemical, Tokyo, Japan	Waugh et al[57]
		Human	SAA VET test; Eurolyser Diagnostica GmbH, Salzburg, Austria	Escribano et al[56]
		Unknown	SpeLIA; Precision System Science Co., Ltd., Chiba, Japan	Yuki et al[30]
	Immunofluorescence	Mouse	Fuji DRI-CHEM immune au cartridge vf-SAA; Fujifilm, Tokyo, Japan	Escribano et al[56]
	ELISA	Feline	Not commercial, developed by authors	Sasaki et al[20]
		Multispecies	PHASE SAA Multispecies; Tridelta Development, Maynooth, County Kildare, Ireland	Leal et al[45] Winkel et al[34] Krasztel et al[43] Giordano et al[58] Kann et al[59,60] Javard et al[63]
		Feline	Cat Serum Amyloid A ELISA (LIFE-SAA-8); Life Diagnostics, Pennsylvania, USA	Dinallo et al[47]
	SPARCL	Feline	SAA-SP-8; Life Diagnostics, Pennsylvania, USA	Liu et al[31]
AGP	ELISA	Feline	Cat alpha-1-acid glycoprotein ELISA (AGP-8); Life Diagnostics, Pennsylvania, USA	Mestrinho et al[46] Glück et al[33] Dinallo et al[47] Glück et al[33]
		Unknown	Avacta Animal Health, Wetherby, UK	Addie et al[40]
	Single-radial immunodiffusion	Feline	Feline α1-acid glycoprotein measurement kit; Saikin Kagaku Institute Co., Sendai, Japan	Correa et al[25] Duthie et al[22]
			PHASE Feline α-1 acid glycoprotein SRID; Tridelta Development, Maynooth, County Kildare, Ireland	Paltrinieri et al[29] Winkel et al[34] Hazuchova et al[37] Giori et al[52] Giordano et al[58] Kann et al[59,60]

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TABLE 2 (Continued)

Acute phase protein	Method	Targeted species	Kit and manufacturer	References
Haptoglobin	Spectrophotometric	Multispecies	PHASE haptoglobin assay; Tridelta Development, Maynooth, County Kildare, Ireland	Stiller et al[64] Hazuchova et al[37] Vilhena et al[23] Love et al[26] Glück et al[33] Krasztel et al[43] Giordano et al[58] Kann et al[59,60] Glück et al[33] Javard et al[63] Silvestre-Ferreira et al[62] Vilhena et al[32]
	ELISA	Feline and canine	TECO feline & canine haptoglobin ELISA; TECOmedical Group, Sissach, Switzerland	Stiller et al[64]
CRP	ELISA	Feline	Cat CRP ELISA; Kamiya Biomedical Company, Washington, USA	Leal et al[45]

Abbreviations: AGP, α1-acid glycoprotein; CRP, C-reactive protein; SAA, serum amyloid A; SPARCL, spatial proximity analyte reagent capture luminescence.

polyclonal rabbit anti-haptoglobin antibodies as capture and detection antibodies.[64] Again, despite an acceptable precision, a significant bias has been observed, and the two methods cannot be used interchangeably.

All the method comparison studies investigating different assays to quantify APPs in cats have identified a significant bias between different assays, which was expected given the heterogenicity of the available analytical techniques and the lack of calibration standards. Each assay uses different calibrators and quality control materials which are not necessarily species-specific for cats. The majority of biomarkers routinely measured in veterinary clinical biochemistry are identical across species and are quantified by standardized chemical reactions using well-established calibrators. Specific protein biomarkers such as APP present a challenge as those proteins often vary across species due to different genomes and protein conformations. The method of choice for quantification of APPs is often an immunoassay; human-based assays with standardized calibration are often not suitable due to lack of cross-reactivity. Moreover, even when species-specific immunoassays are applied, a lack of concordance due to variations in epitope structure between individuals and even within individuals leads to differences in immunoreactivity in different assays.[65] Other issues, such as Hook's effect, whereby antibody saturation prevents sandwich formation and results in a falsely low concentration of analytes of interest, are further potential frustrations for an investigator.[66] A gold standard calibrator of the protein biomarker may only be available by purification procedures which commonly do not yield preparations of 100% purity. Recombinant proteins or synthesized peptides can be used to produce calibrators, but they may not react as native proteins. For instance, glycosylation may be absent in synthesized proteins, or the native conformation may not be achieved, thereby reducing antibody interaction.[67]

To enable the development of species-specific reference preparations, an international harmonization program has been proposed.[67] The inspiration for a globally agreed protocol for the harmonization of assay calibration for veterinary biomarkers was taken from collaborative initiatives organized for human testing under the auspices of the International Federation of Clinical Chemistry (IFCC). In 1994 the IFCC established an international Reference Preparation for Proteins in Human Serum (RPPHS)[68] that provided a pool of human sera with known concentrations of the major biomarkers as determined by the mean value of all laboratories in the collaboration.

The first international harmonization program in veterinary medicine was the European Concerted Action Group on Acute Phase Proteins, established in 2000.[69] Despite a strong effort, assays for animal APPs are still developed with different calibration standards by separate companies. In the end, this means that assay results cannot be compared between different laboratories and reference intervals; therefore, clinical decision points and clinical findings may differ significantly.

In 2018, the International Society for Animal Clinical Pathology (ISACP), agreed to sponsor this process by initiating a working group with the responsibility of preparing a detailed plan for establishing

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International Veterinary Biomarker Reference Preparations in collaboration with the European, Japanese, and American Veterinary Clinical Pathology associations.[67]

6 | FUTURE PERSPECTIVES

The future clinical applications of APPs in veterinary medicine will most likely mimic the applications in human medicine. In human as well as veterinary medicine, the measurement of a single APP (even when sequential measurements are performed), does not have sufficient predictive accuracy to rule in or rule out sepsis in every clinical situation. To improve diagnostic capability, a number of authors have combined APP measurements into sepsis screens with up to 5 different inflammatory markers.[70] The advantages of using an APP profile instead of measuring a single APP have been clearly demonstrated in pediatric human patients with sepsis.[71] A similar combination of multiple inflammatory markers is envisaged in veterinary medicine, and the application of an acute phase index has been proposed.[50] It combines rapid and slow positive APPs with rapid and slow negative APPs in a mathematical formulation to considerably increase the predictive value of APPs in the detection of inflammation.

The proposed index is:

$$\text{index} = \frac{(\text{value of a rapid positive APP}) \times (\text{value of a slow positive APP})}{(\text{value of a rapid negative APP}) \times (\text{value of a slow negative APP})}$$

In cats, SAA is probably the best candidate as a rapid positive APP and AGP as a slow positive APP. Albumin is a slow negative APP; transferrin, retinol-binding protein, transthyretins, and apolipoprotein A-I, are also negative APP, but a distinction into rapid and slow may be difficult due to the lack of knowledge on their kinetics during inflammation.[1,2,7,49,51,72]

The use of the acute phase index rather than the measurement of a single APP enhanced the sensitivity and specificity for detecting inflammation in nonhealthy subjects among populations of normal animals, as demonstrated in dogs with leischmaniasis,[73] cattle at a slaughterhouse,[74] and pigs with six different infectious challenges.[75]

Two major limitations can delay the development of an acute phase index in cats; the higher cost of the APP assays compared with other standard biochemical markers and the different technologies required to quantify the individual APPs (Table 2). In human medicine, numerous sensors for the quantification of biomarkers have been developed (eg, electrochemical, aptamer-based, surface plasmon resonance, and microfluidic sensors).[76,77] These new technologies have numerous advantages compared with the old technologies, such as lateral flow immunochromatographic assays: these include increased sensitivity, increased stability at a broader range of temperatures, higher binding affinity, enhanced induced fit binding property, ease of modification, and capability of miniaturization.[76,77] Most of the new sensors can measure multiple parameters simultaneously, reducing the amount of sample required, the turnaround time, and possibly costs.[78] Future technologies designed for the veterinary market should consider those requirements to significantly impact diagnostic testing in veterinary medicine.

Investigation of clinical applications of APP in feline medicine has been relatively neglected compared with other domestic animals and deserves further exploration. One APP application is the monitoring of animal health and welfare, both for production animals and nondomesticated animals. The presence of different stressors (such as live animal transportation, weaning, and captivity) may affect the well-being of animals, and increased APPs represent an objective tool to assess animal welfare.[79] Good examples are available in pigs,[80–82] cattle,[83–85] chickens,[86] marine mammals,[87–90] fish and,[91] captive and wild nondomesticated animals.[92–98] The majority of investigations on feline APPs have focused on well-defined pathologic conditions; however, APPs can also be used to objectively assess the health status of cats. For example, APPs can be useful in assessing the health and welfare of cats in shelters; shelter housing poses substantial challenges in terms of maintaining positive health and well-being.[99,100] APPs can also be used to monitor the possible side effects of treatments, as demonstrated in hyperthyroid cats treated with radioiodine.[33]

Another future application for APPs is to guide the length of antimicrobial therapies, in accordance with the antimicrobial stewardship core principles and policy.[101] By using APPs as objective markers for the evaluation of therapeutic outcomes, dosing regimens can be refined that are simultaneously effective while not selecting for resistance.[101] A good example comes from a study of dogs with bacterial pneumonia. This study used the normalization of serum CRP concentration to guide the duration of antibiotic treatment, significantly decreasing antimicrobial administration without increasing the number of relapses.[102]

There is ongoing research into new inflammatory markers to improve the diagnostic ability of clinicians. Two new inflammatory markers have been investigated in the last few years: paraoxonase-1 activity (PON-1) and procalcitonin (PCT).

Paraoxonase-1 (PON-1) activity is an inflammatory marker associated with lipid oxidation.[103] PON-1 is a highly promiscuous enzyme synthesized in the liver and capable of hydrolyzing a wide range of substrates. It is intimately associated with high-density lipoproteins (HDLs) in circulation.[104] Given its ability to hydrolyze peroxide phospholipids, PON-1 protects low-density lipoproteins (LDL) from oxidation. Oxidative damage to membrane phospholipids is the starting point for lipid peroxidation that, in turn, may react with proteins, changing their conformation and function and leading to an enhanced inflammatory response.[105] Given the antioxidant role of PON-1, decreased PON-1 activity has been reported in both acute and low-grade inflammatory conditions in various animals, including cats.[106–109] An enzymatic test to quantify PON-1 activity in feline serum has been validated; the study confirmed the suitability of PON-1 activity as a negative acute APP in cats, showing a correlation with AGP but not SAA.[5] PON-1 activity could be an additional option as a negative APP, for the proposed acute phase index. Significantly lower PON-1 activity was observed in cats with FIP compared with healthy cats; moreover, cats with effusive forms

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showed significantly lower PON-1 and higher SAA concentrations compared with cats with noneffusive forms.[109] PON-1 activity can accurately discriminate cats with FIP from cats without FIP, but with similar clinical presentations.[110] A threshold of 78.30 U/L yielded a sensitivity of 100% and a specificity of 50.4%, while a threshold of 24.90 U/L maximized specificity (94.4%) and had a sensitivity of 44.1%, making PON-1 activity a good confirmatory test for FIP.[110]

PON-1 activity significantly decreases in symptomatic and asymptomatic cats naturally infected with *Hepatozoon felis* and *Babesia vogeli* compared with healthy noninfected cats.[23]

Further research is required to investigate additional clinical applications for PON-1 activity, and again, human medicine can be used as a model. In human neonates with sepsis, PON-1 activity measured at enrolment correlated significantly with SAA, CRP, and IL-6 and could discriminate septic from nonseptic neonates.[111] Therefore, PON-1 activity is a promising biomarker of neonatal sepsis. Studies on the diagnostic role of PON-1 activity in cats with sepsis are warranted.

Another marker that has gained increased interest for sepsis investigations in veterinary medicine is procalcitonin (PCT). Procalcitonin is synthesized in monocytes and hepatocytes as a prohormone of calcitonin in response to cytokine stimulation.[112] Bacterial infections are common in cats, and a local bacterial infection can progress to a life-threatening condition.[113,114] As cats with sepsis tend to present with nonspecific clinical signs, diagnosis can be challenging, and diagnostic tools are limited.[115] Currently used APP cannot differentiate inflammation from bacterial infections and noninfectious causes. SAA has only a moderate ability to differentiate between sepsis and nonseptic inflammation in cats, with 79.3% sensitivity and 77.7% specificity (SAA cut-off: >81 mg/L).[28] Procalcitonin is a promising biomarker for the diagnosis of bacterial infections. In humans, PCT increases within 2–4 hours (more rapidly than CRP) and peaks within 6–8 hours after bacterial infection.[116] In cats, PCT has high specificity (93.75%) but low sensitivity (67.5%) for diagnosing bacterial infections, using 366 pg/mL as the cut-off; this study was limited by the inclusion of only cats with confirmed bacterial infections.[112] Further studies to investigate the ability of PCT to discriminate between infectious and noninfectious inflammation are warranted.

In humans, PCT can discriminate between bacterial and viral etiologies.[117] Serum PCT concentrations are considered useful biomarkers for distinguishing bacterial and viral infections in cats.[118] Therefore, serum PCT concentrations could offer guidance in avoiding unnecessary antibiotic use in feline clinical practice.[118]

The investigation of inflammatory markers is flourishing in human medicine, and the new sepsis markers which are currently under investigation in human medicine will most likely be tested in veterinary species. Secretory phospholipase A2 type IIA (sPLA2-IIA) plasma concentrations were shown to be elevated in infants with late-onset bacterial sepsis (LOS) compared with those without LOS, with a sensitivity of 90.7 and specificity of 80.4.[119] Thus, sPLA2-IIA may have clinical utility for the early diagnosis of LOS in very preterm infants, potentially informing clinical management and antibiotic stewardship. Given that sPLA2-IIA is a well-conserved protein, it would be interesting to investigate this new marker in veterinary species.

A major driver in the discovery of new veterinary biomarkers is the application of recent advances in proteomics using liquid chromatography–tandem mass spectrometry (LC–MS/MS) and multiple reaction monitoring (MRM). There are numerous lower-abundance proteins likely to positively or negatively correlated with several disease states, such as stress, inflammation, and subclinical infection.[65] Proteomic techniques permit the identification of a large set of proteins in complex biological samples. Although limited due to incompletely characterized genome sequences and incomplete annotation of gene functions in domestic species,[65] over the last decade, proteomics have been incorporated in a variety of research studies in cats.[120–124] Proteomic analyses of different biological fluids in healthy and diseased cats have been recently performed, setting a new trend in proteomic research.[31,125–127] Nevertheless, there is still a paucity of studies investigating inflammatory markers through proteomics. To the author's knowledge, only one study investigated potential inflammatory markers in healthy cats and those with pancreatitis or pancreatic carcinoma.[127] In that study, three proteins identified by mass spectrometry appeared to differ among the groups: AGP, apolipoprotein-A1 (Apo-A1), and apolipoprotein-A1 precursor (Pre Apo-A1). Neither AGP nor Apo-A1 concentrations were different between groups. Pre-Apo-A1 concentrations appeared to be higher in cats with pancreatic disease, with a significant difference found between cats with pancreatic carcinoma and healthy controls.[127] Proteomics has the potential to be a means of discovery for new APPs, and further research is warranted.

7 | CONCLUSIONS

Increased concentrations of APPs in feline serum are a useful diagnostic tool to demonstrate ongoing systemic acute inflammation. Generally, APPs cannot discriminate between different pathologic processes. FIP is an exception. High AGP concentration in serum or effusion fluid can discriminate between FIP and other conditions with similar clinical presentation. One of the main advantages of the APPs is their 'real-time' secretion in response to cytokine-dependent pathways; as soon as the inflammatory process is in regression, APPs progressively return to baseline concentrations.

Rigorous analytical validation must be the first step in developing new assays and before applying existing assays in research or diagnostic settings. Standardization of calibration is strongly encouraged to avoid biases and significant variations in the selected thresholds observed between different assays that confound the interpretation of published clinical data.

More clinical studies using APPs as objective biomarkers are warranted to guide rational antimicrobial stewardship. Increased specificity could be achieved by combining measurements of multiple inflammatory biomarkers.

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There is active ongoing research to identify new APPs in cats. Moreover, the measurement of APPs will become more accessible for clinicians as an increasing number of POC assays are launched in the veterinary market.

DISCLOSURE

The authors have indicated that they have no affiliations or financial involvement with any organization or entity with a financial interest in, or in financial competition with, the subject matter or materials discussed in this article.

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