

Review

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Review

The Use of Acute Phase Proteins as Biomarkers of Infections Caused by Bovine Respiratory Pathogens, with Particular Reference to *Mycoplasma* spp.

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Abstract

Bovine respiratory disease (BRD) constitutes the predominant group of health problems in cattle. Recently, the role of *Mycoplasma* infections, in particular *Mycoplasma bovis*, as primary infectious agents of BRD has been emphasised. Acute phase proteins (APPs) are a component of the early host response to infection, which is one of the non-specific defensive reactions. The importance of APPs has been widely discussed in various health disorders in cattle, including respiratory problems. This review summarises some of the latest reports on the use of APP assays for bovine respiratory infections involving *Mycoplasma* spp.

Keywords: acute phase proteins; bovine respiratory disease; *Mycoplasma* spp.; bovine respiratory pathogens

1. Introduction

Respiratory disorders in cattle constitute the predominant group of health problems especially in calves. The most significant microorganisms causing respiratory disorders in cattle include mycoplasmas, the most important of which is *Mycoplasma bovis* (*M. bovis*); bacteria from the *Pasteurellaceae* family, including *Pasteurella multocida* (*P. multocida*), *Mannheimia haemolytica* (*M. haemolytica*), and *Histophilus somni* (*H. somni*); *Trueperella pyogenes* (*T. pyogenes*); or viruses such as bovine respiratory syncytial virus (BRSV), parainfluenza virus type 3 (PI3V), bovine coronavirus (BCV) and influenza D virus (IDV) [1–4]. Many are considered primary etiological factors of bovine respiratory disease (BRD).

In cattle, acute phase proteins (APPs) are produced mainly in the liver during the acute phase response (APR), an early systemic physiological reaction, which is a component of the host innate immune response to injury or infection [5]. APPs have been widely used as biomarkers of various health disorders in cattle, including diseases during the transition from pregnancy to lactation in cows, such as fatty liver syndrome, abomasal displacement or metritis; mastitis or infections with different microorganisms [6,7]. Some APPs are also well known as markers of stress in cattle [8,9]. APPs that have been identified in the course of respiratory problems in cattle are listed in Table 1 and 2. APPs perform many diverse significant functions, and generally consist of restoring host homeostasis disturbed under APR conditions, such as binding of hemoglobin or cholesterol, bacteriostatic activity, opsonization, or modulation of some immune functions [7]. In cattle, indicator APPs include serum amyloid A (SAA) and haptoglobin (Hp), which represent a group of proteins that react rapidly or slowly during APR, respectively [10]. Both proteins are positive APPs, that is their concentration increases in serum or plasma under APR conditions [11]. Other positive APPs in cattle with confirmed significance include lipopolysaccharide binding protein (LBP) and fibrinogen

(Fib) [4,12]. The negative APPs whose concentration decreases in response to infection or injury, albumin (Alb) deserve more attention [7,11].

Table 1. Acute phase proteins determined during respiratory disorders in the Bovidae family.

APP	References
SAA	[2,13–18]
Hp	[2,13–19]
LBP	[2]
AGP	[2]
Fib	[4]
A2M	[18]
Alb	[18]

APP - acute phase protein. SAA - serum amyloid A; Hp – haptoglobin; LBP - lipopolysaccharide binding protein; AGP - alpha₁-acid glycoprotein; Fib – fibrinogen; A2M - alpha-2-Macroglobulin; Alb - albumin.

Table 2. Acute phase proteins assessed in the course of infections with bovine respiratory pathogens.

APP	Pathogen	Animal sector	Age or Age group	Specimen	References
SAA	<i>M. bovis</i>	Dairy	4-8 weeks	Serum	[13]
			approximately 5 weeks		[14]
			From few weeks to 4 months/adults		[20]
		Undefined	Calves		[16]
			4 weeks		[18]
	<i>M. bovis</i> <i>P. multocida</i> <i>M. haemolytica</i> <i>H. somni</i> BCV PI3V BRSV	Dairy, beef and veal	9 weeks (endemic) 8 weeks (epidemic)		[17]
	<i>M. dispar</i> <i>M. bovirhinis</i> <i>P. multocida</i> <i>H. somni</i> <i>M. haemolytica</i> <i>T. pyogenes</i> <i>Moraxella</i> sp. BCV	Dairy	From 14 days to 4 months		[15]
	<i>P. multocida</i> <i>Pasteurella</i> sp. <i>M. dispar</i> <i>M. bovirhinis</i> <i>S. suis</i>		From 9 to 32 days		[2]

	<i>Fusobacterium</i> sp.							
	<i>T. pyogenes</i>							
	<i>M. bovis</i>							
	<i>P. multocida</i>							
	<i>H. somni</i>							
	<i>T. pyogenes</i>							
	<i>Bibersteinia</i>							
	<i>trehalosi</i>							
	<i>Gallibacterium</i>							
	<i>anatis</i> ssp.	From 2 to 86 days		[4]				
	<i>haemolytica</i>							
	<i>Mannheimia</i>							
	genus							
	<i>Streptococcus</i>							
	genus							
	and others							
			4-8 weeks	[13]				
		Dairy	approximately 5 weeks	[14]				
	<i>M. bovis</i>		From few weeks to 4 months/adults	[20]				
			Calves	[16]				
		Undefined						
			4 weeks	[18]				
Hp	<i>M. bovis</i>	Dairy, beef and veal	9 weeks (endemic) 8 weeks (epidemic)	Serum	[17]			
	<i>P. multocida</i>							
	<i>M. haemolytica</i>							
	<i>H. somni</i>							
	BCV							
	PI3V							
	BRSV							
	<i>M. dispar</i>	Dairy	From 14 days to 4 months		[15]			
	<i>M. bovirhinis</i>							
<i>P. multocida</i>								
<i>H. somni</i>								
<i>M. haemolytica</i>								
<i>T. pyogenes</i>								
<i>Moraxella</i> sp.								
BCV								
<i>P. multocida</i>								
<i>Pasteurella</i> sp.								
<i>M. dispar</i>								
<i>M. bovirhinis</i>		From 9 to 32 days		[2]				
<i>S. suis</i>								
<i>Fusobacterium</i> sp.								
<i>T. pyogenes</i>								

	<i>M. bovis</i> <i>P. multocida</i> <i>H. somni</i> <i>T. pyogenes</i> <i>Bibersteinia</i> <i>trehalosi</i> <i>Gallibacterium</i> <i>anatis</i> ssp. <i>haemolytica</i> <i>Mannheimia</i> genus <i>Streptococcus</i> genus and others		From 2 to 86 days		[4]
	<i>Mycoplasma</i> <i>Moraxella</i> <i>Mannheimia</i> <i>Pasteurella</i> <i>Ureaplasma</i> and other genera		Prewaning		[19]
LBP	<i>P. multocida</i> <i>Pasteurella</i> sp. <i>M. dispar</i> <i>M. bovirhinis</i> <i>S. suis</i> <i>Fusobacterium</i> sp. <i>T. pyogenes</i>	Dairy	From 9 to 32 days	Serum	[2]
AGP	<i>P. multocida</i> <i>Pasteurella</i> sp. <i>M. dispar</i> <i>M. bovirhinis</i> <i>S. suis</i> <i>Fusobacterium</i> sp. <i>T. pyogenes</i>	Dairy	From 9 to 32 days	Serum	[2]
Fib	<i>M. bovis</i> <i>P. multocida</i> <i>H. somni</i> <i>T. pyogenes</i> <i>Bibersteinia</i> <i>trehalosi</i> <i>Gallibacterium</i> <i>anatis</i> ssp. <i>haemolytica</i> <i>Mannheimia</i> genus <i>Streptococcus</i> genus and others	Dairy	From 2 to 86 days	Plasma	[4]
A2M	<i>M. bovis</i>	Undefined	4 weeks	Serum	[18]
Alb	<i>M. bovis</i>	Undefined	4 weeks	Serum	[18]

APP - acute phase protein; SAA - serum amyloid A; Hp – haptoglobin; LBP - lipopolysaccharide binding protein; AGP - alpha₁-acid glycoprotein; Fib – fibrinogen; A2M - alpha-2-Macroglobulin; Alb – albumin; *M. bovis* - *Mycoplasma bovis*; *M. dispar* - *Mycoplasma dispar*; *M. bovirhinis* - *Mycoplasma bovirhinis*; *P. multocida* - *Pasteurella*

multocida; *H. somni* - *Histophilus somni*; *M. haemolytica* - *Mannheimia haemolytica*; *T. pyogenes* - *Trueperella pyogenes*; *S. suis* - *Streptococcus suis*; BCV - bovine coronavirus; PI3V - parainfluenza virus type 3; BRSV - bovine respiratory syncytial virus

The most commonly used specimen for assessing the presence of APPs in cattle with respiratory disease is blood serum, and the most widely used method is enzyme-linked immunosorbent assay (ELISA), as summarized in Table 3.

Table 3. Methods used for detection of acute phase proteins assessed in the course of infections with bovine respiratory pathogens.

APP	Specimen	Method	References
SAA	Serum	Solid phase sandwich ELISA	[2,4,13–18,20,21]
		Colorimetric assay	[13,14,18–20,22]
Hp	Serum	Monoclonal antibody-based capture ELISA	[15,21]
		Haemoglobin binding assay	[2,4,23,24]
		Competitive ELISA	[16]
		Sandwich ELISA	[17]
LBP	Serum	Solid phase sandwich ELISA	[2]
AGP	Serum	Radial immunodiffusion test	[2]
Fib	Plasma	Heat precipitation method	[4,25]
A2M	Serum	Competitive inhibition ELISA	[18]
Alb	Serum	Competitive inhibition ELISA	[18]

APP - acute phase protein; SAA - serum amyloid A; Hp – haptoglobin; LBP - lipopolysaccharide binding protein; AGP - alpha₁-acid glycoprotein; Fib – fibrinogen; A2M - alpha-2-Macroglobulin; Alb – albumin; ELISA - enzyme-linked immunosorbent assay.

2. The Role of APPs in Assessing the Course of *M. bovis* Respiratory Infections

Some APPs have been used to evaluate the course of experimental infection with *M. bovis* in cattle [13]. Calves intratracheally infected with a field strain of *M. bovis* showed a significant increase in mean SAA and Hp concentrations when compared to the control. This increase was already demonstrated at the first time point (day 3 of the experiment) for both tested APPs, which remained at a significant level until day 7 post infection. Pre-inoculation values for both proteins returned on day 9 of observation. The stimulation of the increase in the concentration of the tested APPs under conditions of *M. bovis* infection is evidence of the activation of APR at that time, which ultimately leads to the restoration of homeostasis disturbed by the infection. This study shows that the selected APPs are good markers of systemic inflammation and, in combination with other inflammatory markers such as eicosanoids, may be used in the initial diagnosis of calves suspected of *M. bovis* infection [13].

A later study confirmed earlier observations of a visible stimulation of the increase in Hp and SAA concentrations following *M. bovis* experimental infection in calves [13,14]. Three *M. bovis* field isolates of different origins were used for intratracheal infection of calves. Regardless of the *M. bovis* isolate used, a visible increase in Hp concentration was demonstrated compared to the control, which persisted for 2 days after infection. In the case of some isolates, further stimulation of the increase in the Hp concentration was also visible on days 14 and 28 after infection. As a rapidly reacting APP, SAA concentration was significantly increased on day 1 post infection, regardless of the isolate used [10,14]. Visibly increased SAA concentration was still observed in some of the tested *M. bovis* isolates on days 2, 3, 5 and 6 after infection [14].

3. Diagnostic significance of APPs

The significant role of Hp as a sensitive indicator of bacterial infections in calves with clinical signs of pneumonic disease was demonstrated in the study of Angen et al. [15]. The study was conducted in Denmark in 2002 on a total of 90 calves, 34 of which were diseased. The trans-tracheal aspirations were tested for the presence of bovine pathogens, including mycoplasmas (*M. bovis*, *M. dispar*, *M. bovirhinis*), bacteria of the *Pasteurellaceae* family (*P. multocida*, *M. haemolytica*, *H. somni*), other bacteria (*Moraxella* sp., *T. pyogenes*) and viruses, comprising BRSV, PI3V and BCoV. Among the bacterial agents, the most frequently detected pathogen in the calves with pneumonia was *P. multocida* (82% of the calves). However, in a slightly smaller percentage of the diseased calves, i.e., 79%, the presence of *M. dispar* and *M. bovirhinis* was detected. Other tested bacteria from the *Pasteurellaceae* family were detected in 41% and 29% of the calves, for *H. somni* and *M. haemolytica*, respectively. The remaining bacteria were detected only in a few percent of the calves with pneumonia, 6 (*T. pyogenes*) or 3% (*Moraxella* sp.), respectively. Most of the tested pathogens were also detected in varying percentages in clinically healthy calves. However, the percentage of positive samples was significantly higher in the diseased calves only in the case of *M. dispar* and *M. bovirhinis* compared to the healthy ones, which may indicate a significant contribution of these microorganisms to the aetiology of pneumonia in the examined calves. In all three herds studied, Hp concentration was significantly higher in the population of diseased animals than in the healthy ones. The most significant difference in the Hp concentration between healthy and diseased populations of calves within the three herds was observed in the herd where high herd prevalences of *P. multocida*, *M. dispar*, *M. bovirhinis* and BRSV were found in animals with pneumonia. In the healthy population of animals from this herd, the prevalence of these microorganisms was visibly lower, and *M. dispar* and BRSV were not detected at all. In the remaining two herds, a significant difference in the concentration of this APP was also observed between the two populations. In these herds, *M. dispar* and *M. bovirhinis* were among the most frequently detected microorganisms in the diseased populations. In comparison, in healthy calf populations from the same herds, the prevalences of these bacteria were visibly lower or not detected. A higher SAA concentration was observed in diseased populations in all three herds studied; however, the difference between diseased and healthy populations for this APP was significant in two of them. In the herd where the most significant difference in concentration of SAA was observed between the diseased animal populations and healthy ones, the presence of the following microorganisms was detected in a high percentage of animals: *H. somni*, *M. bovirhinis*, BRSV, *M. dispar*, *P. multocida* and BCoV in the calf population with pneumonia. Similarly, in this herd, these microorganisms, with the exception of *P. multocida*, were detected in a lower percentage of the calves or were not detected in healthy calf populations. In this study, the increase in SAA concentration in calf populations with pneumonia was less pronounced than Hp, which may indicate the role of the latter as a more sensitive indicator of disease in the herd, especially those with bacterial origin [15].

In another study, the role of selected APPs, such as SAA, LBP, Hp and AGP, was evaluated during a respiratory disease outbreak in Finnish calves for their level of response to the presence of anti-BRSV antibodies [2]. Tracheobronchial lavage samples (TBL) of all calves were tested for the presence of bacteria and viruses, while serum samples were analysed for specific antibodies to the following viral agents, BRSV, PIV3 and BCoV. The most common detected microorganisms in the TBL samples were *P. multocida* and *M. dispar*, which were detected in nine of ten calves examined at week 2, regardless of the BRSV antibody response. At the end of the study in week 6, the presence of these bacteria was found in all the calves investigated. Although BRSV was considered the primary cause of the BRD outbreak, *P. multocida* and *M. dispar* appear to be the major secondary bacterial agents in this respiratory disease. Visibly higher SAA and LBP concentrations were demonstrated in the later stages of BRD (week 3) in calves with low BRSV IgG_i response than in those with the high antibody response, which could be related to the secondary bacterial infection. Significantly higher concentrations of Hp were also observed at this time in these animals. However, unlike Hp, increased SAA and LBP concentrations persisted until the end of the study, indicating that these APPs are

sensitive inflammatory markers of the respiratory disease in young dairy calves. In the case of AGP, no significant differences were observed in the concentration of this APP, regardless of the level of BRSV antibody response or time [2].

The diagnostic significance of Hp and SAA has been demonstrated in Polish cattle with the confirmed presence of anti-*M. bovis* antibodies [20]. The study demonstrated significantly increased mean SAA concentration in the two age groups of cattle examined, i.e., calves and adults seropositive for *M. bovis*, compared to their seronegative counterparts. In the case of Hp, significant differences between seropositive and seronegative animals were observed only in calves. Both APPs appear to be a valuable tool in the diagnosis of calves suspected of being infected with *M. bovis*, supporting the assessment of other immunological parameters, such as total protein and γ -globulins. In adults, the highest diagnostic value was shown for SAA as a rather single marker under these conditions [20].

One of the latest studies has demonstrated the significant importance of SAA and Hp in diagnosing *M. bovis* infections in naturally infected calves of the Bovidae family (cattle and buffalos) in Pakistan [16]. In 200 animals examined in this study, changes in APPs, haematological parameters and oxidative stress factors were assessed intravitaly. The study showed significantly higher concentrations of both SAA and Hp in the calves infected with *M. bovis* compared to the control, which was on average 7- and 5-fold higher, respectively. Additionally, an association was demonstrated between the Hp values and the intensity of respiratory signs in naturally infected *M. bovis* calves [16].

Another study demonstrated the potential importance of selected APPs in the diagnosis of naturally occurring bacterial respiratory infections in preweaning dairy calves in Estonia [4]. The concentration of three APPs, Hp, SAA and Fib, was measured in 150 calves some with suspected lower respiratory tract disease and others with no overt clinical signs; the calves were tested mainly for bacterial pathogens including *M. bovis*, *P. multocida*, *H. somni*, *T. pyogenes*, *Bibersteinia trehalosi*, *Gallibacterium anatis* ssp. *haemolytica*, and genera *Mannheimia*, and *Streptococcus*. Respiratory viruses were not tested at the calf-level. The most frequently detected bacterial microorganisms were *P. multocida*, followed by *M. bovis*, regardless of the calf group. However, both bacteria were more frequently identified in the calves with suspected lower respiratory tract disease. In both groups of calves, the detected median Hp and SAA concentrations exceeded the reference values for these parameters many times over. This was particularly evident in the case of SAA concentration, where the values in the calves with suspected lower respiratory tract disease were nearly 50 times higher than the reference values for this protein. In comparison, in the calves with no clinical signs, this concentration was nearly 30 times higher than the reference values for SAA. Less significant increases in concentration were seen in the case of Hp; however, an almost two-fold increase in this concentration was observed in the clinically healthy calves, whereas a concentration of this APP in the suspected calves was almost 2.5 times higher than the reference value for Hp. For the assessment of Fib, no significant differences were found in the median concentration of this APP between the two groups of calves, and its values remained within the ranges close to the reference values for this parameter. However, a slightly higher median Fib concentration was observed for the calves suspected the disease. Taking into account the median for Fib of all tested calves, in the individuals increased Fib concentration was observed, up to 2.5 times higher than the reference values for this protein (max median of Fib concentration). Additional multivariable analysis showed a significant association between increased concentrations of Fib and SAA and the clinical signs of respiratory disease in calves. In the case of Hp, it was only demonstrated with increased calf rectal temperature. The same analysis demonstrated a significant association between increased Fib and SAA concentrations and the presence of *T. pyogenes*, as well as between increased Fib concentration and the presence of *P. multocida* in the calf TBL samples. No association was found between Hp and the presence of any of the detected respiratory pathogens. The lack of association between the tested APPs and the presence of *M. bovis* in the samples was explained by diagnostic limitations resulting from the use of only the PCR method for this pathogen detection, not culture. However, the possible role of *M. bovis* in the aetiology of the respiratory disease in the calves was partially supported by the

analysis at the herd level, which demonstrated a highest percentage of herds (60%) with *M. bovis* seropositive heifers, compared to other detected pathogens, such as BRSV (47%), bovine herpesvirus 1 (20%) or bovine viral diarrhoea virus (20%). Additionally, increased SAA concentrations and reduced Fib concentrations were observed in the calves from herds with heifers seropositive for *M. bovis* [4].

An attempt was made to assess the association between ultrasound detected lung consolidation at different depths caused by major BRD pathogens and selected APPs in the study of Lowie et al. [17]. The study was conducted on 170 calves, including dairy, beef and veal, in endemic (with history of *M. bovis*) and epidemic (sudden BRD outbreaks) settings in Belgium between 2020 and 2022. The presence of bacteria (*M. bovis*, *P. multocida*, *M. haemolytica* and *H. somni*) and viruses (BRSV, BCV and PI3V), considered the most widespread BRD pathogens in this country, was assessed in non-endoscopic bronchoalveolar lavage samples. In the endemic settings, the most frequently isolated pathogen from cases of lung consolidation, regardless of depth, was *M. bovis*, also demonstrated in evaluating calves with confirmed clinical BRD. However, in epidemic settings, *P. multocida* was the most frequently isolated BRD pathogen in cases with confirmed lung consolidation, although *M. bovis* was detected third after BCV. Additionally, the study demonstrated an association between the presence of consolidation in the lungs of the examined calves, regardless of its depth, and increased Hp concentration. However, differences were found depending on the type of settings studied. More than four times higher Hp concentration was demonstrated in calves with confirmed lung consolidation depth ≥ 1 cm in epidemic settings compared to endemic ones. A significantly higher Hp concentration was associated with greater lung consolidation depth (≥ 3 cm) in endemic settings. However, no association was observed between lung consolidation in the examined calves and changes in SAA concentration in both settings. Similarly, no association was observed between the tested APPs and the clinical BRD, regardless of the settings studied. The study also showed a significant association between higher SAA concentration and the presence of *M. bovis* in calves in epidemic settings. A similar relationship was observed for the second of the analyzed APPs. In the case of endemic settings, a significant association was demonstrated between increased concentration of SAA and the presence of the tested viruses. Unlike the others, no association was observed between any of the tested APPs and the presence of *Pasteurellaceae*, regardless of the settings tested. Moreover, in this study, a cutoff was determined for both APPs depending on the setting tested (endemic or epidemic) to distinguish calves infected with *M. bovis* and showing less depth lung consolidation, as well as those with or without lung consolidation from other animals examined. However, due to the low positive predictive values for the examined APPs for both settings, the specified cutoff values, in the authors' opinion, could not be used in predicting infections due to *M. bovis* based on lung consolidation and the assessed APPs [17].

4. Evaluation of the Efficacy of Respiratory Disorder Therapy

Some APPs, including Hp, SAA, alpha-2-Macroglobulin (A2M) and Alb, have been previously used to evaluate the efficacy of treating experimentally infected calves with *M. bovis* [18]. Three therapy models based on the administration of enrofloxacin alone, enrofloxacin combined with a nonsteroidal anti-inflammatory drug (flunixin meglumine), and enrofloxacin with flunixin meglumine plus pegbovigrastim, an immunostimulator were used. In this study Hp proved to be the most useful marker in assessing the effectiveness of therapy for this infection compared to other APPs. Based on the results of pathological, immunohistochemical and immunological examinations, the efficacy of enrofloxacin administered alone in the treatment of calves with symptoms of pneumonia caused by *M. bovis* infection was demonstrated in comparison to other therapy models. In this study, Hp seems to be a good biomarker for assessing the efficacy of treatment of the infection, which was manifested by a visible reduction in the concentration of this APP after the administration of enrofloxacin alone; previously this increased following experimental infection with *M. bovis* [18].

One of the latest studies has also demonstrated a clear role for Hp in monitoring the efficacy of antimicrobial treatment of preweaning dairy calves with naturally occurring BRD [19]. The study proposed two treatment protocols based on tildipirosin and a combination of florfenicol with flunixin

meglumine. The most abundant genus from the 12 most prevalent bacterial genera in the upper respiratory tract of both diseased and healthy calves during the first 5 days after enrollment was *Mycoplasma*. The applied treatment protocols resulted in a significant reduction in the relative abundance of some bacterial genera at this time, such as *Pasteurella* and *Mannheimia*, in both groups of calves treated with antimicrobials; this contrasted notably with the *Mycoplasma* genus, which was significantly more abundant in calves receiving tildipirosin. In all groups of diseased calves, whether intended for treatment or not, increased Hp concentrations were demonstrated until day 2 after pneumonia diagnosis compared to healthy animals. After this time, a decrease in the Hp concentration in both diseased groups of calves receiving antimicrobials was observed to values similar to those in the healthy ones, in contrast to the untreated sick animals, in which the values for this parameter were still significantly increased. The diagnostic value of Hp was also supported by another observation concerning the last group of calves, which showed a decrease in the concentration of this APP after the start of treatment (after day 5 post-enrollment) to values similar to those in the other examined groups of animals. This study clearly indicates the high diagnostic value of Hp in monitoring the course and efficacy of treatment of calves with BRD symptoms before weaning [19].

5. Conclusions

APP determination is a significant and future diagnostic tool in indirectly detecting infections with pathogens responsible for respiratory disorders in cattle, including BRD. APPs may also constitute a good diagnostic tool in distinguishing diseased from healthy animals, especially when including the assessment of the clinical condition. APP determination can be useful in the initial diagnosis of subclinical respiratory diseases. APPs can also be used to assess the course of infections caused by bovine respiratory pathogens, given their undisputed importance as markers of inflammation in cattle. A valid approach is also the possibility of using APPs to assess the efficacy of respiratory infection treatment in cattle.

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