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REVIEW ARTICLE

Acute phase proteins in cattle and swine: A review

Yolanda Saco | Anna Bassols

Departament de Bioquímica i Biologia Molecular, Servei de Bioquímica Clínica Veterinària, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain

Correspondence
Anna Bassols, Facultat de Veterinària, Departament de Bioquímica i Biologia Molecular, Servei de Bioquímica Clínica Veterinària, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Spain.
Email: anna.bassols@uab.cat

Abstract

The major acute phase proteins (APPs) in cattle are haptoglobin (Hp) and serum amyloid A (SAA), and in swine, are Hp, SAA, C-reactive protein (CRP), and Pig major acute phase protein (Pig-MAP). Many methodologic assays are presently available to measure these parameters, which are still being improved to increase their specificity, sensitivity, user-friendliness, and economic availability. In cattle, the main applications are the diagnosis and monitoring of frequent diseases such as mastitis and metritis in dairy cows and respiratory problems in young calves. In pigs, APPs are useful in the control of bacterial and viral infections, and they may be used at the slaughterhouse to monitor subclinical pathologies and improve food safety. The utility of APP in animal production must not be forgotten; optimization of protocols to improve performance, welfare, and nutrition may benefit from the use of APPs. Other sample types besides serum or plasma have potential uses; APP determination in milk is a powerful tool in the control of mastitis, saliva is a non-invasive sample type, and meat juice is easily obtained at the slaughterhouse. Increasing our knowledge of reference intervals and the influence of variables such as age, breed, sex, and the season is important. Finally, worldwide harmonization and standardization of analytical procedures will help to expand the use of APPs.

KEYWORDS
acute phase response, C-reactive protein, Haptoglobin, ITIH4, pig-MAP, serum amyloid A

1 | MAIN ACUTE PHASE PROTEINS IN CATTLE AND SWINE

Acute phase proteins (APPs) are produced by the liver upon stimulation by pro-inflammatory cytokines, such as interleukins-1β and -6 (IL-1β and IL-6) and tumor necrosis factor-α (TNF-α), in response to infection, inflammation, or trauma. These cytokines are thus used as biomarkers for these conditions in experimental and field studies, and many interesting reviews have been previously published as a general topic[1–8] or about specific animal species.[9–13] Pro-inflammatory cytokines may also be useful in monitoring inflammatory pathologies, but they are cleared from the circulation within a few hours, whereas APP concentrations remain altered for a long time after the stimulus.

APPs are classified as positive (major, moderate, or minor) or negative depending on if concentrations are increased or decreased after a triggering event. There is a consensus as to which are the most relevant APPs in cattle and swine (Table 1).[1,2,5,6,9,14] The major APPs are Haptoglobin (Hp) and Serum Amyloid A (SAA) in both cattle and pigs. C-reactive protein and Pig major acute phase protein (Pig-MAP) are considered major APPs in pigs, and lipoprotein-binding protein (LBP) is a major APP in cattle.[15] Recently, inter-alpha-trypsin

TABLE 1 Main positive (major, moderate, and minor) and negative APPs were identified in cattle and swine.

Species	Major	Moderate	Minor	Negative
Cattle	Hp, SAA, LBP	AGP, ITIH4, CRP	Fb	Albumin, Apo-A1
Swine	Pig-MAP, Hp, SAA, CRP	AGP	Fb	Albumin Apo-A1

Abbreviations: AGP, Alpha-1-acid glycoprotein; Apo-A1, apolipoprotein A1; APP, acute phase proteins; CRP, C-reactive protein; Fb, Fibrinogen; Hp, Haptoglobin; ITIH4, Inter-alpha-trypsin inhibitor heavy chain 4; LBP, lipopolysaccharide-binding protein; Pig-MAP, Pig major acute phase protein; SAA, Serum Amyloid A.

TABLE 2 Analytical techniques for the determination of acute phase proteins in cattle and swine.

Type of analysis	APP	Advantages	Disadvantages
Colorimetric	Hp	Simple, multispecies, basic equipment, easy to automatize	Some interferences Calibration unstable
ELISA	Hp, CRP, Pig-MAP, ITIH4, SAA, LBP	Species-specific	Species-specific Laborious High dilutions
Immunoturbidimetric	Hp, CRP, ITIH4, Pig-MAP	Species-specific Easy to automatize Good reproducibility	Species-specific No or low dilutions Higher precision than ELISA
Radial Immunodiffusion (RID)	SAA, Hp, ITIH4	Species-specific	Species-specific Manual Low number of samples
Point of care	SAA, CRP, Hp	Species-specific On-site testing Hp, MAA also for milk	Species-specific

Abbreviations: APP, acute phase proteins; CRP, C-reactive protein; Hp, Haptoglobin; ITIH4, Inter-alpha-trypsin inhibitor heavy chain 4; LBP, lipopolysaccharide-binding protein; Pig-MAP, Pig major acute phase protein; SAA, Serum Amyloid A.

inhibitor heavy chain 4 (ITIH4) has been identified as an APP in cattle, which is the analog to porcine Pig-MAP.[16]

2 | MAIN METHODOLOGIC TECHNIQUES FOR APP QUANTIFICATION IN SWINE AND CATTLE

An important requirement when determining APPs and other analytical parameters in farm animals is that usually, a large number of samples have to be assayed, and automated techniques are advisable (Table 2). More recently, other technologies and biosensors have been adapted, but they are outside the scope of this review.[17–20]

2.1 | The importance of harmonization and adequate reference values

Harmonization, namely, the preparation of reference materials for the calibration of reagents, is one of the most important requirements needed to expand the use of APPs, and it is indispensable for the standardization of different methodologies and the dissemination of knowledge to the field.[21,22]

Several laboratories, including ourselves, have been involved in the preparation, optimization, and validation of assays based on immunoturbidimetry and ELISA.[22–31] The availability of reagents and assays easily adapted to biochemical analyzers will contribute to the incorporation of APP measurements into routine laboratory testing for monitoring large animal health and welfare.

Likewise, the importance of having accurate reference intervals (RIs) cannot be left aside. Calculation of RIs has to take into account the influence of variables such as age, sex, breed, and type of housing. Published RI for calves and piglets demonstrate significant differences due to age.[32–35]

3 | MAIN APPLICATIONS OF APP IN CATTLE

APPs have been studied in relation to many diseases in cattle and dairy cows,[14,36,37] but only select examples will be summarized here.

3.1 | The transition period

In the dairy cow, the transition period is from the 3 weeks before to 3 weeks after calving. This period is associated with a high incidence of pathologies, such as ketosis, mastitis, hypocalcemia (milk fever), and reproductive problems. The risk of health problems increases during this time, and it is one of the main reasons for culling.

Proper management can significantly reduce the incidence of disease, meaning that the monitoring of the animals is required, and the determination of APP can help in achieving it.

Normal calving induces an acute phase reaction on the days following parturition.[36,38,39] This indicates enhanced activation of the immune system, even in cows with no clinical signs of metabolic stress. In the presence of infection or exacerbated tissue injury, the response is more intense. In all cases, the objective of the inflammatory response is to restore homeostasis and destroy pathogens. The best-studied APP in this context has been Hp in high-yielding dairy cows,[40] cows consuming fresh pasture,[41] and field studies performed at the farm level comparing different APP.[42] SAA has also been used as an inflammatory marker in cows during peripartum[43] and to assess the effect of nutritional management.[44,45]

3.2 | Metritis

Metritis occurs when bacteria from the environment colonize the uterus during parturition. Incidence is high and costly, with 5% to 20% of cows experiencing metritis and, consequently, subfertility and infertility.[46]

As in other infectious diseases, APPs increase during metritis, and it has been proposed that this acute phase inflammatory response precedes clinical metritis. In one study,[47] cows were grouped into 3 health categories after calving (severe metritis, mild metritis, and healthy), and Hp concentrations were measured for several days prior to and after calving. Cows with mild and severe metritis had greater Hp concentrations than healthy cows, and, more importantly, increased Hp concentrations preceded clinical signs of abnormal uterine discharge. Cows with Hp concentrations ≥1 g/L on day +3 after parturition were 6.7 times more likely to develop severe or mild metritis, and this predictive threshold had a sensitivity of 50% and specificity of 87%. Similar results were obtained with Hp and SAA, which were associated not only with the short-term development of metritis but also with chronic subclinical endometritis, other indicators of inflammation, and decreased reproductive performance.[48,49] Recently, attention has been focused on SAA due to its rapid increase in plasma, its short half-life, and the rapid dynamic of changes in blood concentration in metritis and other reproductive problems such as mastitis.[50,51]

The determination of CRP in uterine lavage fluid can be used as a local biomarker for evaluating uterine inflammation since it has been shown to decrease in parallel with the presence of leukocytes during uterine involution.[52]

In conclusion, APP screening may assist in the early detection of metritis, providing increased opportunities for early treatment and prevention.

3.3 | Mastitis

Mastitis is recognized as one of the most important reasons for culling dairy cows. Up to now, the evaluation of somatic cell counts (SCCs) has remained the gold standard for determining udder health. However, APPs are useful as either a valuable complement or even as an alternative to SCC.

In mastitis, there is a general increase in serum APP (Figure 1). The most relevant are Hp,[36] and SAA,[53] although CRP, ITIH4, and LBP also have been identified.[54]

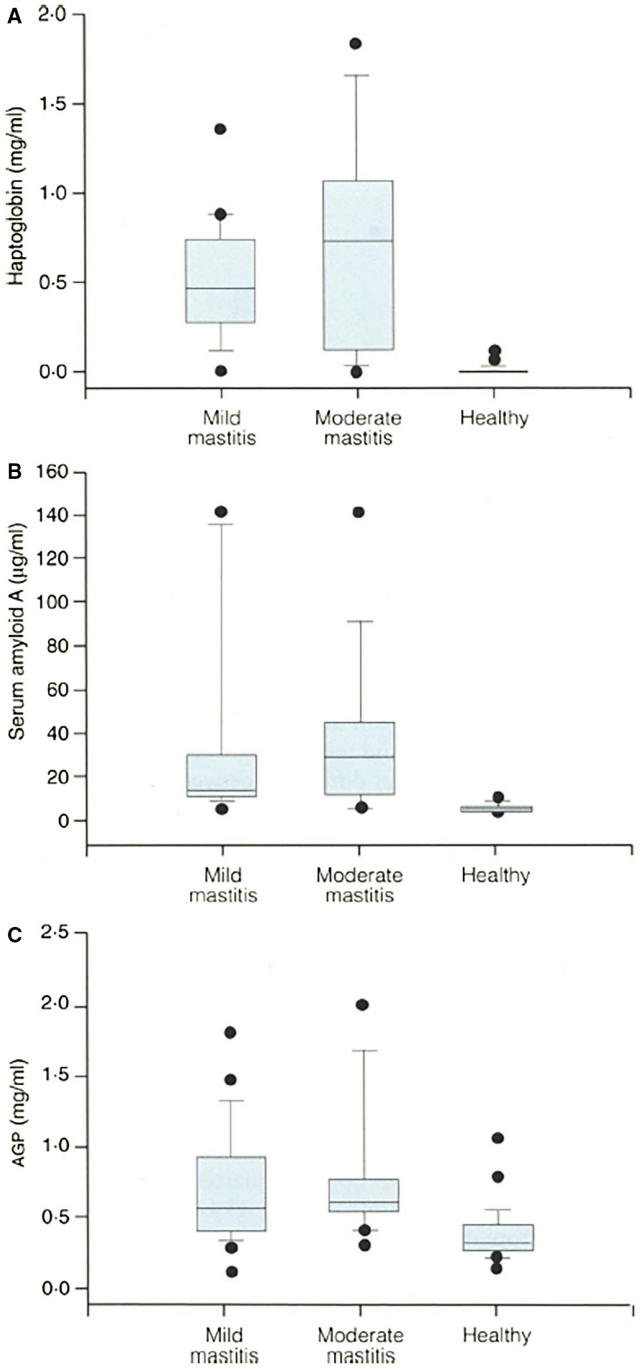

FIGURE 1 Concentrations of (A) haptoglobin, (B) serum amyloid A, and (C) alpha-1 acid glycoprotein (AGP) in serum from dairy cows with mild or moderate clinical mastitis and healthy dairy cows. The plots show the median (line within the box), 25th and 75th percentiles (box), 10th and 90th percentiles (whiskers), and outliers (dots). (From Eckersall et al., 2001[58]; used with permission).

APPs can be measured in milk, which could be advantageous compared with subjective or semiquantitative clinical criteria, such as palpation of the udder or evaluation of SCCs using cow-side tests (eg, California Mastitis Test). Synthesis of SAA and Hp occurs locally in mammary epithelial cells, and this is the source of milk APPs.[55] The SAA isoform present in milk is SAA3 (or milk amyloid A, MAA), different from the plasma isoform. The proteome of a mastitic cow has been studied in serum and milk, and several differences have been identified.[54,56] One is SAA, which does not correlate between the two sample types due to the presence of different isoforms.[57] When several serum and milk APPs were measured in dairy cows, they were found to have a similar diagnostic value to SCCs and proved to have good sensitivity and specificity.[58] Nevertheless, caution must be maintained when stored samples are used for analysis.[59]

Colostrum contains APPs in large quantities; therefore, colostrum intake influences serum APP concentrations in calves. Maternal colostrum SAA and Hp have immunomodulatory roles and may have local protective effects in the gastrointestinal tract of neonatal dairy calves.[60]

In healthy postparturient cows, APP concentrations in milk fall to low levels within 4 days. Therefore, if APPs do not decrease (ie, elevated APPs in milk after 4 days), they could be used as a biomarker of post-parturient mastitis, allowing for an early intervention to reduce disease on dairy farms.[61] Parity has been recognized as a possible confounding factor when diagnosing mastitis using milk Hp concentrations since there is a positive correlation between Hp and parity.[62] Milk SAA3, Hp, and CRP differentiated samples from healthy quarters of cows with subclinical mastitis that do not show clinical signs of intramammary inflammation.[62,63] In experimental studies, inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-10) and SAA3 in milk are correlated with one another and with clinical signs.[57,64] In another study, the kinetics of APP and cytokines in plasma and liver biopsies were presented.[65] Threshold concentrations for these proteins in milk that can be used to differentiate mastitic and healthy udders have been recently published.[66]

The agent of mastitis influences the clinical form of the disease, severity, and treatment. Investigating the secretion patterns of APP into milk may ultimately reflect the etiologic agent. The kinetics of SAA in serum and milk in experimental mastitis induced by *Escherichia coli*,[67] *Pseudomonas aeuriginosa*,[68] and other pathogens[63,64,69,70] were investigated. The highest concentrations of Hp were found in milk in cases of mastitis caused by *E. coli* and *Arcanobacterium pyogenes*, and the lowest concentrations were in cases of mastitis caused by coagulase-negative staphylococci.[69] The median concentration of SAA in milk was over 10 times higher in cases of mastitis caused by *E. coli* than in mastitis caused by other pathogens.[69] *Streptococcus* species are one of the most common etiologic agents of mastitis; the highest concentrations of SAA3 were found in the milk of cows with mastitis caused by *S. agalactiae* and *S. uberis* while SAA3 was lowest in mastitis caused by *S. dysgalactiae*.[70] In a field study performed in dairy farms in Scotland, Hp, SAA3, and CRP measured in milk presented similar profiles in mastitis caused by the same pathogen, and there was a correlation with the clinical symptoms.[63]

3.4 | Respiratory and gastrointestinal problems

Respiratory and gastrointestinal problems are frequent in young calves that are often subjected to husbandry conditions where calves of different origins and health statuses are mixed, provision of milk or solid feed is not always suitable, and prolonged transportation to rearing facilities occurs. At arrival, calves cannot consume the amount of milk and solid feed needed to cover nutritional requirements, and the incidence of disease spikes. The most common disease is a bovine respiratory syndrome (BRD), aggravated by the stress suffered during transportation.[71] The most common agents found in association with BRD are viruses such as bovine respiratory syncytial virus (BRS), parainfluenza-3 virus, adenovirus, and bovine coronavirus. However, secondary bacterial infections are common.[72] In addition to welfare and economic problems, transport and commingling are one of the most important causes of antibiotic use in cattle.

Measurement of Hp, LBP, and SAA have been studied as tools for detecting BRD in feedlot conditions, and the combination of high concentrations together with fever was found to be a very good indicator of disease.[72–76] SAA, LBP, and Hp are sensitive markers of respiratory infection, and they may be useful for exploring the host response to respiratory infections in clinical research.[77,78] Determination of APP at feedlot arrival may be useful in predicting subsequent performance and mortality rates of calves since high Hp concentrations inversely correlate with dry matter intake and body weight.[79] Furthermore, calves with elevated serum Hp concentrations had higher odds of being treated with antibiotics; thus, Hp could be useful for making decisions regarding targeted prophylactic treatment.[79]

Hp concentrations may help predict lung consolidation and have recently been validated as an accurate method for detecting BRD-related lung pathology in dairy calves.[80] Nevertheless, a systematic review of the diagnostic accuracy of Hp, SAA, and fibrinogen vs clinical reference standards for the diagnosis of BRD failed to confirm the utility of APP in the diagnosis of BRD.[81] The authors pointed to the lack of standardization of procedures and clinical criteria to explain this discrepancy.[81]

3.5 | Performance, growth, nutrition, and stress

In large animals, there is an intense investigation of the acute phase response triggered by stress related to several conditions, such as transport, feeding, or housing conditions. These studies are valuable for assessing the animal welfare status of the herds to both improve productivity and obtain products of higher quality.

The effect of weaning, transportation, and commingling on the APP response has been studied, and Hp and SAA have been proposed as the most sensitive APPs to monitor body weight increase to improve the management procedures of young calves.[82–84]

In our laboratory, we have studied how APP can reflect the overall welfare status of cows living in different husbandry conditions.

We have analyzed the serum biochemical profile of Bruna dels Pirineus and Alberes breeds living under different systems of housing and feeding, and SAA and Hp were increased in groups living in the mountains in winter.[85,86] APP have been used to study immune system activation in nutritional studies, as in supplementation with amino acids, where an increase in Hp, SAA, and LBP was observed in cows administered L-Glutamine.[87] APP have been used to monitor the potential inflammatory consequences of a grain-rich diet, which can contain endotoxin, resulting in increased plasma concentrations of Hp and SAA.[88]

4 | MAIN APPLICATIONS OF APP IN SWINE

In pigs, acute inflammation has been induced in non-infectious experimental models using the subcutaneous application of turpentine.[89] The acute phase response has been characterized in this species, and the major APPs have been defined as Hp, CRP, and Pig-MAP.[90]

A large number of experimental studies have been published in pigs with bacterial or viral infections. In addition to diagnostic, prognostic, and etiopathogenesis studies examining APPs, these proteins have also been used in experimental studies as tools for the evaluation of antimicrobial and anti-inflammatory agents and vaccines. In farm control programs aimed at improving the quality of pig production, some studies have supported the idea that analyzing Pig-MAP in one sub-sample of a group of pigs might be a useful tool in routine health and welfare monitoring.[91]

In natural infections, APPs generally have a greater response in animals that present with clinical signs, and the responses are usually of greater magnitude in bacterial infections or concurrent viral and bacterial infections.[92] Conversely, in clinical studies, such as surgical protocols, APPs have been measured in pigs as an animal model to assess inflammation.[93]

4.1 | Bacterial infections

In experimental infections, plasma concentrations of Hp and Pig-MAP increased rapidly and remained elevated for 10–15 days, whereas CRP and SAA show very rapid increases (peaking at 1–2 days post-infection) that decline to normal rapidly (4–5 days post-infection). The kinetics of APP responses have been analyzed in experimental infections with *Streptococcus suis*, *Actinobacillus pleuropneumoniae*,[94–96] *Yersinia enterocolitica*, *Pasteurella multocida*,[97] and *Haemophilus parasuis*.[98] The concentration of APPs correlates with the severity of clinical signs, and in some cases, increases are detected before specific antibodies are increased against the bacteria.[94] APPs have been measured to evaluate the efficacy of antimicrobials against *A. pleuropneumoniae*.[95]

A number of studies have explored the potential for measuring APP concentrations to assess the protective efficacy of a given vaccine since APPs have been observed to usually increase in correlation with antibody titers[99] and with the intensity and duration of clinical signs, as reported in vaccinated pigs prior to inoculation *with H. parasuis* (the etiologic agent of Glässer's disease).[98] However, the APP response is usually lower in vaccinated pigs compared with those with natural infection, as was observed in a study on *Lawsonia intracellularis* vaccination.[100] Taking into account these considerations, APPs could be used as biomarkers to help choose a vaccination protocol that minimizes inflammation, as was proposed in a study of pigs with *Mycoplasma hyopneumoniae*.[101]

Determining CRP concentrations in serum could be relevant for assessing impaired animal welfare in farrow-to-wean, nursery/feeder, and finishing pigs. Swine Inflammation and Necrosis Syndrome (SINS) is a newly identified clinical syndrome in which the translocation of intestinal bacterial products (eg, lipopolysaccharide [LPS]) into the bloodstream is hypothesized to be responsible for the development of inflammation and necrosis in the extremities.[102] Increased CRP concentrations have been detected in pigs affected by SINS due to inflammation and necrosis of the skin, tail, and ears.[103]

4.2 | Viral infections

The APP response in viral diseases is more heterogeneous and depends on if an innate response to the virus is stimulated. Two diseases that currently cause a significant economic impact on pig farms are porcine reproductive and respiratory syndrome (PRRS) and post-weaning multisystemic wasting syndrome (PMWS), caused by the PRRS virus (PRRSV) and porcine circovirus type 2 (PCV2), respectively.

PRRSV is characterized by a weak innate immune response with low production of pro-inflammatory cytokines and, especially, with very low production of interferon-gamma (IFN-γ). Therefore, an efficient acute phase response is not induced.[14,104] CRP and Hp are the most sensitive APPs,[105,106] but concentration variabilities have been reported, probably due to different viral strains or specific aspects of the experimental design.[106–109] The importance of viral strain is clearly demonstrated in our analysis of the response to several PRRSV isolates that produced different clinical outcomes; the APP response (Hp, CRP, and to a lesser degree, Pig-MAP) was heterogeneous and dependent on viral strain but also correlated with the severity of clinical signs (Figure 2).[110]

In PCV2-infected animals, Hp and CRP have been found to correlate with PCV2 viremia, and the clinical course of the disease,[111] but differences in the kinetics are reported depending on the experimental infection protocol.[112]

Swine influenza virus (SIV) is one of the main etiologic agents that produce respiratory disease in pigs. Experimental studies designed to evaluate the acute phase response have demonstrated increases in serum CRP, SAA, and Hp concentrations,[113] with Pig-MAP being less sensitive.[114] The increase in all of these APPs correlated to the severity of clinical signs and lung lesions and was able to

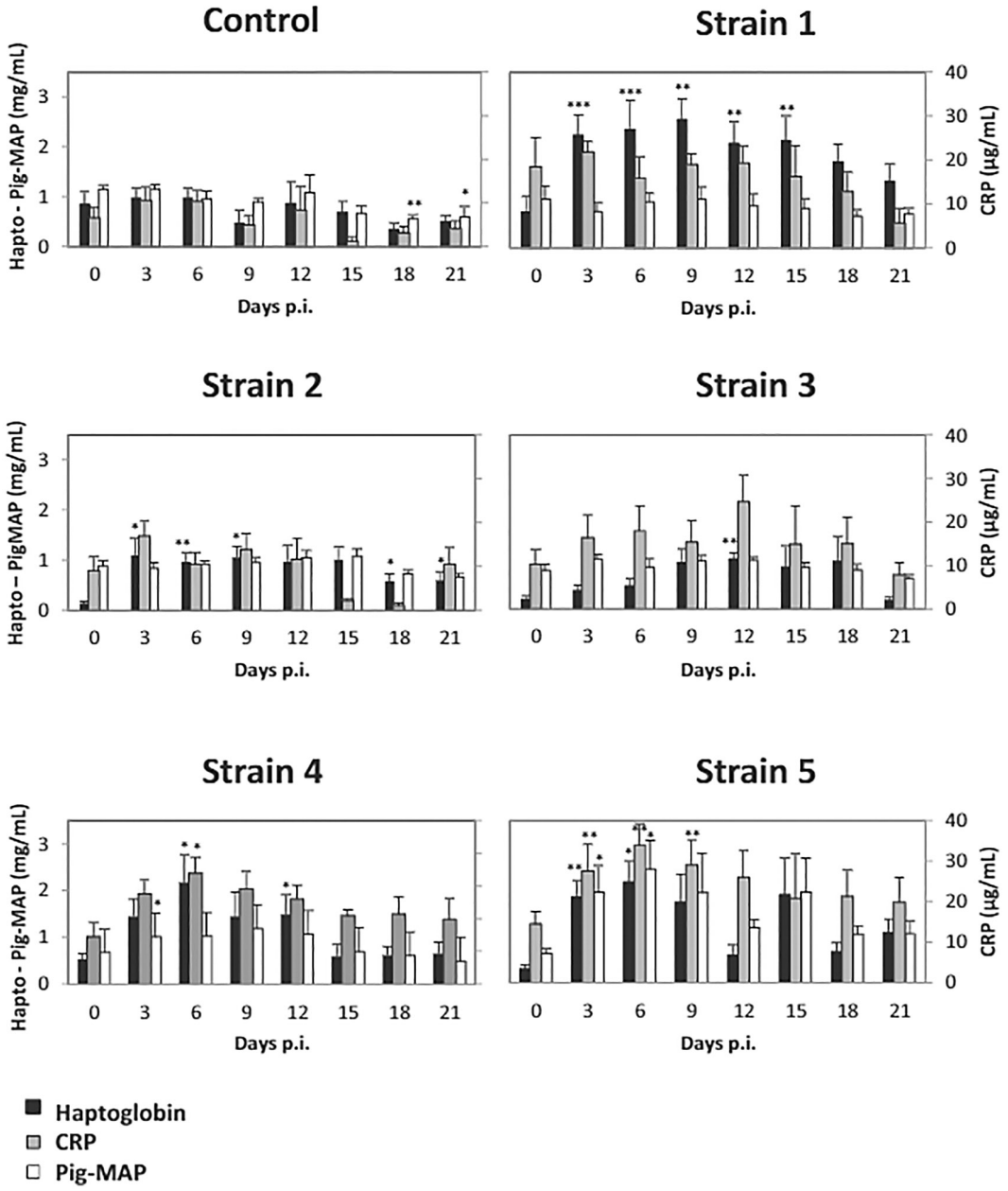

FIGURE 2 Serum concentrations of haptoglobin (mg/mL), C-reactive protein (CRP µg/mL), and Pig major acute phase protein (Pig-MAP mg/mL) in pigs inoculated with several strains of Porcine Respiratory and Reproductive Virus (PRRSV). Mean and S.E.M. for n = 5 pigs in each group are shown. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}p<0.001$ vs t = 0. (From Saco et al., 2016,[110] used with permission).

differentiate subclinical cases,[115] although SAA has been proposed as the best indicator for this pathogen.[116] Coinfection with more than one pathogen has been described for SIV and *H. parasuis*,[117] SIV and *P. multocida*,[116] and SIV and *A. pleuropneumoniae*.[118] In general, increases in APP correlated with the severity of the clinical signs and were more severe than in single-pathogen infections.

In infections caused by the African swine fever virus (ASFV), Aujeszky's disease virus (ADV), or classical swine fever virus (CSFV), different response patterns were observed. In general, the increase in plasma Hp, SAA, and Pig-MAP concentrations are greater than that of CRP for these three viruses, and APP concentrations evolved in parallel with viremia levels.[119] Another study described a significant increase in plasma SAA, CRP, and Hp concentrations in experimental ASFV and CSFV infections, with the increase in the plasma SAA concentrations being the most pronounced, and APP concentrations quickly returning to normal concentrations.[120]

It is also important to emphasize that determination of APP concentration, together with cytokines, is not only useful for diagnostic or monitoring purposes but also for the further study of viral disease pathogenesis.[121,122]

As with vaccines against bacterial infections, APPs can be used as biomarkers in nonclinical vaccine safety studies and can help identify a vaccination protocol that produces the lowest inflammatory reaction with the most effective protection in an individual. The

increase in APPs correlates with clinical signs, and our own results indicate that a vaccine against PCV2, which causes only a very mild and transient increase in rectal temperature did not induce an increase in Hp.[123]

4.3 | Parasites

The APP response in response to parasites is heterogeneous. In experimental infections with three species of *Trichinella*, increased plasma Pig-MAP, CRP, and Hp concentrations were mild and transitory, and none of these proteins was increased in any of the experimental groups of pigs at the same time point after infection.[124]

4.4 | Gastrointestinal diseases

More recently, we analyzed whether Pig-MAP correlated with the gold-standard measure for intestinal wall integrity, which included the villi-to-crypt ratio (V:C ratio) and the measurement of other inflammatory markers (TNF-α) and mucosa integrity markers (serum intestinal fatty acid protein, i-FABP), in pigs with experimental infections with *Salmonella Typhimurium* and the pathogenic *E. coli* strain, ETEC K88. Our results showed that Pig-MAP and TNF-α inversely correlated with the V:C ratio.[125]

4.5 | Other pathologies

APPs have been investigated as markers for lactation problems in sows. Due to complex etiopathogenesis, early diagnosis of postpartum dysgalactia syndrome (PDS) is challenging and usually based on the physical examination performed in the first days after farrowing. Determination of APPs, especially SAA, has been suggested as an early marker of lactation impairment in sows, allowing for a high probability of detecting sows susceptible to lactation disorders.[126]

4.6 | Acute phase proteins under field conditions

In natural infections, the APP response is generally greater in animals with clinical signs and concurrent viral and bacterial infections than in those with no clinical signs or with infections with only one pathogen. An APP response of greater magnitude is described in bacterial diseases (*M. hyopneumoniae*) compared with that observed in pigs affected by PRRS or ADV.[92] Pig-MAP and Hp concentrations are significantly increased in PMWS-affected animals, even before the appearance of clinical signs.[111,127] Increases in Hp and CRP concentrations are greater in pigs with PRRS that have a concomitant infection with *M. hyopneumoniae*.[128]

Some authors propose to measure APPs as a tool for the differential diagnosis of diseases that cause emaciation in fattening pigs. In fact, higher CRP concentrations are observed in pigs with pulmonary consolidation than in pigs with respiratory symptoms associated with the porcine respiratory disease complex (PRDC), while the latter is characterized by significantly higher Hp concentrations.[129]

Some studies have been performed in the field with the objective of assessing whether the extrapolation of APPs from one pig sub-group might be a useful tool in routine health and welfare monitoring programs aimed at improving the quality of global pig production. Using an immunochromatographic method to measure Pig-MAP on pig farms, the analysis of a sub-sample of the pig population was found to be enough to detect diseases or stress conditions that cause significant elevations in Pig-MAP.[91]

4.7 | Acute phase proteins as indicators of zootechnical performance

APPs have been proposed as biomarkers to assess growth performance since there is an inverse correlation between serum APP concentrations and production parameters. This study reasoned that stimulation of the immune system and increased inflammation are accompanied by reduced growth performance due to anorexia, as well as the partitioning of nutrients away from growth to support the immune system.[130] An inverse relationship between serum APP concentrations and production parameters would be anticipated.

In 1992, it was proposed that the determination of serum Hp concentrations in pigs at 7 weeks of age could be an indicator of future weight gain.[131] Similar results were described in 24-week-old animals[132] and animals in the post-weaning period.[133] Thus, Hp was suggested as a surrogate marker for reduced pig growth in a study comparing several nursery feeding programs in pigs raised on commercial farms.[134] In our laboratory, serum Hp concentrations were negatively correlated with improved production parameters (average daily weight gain) throughout the growing and fattening periods of the pigs.[123] More recently, it has been proposed that alpha1-acid glycoprotein (AGP) could be used as an indicator of growth potential in newborn pigs,[135] which may be surprising since AGP is a negative APP in pigs.[136] Newborn runt piglets have higher AGP concentrations than piglets born with normal body weights; this may be the main reason why AGP is considered a marker of growth. Body weight is a potent predictor of preweaning and post-weaning growth, and smaller pigs at birth grow slower.

APPs may be useful as non-specific biomarkers to detect if husbandry conditions, for example, the influence of suboptimal outdoor climates at critical phases of life, will result in production disturbances.[137]

4.8 | Acute phase proteins in nutritional studies

Sub-therapeutic antibiotic doses have been used to prevent infectious diseases, improve performance, and reduce medication costs in pigs. However, due to the association of sub-therapeutic antibiotic dosing in feed with the increasing emergence of antibiotic-resistant

bacteria, the use of antibiotics as feed additives has been banned in the European Union (Regulation [EU] 2019/61 on Veterinary Medicines and Regulation (EU) 2019/4 on Medicated Feed). Alternatives to the use of antibiotics are urgently needed, and APP measurements may be helpful in monitoring the effectiveness of alternatives. In this context, APPs have been used to assess the status of the immune system in studies examining the efficacy of probiotics and immunomodulators as better alternatives to antibiotic feed additives.[138–140]

Likewise, serum Hp has been used to evaluate the effects on the immune status in studies examining supplementation with amino acids during disease challenge[141] and diets supplemented with essential amino acids.[142]

4.9 | Acute phase proteins in slaughterhouse pigs as health status markers

APPs have been used as a complement to ante-mortem and post-mortem inspection of swine. On arrival at the slaughterhouse, APPs could offer information on herd health on the farms from which the pigs originate and aid in detecting chronic disease in apparently asymptomatic animals. One study found that Hp concentration in pigs from farms with different herd health and husbandry conditions have different mean values.[143] Therefore, the determination of Hp in the slaughterhouse can be of potential use for identifying herd problems on farms.[144]

Cranio-ventral pulmonary consolidation (CVPC) and pleuritis are the most common pathologic lesions found in the lungs of pigs at the slaughterhouse, with *M. hyopneumoniae* and *A. pleuropneumoniae* being the most important primary respiratory pathogens, respectively.[145] These diseases are associated with significant economic losses. At the slaughterhouse, Hp concentrations were significantly higher in animals with CVPC lesions compared with animals without these types of lesions.[146] Significant differences in CRP and Hp concentrations have also been described in animals without clinical symptoms but with pulmonary lesions.[147] A study of 24 farms prescreened for the presence of either CVPC or pleuritis indicated that Pig-MAP and possibly Hp are potential markers for characterizing and discriminating respiratory lesions at slaughter.[148] Using a point-of-care assay, Pig-MAP concentrations from blood samples obtained at slaughter were increased in association with lesions found on carcass inspection,[91] suggesting that this may be useful for real-time evaluation. An extended study indicated that APPs could also be valuable as predictive indicators for risk assessment in meat inspection, as increased Hp and Pig-MAP concentrations in slaughter blood indicated a 16- and 10-fold higher risk for organ abnormalities, respectively.[149]

4.10 | Acute phase proteins response in stressful situations

Swine species are generally exposed to stressful environmental conditions that can affect the immune response and increase the risk of disease. Transportation, social stress, heat, and dietary changes are some of the main causes that produce stress.[150] In response to stress, the hypothalamic–pituitary–adrenal (HPA) axis is activated, stimulating glucocorticoid production in the adrenal gland. Although the traditional view is that glucocorticoids are anti-inflammatory, there is an increase in proinflammatory cytokines when there is a cross-activation of the immune system and glucocorticoids, especially in conditions where stress precedes inflammation or in conditions of chronic stress.[151–153] The multiple physiologic responses to stress are illustrated in Figure 3. The paradigmatic stress hormone, cortisol, can be used as a stress marker but has large intraindividual variability, may be altered by other physiologic causes such as exploration of the environment, exhibits a circadian rhythm, and is a poor marker for chronic stress.[154]

The specific effect of stress on APP concentrations is difficult to evaluate since, in many situations (eg, housing, transport),

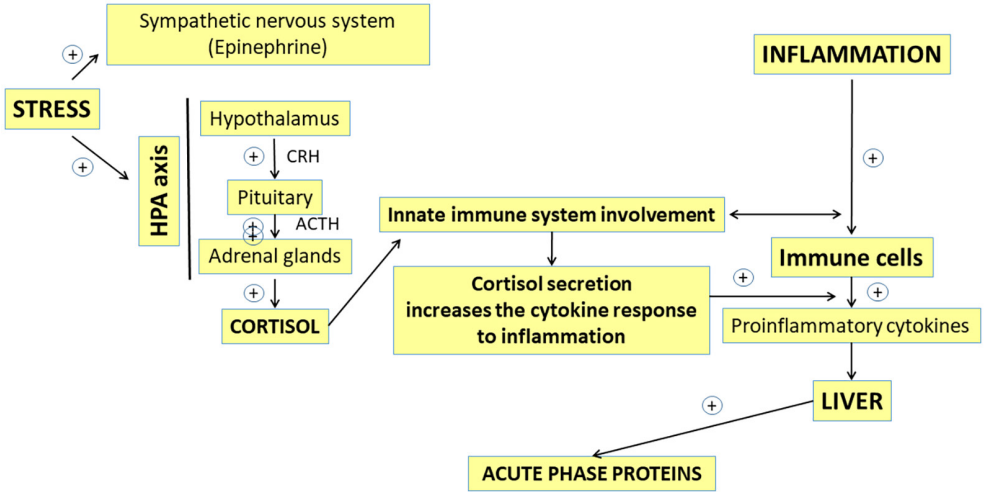

FIGURE 3 Relationship between stress and the immune system. CRH: Corticotropin-releasing hormone; ACTH: Adrenocorticotropic hormone.

there is concurrent psychologic stress, subclinical infections, and traumatic lesions inherent in the crowding of animals. Besides the ethical aspects, the welfare of the animals during transport to and lairage in the slaughterhouse is important since the impact of stress is closely related to meat quality.[155] The duration of transport affects Pig-MAP and Hp responses; increased concentrations are seen with longer transport times, and CRP and SAA concentrations increase after shorter transport times, probably because they are faster-responding proteins.[156–159] Conditions accompanying transport (eg, access to water, food, or the presence of sawdust) and alterations in feeding patterns can also affect animal welfare, cause stress, and induce higher concentrations of Pig-MAP, Hp, and CRP.[157,160] Heat stress has also been reported to induce an acute phase response.[161]

Stress in pigs has been widely studied in our laboratory. Pigs that are housed in high-density pens had higher Pig-MAP concentrations than those kept in larger spaces.[162] Sows have commonly been housed under field conditions in individual stalls throughout pregnancy because it eases animal handling, reduce social stress, and allows appropriate feeding. Because this individual housing system is considered stressful and harmful for animals, this practice has been banned by the European Union (CD 2001/88/EC). Our work in gilts demonstrated that Hp and Pig-Map were good markers for this kind of housing-induced stress.[163] In our work on mixing stress and human-animal relationships, we found correlations between Hp, Pig-MAP, and CRP and stress status.[164]

4.11 | Acute phase proteins in alternative fluids

In addition to blood serum or plasma, APP measurements in other fluids can be practical. Meat juice might provide an adequate matrix in which the health status of the animal can be reflected, which can easily be obtained at slaughter for end-point analysis. Pig-MAP and Hp concentrations in meat juice are closely correlated with those in plasma.[165] Other studies support the usefulness of CRP and Hp in the identification of carcasses with pathologic findings and show high sensitivity and specificity.[166,167] These results open new possibilities for the assessment of animal health in pig production, with implications for food safety and meat quality.

An exhaustive evaluation of APP measurements in the saliva is beyond the scope of the present review since a recent review has been published on this topic,[168] but it deserves some comments. APP such as Hp and SAA have been measured in saliva as non-invasive indicators of the health status of farms.[169,170] Results are variable, but Hp and SAA have been proposed to be increased in some stress conditions such as transport, housing, isolation, and restraint.[171–173] Some salivary APPs are affected by circadian patterns and can be influenced by sex.[174] There is a good agreement between APPs quantified in saliva and serum, suggesting that salivary APP determinations could be used as an alternative to serum in the pig.[170] In experimental conditions, salivary Hp is a good biomarker of systemic inflammatory responses in pigs challenged with LPS.[175]

5 | CONCLUSIONS

The main limitation of using APPs is the lack of specificity. Nevertheless, this is also the main strength. Acute phase proteins have been extensively investigated in diseases, but their use as monitoring tools for production and welfare purposes deserves to be recognized and further explored. One important bottleneck identified long ago is the standardization and harmonization of diagnostic testing and the establishment of reference intervals.

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ORCID

Anna Bassols https://orcid.org/0000-0003-4213-2274

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