OPEN ACCESS
Advances in Animal and Veterinary Sciences

Review Article

Different Predictive Tools for the Bovine Respiratory Disease and it's Unfavorable Outcomes

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Abstract | In this review, the literature was searched to give insight into the predictive tools used for the Bovine respiratory disease "BRD" and its detrimental outcomes. BRD continues to be the most economically significant disease in feedlots and one of the most important causes of morbidity and mortality in dairy and veal calves. Despite the use of new-generation antimicrobials, vaccines, prophylactic and metaphylactic strategies in the past decade, the prevalence of BRD has been reported to increase. Challenges regarding early, accurate diagnosis and prognosis of diseased cases are raised to avoid misclassification "false negative cases" also non-prudent use of antimicrobials "false positives".Thoracic ultrasonography "TUS" and blood haptoglobin were able to predict cases at high risk of being morbid also diseased ones at risk of detrimental outcomes. Future large scaled on-field studies will help in proposing a schematic criterion for BRD prognostic tools.

Keywords | Respiratory disease, Calves, Ultrasonography, Acute phase proteins, Lactate.

Received | June 25, 2019; **Accepted** | August 19, 2019; **Published** | October 25, 2019
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Citation | Abdallah AA (2019). Different predictive tools for the bovine respiratory disease and it's unfavorable outcomes. Adv. Anim. Vet. Sci. 7(11): 929-936.
DOI | http://dx.doi.org/10.17582/journal.aavs/2019/7.11.929.936
ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331

INTRODUCTION

Bovine Respiratory Disease (BRD) is a respiratory disease complex that accounts for a significant portion of cattle/calf losses, medication costs, labor and production losses in the beef and dairy industry (Camkerten et al., 2010). The BRD complex has a multifactorial etiology and different predisposing factors including prenatal and preweaning nutrition, health management and post weaning factors, which include the duration of the weaning period prior to transport, transportation and marketing stress, commingling, nutrition and health management (Holland et al., 2011).

The detrimental economic effects of BRD increase with disease severity and the number of treatments administered (Wolfger et al., 2015). In a recent US study (USDA, 2012), BRD accounts for 18.1% of preweaned dairy heifers'morbidity and 2.3% their mortality, in another study (USDA, 2013) it is responsible for 16.2% of feedlot cattle morbidity.

Early and accurate antemortem diagnosis of BRD still a big challenge for veterinarians and cattle producers, previous reviews discussed the accuracy of clinical illness (Timsit et al., 2016), acute phase proteins (Abdallah et al., 2016) and other diagnostic tools (Wolfger et al., 2015) versus different reference or gold standards for BRD diagnosis in feedlot and dairy cattle, this is considered as a confounding factor due to various definitions of BRDpos and BRDneg cases that did not allow those authors to conclude the added value of the selected diagnostic tools to role in or role out BRD cases, so standardization of BRD case or non case definitions is highly recommended.

Thoracic ultrasonography (TUS) and some blood biomarkers used as predictive tools in previous studies to identify cattle at risk for unfavorable outcomes of BRD (death, relapses,early culling, poor productive and reproductive performance) (Coghe et al., 2000; Carter et al., 2012; Berry et al., 2004; Abutarbushet al., 2012; Buczinski et al., 2013; Buczinski et al., 2014; Rademacher et al., 2014; Buczinski et al., 2015a; Buczinski et al., 2015b).

Table 1: Characteristics of the studies utilized TUS as a predictor of negative BRD outcomes.

References	Type of cattle	Study design	Outcome	N	BRD	C
(Ollivett et al., 2011)	Dairy calves	Prospective longitudinal	Subclinical pneumonia diagnosed using TUS and was associated with significant **impaired growth**	91	NR	NR
(Abutarbush et al., 2012)	Feedlot cattle	Prospective longitudinal	TUS examination performed at enrollment, 2, 4 and 6 weeks after had no prognostic value, just TUS examination of fever cases at study enrollment (if lung lesion detected) Help in improving **ADG** (P=0.007) 34 days post arrival	174	116	58
(Buczinski et al., 2013)	Dairy calves	Case control (operators were blinded during TUS examination)	Consolidation Depth considered a good predictor of a calf being **treated** or not for BRD (AUC=0.896)	10	6	4
(Buczinski et al., 2014)	Dairy calves	Prospective cohort	The number of consolidated sites and the maximal depth of consolidated lung appeared to be potential predictors of **death** within 1 month after the examination (AUC=0.809, 0.743 respectively)	106	56	NR
(Rademacher et al., 2014)	Feedlot calves	Case control	The number of sites with consolidation, number of sites with pleural irregularities, maximal depth of consolidation, maximal area of consolidation, and total consolidated area considered good predictors for **BRD deaths** before end of study period (*P*=0.008, 0.045, 0.005, 0.02 and 0.005 respectively)	44	29	15
(Adams and Buczinski, 2016)	Dairy calves	Prospective cohort	Calves with extensive lung consolidation ≥6 cm in one or more locations at 3 months age had greater risk of **dying** or being **culled** [26% (95% credibility interval: 13–47%)] (*P* < 0.01) than those with ≥1 location of lung consolidation (≥1cm and < 6 cm), those with pleural irregularities or normal ones.	239	142	97
(Teixeira et al., 2017)	Dairy calves	Prospective cohort	Heifers with lung consolidation at weaning were less likely to get pregnant (HR=0.7, *P*=0.006) and more likely to be **culled** before their first parturition (HR=4.7, *P*<0.001) than heifers without lung consolidation	613	124	489

NR: not reported, TUS: thoracic ultrasonography, BRD: bovine respiratory disease, ADG: average daily gain, AUC: area under curve, HR: hazard ratio

Improved means of prognosing of BRD will allow animals to have less stress, lower rates of illness, and allow correct effective treatment. Cattle with BRD can potentially have decreased gains and meat quality. With improved methods of prognostics, meat quality and feedlot efficiencies will increase. Based on what was previously stated, in the current review article, we aimed to give an insight from the literature about some of the formerly reported predictive tools for BRD and its unfavorable outcomes, articles discussed the thoracic ultrasonography, blood acute phase proteins (APP) and lactic acid roles in BRD prognosis are exclusively included.

Thoracic Ultrasonography (Tus)

The pathophysiology of BRD is such that cellular infiltrates and cellular debris effectively displace air from the lung tissue, resulting in non-aerated and/or consolidated lung lesions that are detectable by ultrasonography. These lesions alter the lung character, changing the ultrasonographic image from that of a strong reflector with reverberation artifact to a homogenous, hypoechoic structure like that of liver (Reef et al., 1991). These changes might make it possible to arrive at an TUS diagnosis of lung lesions regardless of the clinical state of the animal (Ollivett, 2014).

Thoracic ultrasound has been proposed as a calf-side tool to aid BRD diagnosis, detect pulmonary lesions, and reduce the use of antimicrobials (Teixeira et al., 2017), TUS holds promise due to its reported accuracy for diagnosis of parenchymal lung lesions, especially consolidation associated with infectious bronchopneumonia (Babkine and Blond, 2009). Additionally, TUS is well correlated with gross lesions found at the post-mortem examination of dairy calves suffering from naturally occurring respiratory disease (Rabeling et al., 1998; Flöck, 2004) and may , therefore, be used for the antemortem assessment of the severity and extent of pulmonary lesions (Rademacher et al., 2014).

In a recent study in preweaned dairy calves (Buczinski et al., 2015b) TUS was specific (SpTUS: 93.9%; 95% Bayesian credible intervals [BCI]: 88.0–97.6%) and relatively sensitive (SeTUS: 79.4%; 95% BCI: 66.4–90.9%) for BRD diagnosis, another study reported that the sensitivity and specificity of TUS for detecting lung lesions were 94% (95% CI, 69–100%) and 100% (95% CI, 64–100%), respectively compared to post-mortem examination as a gold standard for BRD diagnosis (Ollivett et al., 2015).

TUS prognostic ability for different BRD outcomes was tested in previous studies that were conducted on feedlot or dairy herds (Ollivett et al., 2011; Abutarbush et al., 2012; Buczinski et al., 2013; Buczinski et al., 2014; Rademacher et al., 2014; Adams and Buczinski, 2016; Teixeira et al., 2017) the results were summarized in Table 1, all those studies conducted on calves except one study (Abutarbush et al., 2012) in which adult cattle were recruited.

Consolidation depth reported in different studies as a valuable predictor with greater ability compared to other TUS indices (Buczinski et al., 2013; Buczinski et al., 2014; Rademacher et al., 2014), one study (Rademacher et al., 2014) reported 9 sites (5 on the left and 4 on the right) on both sides of the thoracic cavity have higher odds > 1 ($P<0.05$) when relating the presence of consolidation at initial examination to a negative BRD outcomes, the confounding factor of this study that BRD cases were left without treatment through the study period that may exacerbate BRD negative outcomes rather than in diseased cases that usually subjected to treatment.

A recent study (Teixeira et al., 2017) elucidated that heifers detected with lung consolidation at 60 days of life had a higher age at first calving (AFC) in contrast to another one (Adams and Buczinski, 2016) that reported no difference of AFC for calves found with extensive lung consolidation (≥6 cm in one or more locations) by 3 months of age with those with ≥1 location of lung consolidation (≥1cm and < 6 cm), those with pleural irregularities or normal ones, both studies agreed that calves of weaning age with lung consolidation had a greater hazard of death or culling than those with out lung lesions.

No association found between lung lesions detected at time of enrollment, 2, 4, or 6 weeks post-enrollment in feedlot cattle and different health outcomes (treatment, wastage, or mortality), just in arrival fever cases, cattle detected with lung lesions at time of enrollment had significantly better short-term rates of gain (average daily gain to last ultrasound, P=0.007) compared with animals without lung lesions (Abutarbush et al., 2012), in this study TUS was performed just in the right side of the thoracic cavity that may underestimate results by increasing probability of missing diseased cases (false negatives) in which lung lesions may be present in the left side.

Blood Biomarkers

The diagnostic and prognostic potential of measuring acute phase proteins in cattle with BRD has been suggested (Eckersall, 2007), their concentrations usually change after infection, inflammation, surgical trauma, or stress with either increase (positive APP) or decrease (negative APP), haptoglobin (Hp), serum amyloid A (SAA), and fibrinogen (Fb) are among the most commonly reported positive APP measured during naturally or experimentally induced BRD in dairy and beef cattle (Gånheim et al., 2007;Timsit et al., 2009; Tothova et al., 2011; Wolfger et al., 2015).

Seven studies (Garry, 1984; Wright et al., 1995; Wittumet al., 1996; Purdy et al., 2000; Carter et al., 2002; Berry et al., 2004; Humblet et al., 2004) were included to investigate the prognostic utility of the fore mentioned APP (Table 2). Hp concentrations significantly decreased in treated (recovered) versus diseased cases in all those studies, one study (Carter et al., 2002) reported that Hp levels measured by feedlot arrival were correlated with number of treatments required after, another one (Berry et al., 2004) found that it´s level increased with number of treatments, in contrast to other studies (Wittum et al., 1996; Step et al., 2008, Brooks et al., 2011) in which Hp concentrations in samples collected by feedlot arrival or BRD diagnosis were not related to case severity or treatment needed, while it may have a limited merit for taking treatment decisions (Holland et al., 2011).

Fb levels were significantly lowered post treatment (Garry, 1984; Carter et al., 2002; Humblet et al., 2004), while it did not significantly differ before and after treatment (Purdy et al., 2000) and was not associated with number or required treatments (Berry et al., 2004). SAA levels were significantly and non-significantly changed between treated versus diseased cases in two studies (Carter et al., 2002; Berry et al., 2004) respectively.

Respiratory disease may affect the oxygen transport chain in various ways, there may be a reduced oxygen transfer

Table 2: Acute phase proteins changes pre and post bovine respiratory disease treatment/predictive value for required treatments.

References	Study design/type of cattle	Studied APP	Sampling time	Outcome
(Garry, 1984)	Prospective cohort/NR	Fb	Initial examination of all calves	Mean Fb levels were sig. lower (P=0.001) in recovered than poorly prognosed ones. 88.9% of calves with Fb levels ≥800 mg/dl (cut off) → died or performed poorly. 89% of calves with Fb levels<800 mg/dl→ good recovery.
(Wright et al., 1995)	Randomized trial/feedlot	Hp	Arrival day (0), 7, 14, 21 and 28 days in feed	Hp levels sig. ↓ (P<0.05) in recovered vs morbid cases.
(Wittum et al., 1996)	Randomized trial/feedlot	Hp	Initial and final examination (by recovery)	Hp concentrations by final ex. ↓ significantly (P < 0.01) in treated group than non-treated one. Hp levels (in treatment group) did not changed between new and relapsed cases (Hp conc. unrelated to case severity or treatment need).
(Purdy et al., 2000)	Prospective Cohort/feedlot	Hp and Fb	Treatment day and 4 days after (by recovery)	Mean Hp level was sig.↓ (by 2.36-fold) post treatment (P < 0.001). Fb level non-sig. changed between sick and recovered calves.
(Carter et al., 2002)	Randomized trial/feedlot	Hp, SAA, Fb and (AGP)	Treatment day and 14 days after	Hp, SAA and Fb sig. ↓ 14 days post treatment (P<0.05) than that of initial time for calves treated once or more, AGP level sig. ↓ for those who treated once. Hp level only at initial processing day found to be correlated with the number of treatments required.
(Berry et al., 2004)	Randomized trial/feedlot	Hp, SAA and Fb	Treatment day and 7 days after	Hp sig. ↓ (<0.05) post treatment, also it´s level ↑ with No. of treatments. SAA level did not differ in morbid vs treated and did not changed sig. with No. of treatments. Fb concentrations did not influence by number of antimicrobial treatments.
(Humblet et al., 2004)	Retrospective longitudinal/NR	Hp & Fb	Before examination or treatment, 2nd sample three weeks later (after recovery)	Hp and Fb levels sig. ↓ (P≤0.05) in recovered vs diseased cases. 78% of treated calves needed an anti-inflammatory (AI) drug and 75% of calves did not require AI according to their Hp values. 80% of treated calves needed AI if Fb values were considered.

APP: acute phase proteins, NR: not reported, Fb: fibrinogen, Hp: haptoglobin, SAA: serum amyloid A, AGP: α-1 acid glycoprotein.

Table 3: Blood lactate as a predictor for BRD occurrence, relapses and death.

Study ID	Study design/ type of cattle	Lactate measurement methods	Sampling time	Outcome
(Coghe et al., 2000)	Retrospective cohort/NR	1-Portable lactate analyser (Accusport, Boehringer Mannheim) (index) 2-Enzymatic-photometric method (Socolab, Limal) (reference)	By BRD diagnosis and repeated daily with aggravating clinical signs	Plasma lactate level >4 and 3.6mmol/L for both of measurement methods (index versus reference) were prognostic indicators for death within 24h.
(Nagy et al., 2006)	Consecutive case series/NR	Automatic biochemical analyser ALIZÉ (Lisabio, France) and test kits (BioMérieux)	Beginning of observation, after clinical examination or during the therapy (more than 24 h before the death or before returning to the owner)	Plasma lactate was sig. lower (P < 0.001) in survivor versus non-survivors. In non-survivor calves, lactate level increased 24h before death.
(Aich et al., 2009)	Randomized trial (BHV-1 + *Mannheimia haemolytica*) / feedlot	H Nuclear Magnetic Resonance Spectroscopy	One day before and 4 successive days after viral challenge	Serum lactate could be predictive for BRD deaths.
(Montgomery et al., 2009)	Randomized trial /feedlot	Glucose-lactate auto analyzer (2300 Stat Plus, YSI Inc., Yellow Springs, OH)	1st day of receiving period	Plasma lactate was sig. ↓ (P < 0.01) by sampling time in calves treated for BRD later in early feeding period.
(Buczinski et al., 2015b)	Prospective longitudinal/ feedlot	Handheld lactate-meter (Lactate Pro, Arkray,Kyoto, Japan)	Processing day/ by BRD confirmation (day 0), 3, 6, 9 and 15 days later	Plasma lactate level >5mmol/L at processing can help in metaphylactic treatment decision (Y/N). ↑plasma lactate level in BRD cases sig. associated (P < 0.01) with ↑ hazard of **dying** before next pull also help to select cases need supportive treatment.

NR: not reported, BRD: bovine respiratory disease, BHV: bovine herpesvirus, Y: yes, N: no.

from the lungs to the arterial blood, an elevated oxygen consumption due to an increased work of breathing (Coghe et al., 2000) and sometimes cardiovascular dysfunction (Desmecht et al., 1994), cause increase in the anaerobic metabolism that becomes more prominent resulting in an increase in blood lactate levels (Coghe et al., 2000), based on that, blood l-lactate concentration (LAC) has been studied in previous researches (Coghe et al., 2000; Nagy et al., 2006; Aich et al., 2009; Montgomery et al., 2009; Buczinski et al., 2015b) to evaluate it´s ability to predict BRD cases in feedlot calves early by their arrival to feedlot or BRD outcomes (relapses and mortality) in diagnosed cases during the production cycle, those findings summarized in Table 3.

No association was found between lactate level measured by feedlot arrival and further BRD morbidity (Aich et al., 2009). Other studies (Coghe et al., 2000; Nagy et al., 2006; Aich et al., 2009) found that increased blood lactate level could be a predictive for mortality within 24h, the former study attributed absence of association between lactate level and further morbidity to the stress of transport lead to depletion glycogen stores, other studies reported a positive relation between blood lactate levels and near death within 24h as they sampled the diseased animals by time of BRD diagnosis or during disease progress that may support the formerly illustrated explanation about BRD interference with oxygen transfer and increased anaerobic metabolism lead to increased lactate level (Coghe et al., 2000).

In the remaining study (Buczinski et al., 2015b) the blood lactate level>5mmol/L by processing was associated with metaphylactic treatment decision help in minimizing misclassification costs with low sensitivity (49%) and relatively high specificity (77%) also increased lactate level in BRD confirmed cases by it´s diagnosis was related to increased hazard of death before next examination but not predictor of death through out the study period as the mentioned.

CONCLUSIONS AND LIMITATIONS

Effective control of BRD has proven to be difficult in the North American dairy and beef industries, at least in part due to the complexity of disease pathogenesis and the ubiquity of BRD-associated pathogens (Gorden and Plummer, 2010). Early identification of sick cattle is a major concern in the feedlot and dairy industry, mainly due to the negative impact of BRD on affected calves including relapses, mortality, propagation of infectious agents and retarded growth (Gardner et al., 1999; McGuirk, 2008) also this syndrome is the leading cause of antimicrobial use in the feedlot industry (Edwards, 2010).

In this review, we tried through searching the literature to better understanding some of BRD predictive tools, promising results obtained from using TUS and some blood biomarkers to predict cases at high risk of being morbid also diseased ones at risk of detrimental outcomes.

TUS can be considered in different cattle industries (beef, dairy or veal) that mean one examination of animals by their arrival to raising facilities could help in detecting morbid cases that may be missed subclinically, also follow up diseased cases with another examination 1 week post treatment that help in confirming recover, retreatment or considering chronic cases that may be culled early, all should done with special attention to common sites for detecting lung lesions previously reported (Rademacher et al., 2014; Ollivett and Buczinski, 2016) also consolidation depth as a useful prognostic indicator.

Hp found to be the most useful APP that frequently estimated in dairy and beef calves by their arrival, time of diagnosis also post treatment and have better performance than other APP in diagnosis of naturally occurring BRD (Abdallah et al., 2016), results showed that Hp could be indicator of treatment success, in some cases it was related to number of required treatments, depending on that Hp estimation by time of diagnosis/treatment also post treatment can give idea about disease progress either with recovery or relapses, also blood lactate measurement by diagnosis and if the clinical signs augmented may be useful indicator to complete treatment or slaughter of poor prognostic cases according to lactate level.

All possible prognostic tools did not discussed here, also TUS and the reported biomarkers may be not available to be easily used at individual and farm level that considered a limitation of this review,even though, this review aimed to give insight about previously evaluated BRD prognostic tools and try to figure out in quick messages a small schema that may be valuable if used to predict BRD negative outcomes, also further research is recommended on large scale to propose and validate different tools that could be used to predict BRD unfavorable outcomes.

CONFLICT OF INTEREST

Author disclose no conflict of interest.

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