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European Buiatrics Forum

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Mechanisms of Action and the Role of Anti-Pyretic and Anti-Inflammatory Intervention in the Treatment of Bovine Respiratory Disease

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“Humanity has but three great enemies: fever, famine, and war, and of these by far the greatest, by far the most terrible, is fever”
(Sir William Osler; 1849-1919)

1. Introduction

A hallmark sign of infection is an elevation in body temperature. Purists may argue the need to treat an elevated body temperature but the elevation in body temperature is accompanied by a complex set of noxious symptoms. These clinical consequences of the febrile response are well known to anyone who has suffered from an infectious disease or has tended to an afflicted patient. It is not difficult to recognize and score this “clinical depression” in calves with Bovine Respiratory Disease (BRD) as the fever is accompanied by other symptoms such as anorexia and malaise (Figure 1). While difficult to score in animals, humans typically complain of arthralgia, myalgia, headache, and nausea associated with their elevation in body temperature. As Osler suggests, the phenomenon can be debilitating. While the febrile response is routinely treated in pediatric medicine, and in companion animal medicine, even fevers of 40.5°C or 41.0°C in a calf are often not regarded as a reason for immediate pharmacological intervention.

Instead, BRD is universally treated with antibiotics but the antipyretic effect and associated overt clinical symptomatic relief of antimicrobial therapy may not be realized for hours. Besides raising animal welfare concerns, ignoring the febrile response can be detrimental to husbandry. For example, BRD is often associated with recently weaned and transported calves trying to cope with the stress of adapting to their new environment. The ability to cope is difficult at the best of times but is severely impeded by the debilitation caused by the febrile response. The co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) rapidly curtails the febrile response buying time until the effects of the antibiotic become clinically manifest.

NSAIDs have also been reported to confer anti-inflammatory benefits to pneumonic calves. Moreover, there is evidence that some antibiotics possess anti-inflammatory or immunomodulatory effects. The anti-pyretic and anti-inflammatory aspects of both active ingredients in Resflor®, the combination drug containing the antibiotic florfenicol and the NSAID flunixin meglumine, are discussed.
2. Normal Thermoregulation and the Pathogenesis of Fever

Fever is “a state of elevated core temperature, which is often, but not necessarily, part of the defensive response of multicellular organisms (hosts) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host” (IUPS Thermal Commission, 1987). Fever is extremely well preserved throughout evolution. It has been found in numerous phyla and is estimated to be more than four million years old (Mackowiak 2000). Fever is seen in mammals, reptiles, amphibians, and fish as well as in some invertebrates. Not only is it found in endothermic (warm-blooded) animals, it is also seen in ectothermic (cold-blooded) animals (Kluger et al., 1996). In response to infection, lizards will elevate their body temperature by selecting a warmer microclimate (Bernheim and Kluger, 1976).

It has been argued that this preservation and universality of fever must have a purpose. Thus, it has been hypothesized that suppression of this physiological response can be detrimental to overall treatment outcome. The author does not disagree that, at a certain level, the elevation in body temperature is an attempt to create an inhospitable environment for a foreign invader. In the case of BRD, however, we know that this innate immunological defense mechanism is overwhelmed and veterinary intervention is needed. As symptoms progress it is doubtful that the febrile response, or the inflammatory changes taking place in the lungs, are serving any beneficial purpose. In the author’s 20 year experience using flunixin meglumine, as per label directions, as adjunctive therapy in the treatment of BRD, no antagonism with antibiotics has ever been observed. Moreover, in a mass North American industrial feedlot study, calves treated with florfenicol-flunixin had a lower crude case fatality rate (p = .0047) than calves treated with a conventional antibiotic alone (Van Donkersgoed et al., 2009).

Maintenance of body temperature (thermoregulation) is dependent on an integrated network of neural connections involving the hypothalamus, limbic system, lower brainstem, the reticular formation, spinal cord, and the sympathetic ganglia (Boulant, 1997). An area in and near the rostral hypothalamus is also important in orchestrating thermoregulation. This region, the “preoptic area,” includes the preoptic nuclei of the anterior hypothalamus (POAH) and the septum pallusolum. It has been referred to as the organum vasculosum of the laminae terminalis or OVLT (Ryan and Levy, 2003).

In simple terms, the OVLT acts as an internal thermostat, maintaining mean body temperature around a set point. Fever can be described as a regulated rise in body temperature after an increase in the hypothalamic set point (Saper and Breder, 1994). Under the influence of the hypothalamus, physiologic and behavioral functions favoring heat production and heat retention are stimulated until arriving at a newly elevated set point temperature (Saper and Breder, 1994).
In response to certain exogenous pyrogens, such as microbial surface components, white blood cells are stimulated to produce endogenous pyrogens. The most potent of these endogenous pyrogens are interleukin-1 (IL-1), and tumor necrosis factor alpha (TNF-α) (Leon, 2002). Other endogenous pyrogens that are integral in the febrile response include interleukin-6 (IL-6) and the interferons (Netaa, Kullberg and Van der Meer, 2000). These endogenous pyrogens act on the central nervous system at the level of the OVLT. The exact mechanism of how circulating cytokines in the systemic circulation are sensed by neural tissue is not completely known. It has been hypothesized that a leak in the blood-brain barrier at the level of the OVLT allows the central nervous system to sense the presence of endogenous pyrogens. Additional proposed mechanisms include active transport of cytokines into the OVLT or activation of cytokine receptors in endothelial cells of the neural vasculature. These endogenous pyrogens trigger the release of other mediators, most notably prostaglandin E2 (PGE2), in the region of the OVLT. This appears to be mediated by cyclooxygenase-2 (COX-2) as genetically-engineered mice that lack the COX-2 gene were unable to mount a febrile response to endotoxin (Li et al., 1999). Moreover, COX-2-specific NSAIDs are effective anti-pyretic agents (Schwartz et al., 1999). The most likely cell type responsible for producing PGE2 is the microvascular endothelial cell within the CNS, which expresses COX-2 exuberantly after stress (Li et al, 1999; Cao et al., 1996; Matsumura et al., 1998). PGE2 is believed to be the proximal mediator of the febrile response. Pre-optic neurons bearing E-prostanoid receptors alter their intrinsic firing rate in response to PGE2, evoking an elevation in the thermoregulatory set point (Ushikubi et al., 1998; Oka et al., 2000). The elevation in the pre-optic neuron firing rate is communicated via a complex neural and endocrine network and results in physiological alterations which include cutaneous vasoconstriction, shivering, and non-shivering thermogenesis via enhanced release of thyroid hormones, glucocorticoids, and catecholamines (Boulant, 1997). Typical early behavioral changes prior to fever include seeking a warmer environment or adding clothing (Figure 2).
3. The Anti-Pyretic Efficacy of NSAIDs

The primary mechanism for the antipyretic activity of NSAIDs is by blocking the action of COX-2 in the CNS and thus preventing production of the proximal mediator of the febrile response (PGE$_2$). This allows the thermoregulatory set point to return to normal.

Flunixin meglumine remains the most widely used NSAID in livestock medicine. It is the only NSAID approved for use in food-producing animals in the United States. Its popularity in veterinary medicine is no doubt due to the rapidity of clinical onset - the effect often being apparent before the veterinarian leaves the farm.

The antipyretic effect of Finadyne®/Banamine® Injection (flunixin as meglumine 50 mg/mL; Intervet Inc.) in the treatment of BRD has been described by Lockwood, Johnson and Katz (2003). It is evident that while all NSAIDs inhibit cyclooxygenase and have the ability to alleviate pyrexia, in any given circumstance, differences in efficacy between NSAIDs can be observed (Figure 3, Figure 4). The combination product, Resflor, exhibits an antipyretic effect which is indistinguishable from that of the single-entity flunixin meglumine formulation, Banamine/Finadyne (Weingarten et al., 2006) (Figure 5, Figure 6, Figure 7, Figure 8).

While direct inhibition of COX enzyme activity is a major mechanism to effect an antipyretic response, it is evident that other means exist. For example, sodium salicylate, aspirin’s major metabolite, exhibits similar anti-inflammatory and antipyretic properties as aspirin, yet, it is a poor inhibitor of COX in vitro (Weissmann, 2000; Riendeau et al., 1997). Its in vivo efficacy is likely due to down-regulation of COX expression by disabling the transcriptional activator nuclear factor - κB (NF-κB) (Kopp and Ghosh, 1994; Yin, Yamamoto and Gaynor, 1998).

![Antipyretic Effect of Finadyne®/Banamine® in Cattle with BRD](image)

**Figure 3**

Lockwood et al, 2003 Vet Record 152, 392-4

- a: different than ceftiofur p<0.05
- b: different than ceftiofur + carprofen  p<0.05  n=16
Figure 4

**Antipyretic Effect of Finadyne®/Banamine® in Cattle with BRD**

- ceftiofur
- ceftiofur + flunixin
- ceftiofur + meloxicam

a: different than ceftiofur p<0.05
b: different than ceftiofur + meloxicam p<0.05  n=23

Figure 5:

In the development of Resflor, the effect of dose of flunixin within RESFLOR on antipyretic response in cattle with naturally-occurring Bovine Respiratory Disease was examined in order to determine the optimal concentration of flunixin within the combination product. Three treatments were administered subcutaneously once at 40 mg/kg of florfenicol (20 mL/150 kg). Nuflor is the commercial single-agent product containing 300 mg/mL of florfenicol. RESFLOR 1FLX is the current commercial formulation of Resflor containing 300 mg/mL of florfenicol but with twice the concentration of flunixin (co-delivered flunixin at a dose of 4.4 mg/kg BW). On hours 2, 6 and 10 post-dose RESFLOR 1FLX and RESFLOR 2FLX provided a superior antipyretic response than NUFLOR (p<0.0001). There was no difference in the antipyretic response provided by RESFLOR 1FLX and RESFLOR 2FLX at any timepoint (from Weingarten et al., 2006).
Effect of Treatment on Mean Rectal Temperature in US Cattle with BRD (n=170)

Effect of Treatment on Mean Rectal Temperature in EU Cattle with BRD (n=104)

Change in mean group rectal temperatures up to 10 days post treatment

Figure 6

Figure 7

Figure 8:
The antipyretic effect of Resflor in calves with BRD induced by bronchial inoculation of a Mycoplasma bovis culture. Mean group temperatures in the Resflor group had fallen to near baseline levels by approximately 12 hours post treatment (Resflor vs. Saline p<0.05 for all timepoints up to Day 7) (n=23).
4. **The Anti-Inflammatory Efficacy of NSAIDs in the Treatment of BRD**

The ability of flunixin to modulate the lung’s response to the inflammation evoked by infection was first described by Selman et al. (1984; 1986). Lockwood, Johnson and Katz (2003) demonstrated that NSAIDs commonly used in veterinary medicine were capable of reducing lung consolidation in calves afflicted with BRD (Figure 9). This has since been confirmed with Resflor treatment (Figure 10). In order for these benefits to be realized, treatment should be initiated before irreversible damage to the lungs occurs.

The mechanism of action for the decrease in lung consolidation is likely similar to that described above for fever reduction, i.e., direct inhibition of COX enzyme activity and down-regulation of COX expression. It is important to note that the duration of activity of flunixin at the site inflammation is much longer than that predicted by its plasma half-life because of preferential distribution into inflammatory exudate and slow clearance from this space (Espinasse et al., 1994, Landoni et al., 1995).

Additionally, NSAIDs have effects on leukocytes and endothelial cells. Leukocyte adhesion to, and migration through, activated vascular endothelium can be inhibited by NSAIDs (Weissman, 2000; Pierce et al, 1996). Aspirin and sodium salicylate, for example, inhibit leukocyte accumulation at sites of tissue injury (Cronstein et al., 1999). The influx and accumulation of phagocytic and reactive immune cells in the airways and alveolar spaces compromise the ability of the lungs to exchange oxygen. Phagocytic cells that have been attracted to the area take up bacteria and debris while simultaneously releasing tissue-damaging enzymes, cell-attracting chemokines, and cytokines, which further increases inflammation in the area. As cells and inflammatory debris clog the bronchioles and alveoli, the exchange of oxygen is reduced in the area and carbon dioxide increases causing respiratory distress. All of these processes—which are often necessary to control invading pathogens or induce healing—can result in diminished air return and reduced production performance or even death (Thacker, 2008). NSAIDs used in conjunction with antibiotics provide a much greater improvement in respiration in pneumonic calves than antibiotic therapy alone (Weingarten et al., 2006; Figure 11).

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**Figure 9**

Effect of Finadyne®/Banamine® on Lung Consolidation in Cattle with BRD

- Ceftriaxone
- Ceftriaxone + carprofen
- Ceftriaxone + ketoprofen
- Ceftriaxone + flunixin

Lockwood et al, 2003 Vet Record 152, 392-4

n=16

*p < 0.05

**Figure 10**

Effect of Flunixin Concentration Within RESFLOR® on Lung Consolidation

- Nuflor
- Resflor 1FLX
- Resflor 2FLX

Weingarten et al., 2006

a vs. b; p < 0.05
5. The Anti-Inflammatory Efficacy of Antibiotics in the Treatment of BRD

The killing and removal of a bacterial pathogen by an effective antimicrobial agent results in clinical improvement including decreased fever and inflammation. While the focus of this paper has been on the mechanisms of action and justification of the use of NSAIDs in the treatment of BRD, it is noteworthy that some antibacterials can modulate the inflammatory responses by directly affecting host cell function. Zhang et al (2008) demonstrated that florfenicol inhibited early cytokine responses, particularly production of TNF-α and IL-6, by macrophages stimulated in vitro with endotoxin. Moreover, florfenicol increased survival in a murine model of endotoxemia. Florfenicol significantly attenuated the tissue injury of lungs in a mouse model of endotoxin-induced inflammatory lung injury (Zhang et al, 2009). A single dose of florfenicol significantly decreased the W/D ratio (the wet to dry ratio - a measure of lung edema) of lungs and protein concentration in the bronchoalveolar lavage fluid (BALF), and significantly reduced the number of total cells, neutrophils and macrophages in the BALF at 24 hours after endotoxin challenge. The clinical significance of these findings to a calf with bacterial pneumonia is not clear but it is important to note that Resflor, a florfenicol - flunixin combination product, has dual pharmacology and that both active ingredients contribute to the drug’s antipyretic and anti-inflammatory efficacy.

6. Conclusion:

BRD remains the leading cause of illness and death in feedlots. Classically, the efficacy of medicinal agents to treat BRD has been measured by a decrease in mortality or labour costs (e.g., retreatment rates), or improved weight gains. However, an increasingly more sophisticated consumer is interested not only in the cost-efficiency of animal protein production but in how the animal is treated while under our care. Twenty years ago, it was rare for veterinarians to use post-operative analgesia in canine or feline medicine. Today it is routine. Similarly, ignoring the discomfort of a calf with a febrile response is being re-evaluated by the veterinary community.

The addition of an NSAID as adjunctive therapy, or as combination therapy, in the treatment of BRD rapidly provides anti-pyretic relief, and improvement in clinical depression and respiration.
7. References


Rational treatment of respiratory disorders in young bulls, at fattening units in France

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1. Introduction

One third of French beef is produced in fattening units for young bulls (YB). These are non-castrated males, penned at 6-8 months old, a live weight of 270-300 kg and fattened intensively up to 18-24 months of age. In these units, 70% of health problems concern respiratory disorders and an average of 20% of YB are treated for respiratory disease in the first weeks after arrival. Depending on the severity of the situation, respiratory disease reduces the operating income in the Pays de la Loire region by 11 to 26%.

In these units, the farmer feeds and observes the YB once or twice daily. It is the farmer who detects sick animals and decides on treatment with medicines available (or, if he deems necessary, calls the veterinarian). This treatment is aimed, on the one hand, at controlling the bacterial infectious agents (Mannheimia haemolytica, Pasteurella multocida) that play a role in respiratory disease occurring after arrival through the use of antibiotics and, on the other hand, at controlling the inflammatory reaction through the use of an anti-inflammatory (primarily NSAID). The zootechnical objectives of such treatment are to reduce the mortality of YB and reduce the impact of respiratory diseases on the subsequent growth of the animal.

The farmers and/or the veterinarians can also decide to use metaphylactic treatment. Such treatment begins after detection of the first sick animal in a group and consists of group treating the YB, including the sick ones but also the apparently healthy YB that have been in contact. This eliminates the need for accurate detection of all clinical cases and enables rapid treatment of any YB in the early stages of the disease, thus preventing new cases in the group. However, the main risk of metaphylaxis is excessive YB treatment. A key prerequisite of the rational use of metaphylaxis is knowing, at the moment the farmer detects the first clinical case, the proportion of YB actually sick. In other words, the under-detection of cases by the farmers must be quantified. A second prerequisite it the importance of knowing how the treated and the untreated YB will progress clinically (will they become ill?).

The purpose of this study is to discuss, based on the continuous clinical observation and monitoring of the temperature of 12 groups of YB, (i) the level of under-detection of sick animals by the farmers and (ii) the clinical development of both treated and untreated bulls.

2. Observation of young bulls and data collection

In the period between November 2007 and February 2008, 112 young beef bulls (YB) aged between 7 and 11 months (272 ± 40 days) and weighing between 300 and 500 kg (392 ± 45 kg) were observed during the 40 days after arrival. The YB were bought on cattle markets and came from different farms. They were divided into groups of 8 to 12 animals per pen (defined as a group) at 3 commercial cattle farms chosen because of their good animal husbandry practices. A total of 12 pens (=12 groups) of YB were observed. None of the YB had received a vaccine or antibiotic at the time of arrival. Shortly after arrival, all YB on study were given an intraruminal bolus containing a temperature sensor (L=9 cm, Ø=3 cm) which, after being ingested by the animal, was to remain in the reticulo-rumen throughout the animal’s life. The sensor measures and registers the animal’s ruminal temperature, transmitting the data to a computer every 15 minutes. The data from the bolus were analyzed retrospectively using a program that allows (i) correcting for ruminal hypothermia resulting from drinking, (ii) defining a reference ruminal temperature for each animal, and (iii) detecting differences between the ruminal temperature and the reference ruminal temperature, also called ruminal hyperthermia (Figure 1).
3. Description of the clinical patterns at the time of veterinary examination

Based on the data obtained during the examinations and the serum haptoglobin measurements, five different clinical patterns were seen (Cf. Figure 2): (1) "clinically healthy" YB (n=23), (2) clinically healthy YB with a serum haptoglobin concentration ≥0.25 g/l (sensibility=76%, specificity=94%) (n=6), (3) YB with "clinical signs of respiratory disease without hyperthermia" (n=31), (4) YB with "hyperthermia (T°rect ≥39.7°C) without clinical signs of respiratory disease" (n=10) and (5) YB with "hyperthermia (T°rect ≥39.7°C) with clinical signs of respiratory disease" (n=42).
In the 12 groups monitored, the farmers found at least 1 case of respiratory disease in the 13 days following arrival (min: 1d, max: 13d, med: 4d). Within the groups, the clinical patterns were very heterogeneous at the time of detection, while at least 3 different clinical patterns were observed (Figure 3). Between the groups, this strong heterogeneity was observed both in groups without any “clinically healthy” YB (lot 3.3) as well as groups with “clinically healthy” YB, representing half the total number (lot 1.3). However, regardless of the group, the proportion of “clinically healthy” animals was very low (< 50 %), which could be the result of late detection or even failure of detection, by the farmers.

Figure 2: Clinical patterns based on clinical symptoms and serum haptoglobin (Hap) levels.

Figure 3: Description of clinical patterns at the time of initial veterinary examination for each of the 12 groups.
3.1. Late detection of sick bulls by the farmers

The use of an intraruminal bolus made it possible to demonstrate the late detection of sick YB by the farmers. Actually, the treated YB (T°r>39.7°C with ≥ 2 clinical signs of respiratory problems) had ruminal hyperthermia (temperature above the reference temperature) on average 47 hours before treatment (min: 1.48h ; max: 166.39h) (Figure 4).

This late detection of sick YB may be explained by the fact that the clinical signs on which the farmer bases his decision appear late in relation to the onset of the disease. In general, YB farmers mainly look for depression and/or a reduction in feed intake, signs that mostly do not appear until the advanced stages of respiratory disease. Late detection therefore reduces the chances of recovery and aids the transmission of infectious pathogens from sick to healthy animals through contact.

With the use of more advanced detection methods (intraruminal bolus with temperature sensor, infrared thermography), sick animals could be treated several days before the appearance of clinical signs detectable by the farmer. Schaefer et al. have demonstrated that the use of infrared thermography in feedlots enables detection of sick animals 4 to 6 days prior to the appearance of clinical signs. However, these methods are very expensive for use on commercial farms. An alternative could be the regular monitoring of the rectal temperature of YB during the first days after arrival.
3.2. Under-detection of unhealthy animals by farmers

In our study, the farmers detected very few unhealthy animals. Only 6 out of 32 unhealthy YB (Se=19%) were detected by the farmer on farm 1, 9 out of 29 (Se=31%) on farm 2 and 6 out of 27 (Se=22%) on farm 3, compared to detection through a combined veterinary clinical examination and serum haptoglobin measurement.

Analysis of the ruminal temperature data recorded by the intraruminal bolus, revealed numerous cases of hyperthermia not detected/detectable by the farmers, prior to the farmer’s detection of the first clinical case (Figure 5).

Figure 5: Example of a group of 9 young bulls of which 4 were treated after detection by the farmer. This figure shows that 3 out of 5 of the non-treated YB had ruminal hyperthermia in preceding days.

This result is consistent with prior studies of the French YB system: farmers do not detect all animals with respiratory disease. A study based on inspection of the lungs of 2,345 YB in the abattoir, for example, showed that some 60% of YB that were not treated during the fattening period had pulmonary lesions. Therefore, respiratory disease that is left undetected by the farmers not only has a negative effect on the well-being of the young bulls, but also on their growth.

In fact, untreated YB in contact with treated YB show a reduction in average daily gain of 53 g/d compared to YB in groups in which none of the YB were treated. Comparable numbers of under-detection of sick animals was also seen in North American and South African feedlots.

The existence of under-detection of unhealthy YB in our study, justifies an evaluation of the importance of metaphylaxis in YB. Catry et al. have shown that the metaphylactic treatment of lots of beef calves in which at least 10% of new cases was detected within 72 h significantly improved the growth performance of the “apparently healthy” calves in contact with treated calves. However, this potential increase in growth performance is yet to be demonstrated for YB. Moreover, an economic analysis must take into account not only the improvement in growth performance, but also the increased treatment cost (increase in the number of animals treated) to ascertain the profitability of such a therapeutic approach.
4. Clinical development of treated and untreated young bulls

4.1. Clinical Development of YB treated at the first veterinary visit

At the time of detection by the farmer, between 2 YB out of 8 (25%) and 8 YB out of 12 (66%) had a T\textsuperscript{rect} ≥39.7°C with at least 2 clinical signs of respiratory disease. These YB were given Resflor\textsuperscript{®} subcutaneously in a dosage of 2 ml per 15 kg of bodyweight. In 91.9% of the treated YB, therapeutic success was reached 4 days after treatment. After the subcutaneous injection with Resflor\textsuperscript{®}, the ruminal temperature decreased rapidly to below 39.5°C (“normal” ruminal temperature) within 4 hours (Figure 6). As ruminal temperature is strongly correlated to body temperature ($r^2 = 0.8$), it can be said that the body temperature returned to normal within 4 hours after treatment.
The serum haptoglobin concentrations were also elevated on the day of treatment (Figure 7). However, after treatment with Resflor®, these concentrations rapidly decreased to values below 0.25 g/L (Figure 7), the threshold differentiating healthy YB and YB with respiratory problems (Se=76% and Sp=94%).

In our study, the majority of the treated animals had elevated haptoglobin concentrations on the day of treatment, suggesting the presence of inflammation and therefore justifying the use of an anti-inflammatory. Moreover, Pasteurellaceae (Mannheimia haemolytica and Pasteurella multocida) and/or Mycoplasma bovis were isolated from lungs in 76% of the treated bulls (data not shown) which underscores the importance of antibiotic therapy in YB with respiratory disease in the days following arrival.
4.2. Clinical development of YB not treated at the time of the first veterinary visit

After the initial veterinary visit in response to the first case/cases detected by the farmers, further visits were scheduled every 3 days to identify possible new cases of respiratory disease.

In 10 groups out of 12, between 25% and 100% of YB that were not treated during the first veterinary visit (66% on average) were diagnosed sick and treated during the 2 to 10 days following this first visit (Figure 7). Among the YB treated after the first visit, 12 were “clinically healthy” at the time of the first visit (n=23), 2 were “clinically healthy with a serum haptoglobin level of ≥ 0.25 g/l” (n=6), 17 had “signs of clinical respiratory disease without hyperthermia” (n=31) and 4 had a “T°rect ≥ 39.7°C without clinical signs of respiratory disease” (n=10). Thus, amongst the 4 clinical patterns for which no treatment was given during the first veterinary visit, all appeared to be at equal risk of requiring treatment later on.

In the groups in which a significant number of new cases were detected after the first visit (Figure 8), metaphylactic treatment could be considered as a means of reducing the number of secondary cases. This effect of metaphylactic treatment has been demonstrated by Catry et al. In their study, metaphylactic treatment of lots (in which at least 10% of new cases were detected during a period of 72 hours), significantly reduced the number of new cases during the 20 days post-treatment (OR=9.37).

However, in the study groups in which none or only a few secondary cases were detected (Figure 8), this beneficial effect of metaphylaxis is less clear. It thus seems that in order to accomplish effective metaphylaxis, it is necessary to predict the number of new cases to expect after detection of the first case. However, as yet, there are no criteria allowing such a prediction to be made.

Figure 8:
Treatment of sick animals in 2 groups of YB in the study. In group 4 from farm 2, none of the YB not treated at the time of the first visit were subsequently treated, while in group 3 from farm 2, 4 YB not treated during the first visit were treated within 8 days after this visit.
5. Conclusion

In the 12 pens (=groups) of young bulls in this study, the detection of respiratory disease by farmers was late and incomplete. On average, they detected the disease more than 47h after the onset of hyperthermia. Moreover, they detected less than 31% of unhealthy animals compared with the clinical examination by a veterinarian combined with the measurement of serum haptoglobin levels. Given these difficulties in detecting unhealthy animals, metaphylactic treatment of all animals in the group could be indicated. However, it is important to further confirm the clinical and economic benefits of such approach.

Furthermore, in this study the clinical development of untreated animals in contact with treated animals was variable. In certain groups, the untreated animals later became sick, favoring the use of metaphylaxis. Conversely, in other groups the absence of new clinical cases advocates against this approach. It is important, therefore, to be able to first predict the number of secondary cases to be expected. As yet, there are no criteria allowing such a prediction to be made.

In this study, despite the often late detection and late treatment of respiratory disease, the use of a treatment comprising an antibiotic and an anti-inflammatory (Resflor®) yielded a therapeutic success of 91.9 % (4 days post-treatment) and brought about a rapid decrease in body temperature (<4 h) and serum haptoglobin levels ([Hap] <0.25g/l during the 6 days post-treatment) in the treated animals.
6. References


Notes