Received: 6 May 2022 | Revised: 10 August 2022 | Accepted: 6 September 2022

DOI: 10.1111/vcp.13195

Veterinary Clinical Pathology
An International Journal of Laboratory Medicine
WILEY

REVIEW ARTICLE

Use of serum amyloid A in equine medicine and surgery

Stine Jacobsen

Department of Veterinary Clinical Sciences, Section Medicine & Surgery, University of Copenhagen, Copenhagen, Denmark

Correspondence
Stine Jacobsen, Department of Veterinary Clinical Sciences, Section Medicine & Surgery, University of Copenhagen, Agrovej 8, DK-2630 Taastrup, Denmark.
Email: stj@sund.ku.dk

Abstract

Serum amyloid A (SAA) has become an indispensable part of the management of equine patients in general practice and specialized hospital settings. Although several proteins possess acute phase properties in horses, the usefulness of SAA exceeds that of other acute phase proteins. This is due to the highly desirable kinetics of the equine SAA response. SAA concentrations exhibit a rapid and pronounced increase in response to inflammation and a rapid decline after the resolution of inflammation. This facilitates the detection of inflammatory disease and real-time monitoring of inflammatory activity. SAA may be used in all stages of patient management: (1) before diagnosis (to rule in/rule out inflammatory disease), (2) at the time of diagnosis (to assess the severity of inflammation and assist in prognostication), and (3) after diagnosis (to monitor changes in inflammatory activity in response to therapy, with relapse of disease, or with infectious/inflammatory complications). By assessing other acute phase reactants in addition to SAA, clinicians can succinctly stage inflammation. White blood cell counts and serum iron concentration change within hours of an inflammatory insult, SAA within a day, and fibrinogen within 2–3 days; the interrelationship of these markers thus indicates the duration and activity of the inflammatory condition. Much research on the equine SAA response and clinical use has been conducted in the last decade. This is the prerequisite for the evidence-based use of this analyte. However, still today, most published studies involve a fairly low number of horses. To obtain solid evidence for use of SAA, future studies should be designed with larger sample sizes.

KEYWORDS
acute phase response, assay, equine, inflammation, SAA

1 | THE EQUINE ACUTE PHASE RESPONSE AND ACUTE PHASE PROTEINS

The acute phase response (APR) is the immediate systemic reaction to various types of tissue injury including inflammation, infection, and trauma. It is elicited by pro-inflammatory cytokines and other inflammatory molecules and results in disease-related physiological changes such as fever and hormonal and metabolic alterations as well as the hepatic and extra-hepatic synthesis of acute phase proteins (APPs).[1,2]

In the horse, several proteins are positive APPs, that is, proteins that are synthesized de novo in response to inflammation and

In agreement with the editors of Veterinary Clinical Pathology and the meeting organizers, this review is based on the author's contribution to the proceedings of premeeting workshop, "Understanding the crucial role of acute phase proteins in veterinary clinical pathology," of the 2021 ACVP/ASVCP Virtual Annual Meeting.

released into the circulation. Serum amyloid A (SAA) is a major APP in horses and its concentration can increase many-fold in response to inflammation (>10 times above the reference interval, but often 1000 times or more).[3] In contrast, fibrinogen is a moderate APP, and increases in fibrinogen concentration are more modest (most often 1–3 times above the reference interval).[4,5] Several APPs that are very useful in other species have been shown to be of limited value in horses. For example, haptoglobin[6–8] and C-reactive protein (CRP)[6,9] have high concentrations in healthy horses and minor or no increase in plasma concentrations in horses suffering from inflammatory or infectious conditions.[6–9]

Negative APPs are proteins, whose plasma concentration decreases during the APR.[10] Hepatic synthesis of albumin decreases during the APR, resulting in a modest decrease in plasma concentration.[11] Also paraoxonase-1 levels have been shown to decrease during the APR in several species including horses.[12–14] Combining positive and negative APPs in an index has been suggested to increase sensitivity,[15] but this has not been further explored in equine medicine.

Recent studies have suggested that other proteins have the potential to be useful APPs in the horse such as procalcitonin[16–18] and neutrophil gelatinase-associated lipocalin (NGAL).[19–21] NGAL seems to be a promising biomarker with a response pattern that is similar to that of SAA. Rapid and pronounced NGAL responses have been demonstrated in serum and synovial fluid of horses with experimentally induced and naturally occurring arthritis,[19] and in serum and peritoneal fluid of horses with acute inflammatory abdominal disease such as colitis and peritonitis.[21] Currently, there are very few studies evaluating this protein in horses, and more research is needed to support the use of NGAL in evidence-based equine medicine.

Response patterns of the APPs differ substantially, with some having a fast and others having a slower response to an inflammatory stimulus (Figure 1).[3] The SAA response is fairly rapid, with plasma concentrations increasing 8–12 hours after induction of experimental inflammation,[22,23] and peaking after 48–72 hours.[5,22,23] The amplitude of the SAA response is impressive; plasma concentrations can increase from within the reference interval (<0.5 mg/L, Table 1) to 5000 mg/L or more in horses with severe inflammation.[24] Due to its short half-life (30–120 minutes),[25,26] serum concentrations of SAA decrease rapidly as the inflammation resolves, as demonstrated in horses exposed to a single experimental inflammatory stimulus[22,23] or surgery.[5] This is in contrast to fibrinogen. Plasma fibrinogen concentrations take a bit longer to increase in response to inflammatory stimuli, and because of a long half-life in circulation, plasma concentrations remain increased for days or weeks after inflammation has subsided (Figure 1).[5,22] With its concentration closely paralleling changes in inflammatory activity, SAA is very useful for real-time monitoring of inflammation.[3] This is a highly desirable characteristic for clinicians using SAA measurements to support their clinical decision-making, as there is minimal lag-time between change in inflammatory activity (eg, in response to effective therapy) and change in serum SAA concentration.

A clinically useful approach is to measure some APPs and other inflammatory markers with fast and some with slower response patterns.[27] This ensures that peracute, acute, and subacute inflammation can be detected and monitored. It is important to keep in mind that, despite their name, APPs are produced not only in acute inflammation. APPs are synthesized and can be detected as long as there is active or ongoing inflammation, over days to weeks. At the Large Animal Teaching Hospital (LATH) at the University of Copenhagen, we routinely use a panel of inflammatory markers for assessing inflammation in horses that includes total leukocyte count (WBC), differential leukocyte counts, iron, SAA, and fibrinogen. This LATH panel combines very fast (WBC and serum iron that change in as little as 2 hours),[22] fast (SAA), and slower (fibrinogen) reacting markers of inflammation (Figure 1). Thus, very robust characterization of the horse's inflammatory status is achieved.

1.1 | Compartment-specific assessment of SAA

In addition to hepatic production of SAA resulting in the release of the protein into the systemic circulation where it can be measured in blood, plasma, or serum, SAA is also synthesized in extrahepatic tissues.[28–31] SAA release to local compartments has been shown to occur in healthy and in pathological conditions. In horses, SAA has been found in normal colostrum[31,32] and in inflamed saliva,[33] synovial fluid,[22,34,35] and peritoneal fluid.[36] Measuring SAA in these biological fluids may provide information on the compartment-specific inflammatory activity. In synovial fluid, SAA concentrations increase 12-16 hours after induction of experimental arthritis.[22,23,34] Accumulation of SAA protein in synovial fluid may be the result of extravasation from the blood, but local production in the joint also plays a role. Cytokine-stimulated equine chondrocytes and fibroblast-like synoviocytes have been shown to synthesize SAA in vitro,[30] and in synovial fluid from horses with experimental and naturally occurring arthritis a specific extrahepatic isoform of SAA (SAA3) has been identified.[34,35] Measuring this specific isoform could potentially enhance diagnostic accuracy, but this potential has not been explored in equine medicine.

It has been suggested that measurements of SAA in the synovial fluid could help diagnose synovial sepsis. Significantly higher SAA concentrations were found in synovial fluid from horses with septic synovitis than in synovial fluid from horses with aseptic arthritis or from healthy horses.[37,38] Declining concentrations of SAA in synovial fluid were shown to reflect eradication of intraarticular infection in experimental *Escherichia coli* arthritis[39] and in naturally occurring septic synovitis.[35] SAA has the advantage that concentrations are less affected by therapeutic interventions than are other routine synovial fluid measurands. Diagnostic and therapeutic procedures, such as arthrocentesis,[35] through-and-through lavage,[40] intra-articular injection of drugs (amikacin, hyaluronic acid, or platelet-rich plasma),[41–43] or arthroscopy,[44] have been shown to cause no changes in SAA concentrations in synovial fluid. In contrast, WBC, differential count, and total protein increased in response to these interventions, in many instances approaching levels found in patients with septic synovitis (total protein >30 g/L, WBC > 20×10^9/L, neutrophil % >80).[35,43,44] Based on this, synovial fluid, SAA may prove more

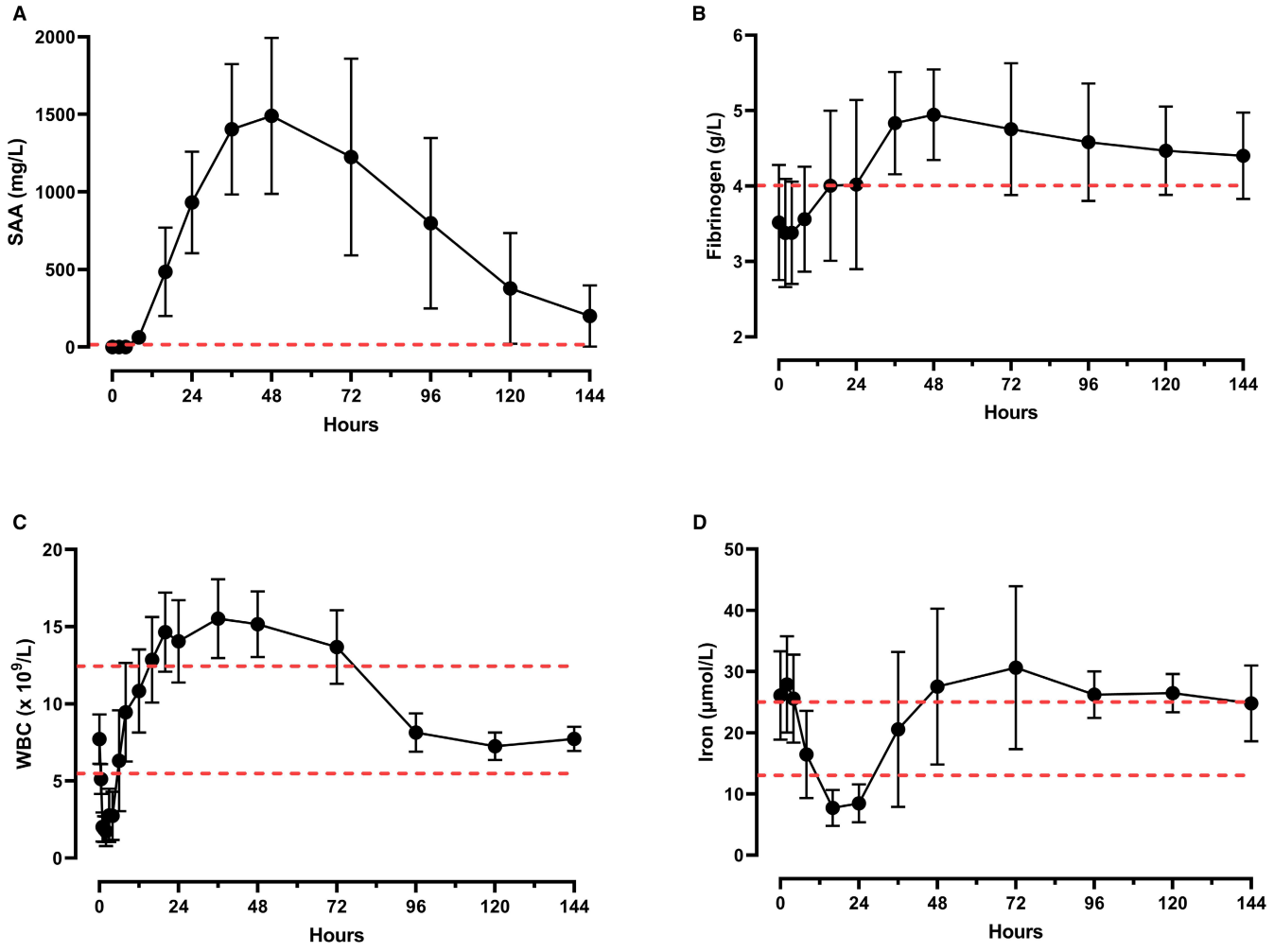

FIGURE 1 Response patterns for serum amyloid A (SAA, A), fibrinogen (B), total leukocyte count (WBC, C), and serum iron (D) after a single inflammatory stimulus. Data were derived from six adult horses subjected to intravenous injection of 1 µg/kg *Escherichia coli* lipopolysaccharide (LPS) (unpublished data). LPS was injected at time point 0. Interrupted lines delineated reference intervals.

useful for monitoring therapeutic efficacy than other commonly used inflammatory markers, as treatment-induced elevations in total protein, WBC, and/or neutrophil % may mask a response to treatment and lead to the erroneous conclusion that infection is ongoing.

Increased concentrations of SAA and other APPs (haptoglobin and fibrinogen) have been detected in peritoneal fluid after experimental exploratory laparotomy[45,46] and in horses with abdominal disease such as intestinal strangulations and inflammatory conditions (acute enteritis, typhlocolitis, or peritonitis).[36,47] Measuring APPs in peritoneal fluid could thus have diagnostic potential. In one study, however, assessment of SAA in peritoneal fluid did not improve the ability to discriminate medical and surgical conditions in horses with severe colic compared to the more straightforward measurement of SAA in serum.[7]

2 | METHODS FOR MEASURING SAA

An analyte, such as SAA, whose response pattern is characterized by very pronounced concentration changes from essentially unmeasurable in the healthy horse to several thousands of mg/L in response to inflammation, is very difficult to quantify reliably in the entire concentration range. We recently validated an automated latex bead-based immunoturbidometric assay (VET-SAA, Eiken Chemical Co., Japan) with a very broad working range,[24] which measured equine SAA with acceptable reliability in the concentration range of 0 to >6000 mg/L. The assay was set up to perform 1:14 reflex dilutions at an SAA concentration >200 mg/L and could thus measure SAA in the entire attainable concentration range. For samples with very high SAA concentrations, repeated dilutions were necessary. There was a statistically significant inaccuracy in the high concentration range. However, inaccuracy was slight, and – considering SAA's rapid and pronounced concentration changes – deemed to be clinically insignificant.[24] When using SAA measurements for monitoring purposes in horses with severe inflammation, it is important to choose an assay that can reliably detect concentration changes in the high concentration range.

Several horse-side point-of-care (POC) assays have been developed and have shown reasonable performance in validation

TABLE 1 Reference intervals of inflammatory markers used at The Large Animal Teaching Hospital, University of Copenhagen, Denmark (https://vetdiagnostik.ku.dk/english/)

Inflammatory marker/acute phase reactant	Reference interval	Methodology
White blood cell count ($\times 10^9$/L)	5.45–12.65	Automated counting (ADVIA 2120i Siemens Healthineers, Germany)
Differential leukocyte counts (%)	Neutrophils 28.0–82.8 Lymphocytes 19.8–58.9 Monocytes 1.4–10.5	Automated counting (ADVIA 2120i, Siemens Healthineers, Germany) and manual counting
Iron (μmol/L)	13.10–43.00	Colorimetric spectrophotometry (Atellica Solution, Siemens Healthineers, Germany)
Serum amyloid A (mg/L)	<0.5	VET-SAA, Eiken Chemical Co., Japan, (Atellica Solution, Siemens Healtineers, Germany)
Fibrinogen (g/L)	1–4	HemosIL RecombiPlastin (PT-based assay) (ACLTop 500, Instrumentation Laboratory, Massachusetts, United States)
Haptoglobin (mg/L)	728-4265	Phase Range Hp Assay; Tridelta Development Ltd., Ireland (Attelica Solution, Siemens Healthineers, Germany)

studies.[48–50] These assays are marketed for different SAA concentration ranges, for example, up to 3000 mg/L for the StableLab assay (https://www.stablelab.com/pages/serum-amyloid-a-blood-test)[49] and the VMRD assay system (https://vmrd.com/core/files/vmrd/uploads/files/SAA%20circular%20version%202.pdf);[50] up to 180 mg/L for the EquiCheck system (https://www.targetvet.com/equine-progesterone-igg-and-saa-testing/visual-equichek-saa-test-or-quantitative-saa-chek/); up to 500 mg/L for the Eurolyser (https://www.eurolyser.com/veterinary-diagnostics/poc-test-parameters/saa-test/); and up to 1000 mg/L for the LifeAssays test system (https://www.lifeassays.com/equine-serum-amyloid-a-saa-test/). StableLab (Zoetis) is available in Europe and the USA. This assay has been validated and compared with the most commonly used immunoturbidometric SAA assays (LZ-SAA and VET-SAA, both from Eiken Chemical Co.).[49,51] Kiemle et al (2022)[51] demonstrated a high degree of constant and proportional concentration bias between the StableLab assay and the immunoturbidometric SAA assays. The StableLab assay had high intra- and interassay coefficient-of-variation, poor recovery rate, and a hook effect. All these findings may severely limit the validity of results obtained with the assay, which users should be aware of. Based on the demonstration of the hook effect, the authors recommended that "it is advisable to perform repeat SAA measurements using the manufacturer's dilution protocol when clinical appearance of a horse and SAA results do not correlate and hence may represent falsely low concentrations secondary to a possible hook effect."[51]

POC assays are generally user-friendly, but considering the limited working range and inferior reliability, these assays are mainly useful for basic detection of inflammation in the field or after-hours, where fast results are needed and/or samples cannot be shipped to larger reference laboratories. It is important to keep in mind that there may be quite substantial concentration bias between methods, so measured concentrations cannot be compared across assay systems. Very high intra- and interassay coefficient-of-variations (8%–45%) demonstrated in the StableLab POC[49,51] means that repeated measurements need to be interpreted with caution, as changes in concentration may result from analytical as well as biological variation.

It has been suggested that SAA is a highly stable protein and that storage of equine serum samples at 4 or 22°C for up to 17 days did not change SAA concentration.[52] It is, however, important to note that the assay used in the study only measured SAA concentration up to 270 mg/L. At −80°C, SAA has been shown to be stable for 2.5 years.[51]

2.1 | Reference intervals

Many textbooks and reviews state reference intervals for equine APPs. But reference intervals can only be shared across laboratories using the exact same methodology.[53] Each laboratory must therefore establish its own reference intervals, preferably de novo, or by transference using a small number of samples according to established guidelines.[54]

For SAA, reference intervals reported in different studies differ slightly, but most have suggested that serum concentrations in healthy adult horses are <10–20 mg/L. The reference intervals for inflammatory markers used at the LATH are shown in Table 1.

Reference intervals in neonatal foals have been described.[55–57] A recent study found that the mean serum SAA in 151 healthy neonatal foals (<19 hours old) was 27.7 mg/L.[57] In contrast, two small studies have suggested that healthy foals have slightly higher serum concentrations of SAA than adult horses, with a peak concentration of up to 120 mg/L at 24–72 hours after birth.[55,56] These slightly higher concentrations could be associated with passive transfer of SAA, as SAA has been found in colostrum,[31,32] or from endogenous production as a consequence of the foal sustaining mild trauma while passing through the birth canal. It is not clear whether placentitis in the

mare will give rise to increases in serum SAA concentration in the foal, as both normal[58,59] and slightly elevated concentrations[60] have been demonstrated in nonseptic foals and fetuses from mares with placentitis. It is not clear at which age SAA concentrations level out, but presumably within a few weeks after birth.

3 | USE OF SAA IN EQUINE MEDICINE AND SURGERY

SAA and other APPs can be valuable at all stages of patient management[3]:

- Before a diagnosis has been made: SAA can be used to assess inflammation and prioritize differential diagnoses with and without inflammation or to detect subclinical inflammatory disease.
- Once a diagnosis has been established: SAA might serve as a prognostic indicator.
- Monitoring disease progression and response to therapy: SAA is highly suited for monitoring changes in inflammation in the intervention phase of patient management; repeated measurements are useful for assessment of response to therapy, detection of relapse, or occurrence of infectious or inflammatory complications. SAA can also be used to support the decision to stop antimicrobial therapy.

Table 2 provides an overview of circumstances, where SAA may be useful. Several reviews on the equine acute phase response, and more specifically, SAA in a variety of clinical conditions is available.[3,61–63] Veterinary clinicians need to have a thorough understanding of the SAA response to interpret measurement results. One important aspect to keep in mind is the effect of the duration of the disease on SAA. The time dependence is related to the large amplitude of the SAA response, where concentrations can increase manyfold within hours.[3] This was demonstrated in horses with the abdominal disease, where SAA and haptoglobin concentrations in serum and peritoneal fluid were markedly influenced by the duration of the disease prior to sample collection.[47]

3.1 | Patient assessment and diagnosis

Hepatic synthesis of SAA only occurs during inflammation; noninflammatory disease does not result in increased blood concentrations of SAA, as demonstrated in foals[64–66] and adult horses.[24] SAA is thus a specific marker of inflammation and infection. This is in contrast to other commonly used inflammatory markers, where levels can change in response to a variety of noninflammatory stimuli. Leukocytosis can occur after vigorous exercise, in frightening or painful conditions, during stress, or after corticosteroid treatment;[67] iron deficiency caused by blood loss, parasitism, and other noninflammatory conditions can result in hypoferremia;[68] and fibrinogen concentrations can change as a result of coagulation and coagulopathies.[69]

TABLE 2 Clinical circumstances where Serum amyloid A can improve patient management

	Horses with disease			
	Diagnosing		Monitoring	
Healthy horses	Individual horses	Herd/group level	Individual horses	Herd/group level
To determine fitness/health before surgery, race or contest (through detection of subclinical disease)	To prioritize differential diagnoses into those with and those without inflammation	To screen for/achieve early detection of infectious disease, eg, *Rhodococcus equi* pneumonia in endemically infected farms	To adjust treatment, eg, change or stop antimicrobials	To monitor the spread of disease through groups of horses with the purpose of sectioning herds to prevent the spread of disease
To adjust training intensity	To tailor individual treatment, eg, the decision to use antimicrobials or not		To detect relapse	
Certify welfare of training, competitions (eg, endurance competitions), transportation, or other potentially harmful/stressful management situations			To detect secondary infection and surgical site infection	
			To assist decision-making re. return to work after the convalescence period, eg, after airway infections	

Interpretation of SAA is therefore more straightforward than other inflammatory markers.

For certain patient groups, it may be necessary to rule in or rule out inflammation to properly prioritize differential diagnoses. In horses with severe acute abdominal pain (colic), it is crucial to quickly categorize the underlying condition as either surgical or medical in nature. Horses with inflammatory abdominal conditions, where medical treatment is most appropriate (duodenitis, proximal jejunitis, acute typhlocolitis, or peritonitis), may be clinically indistinguishable from horses with conditions that require surgical intervention (strangulations, displacements, or severe impactions). Both groups often present with similar severe clinical findings of shock, pain, positive gastric reflux, and/or abnormal peritoneal fluid parameters. One study showed that assessment of serum SAA concentration resulted in significantly more horses (90%) correctly classified as inflammatory colic requiring medical therapy or surgical colic, compared with a prediction model not including SAA, where 86% were correctly classified.[7]

Assessment of SAA is useful for neonatal patient management. Diagnosing infections in neonatal foals can be a challenge because the clinical signs are nonspecific, and diseases with a noninfectious cause, such as prematurity, failure of passive transfer, neonatal maladjustment syndrome, and isoerythrolysis, can manifest similar to infectious diseases such as sepsis. SAA may thus help differentiate infectious from noninfectious disease[56,65,66,70] and aid the clinician in obtaining a correct diagnosis and making a more informed decision on whether to start antimicrobial therapy while waiting for bacteriology results.

In apparently clinically healthy horses, assessment of inflammatory markers may be of value to detect subclinical inflammation and may be a helpful predictor of surgical risk in horses undergoing elective surgery. In horses undergoing castration, postoperative infectious complications occurred more frequently in horses with preoperatively increased serum SAA than in horses with normal SAA concentrations.[71] Subclinical airway infections potentially increase anesthetic risk as has been shown in some human medical studies.[72,73] At the LATH, in addition to clinical examination, every horse undergoing elective surgical procedures has a panel of inflammatory markers assessed preoperatively. If any of these are abnormal, the owner is advised to postpone surgery to mitigate the increased anesthetic and surgical risk in patients with preexisting inflammation or infection.

Measurement of SAA or other APPs in apparently healthy horses could also be relevant to other purposes, for example, to ensure fitness or document animal welfare in potentially stressful situations (Table 2). During transportation, APPs have been shown to reflect stress.[74] One study used SAA to screen for air travel-associated infections; sensitivity and specificity of SAA measured 24 hours postarrival (cutoff value = 23 mg/L) was 93.3 and 91.3%, respectively.[75] This was in contrast to fever, which had a sensitivity of only 3% and specificity of 100%.[56] The authors concluded that SAA was very sensitive and could be used to detect infection before clinical signs occurred.[75]

There is fairly substantial literature describing changes in APPs in response to training and exercise in healthy horses. Fibrinogen, haptoglobin, and SAA concentrations increase slightly during training programs of several months' duration.[76,77] It has been suggested that SAA could indicate training exceeding the horse's fitness level. Inexperienced endurance horses had increased serum SAA concentrations after a training session, while experienced ones did not.[78] Blood concentrations of SAA and other APPs increased after strenuous exercises such as endurance rides, races, and eventing.[6,78–82] It is not clear whether the APR represents adaptational changes or indicates that the exercise exceeded the horse's fitness. Musculoskeletal trauma has been shown to cause increased serum SAA concentrations,[83,84] so subclinical muscle injury could be part of the explanation. Assessing SAA before the competition was not useful for predicting elimination during competition in endurance horses,[85] and blood concentrations APPs do not seem to be consistently elevated in horses exhibiting poor performance.[86,87] In overweight ponies and horses, low-intensity exercise reduced blood concentrations of SAA and haptoglobin, suggesting that health benefits and positive effects of training on obesity-related inflammation can be monitored by APPs.[88,89]

Similar to other inflammatory markers, SAA will be produced in response to inflammation independent of etiology, so SAA cannot be used to make etiological diagnoses. Aseptic tissue injury and inflammation (accidental or iatrogenic, eg, vaccination or surgery) as well as infectious diseases will elicit an SAA response,[24,71,83,90–94] It has been suggested that viral disease is accompanied by lower serum SAA concentrations than the bacterial disease.[94] However, overlap between groups is substantial, and while SAA may give an indication of etiology, it cannot categorically distinguish viral infections from bacterial ones.

Although SAA has been repeatedly shown to reliably indicate the presence of systemic inflammation in horses,[35,91,92,95–98] it has been suggested that local inflammation gives rise to lower plasma SAA concentrations.[24,98] Certain specific conditions such as gastric ulcer syndrome,[99] intestinal cyathostominosis,[100] inflammatory airway disease,[101] and ulcerative keratitis and anterior uveitis[102] do not seem to reliably elicit an SAA response. This is not surprising nor considered a specific drawback of SAA in comparison with other inflammatory markers, as patients suffering from these conditions have insufficient systemic inflammation to consistently cause alterations in blood levels of any of the inflammatory markers routinely assessed.[100–102] In several older studies, SAA concentrations were found to be normal or low in horses with abscesses (i.e., walled-off inflammation).[65,103] Two recent case reports have questioned this generalization, as increased serum SAA concentrations were detected in a horse with an abdominal abscess[104] and a horse with a pararectal abscess.[105] In foals with *Rhodococcus equi* pneumonia, SAA has been suggested to be of limited diagnostic value. Measurement of serum SAA weekly or every 2 weeks was not useful for screening foals at farms endemically affected by *Rhodococcus equi* infection as a means to achieve early recognition.[103,106,107] In foals with clinical signs of *Rhodococcus equi*

pneumonia (fever, nasal discharge), serum SAA levels were found to be significantly elevated and to decline in response to successful treatment,[70,106,108] with the decline preceding normalization of ultrasonographically determined lung abscess scores[108] or plasma fibrinogen concentrations.[70] Lankenfeld et al (2021)[108] cautioned against relying solely on SAA for the detection of *Rhodococcus pneumonia*, as approx. 50% of foals with pulmonary abscesses and normal temperatures had normal serum SAA. Fibrinogen was suggested to be superior to SAA for screening purposes in farms with endemic *Rhodococcus equi* in a study with 10 foals,[107] while a larger study involving 54 foals found similar predictive capacity of the two APPs.[106] In horses with *Streptococcus equi* infection, El-Deep et al (2017)[109] found only modestly, although statistically significant, increased serum SAA concentrations compared with healthy controls. However, case descriptions were inadequate to determine whether this was related to sampling occurring in the very early stages of the infection or whether it was due to infection being walled off in abscesses. In the LATH caseload, horses with strangles generally show markedly elevated SAA concentrations (>2000 mg/L, author's unpublished observations). Taken together, the current literature suggests that serum SAA concentrations must be interpreted with some caution in abscessing infections.

3.2 | Predicting outcome

Based on the assumption that more severe or sustained inflammatory disease carries a worse prognosis, SAA may, by its excellent ability to reflect the intensity of the inflammatory response, serve as a prognostic indicator. However, results of studies attempting to link early assessment of SAA to outcome are generally discouraging, as most equine studies have failed to demonstrate a reliable prognostic value of measuring SAA.[93,97,110,111]

To evaluate the ability of SAA and haptoglobin to predict survival, Westerman et al (2015)[97] measured plasma SAA and haptoglobin concentrations at the time of admission in 53 horses (36 survivors and 17 nonsurvivors) with a variety of inflammatory conditions (peritonitis, colitis, trauma, renal insufficiency and cystitis, pneumonia, cellulitis, fever of unknown origin, and miscellaneous). The authors found that a single-point measurement of the two APPs was not significantly associated with survival outcomes and suggested that serial analysis during treatment might be a better prognostic tool.[97] This notion was corroborated by a study using repeated perioperative assessment of SAA and fibrinogen in horses undergoing exploratory laparotomy to predict postoperative complications and survival to discharge.[110] Preoperative concentrations did not differ between groups, but SAA concentrations day 1–5 after surgery differed significantly between horses that did and did not survive to discharge. In contrast to these findings, daily measurements of SAA in horses being treated for synovial sepsis were unable to predict outcome (survival/nonsurvival).[93]

Using admission concentrations of SAA for predicting outcome in horses admitted with colic has been investigated in three studies.[8,111,112] A retrospective study investigated SAA concentration at admission in 718 horses with acute abdominal pain admitted to two centers.[112] In survivors, serum SAA concentration was significantly lower (median 1.4 mg/L) than in horses that died or were euthanized (median 10.8 mg/L); when a cutoff value of 50 mg/L was applied, a significantly larger proportion of nonsurvivors than survivors had serum SAA concentrations greater than the cutoff.[112] A study evaluating 42 horses admitted with colic found that horses with SAA>5 mg/L at admission were more likely to develop thrombophlebitis or be euthanized due to a poor prognosis (odds ratio 7.6, 95% confidence interval 1.1–52.4) than horses with normal SAA.[8] In contrast, Dondi et al (2015)[111] found no difference in admission SAA concentrations between colic survivors and nonsurvivors. Although the former two studies seem encouraging, concentration differences in survivors and nonsurvivors were too small to be useful in practice.

Apart from disease severity, other factors may influence SAA concentrations, including the timing of sampling (a horse with the peracute disease may be admitted before SAA concentrations have increased), mass and type of tissue affected, and disease etiology. At The LATH, patients with peritonitis, colitis, acute cellulitis-lymphangitis, and septic arthritis have the highest serum SAA concentrations, with concentrations of 6000–8000 mg/L SAA observed often, and up to 12,000–15,000 mg/L occasionally encountered (author's unpublished observations). These factors may explain why many studies fail to demonstrate a strong association between admission SAA concentration and outcome, but more research is needed to fully understand factors determining SAA concentrations.

3.3 | Monitoring response to therapy

SAA is very useful for patient monitoring. In patients being treated for infectious conditions, declining SAA concentrations in samples taken every 2–4 days help clinicians ascertain that infection is being eradicated and inflammation is resolving. This is particularly useful in cases awaiting culture results, where the choice of antibiotics is initially based on preliminary clinical evidence and the clinician's experience. Declining SAA concentration has been demonstrated to parallel successful treatment of synovial sepsis[93,113] and pneumonia in foals.[108]

In horses undergoing exploratory laparotomy, SAA initially increases in response to the surgical trauma and then, in the absence of surgical site or other infections, declines toward normal within 4–6[96,114] and 11 days,[5] depending on the extent of the surgical trauma. Fibrinogen also increases in response to laparotomy, but due to the long half-life of the protein, plasma concentrations stay elevated for longer periods, making fibrinogen of limited value for real-time monitoring of postsurgical inflammation.[5,96,114] When APPs are used to monitor for infectious complications, the expected APP response for the primary disease must be characterized before deviations, such as sustained increases or unexpectedly high APP concentrations, can be identified.[3] In horses that developed complications after exploratory laparotomy (eg, diarrhea, ileus, thrombophlebitis, fever),

postoperative SAA,[96,114] and fibrinogen[114] concentrations were significantly higher than those found in horses without complications. In horses undergoing castration, sustained high SAA[115] or haptoglobin and fibrinogen concentrations[116] were identified in horses classified clinically as having excessive inflammation. Unexpectedly high concentrations of SAA and other APPs postoperatively should thus prompt a thorough examination of the patient to identify the site of infection.

The effect of concurrent inflammatory conditions may be additive and result in higher than expected SAA concentrations. This can be exploited to identify bacterial superinfection in horses with viral infections. For example, with experimental influenza infection, horses that developed clinical signs of secondary bacterial infection had persistently high plasma SAA concentrations.[117]

There are no investigations into biomarker-guided antimicrobial stewardship in horses. In people, APPs are used both to guide initiation or initial withholding of antibiotic treatment and to determine when it is safe to discontinue treatment. Procalcitonin and CRP are used either as single decision criteria or in algorithms, and randomized controlled trials and meta-analyses have shown that this is a safe approach, leading to no increase in morbidity, mortality, or relapse rate; in many cases, this resulted in reduced use of antimicrobials.[118–120] In a small group of dogs with bacterial pneumonia, it appeared safe to use CRP to guide the duration of antibiotic treatment; this resulted in a significantly shorter treatment duration without an increased number of relapses compared to conventional subjective decision-making.[121] Similar use of SAA in equine medicine should be investigated, as SAA is likely to perform as well as the species-specific major APPs assessed in humans (procalcitonin, CRP) and dogs (CRP).

4 | CONCLUDING REMARKS

It is now more than 35 years ago since Husebekk et al (1986)[122] first isolated SAA from serum from a horse that had suffered a septic abortion. For the last decade, more than 30 papers on equine SAA have been published annually. The use of SAA undoubtedly increases the quality of patient assessment in equine medicine and surgery. However, there is a continued need for research into the usefulness of SAA in equine clinical medicine to provide increasingly robust evidence for how and when SAA should be used, particularly in larger and prospective studies. It is unfortunate that even quite recent studies have very small sample sizes of 5–15 horses per group and/or address a clinical problem or have a study design, where SAA measurements seemed to be of limited relevance (eg, through improper timing of blood sampling, attempts to correlate SAA to pathological events occurring staggered in time relative to the SAA response, or use of SAA in clinical situations, where there is a little pathophysiological rationale for assuming that SAA will provide diagnostic or other information).[108,113,123,124] This can make the studies prone to type II errors or erroneous conclusions regarding the potential usefulness of assessing SAA.

DISCLOSURE

The author received funding from Eiken Chemical Company, Japan in 2018 to perform analytical and clinical validation of the VETSAA assay. Otherwise, the author has indicated that she has 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.

ORCID

Stine Jacobsen https://orcid.org/0000-0002-2380-4576

REFERENCES

1. Sack GH Jr. Serum amyloid A - a review. *Mol Med*. 2018;24:46.
2. Zhang Y, Zhang J, Sheng H, Li H, Wang R. Acute phase reactant serum amyloid A in inflammation and other diseases. *Adv Clin Chem*. 2019;90:25-80.
3. Kjelgaard-Hansen M, Jacobsen S. Assay validation and diagnostic applications of major acute-phase protein testing in companion animals. *Clin Lab Med*. 2011;31:51-70.
4. Borges AS, Divers TJ, Stokol T, Mohammed OH. Serum iron and plasma fibrinogen concentrations as indicators of systemic inflammatory diseases in horses. *J Vet Intern Med*. 2007;21:489-494.
5. Jacobsen S, Nielsen JV, Kjelgaard-Hansen M, et al. Acute phase response to surgery of varying intensity in horses: a preliminary study. *Vet Surg*. 2009;38:762-769.
6. Cywinska A, Szarska E, Gorecka R, et al. Acute phase protein concentrations after limited distance and long distance endurance rides in horses. *Res Vet Sci*. 2012;93:1402-1406.
7. Pihl TH, Scheepers E, Sanz M, et al. Acute-phase proteins as diagnostic markers in horses with colic. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:664-674.
8. Westerman TL, Foster CM, Tornquist SJ, Poulsen KP. Evaluation of serum amyloid A and haptoglobin concentrations as prognostic indicators for horses with colic. *J Am Vet Med Assoc*. 2016;248:935-940.
9. Zabrecky KA, Slovis NM, Constable PD, Taylor SD. Plasma C-reactive protein and haptoglobin concentrations in critically ill neonatal foals. *J Vet Intern Med*. 2015;29:673-677.
10. Aldred AR, Schreiber G. The negative acute phase proteins. In: Mackiewicz A, Kushner I, Baumann H, eds. *Acute Phase Proteins. Molecular Biology, Biochemistry, and Clinical Applications*. 1st ed. CRC Press; 1993:21-37.
11. Allen BV, Kold SE. Fibrinogen response to surgical tissue trauma in the horse. *Equine Vet J*. 1988;20:441-443.
12. Ruggerone B, Paltrinieri S, Giordano A, et al. Paraoxonase-1 activity evaluation as a diagnostic and prognostic marker in horses and foals. *J Vet Intern Med*. 2020;34:949-954.
13. Ruggerone B, Scavone D, Troia R, Giunti M, Dondi F, Paltrinieri S. Comparison of protein carbonyl (PCO), paraoxonase-1 (PON1) and C-reactive protein (CRP) as diagnostic and prognostic markers of septic inflammation in dogs. *Vet Sci*. 2021;8:93.
14. Scavone D, Sgorbini M, Borges AS, Oliveira-Filho JP, Vitale V, Paltrinieri S. Serial measurements of paraoxonase-1 (PON-1) activity in horses with experimentally induced endotoxemia. *BMC Vet Res*. 2020;16:422.
15. Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ, van Dijk E, Meloen RH. Monitoring health by values of acute phase proteins. *Acta Histochem*. 2006;108:229-232.
16. Bonelli F, Meucci V, Divers T, et al. Evaluation of plasma procalcitonin concentrations in healthy foals and foals affected by septic systemic inflammatory response syndrome. *J Equine Vet Sci*. 2015;35:645-649.
17. Bonelli F, Meucci V, Divers TJ, et al. Plasma procalcitonin concentration in healthy horses and horses affected by systemic inflammatory response syndrome. *J Vet Intern Med*. 2015;29:1689-1691.

18. Kilcoyne I, Nieto JE, Dechant JE. Diagnostic value of plasma and peritoneal fluid procalcitonin concentrations in horses with strangulating intestinal lesions. *J Am Vet Med Assoc*. 2020;256:927-933.
19. Frydendal C, Nielsen KB, Berg LC, et al. Influence of clinical and experimental intra-articular inflammation on neutrophil gelatinase-associated lipocalin concentrations in horses. *Vet Surg*. 2021;50:641-649.
20. Jacobsen S, Berg LC, Tvermose E, Laurberg MB, van Galen G. Validation of an ELISA for detection of neutrophil gelatinase-associated lipocalin (NGAL) in equine serum. *Vet Clin Pathol*. 2018;47:603-607.
21. Winther MF, Haugaard SL, Pihl TH, Jacobsen S. Concentrations of neutrophil gelatinase-associated lipocalin are increased in serum and peritoneal fluid from horses with inflammatory abdominal disease and non-strangulating intestinal infarctions. *Equine Vet J* 2022. Online ahead of print. doi:10.1111/evj.13603
22. Andreassen SM, Vinther AML, Nielsen SS, et al. Changes in concentrations of haemostatic and inflammatory biomarkers in synovial fluid after intra-articular injection of lipopolysaccharide in horses. *BMC Vet Res*. 2017;13:182.
23. Lindegaard C, Gleerup KB, Thomsen MH, Martinussen T, Jacobsen S, Andersen PH. Anti-inflammatory effects of intra-articular administration of morphine in horses with experimentally induced synovitis. *Am J Vet Res*. 2010;71:69-75.
24. Jacobsen S, Vinther AM, Kjelgaard-Hansen M, Nielsen LN. Validation of an equine serum amyloid A assay with an unusually broad working range. *BMC Vet Res*. 2019;15:462.
25. Uhlar CM, Whitehead AS. Serum amyloid A, the major vertebrate acute-phase reactant. *Eur J Biochem*. 1999;265:501-523.
26. Hoffman JS, Benditt EP. Plasma clearance kinetics of the amyloid-related high density lipoprotein apoprotein, serum amyloid proten (apoSAA), in the mouse. Evidence for rapid apoSAA clearance. *J Clin Invest*. 1983;71:926-934.
27. Cerón JJ, Ohno K, Caldin M. A seven-point plan for acute-pahse protein interpretation in companion animals. *Vet J*. 2008;177:6-7.
28. Berg LC, Thomsen PD, Andersen PH, Jensen HE, Jacobsen S. Serum amyloid A is expressed in histologically normal tissues from horses and cattle. *Vet Immunol Immunopathol*. 2011;144:155-159.
29. Christoffersen M, Woodward E, Bojesen AM, et al. Inflammatory responses to induced infectious endometritis in mares resistant or susceptible to persistent endometritis. *BMC Vet Res*. 2012;8:41.
30. Jacobsen S, Ladefoged S, Berg LC. Production of serum amyloid A in equine articular chondrocytes and fibroblast-like synoviocytes treated with proinflammatory cytokines and its effects on the two cell types in culture. *Am J Vet Res*. 2016;77:50-58.
31. McDonald TL, Larson MA, Mack DR, Weber A. Elevated extrahepatic expression and secretion of mammary-associated serum amyloid A 3 (M-SAA3) into colostrum. *Vet Immunol Immunopathol*. 2001;83:203-211.
32. Duggan VE, Holyoak GR, MacAllister CG, Cooper SR, Confer AW. Amyloid a in equine colostrum and early milk. *Vet Immunol Immunopathol*. 2008;121:150-155.
33. Jacobsen S, Adler DMT, Bundgaard L, Sørensen MA, Andersen PH, Bendixen E. The use of liquid chromatography tandem mass spectrometry to detect proteins in saliva from horses with and without systemic inflammation. *Vet J*. 2014;202:483-488.
34. Jacobsen S, Niewold TA, Halling-Thomsen M, et al. Serum amyloid A isoforms in serum and synovial fluid in horses with lipopolysaccharide-induced arthritis. *Vet Immunol Immunopathol*. 2006;110:325-330.
35. Jacobsen S, Thomsen MH, Nanni S. Concentrations of serum amyloid A in serum and synovial fluid from healthy horses and horses with joint disease. *Am J Vet Res*. 2006;67:1738-1742.
36. Pihl TH, Andersen PH, Kjelgaard-Hansen M, Morck NB, Jacobsen S. Serum amyloid A and haptoglobin concentrations in serum and peritoneal fluid of healthy horses and horses with acute abdominal pain. *Vet Clin Pathol*. 2013;42:177-183.
37. Stack JD, Cousty M, Steele E, et al. Comparison of serum amyloid A measurements in equine synovial fluid with routine diagnostic methods to detect synovial infection in a clinical environment. *Front Vet Sci*. 2019;6:325.
38. Robinson CS, Singer ER, Piviani M, Rubio-Martinez LM. Are Serum amyloid A or D-lactate useful to diagnose synovial contamination or sepsis in horses? *Vet Rec*. 2017;181:425.
39. Yoshimura S, Koziy RV, Dickinson R, et al. Use of serum amyloid A in serum and synovial fluid to detect eradication of infection in experimental septic arthritis in horses. *Can J Vet Res*. 2020;84:198-204.
40. Sanchez-Teran AF, Bracamonte JL, Hendrick S, et al. Effect of repeated through-and-through joint lavage on serum amyloid A in synovial fluid from healthy horses. *Vet J*. 2016;210:30-33.
41. Sanchez Teran AF, Rubio-Martinez LM, Villarino NF, Sanz MG. Effects of repeated intra-articular administration of amikacin on serum amyloid A, total protein and nucleated cell count in synovial fluid from healthy horses. *Equine Vet J*. 2012;Suppl 43:12-16.
42. Johnston GCA, Wood KA, Jackson KV, Perkins NR, Zedler ST. Evaluation of the inflammatory response to two intra-articular hyaluronic acid formulations in normal equine joints. *J Vet Pharmacol Ther*. 2020;43:38-49.
43. Smit Y, Marais HJ, Thompson PN, Mahne AT, Goddard A. Clinical findings, synovial fluid cytology and growth factor concentrations after intra-articular use of a platelet-rich product in horses with osteoarthritis. *J S Afr Vet Assoc*. 2019;90:a1721.
44. Sanchez-Teran AF, Bracamonte JL, Hendrick S, et al. Effect of arthroscopic lavage on systemic and synovial fluid aerum amyloid A in healthy horses. *Vet Surg*. 2016;45:223-230.
45. Bowlby C, Mudge M, Schroeder E, Godman J, Hurcombe S. Equine inflammatory response to abdominal surgery in the absence of gastrointestinal disease. *J Vet Emerg Crit Car*. 2021;31:601-607.
46. Alonso JD, Schmidt EMS, Eckersall PD, et al. Inflammatory response of healthy horses subjected to small colon enterotomy and treated or not with heparin. *J Equine Vet Sci*. 2020;90:102989.
47. Pihl TH, Scheepers E, Sanz M, et al. Influence of disease process and duration on acute phase proteins in serum and peritoneal fluid of horses with colic. *J Vet Intern Med*. 2015;29:651-658.
48. Jacobsen S, Kjelgaard-Hansen M. Evaluation of a commercially available apparatus for measuring the acute phase protein serum amyloid A in horses. *Vet Rec*. 2008;163:327-330.
49. Schwartz D, Pusterla N, Jacobsen S, Christopher MM. Analytical validation of a new point-of-care assay for serum amyloid A in horses. *Equine Vet J*. 2018;50:678-683.
50. Karam B, Hines S, Skipper L, Pusterla N. Whole-blood validation of a new point-of-care equine serum amyloid A assay. *J Equine Vet Sci*. 2020;94:103222.
51. Kiemle J, Hindenberg S, Bauer N, Roecken M. Comparison of a point-of-care serum amyloid A analyzer frequently used in equine practice with 2 turbidimetric immunoassays used in human and veterinary medicine. *J Vet Diagn Invest*. 2022;34:42-53.
52. Hillstrom A, Tvedten H, Lilliehook I. Evaluation of an in-clinic serum amyloid A (SAA) assay and assessment of the effects of storage on SAA samples. *Acta Vet Scand*. 2010;52:8.
53. Friedrichs KR, Jensen AL, Kjelgaard-Hansen M. Reference intervals and decision limits. In: Brooks MB, Harr KE, Seelig DM, Wardrop KJ, Weiss DJ, eds. *Schalm's Veterinary Hematology*. 7th ed. Wiley Blackwell; 2022:1273-1282.
54. Friedrichs KR, Harr KE, Freeman KP, et al. ASVCP reference interval guidelines: determination of de novo reference intervals in veterinary species and other related topics. *Vet Clin Pathol*. 2012;41:441-453.
55. Duggan VE, Holyoak GR, MacAllister CG, Confer AW. Influence of induction of parturition on the neonatal acute phase response in foals. *Theriogenol*. 2007;67:372-381.

56. Paltrinieri S, Giordano A, Villani M, Manfrin M, Panzani S, Veronesi MC. Influence of age and foaling on plasma protein electrophoresis and serum amyloid A and their possible role as markers of equine neonatal septicaemia. *Vet J*. 2008;176:393-396.
57. Nieman NM, Chan DS. Comparison of the diagnostic predictability of Serum amyloid A, white blood cell count and immunoglobulin G tests as indicators of early-onset, acute-phase morbidities in newborn foals. *Equine Vet Edu*. 2021;early view. doi:10.1111/eve.13557
58. Borba LD, Nogueira CEW, Bruhn FRP, et al. Peripheral blood markers of sepsis in foals born from mares with experimentally induced ascending placentitis. *Vet Rec*. 2020;187:29.
59. Boakari YL, Esteller-Vico A, Loux S, et al. Serum amyloid A, Serum amyloid A1 and haptoglobin in pregnant mares and their fetuses after experimental induction of placentitis. *Anim Reprod Sci*. 2021;229:106766.
60. Erol E, Jackson C, Horohov D, Locke S, Smith J, Carter C. Elevated serum amyloid A levels in cases of aborted equine fetuses due to fetal and placental infections. *Theriogenol*. 2016;86:971-975.
61. Jacobsen S, Andersen PH. The acute phase protein serum amyloid A (SAA) as a marker of inflammation in horses. *Equine Vet Edu*. 2007;19:38-46.
62. Witkowska-Pilaszewicz OD, Zmigrodzka M, Winnicka A, Miskiewicz A, Strzelec K, Cywinska A. Serum amyloid A in equine health and disease. *Equine Vet J*. 2019;51:293-298.
63. Long A, Nolen-Walston R. Equine inflammatory markers in the twenty-first century: a focus on serum amyloid A. *Vet Clin Equine*. 2020;36:147-160.
64. Gardner RB, Nydam DV, Luna JA, Bicalho MLS, Matychak MB, Flaminio MJBF. Serum opsonization capacity, phagocytosis, and oxidative burst activity in neonatal foals in the intensive care unit. *J Vet Intern Med*. 2007;21:797-805.
65. Stoneham SJ, Palmer L, Cash R, Rossdale PD. Measurement of serum amyloid A in the neonatal foal using a latex agglutination immunoturbidometric assay: determination of the normal range, variation with age and response to disease. *Equine Vet J*. 2001;33:599-603.
66. Chavatte PM, Pepys MB, Roberts B, et al. Measurement of serum amyloid A protein (SAA) as an aid to differential diagnosis of infection in newborn foals. In: Plowright W, Rossdale PD, Wade JF, eds. *Proceedings of the 6th International Conference on Infectious Diseases, Newmarket, UK, 7-11 July*. R & W Publications; 1991:33-38.
67. Welles EG. Interpretation of equine leukocyte responses. In: Weiss DJ, Wardrop KJ, eds. *Schalm's Veterinary Hematology*. 6th ed. Wiley-Blackwell; 2010:314-320.
68. Harvey JW. Iron metabolism and its disorders. In: Kaneko JJ, Harvey JW, Bruss ML, eds. *Clinical Biochemistry of Domestic Animals*. 6th ed. Elsevier; 2008:259-285.
69. Gentry P, Burges H, Wood D. Hemostasis. In: Kaneko JJ, Harvey JW, Bruss ML, eds. *Clinical Biochemistry of Domestic Animals*. 6th ed. Elsevier; 2008:287-330.
70. Hultén C, Demmers S. Serum amyloid A (SAA) as an aid in the management of infectious disease in the foal: comparison with total leukocyte count, neutrofil count and fibrinogen. *Equine Vet J*. 2002;34:693-698.
71. Busk P, Jacobsen S, Martinussen T. Administration of perioperative penicillin reduces postoperative Serum amyloid A response in horses being castrated standing. *Vet Surg*. 2010;39:638-643.
72. Kara D, Gürsoy F. Infectious diseases and anesthesia in children. *Trends Pediatr*. 2021;2:109-113.
73. Lee HJ, Woo JH, Cho S, Oh HW, Joo H, Baik HJ. Risk factors for perioperative respiratory adverse events in children with recent upper respiratory tract infection: a single-center-based retrospective study. *Ther Clin Risk Manag*. 2020;16:1227-1234.
74. Casella S, Fazio F, Giannetto C, Giudice E, Piccione G. Influence of transportation on serum concentrations of acute phase proteins in horse. *Res Vet Sci*. 2012;93:914-917.
75. Oertly M, Gerber V, Anhold H, Chan DS, Pusterla N. The accuracy of serum amyloid A in determining early inflammation in horses after long-distance transportation by air. *J Equine Vet Sci*. 2021;97:103337.
76. Mack SJ, Kirkby K, Malalana F, McGowan CM. Elevations in serum muscle enzyme activities in racehorses due to unaccustomed exercise and training. *Vet Rec*. 2014;174:145.
77. Fazio F, Assenza A, Tosto F, Casella S, Piccione G, Caola G. Modifications of some acute phase proteins and the white blood cell count in thoroughbreds during training. *Vet Rec*. 2010;167:370-372.
78. Cywinska A, Witkowski L, Szarska E, Schollenberger A, Winnicka A. Serum amyloid A (SAA) concentration after training sessions in Arabian race and endurance horses. *BMC Vet Res*. 2013;9:91.
79. Turlo A, Cywinska A, Czopowicz M, Witkowski L, Jaskiewicz A, Winnicka A. Racing induces changes in the blood concentration of serum amyloid A in thoroughbred racehorses. *J Equine Vet Sci*. 2016;36:15-18.
80. Witkowska-Pilaszewicz O, Baska P, Czopowicz M, et al. Changes in serum amyloid A (SAA) concentration in arabian endurance horses during first training season. *Animals (Basel)*. 2019;9:330.
81. Valle E, Zanatta R, Odetti P, et al. Effects of competition on acute phase proteins and lymphocyte subpopulations - oxidative stress markers in eventing horses. *J Anim Physiol Anim Nutr (Berl)*. 2015;99:856-863.
82. Arfuso F, Giannetto C, Fazio F, Panzera F, Piccione G. Training program intensity induces an acute phase response in clinically healthy horses. *J Equine Vet Sci*. 2020;88:102986.
83. Turlo A, Cywinska A, Czopowicz M, et al. The effect of different types of musculoskeletal injuries on blood concentration of serum amyloid A in thoroughbred racehorses. *PLoS One*. 2015;10:e0140673.
84. Turlo A, Cywinska A, Czopowicz M, Witkowski L, Szarska E, Winnicka A. Post-exercise dynamics of serum amyloid A blood concentration in thoroughbred horses classified as injured and non-injured after the race. *Res Vet Sci*. 2015;100:223-225.
85. Cywinska A, Gorecka R, Szareska E, Witkowski L, Dziekan P, Schollenberger A. Serum amyloid A level as a potential indicator of the status of endurance horses. *Equine Vet J*. 2010;42(Suppl. 38):23-27.
86. Fraipont A, Van Erck E, Ramery E, et al. Subclinical diseases underlying poor performance in endurance horses: diagnostic methods and predictive tests. *Vet Rec*. 2011;169:154.
87. Richard EA, Fortier GD, Pitel PH, et al. Sub-clinical diseases affecting performance in Standardbred trotters: diagnostic methods and predictive parameters. *Vet J*. 2010;184:282-289.
88. Bamford NJ, Potter SJ, Baskerville CL, Harris PA, Bailey SR. Influence of dietary restriction and low-intensity exercise on weight loss and insulin sensitivity in obese equids. *J Vet Intern Med*. 2019;33:280-286.
89. Menzies-Gow NJ, Wray H, Bailey SR, Harris PA, Elliott J. The effect of exercise on plasma concentrations of inflammatory markers in normal and previously laminitic ponies. *Equine Vet J*. 2014;46:317-321.
90. Pollock PJ, Prendergast M, Schumacher J, Bellenger CR. Effects of surgery on the acute phase response in clinically normal and diseased horses. *Vet Rec*. 2005;156:538-542.
91. Andersen SA, Petersen HH, Ersboll AK, Falk-Ronne J, Jacobsen S. Vaccination elicits a prominent acute phase response in horses. *Vet J*. 2012;191:199-202.
92. Nunokawa Y, Fujinaga T, Taira T, et al. Evaluation of serum amyloid A protein as an acute-phase reactive protein in horses. *J Vet Med Sci*. 1993;55:1011-1016.

93. Sinovich M, Villarino NF, Singer E, Robinson CS, Rubio-Martinez LM. Can blood serum amyloid A concentrations in horses differentiate synovial sepsis from extrasynovial inflammation and determine response to treatment? *Vet Rec*. 2020;187:235.
94. Viner M, Mazan M, Bedenice D, Mapes S, Pusterla N. Comparison of serum amyloid A in horses with infectious and noninfectious respiratory diseases. *J Equine Vet Sci*. 2017;49:11-13.
95. Belgrave RL, Dickey MM, Arheart KL, Cray C. Assessment of serum amyloid A testing of horses and its clinical application in a specialized equine practice. *J Am Vet Med Assoc*. 2013;243:113-119.
96. Daniel AJ, Leise BS, Burgess BA, Morley PS, Cloninger M, Hassel DM. Concentrations of serum amyloid A and plasma fibrinogen in horses undergoing emergency abdominal surgery. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:344-351.
97. Westerman TL, Tornquist SJ, Foster CM, Poulsen KP. Evaluation of serum amyloid A and haptoglobin concentrations as prognostic indicators for horses with inflammatory disease examined at a tertiary care hospital. *Am J Vet Res*. 2015;76:882-888.
98. Hooijberg EH, van den Hoven R, Tichy A, Schwendenwein I. Diagnostic and predictive capability of routine laboratory tests for the diagnosis and staging of equine inflammatory disease. *J Vet Intern Med*. 2014;28:1587-1593.
99. Spanton JA, Smith L, Mair TS. Is serum amyloid A elevated in horses with equine gastric ulcer syndrome? *Equine Vet Edu*. 2020;32:16-19.
100. Nielsen MK, Betancourt A, Lyons ET, Horohov DW, Jacobsen S. Characterization of the inflammatory response to anthelmintic treatment of ponies with cyathostominosis. *Vet J*. 2013;198:457-462.
101. Leclere M, Lavoie-Lamoureux A, Lavoie JP. Acute phase proteins in racehorses with inflammatory airway disease. *J Vet Intern Med*. 2015;29:940-945.
102. Labelle AL, Hamor RE, Macneill AL, Lascola KM, Breaux CB, Tolar EL. Effects of ophthalmic disease on concentrations of plasma fibrinogen and serum amyloid A in the horse. *Equine Vet J*. 2011;43:460-465.
103. Cohen ND, Chaffin MK, Vandenplas ML, et al. Study of serum amyloid A concentrations as a means of achieving early diagnosis of *Rhodococcus equi* pneumonia. *Equine Vet J*. 2005;37:212-216.
104. Pilati N, Corsalini J, Beccati F, Nannarone S, Gialletti R. Surgical treatment of an abdominal abscess caused by a migrating iron wire from the ventral colon, a case report. *J Equine Vet Sci*. 2017;54:103-106.
105. Ortolani F, Nannarone S, Scilimati N, Gialletti R. Successful surgical and medical management of a pararectal abscess in a horse. *J Equine Vet Sci*. 2021;99:103387.
106. Giguère S, Hernandez J, Gaskin J, Miller C, Bowman JL. Evaluation of white blood cell concentration, plasma fibrinogen concentration, and an agar gel immunodiffusion test for early identification of foals with *Rhodococcus equi* pneumonia. *J Am Vet Med Ass*. 2003;222:775-781.
107. Passamonti F, Vardi DM, Stefanetti V, et al. *Rhodococcus equi* pneumonia in foals: an assessment of the early diagnostic value of serum amyloid A and plasma fibrinogen concentrations in equine clinical practice. *Vet J*. 2015;203:211-218.
108. Lankenfeld A, Weber C, Rohn K, Venner M. Kinetics of serum amyloid A during the treatment period of foals with pneumonia. *Pferdeheilkunde*. 2021;37:128-136.
109. El-Deeb WM, Elmoslemany AM, Salem MA. Cardiac troponin I and immune-inflammatory response in horses with strangles. *J Equine Vet Sci*. 2017;51:18-23.
110. De Cozar M, Sherlock C, Knowles E, Mair T. Serum amyloid A and plasma fibrinogen concentrations in horses following emergency exploratory celiotomy. *Equine Vet J*. 2019;52:59-66.
111. Dondi F, Lukacs RM, Gentilini F, Rinnovati R, Spadari A, Romagnoli N. Serum amyloid A, haptoglobin, and ferritin in horses with colic: association with common clinicopathological variables and short-term outcome. *Vet J*. 2015;205:50-55.
112. Vandenplas ML, Moore JN, Barton MH, Roussel AJ, Cohen ND. Concentrations of Serum amyloid A and lipopolysaccharide-binding protein in horses with colic. *Am J Vet Res*. 2005;66:1509-1516.
113. Haltmayer E, Schwendenwein I, Licka TF. Course of serum amyloid A (SAA) plasma concentrations in horses undergoing surgery for injuries penetrating synovial structures, an observational clinical study. *BMC Vet Res*. 2017;13:137.
114. Aitken MR, Stefanovski D, Southwood LL. Serum amyloid A concentration in postoperative colic horses and its association with postoperative complications. *Vet Surg*. 2019;48:143-151.
115. Jacobsen S, Jensen JC, Frei S, Jensen AL, Thoefner MB. Use of serum amyloid A and other acute phase reactants to monitor the inflammatory response after castration in horses: a field study. *Equine Vet J*. 2005;37:552-556.
116. Miller MS, Moritz A, Röcken M, Litzke L-F. Bestimmung von serum-amyloid A, haptoglobin und fibrinogen als Entzündungsparameter nach Kastration von Hengsten (evaluation of serum amyloid A, haptoglobin and fibrinogen as inflammatory markers after castration of stallions). *Tierärtzl Prax*. 2007;35:69-74.
117. Hultén C, Sandgren B, Skioldebrand E, Klingenborg B, Marhaug G, Forsberg M. The acute phase protein serum amyloid A (SAA) as an inflammatory marker in equine influenza virus infection. *Acta Vet Scand*. 1999;40:323-333.
118. Albrich WC, Harbarth S. Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting. *Intens Care Med*. 2015;41:1739-1751.
119. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463-474.
120. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2017;10:CD007498.
121. Viitanen SJ, Lappalainen AK, Christensen MB, Sankari S, Rajamaki MM. The utility of acute-phase proteins in the assessment of treatment response in dogs with bacterial pneumonia. *J Vet Intern Med*. 2017;31:124-133.
122. Husebekk A, Husby G, Sletten K, Marhaug G, Nordstoga K. Characterization of amyloid protein AA and its serum precursor SAA in the horse. *Scand J Immunol*. 1986;23:703-709.
123. Muller AC, Buttner K, Rocken M. Systemic serum amyloid A in early (<24 h) diagnosis of acute synovial structure involvement in horses with penetrating limb injuries. *Vet J*. 2021;277:105759.
124. Flick M, Vinther AML, Jacobsen S, et al. Effect of exercise on serum neutrophil gelatinase-associated lipocalin concentration in racehorses. *Vet Clin Pathol*. 2021;50:551-554.

How to cite this article: Jacobsen S. Use of serum amyloid A in equine medicine and surgery. *Vet Clin Pathol*. 2023;52(Suppl. 1):8-18. doi: 10.1111/vcp.13195