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Review

Diagnostic Use of Serum Amyloid A in Dairy Cattle

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Abstract: Checking the health status of the individual animal and/or herd in a farm is one of the most important factors in diary production. Because of its high economical value, the early detection of ongoing disease is of high interest in breeders and veterinary clinical practitioners. The acute phase response (APR) is a non-specific systemic reaction for any type of tissue injury leading to disturbances in homeostasis. During this reaction, the production of acute-phase proteins (APPs) is changed. APPs may act as biomarkers of inflammation, allowing researchers to study the progression of the inflammatory response. One of the major APPs in cows is serum amyloid A (SAA). Due to its short half-life and the fast dynamic of changes in blood concentration, SAA seems to be a reliable indicator of several pathologies and treatment effectiveness. Because the blood-based and milk protein biomarkers of the herd's health status are of great interest, this article reviews the current information about changes in SAA concentrations in the blood and milk of cattle in health and disease. It summarizes its clinical usefulness as a health status indicator in diary production.

Keywords: cow; milk production; heard health status; APPs; SAA

Citation: Trela, M.; Domańska, D.; Witkowska-Piłaszewicz, O. Diagnostic Use of Serum Amyloid A in Dairy Cattle. *Agriculture* **2022**, *12*, 459. https://doi.org/10.3390/agriculture12040459

Academic Editors: Cong Li and Zhi Chen

Received: 16 February 2022
Accepted: 22 March 2022
Published: 25 March 2022

1. Introduction

The unspecific response to a variety of stimuli including trauma, infection, surgery, neoplasia, presence of a chronic disease, or ongoing inflammatory processes is called the acute phase response (APR) [1]. The main task of this early defense system is to eliminate the agent(s) which disturb the animal's homeostasis. The integral part of the APR is acute-phase protein (APP) synthesis. Depending on the fold and the dynamic of the changes, the APPs are classified as major (10- to 100-fold increase within the first 48 h with a rapid decline), moderate (2- to 10-fold increase with prolonged in duration), or minor (slight increase with prolonged duration) [1]. The pattern of changes in the concentrations of APPs in blood is species specific.

In cattle, the one of the major APPs is serum amyloid A (SAA), the concentration of which starts to increase within the first 4 h with a pick after 24–48 h [1]. In the dairy cow, seven isoforms have been recognized in the blood, but SAA1 and SAA2, which are mainly expressed in the liver, are the major ones that are overproduced during the APR [1]. SAA3 is expressed extrahepatically by adipose tissue, the mammary gland, intestinal epithelial cells, the lungs, ovarian granulosa, skeletal muscles, synovial membrane, the thymus, the thyroid gland, and the uterus but also by macrophages; thus, it is present in the blood but at a very low level in healthy animals [2]. SAA belongs to a family of apolipoproteins which have been very well conserved throughout evolution and have a wide range of functions (Figure 1).

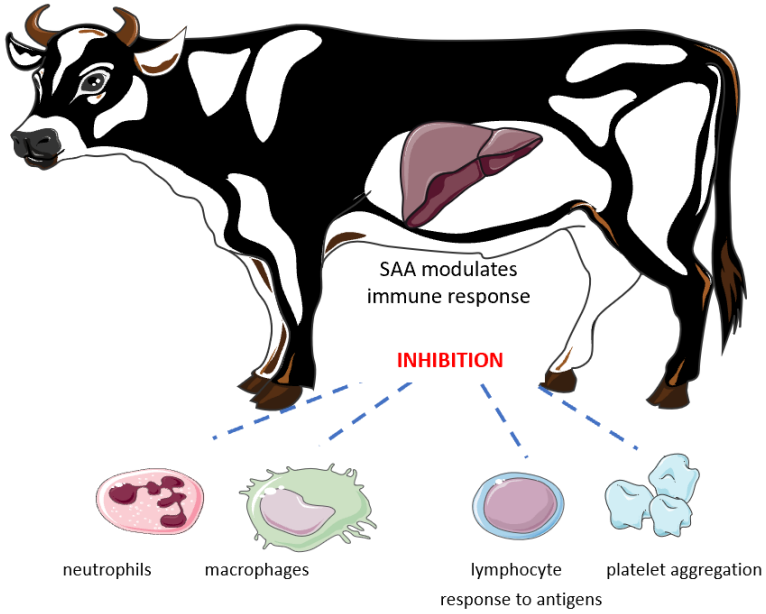

Figure 1. Systemic inflammation stimulates SAA production in cattle.

In healthy dairy cattle, the reference range of SAA concentration is variable (0–70 mg/L) [3]. It was suggested to use as a cut point the value of >600 mg/L for detecting the presence of the inflammatory process [3]. However, this cut-off value may be set up too high taking into account other reports (ex. 162.19 or 447.8 mg/L during mastitis) [4]. It is known that SAA is over expressed during several disorders; thus, changes in its concentration are considered as blood-based protein biomarkers in adult cows (Table 1) and calves. It is commonly used in clinical practice [1]. However, there is no APP which is specific for a particular disease. The APP concentration is elevated in animals with many different diseases, having very poor diagnostic specificity in detecting the cause. Thus, they need to be interpreted in the full clinical context. Despite the challenges in the determination of APPs, their usefulness has been proven, especially in the early detection of sub-clinical disorders or alterations of the health status/individuals.

Table 1. Examples of diseases/environmental conditions upregulating SAA blood concentration in adult cattle.

Diseases/Environmental Conditions	SAA Reported Values/Fold Increase [mg/L] (Reference Values: 0–70 Blood, Milk 0.6–50) [3,5]
high grain concentration dry matter (30–45%)	19–46 [6]
heat stress	4 fold [7]
long-term transportation (4–6 h)	1–2 fold [7]
ketosis	89.2 [8]
subacute ruminal acidosis	313.9 (at least one fold) [9]
fatty liver	80 [10]
abomasal displacement	>126 [3]
traumatic reticuloperitonitis	159 [11]
paratuberculosis	one fold [12]
brucellosis	123.75 [13]
babesiosis	mild 169.8; severe 183.4 [14]
Anaplasma marginale	167–180 [15]
one week postpartum	94 [16]
endometritis	low 20.25; mild 28.17; severe 34.62 [17]
pyometra	62.5 [18]
acute laminitis	281.26–590 [19]
mastitis	447.9 (milk 1315.9) [4]

2. SAA Concentrations in Healthy Cattle—Impact of Nutrition and Stress

Intensive dairy cow management supporting high milk yields requires the inclusion of large amounts of concentrates in the diet. Thus, significant economic losses in the dairy industry may be caused by unsuitable feeding. The maintenance of proper levels of fiber, dry matter intake, and the energy density of the diet are the most important factors in formulating diets to prevent problems connected with feeding. However, slight incompatibility in cows' production levels and improper feeding levels may go unnoticed. Cows with concentrations of nonesterified fatty acids (NEFA) above 0.35 mmol/L have higher mean serum concentrations of SAA (90.3 mg/L) than cows with NEFA concentrations less than (0.35 mmol/L to 27.0 mg/L) [20], but it is still within reference value. SAA concentration was found to be enhanced in cows fed with high grain concentration [6,21]. The higher dry matter (30–45%) of barley grain influences higher SAA concentrations (19–46 mg/L) in comparison to lower dry matter contents (0–15%; SAA 2–12 mg/L) in cows blood [6]. In addition, the concentrate level and neutral detergent fiber (NDF) content in the diet are connected with the development of inflammatory conditions characterized by increased SAA blood levels [22]. Probably, it is caused by an increased endotoxin level in the rumen. The results of Zebeli et al.'s study indicate that the feeding of more than 44% concentrate or less than 39.2% NDF in the diet linearly increases the SAA blood concentration. The one percent increase in NDF content is connected with decreased concentration of plasma SAA of 9.2 mg/L. Worth noting is that the level of the systemic inflammation resulting from improper diets vary in different cattle breeds (ex. Holstein vs. Jersey) [21].

Fortunately, some feeding supplements may downregulate the systemic inflammatory reaction. Saccharomyces cerevisiae fermentation product (SCFP) decreases the SAA blood levels by 33% after 5 days after beginning the supplementation in cows with heat stress [23]. Heat stress, which has a negative impact on animal welfare and productivity, stimulates the APR characterized by a four-fold increase in SAA blood concentration.

Other stressors in addition to heat stress are weaning and transport. It was documented that the concentration of SAA and other APPs, such as haptoglobin (Hp), increase significantly in response to long-term transportation (4–6 h) [7]. In addition, in this study, SAA response occurred in every cow, whereas only five of the eight animals showed Hp responses. Thus, improper management may strongly influence SAA concentration.

3. SAA as a Diagnostic Tool in Metabolic Disorders in Adult Dairy Cows

In dairy cows, one of the most common metabolic diseases is ketosis, which often occurs during the parturition transition period. Thus, the early identification of this disease at a subclinical level is important in dairy cow health prevention. It was documented that concentration of SAA is increased in blood (41.2 vs. 89.2 mg/L) but reduced in urine in cattle during ketosis [8]. It may be connected with changed high-density lipoproteins metabolism. Another common metabolic disease (in up to 19% of early lactation dairy cows and 26% of mid-lactation) is subacute ruminal acidosis (SARA). It is caused by inappropriate feeding, leading to rumenitis caused by low rumen pH (below 5.6 lasting at least 3 h/day). It is documented that SAA blood concentration is increased at least one-fold in cows with SARA (168 vs. 313.9 mg/L) [9]. The concentration of SAA in the bloodstream of cows affected by fatty liver reached a peak value of 80 mg/L and is higher than average concentrations in healthy cows [10].

4. SAA as a Diagnostic Tool in Gastrointestinal Disorders in Adult Dairy Cows

Common gastrointestinal disorders in high-producing dairy cows is abomasal displacement (AD). It is connected with extensive dietary, metabolic, endocrine, and immunological changes in dairy cows during the period occurring two weeks prepartum through two to four weeks. In cows below 2, lactation SAA is 126, and above 2, lactation is at 132 mg/L during left AD (LAD). In comparison, in healthy animals it was 59 mg/L and 60 mg/L, respectively. In another study, the values of the SAA varied: In LAD it was 55 mg/L and right AD-90 mg/L in comparison to healthy ones (12 mg/L) [3]. It was postulated that

APR during AD may be connected with a negative energy balance in postparturient dairy cows with LAD, which may lead to the release of proinflammatory cytokines.

Traumatic reticuloperitonitis is a relatively common disease caused by a foreign body ingested by the cow and migrated to the reticulum. Also during this disorder, the SAA concentration increases to 159 mg/L and has 100% sensitivity and 86.1% specificity. It was suggested that the optimal cut-off point is set at 68 mg/L for SAA and at 0.74 mg/L for Hp in this condition [11].

In dairy cattle production, a popular gastrointestinal infectious disease is paratuberculosis (PTB), which is a chronic disorder caused by *Mycobacterium avium* subspecies *paratuberculosis* (Map). It also effects the inflammatory response. In a large scale study in which 190 cows were examined, it was documented that in animals with different types of lesions, SAA increases regardless of the type (focal 13.10; multifocal 13.56; diffuse paucibacillary 19.82; diffuse multibacillary 6.44 mg/L) in comparison to healthy controls (6.91 mg/L) [12].

5. SAA as a Diagnostic Tool in Respiratory Tract Infections

The relative usefulness of changes in the leukocyte number and some APPs such as fibrinogen and Hp in predicting infectious diseases during the incubation period is not always satisfactory, especially in cattle. In this case, SAA seems to be more sensitive. In viral pneumonias, SAA responded more rapidly to infection than Hp [1]. Also during brucellosis, the SAA blood concentration is increased in comparison to healthy controls (32.92 vs. 123.75 mg/L) [13], whereas Hp concentration is not changed during this disorder. However, most studies connected with SAA changes in respiratory tract infections are performed in calves; this part is discussed in paragraph 10.

6. SAA as a Diagnostic Tool in Parasitic Infections

In addition, SAA may be a good indicator of the inflammatory process in cattle naturally infected with several species of parasites. It was documented that in bovine babesiosis (*Babesia bigemina*), SAA testing had 100% specificity and 100% sensitivity, with values for mild (169.8) and severe (183.4 mg/L) parasitemia (healthy animals 4.79 mg/L) [14]. *Anaplasma marginale* infection also causes the APR connected with a high concentration of several APPs (Hp, SAA, ceruloplasmin, and fibrinogen); however, SAA is suggested to be the most sensitive diagnostic factor in this case (167–180 vs. healthy 5.17 mg/L) [15]. In another study, the infected cows showed a significant, but as high as the previous one, increase in SAA (134 mg/L) [24]. During cystic echinocccosis in the liver and/or lungs caused by the larval stage of *Echinococcus granulosus* and connected with infection with microbial agents such as *Staphylococcus aureus*, *Escherichia coli, Corynebacterium* spp. and *Campylobacter* spp., *Candida* spp., *Streptococcus* spp., *Mannheimia haemolytica*, *Corynebacterium* spp., and *Micrococcus* spp., the concentration of SAA was increased twofold (7.51 $\pm$ 0.41 mg/L) in the infected cattle blood [25]. However, this is within reference value.

7. SAA in Reproduction

SAA serum concentration in healthy cows is not related with the physiological estrus phase. High values of SAA have been found in cows with ovarian cysts such as luteal (>35 mg/L) and follicular cysts (>50 mg/L) (healthy cows < 10 mg/L) [1,26]. Alsemgeest et al. (1993) reported that, in cows, 48 h before delivery, the mean SAA concentration was low. According to results obtained at 24, 48, 72, and 96 h after delivery, the mean SAA concentrations were significantly increased [27]; the highest concentration of SAA was reached 48 h after calving. The results of Ametaj et al. (2005) are in contrast with these findings, as immediately after parturition, increases in two main bovine APPs, hepcidin and SAA, were confirmed in cows [10]. Thus, higher concentrations of SAA in the blood and cervico-vaginal mucus of healthy animals in late postpartum may be important to modulate physiological inflammation and prevent tissue damage caused by severe inflammation [28].

In healthy fresh lactating cows (within one week postpartum) from 10 farms, the serum SAA concentration was 94 mg/L [16]. Differences among farms have been observed. These may be caused by different sensitivity in detecting the farm-specific inflammatory reactions induced be environmental factors such as regrouping and farm-specific diseases, such as mastitis and metritis [29]. Cows with metritis between the first and third week postpartum had greater (11.44 mg/L) concentrations of SAA compared to healthy cows in this time (10.40 mg/L). SAA levels in metritic cows at 8 (17.95 mg/L) and 4 (60.03 mg/L) weeks prior to parturition were also greater than in the control groups during the same time (84.47 and 34.61 mg/L, respectively). The study of Zhang et al. showed that both the protein and mRNA of SAA were increased in endometritis or in LPS-stimulated cells, and the increases were positively correlated with the severity of endometritis in vivo or LPS stimulation strength in vitro [30]. In another study, the correlation between the level of endometritis and SAA plasma concentration was observed. The average levels of SAA were noted: in healthy cows—14.24 mg/L; cows with low level endometritis—20.25 mg/L; mild endometritis—28.17 mg/L; and severe endometritis—34.62 mg/L [17]. It was also confirmed that blood and uterine concentrations of SAAs might be used as a diagnostic tool for subclinical endometritis during postpartum [18]. Thus, SAA might be used as useful parameter to evaluate the condition of the reproductive system and its problems. In addition, data suggest that serum SAA can be used to screen cows for the potential occurrence of uterine infections prior to calving [31].

The level of SAA was significantly higher in the serum of cows with pyometra (62.5 $\pm$ 9.01 mg/L) compared to healthy animals (35.4 $\pm$ 6.90 mg/L). In addition, in healthy cows, the level of SAA was significantly higher in the serum than in uterine washings (27.5 $\pm$ 6.62 mg/L) [18]. Thus, the SAA uterine/plasma ratio may be a valuable tool for pyometra detection.

8. SAA in Limb Diseases

Limb diseases in dairy herds are a serious clinical problem that directly affects the milk yield of cows. A lame cow loses on average 350 kg of milk (from 160 to 550 kg) during its lactation. Lameness in dairy cows means that these animals have a problem with moving, take longer to return from the milking parlor, and experience pain and discomfort. The most common causes for lameness in dairy cattle are inflammatory claw diseases such as sole ulcer, papilomatous digital dermatitis, interdigital necrobacilosis, septic pododermatitis, and white line disease [32]. In general, the clinical form of limb diseases can be easily diagnosed through a clinical examination, while the diagnosis of subclinical limb diseases remains a challenge. However, very often, the only symptom is lower milk production, which can persist for as much as four months before lameness is diagnosed and treatment applied, and may even last up to five months after treatment. That is why it is so important to look for a more sensitive diagnostic marker of lameness.

In previous studies, SAA seems to be a sensitive marker of lameness. Acute laminitis, sole ulcer, and digital dermatitis are responsible for the increase in SAA concentration of 442.76 mg/L, 590.00 mg/L, and 281.26 mg/L, respectively [19]. In contrast, diseases with an absence of lameness, such as heel erosions and white line disease in the primary stage (without secondary infections), did not induce a significant increase in APPs. However, in another study, SAA performed in cows 4 and 8 weeks before parturition the level of SAA was 2–3 times higher in lame animals [33]. Similar findings were also confirmed in another study in which SAA concentration increased approximately 3 times in lame cows in comparison with healthy controls (22.19 vs. 8.89 mg/L); however, Hp was 20 times higher (217.1 vs. 1.17 mg/L) [34]. Thus, SAA may be a marker for lameness connected mostly with inflammatory process.

In addition, SAA is useful for treatment monitoring [35]. In this study there were three groups: the first one in which systematic decreases in APPs levels in subsequent blood collections were recorded; the second in which an increase in the level of one or more APPs in the second or third blood collection was recorded; and the control group. In both study

groups, the SAA concentration decreased during treatment (220.8 to 130.7 and 130.1 to 99.2 mg/L, respectively). Thus, SAA seems to be a promising marker in lameness detection and recovery in dairy herds.

9. SAA in Mastitis

Bovine mastitis is a major cause of economic loss in the dairy industry. The consequence of mastitis is a decrease in milk yield, quality reduction, and an influence on the composition of the milk and the processing properties of milk [36]. Methods that will enable fast and precise diagnosis, especially of subclinical mastitis, are still being sought. Among such methods, the determination of APPs deserves attention. SAA is produced in the liver in response to acute phase stimulus but also in other extra-hepatic tissues, including the mammary gland. Among the main three isoforms, SAA_3 is produced predominantly in milk and has been called mammary-associated amyloid A (MAA-S3) [37].

MAA-S3 has at the N-end of its sequence four amino-acid motif amino acids (TFLK), regardless of species (horse, cow, sheep), that are absent in the isoform of the liver synthesis protein [37]. MAA-S3 contains 83% of the same amino acid sequence as SAA. The highest concentration of MAA-S3 (267 mg/L) occurs in the colostrum of healthy cows on the first day after parturition. MAA-S3 stimulates the expression of mucin in enterocytes, indicating a possible protective action on the digestive tract of newborns, especially in the case of necrotizing enterocolitis [38]. During the days following birth, the concentration gradually drops to a value of 2.63 mg/L. In a more recent study, the MAA-S3 concentration in milk in healthy cows with a normal somatic cell count (SCC) was <0.6–50 mg/L [5].

The secretion of MAA-S3 is stimulated by prolactin, LPS contained in the wall of Gram-negative bacteria, and also by lipoteichoic acid (TLA) contained in the wall of Gram-positive bacterial [37] and may influence the development of local immunity in the mammary gland. Thus, thanks to ability to stimulate integral bacterial elements to MAA-S3 synthesis, MAA-S3 seems to be a good indicator of udder inflammation. It was documented that MAA-S3 is a marker of early inflammation of the mammary gland, especially subclinical inflammations [2]. The MAA-S3 increases faster than SAA in blood because it occurs after 12 h, whereas, in plasma, it is after 24 h. Additionally, the concentration of MAA-S3 during mastitis in the cows inoculated with the *E. coli* is much higher compared to blood (1315.9 vs. 447.9 mg/L), unlike Hp [4]. This was also confirmed in very recent study [39]. In addition, the highest MAA-S3 levels were found in cows with chronic mastitis and the lowest in cows with subclinical mastitis, but still, the obtained values were several times higher than in healthy cows [40]. It is hypothesized that faster and higher increase in MAA-S3 is connected with the early phase of inflammation when the systemic defense response of the organism has not yet been initiated. There is also a possibility that SAA from blood is transported to the mammary gland, where the appearance of pathogens triggered an APR, thus causing the significant increase in MAA-S3 and resulting in a high level of MAA-S3 in milk. In addition, MAA-S3 may be mostly produced locally, which is the most likely cause, as there is a different amino acid sequence from SAA [37]. Eckersall (2010) proved that in cows with mastitis, the sensitivity of the determination of SAA in serum is 83%, and in milk, 93%, while the specificity is 90% in serum and 100% in milk [2].

It was documented that the increase in the MAA-S3 concentration in milk depends on the type of pathogenic factor. In infections caused by *E. coli*, the increase in APPs concentrations was the greatest compared to infections caused by streptococci (*Strep. agalactiae, Strep. uberis, Strep. dysgalacyiae*) and *Staphylococcus aureus*. In contrast, significant differences in the level of SAA concentration in the serum depending on the pathogens in more recent study was not detected (*Strep. agalactiae* 210 mg/L, *Strep. dysgalactiae* 210 mg/L *and Strep. uberis* 229 mg/L) [41]. However, measuring the SAA or MAA-S3 should not be consider as method for evaluating the need of antibiotic use. Susceptibility testing and the targeting of pathogens should always be performed to counteract increased global problem with antibiotic resistance.

10. SAA in Calves Diseases

In available publications, there are many studies describing SAA and its concentration in calves. It was documented that SAA concentration is higher in calves than adult cows, which may be caused by various physiological needs and challenges faced by the calves during maturation. The average concentration of SAA in one-month-old healthy calves is 59 mg/L, and at the age of six months, it is 19 mg/L [42]. Dudek et al. (2014) tested the influence of vaccination in pregnant cows with inactivated vaccine composed of BRSV-PI3V-*M. haemolytica* antigens on the SAA serum concentration in their calves [43]. The SAA concentration was significantly higher in the experimental calves (>150 mg/L) compared to the control calves (from nonvaccinated dams until the ninth week). Then, the SAA concentration increased in the control group (>300 mg/L) while the experimental group declined, giving statistically significant differences until week 12 [43].

Moreover, during respiratory tract infections, there is an increase in SAA. In calves with bronchopneumonia, Coskun et al. (2012) found higher concentrations of SAA in bronchoalveolar lavage fluid (BALF) than in healthy calves [24,44]. In viral infection such as syncytial virus and secondary bacterial infections, the increase in SAA in the first week of infection was observed with the maximal level at the third week and a decrease up to week six (>20 mg/L) [45]. In the other study, the SAA level was used for treatment monitoring. In calves with respiratory diseases (SAA = 725.11 $\pm$ 7.19 mg/L vs. healthy ones 304.00 $\pm$ 25.69 mg/L), the SAA level started to drop during antibiotic therapy from 824.55 $\pm$ 14.73 mg/L on day 0 to 526.05 $\pm$ 27.39 mg/L on day 10 [46]. However, it should be highlighted that because of the increased global problem with antibiotic resistance, antibiogram and the pathogen(s) testing should be performed as often as possible.

One of the more costless problems in calf health management are diarrheas. SAA blood concentration as response to stress, inflammation, infection, or tissue injury during diarrhea in calves has been developed. In post-weaned calves with diarrhea caused by bovine coronavirus (BCoV), SAA blood concentration was higher (46.2 $\pm$ 7.6 mg/L) than in recovered animals (28.5 $\pm$ 7.4 mg/L), but this increase was not statistically significant [47]. This study showed that changes in SAA were less pronounced in post-weaned calves (aged 117–155 days) with diarrhea.

The blood concentration of SAA seems to be a more sensitive marker of stress than disease in calves, but several factors can also affect SAA results [1]. In one study, the SAA concentration was checked in calves in physical stress conditions. Alsemgeest et al. observed that the plasma SAA concentrations were significantly raised in animals housed on the floor-type associated with the highest level of physical stress (17.9 $\pm$ 1.8 mg/L vs. 2.8 $\pm$ 0.9 mg/L), although the concentrations were within the normal range for healthy cattle [27]. Changes in aldolase and cortisol concentrations have not been observed, which suggest the presence only physical stress, not neuro-hormonal. Other authors reported significant elevations in SAA concentrations (from 3.2 $\pm$ 2.9 mg/L) after dehorning procedures in calves during 48 h (to 36.9 $\pm$ 30.3 mg/L) [48].

The measurement of SAA concentrations may also be used in the diagnosis of bacterial infections in stillborn calves (53.3 mg/L) in comparison to unexplained stillbirth (10.7 mg/L) [49]. In perinatal dead calves' plasma, authors observed lower SAA concentration when uterine infection was not present in the dams (6.3 mg/L) in comparison to dead calves where infection was present in the dam's uterus (13.8 mg/L) [50]. Summarizing, the changes in SAA levels may be an unspecific indicator of health status in calves; however, the different values than in adult cows should be taken into consideration. It should be highlighted that there is a shift toward more productive cows and larger herds [51]. Thus, it is associated with more health problems.

11. Conclusions

As non-specific markers of inflammation, changes in SAA blood concentration may be a beneficial tool to help recognize the inflammatory process in dairy cattle. One of the most important conclusions that changes in SAA concentration are very dynamic in connection

to very short half-life time. Thus, it may be useful in some cases in the quantification of inflammatory activity. However, in most cases, it does not allow one to recognize the etiology of disease. However, monitoring diseases and their treatments by means of SAA may allow cattle farmers to determine the efficiency and efficacy of a specific treatment.

SAA testing is a useful tool for the assessment of health in general, to monitor the health state, and prevent the spread of infection in the whole herd. Very often, the research is performed on large cow populations. Thus, SAA seems to be a promising unspecific biomarker of the inflammatory process. In addition, it may also help in antemortem inspections of large herds in slaughter houses. Thus, the early diagnosis of several diseases is extremely important because of their significant economical and zoonotic impact.

However, the clinical application of SAA has some practical limitations associated with measurement methods. Mostly, they are time-consuming and relatively expensive, such as ELISA tests; thus, rapid field tests that allow the determination of SAA are still needed. Moreover, in veterinary practice, it is not always obvious that one isolated condition needs to be assessed. Thus, clinical examination should be performed, and SAA cannot be evaluated alone. Future research should be focused on creation rather the APPs diagnostic profiles.

Author Contributions: Conceptualization, M.T., D.D. and O.W.-P.; writing—original draft preparation, M.T., D.D. and O.W.-P.; writing—review and editing, M.T., D.D. and O.W.-P.; supervision, O.W.-P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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