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The Bovine Respiratory Syncytial Virus: Short-and Long-Term Consequences

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Introduction

The Bovine Respiratory Disease Complex (BRDC) is a huge problem worldwide. Cost estimations reach 3 billion dollars every year for the cattle industry[1]. Among the pathogens implicated in the complex, the Bovine Respiratory Syncytial Virus (BRSV) has been associated with 45% of BRDC cases[2] (and 60% in case of enzootic calf pneumonia[3]). These simple numbers show by themselves the tremendous importance of BRSV in cattle production.

Acute disease

Overview

The acute harmful effects of a virulent strain of BRSV circulating among young calves can be obvious. They are usually noticed in the group of calves aged between 1 and 6 months (yet, it is noteworthy that the age is not protecting by itself. If cattle are immunologically naive, they might die of the consequences of the infection at any age[4]). Those effects appear as a severe contagious respiratory disease: the morbidity can reach 80% of calves and mortality 20%[5]. In practice, even the most aggressive therapy is not successful in treating the most affected animals.

Image 1: BRSV is one of the most common cause of respiratory disease worldwide

BRSV specificity

Such a life-threatening acute disease, frequently seen with BRSV, is rarely observed with PI-3. However, these two viruses induce necrosis of epithelial cells of bronchioles. Thus, the origin of the lethal consequences of BRSV infection cannot be found in its direct cytopathic effect but in the ability of the virus to trigger a severe acute inflammation in the whole organ.

Lesions

Macroscopically, this inflammation shows the hallmarks of an acute bronchointerstitial pneumonia with emphysema. The lungs of calves that died after an acute BRSV infection are **highly congestive**. The congestion is irregular giving a heterogenous aspect to the parenchyma. In most cases, the antero-ventral region of the lungs is the most congestive and show some atelectatic portions. The **lymph node reaction** is always present and is usually obvious as the lymph nodes swelling can exceed 10 times the normal size. The **emphysema** also is characteristic of the disease. The histopathological exams reveal a clear damage of bronchioles: epithelial cells necrosis, the presence of large multinucleated syncytial cells (that gave its name to the virus), and a mixed infiltration of neutrophils and some eosinophils (unusual in classical viral lesions). The epithelial necrosis can also involve the pneumocytes. As a consequence, re-epithelialisation of the alveolar wall by type 2 pneumocytes is often present.

Pathogenicity

Although there are still lots of questions about the pathogenicity of the disease, the literature focusing on the disease caused by Pneumovirus (the human and the bovine syncytial virus) indicates that the worst clinical evolutions are induced by a **Th2 biased immunoreaction**[5]. That kind of reactions are close to type I hypersensitivity and implicate the action of the IgE, the eosinophils and sometimes the neutrophils[6]. In calves, the neutrophils seem to play a key role in this pathogeny[7]. Why, in the same herd, some animals trigger this biased deleterious inflammatory reaction and some other not, remains a tough question.

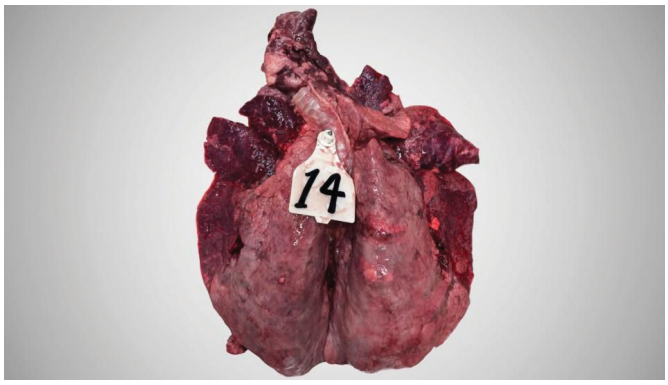

Image 2: Typical macroscopic BRSV lesions found in the lung are emphysema and atelectasis

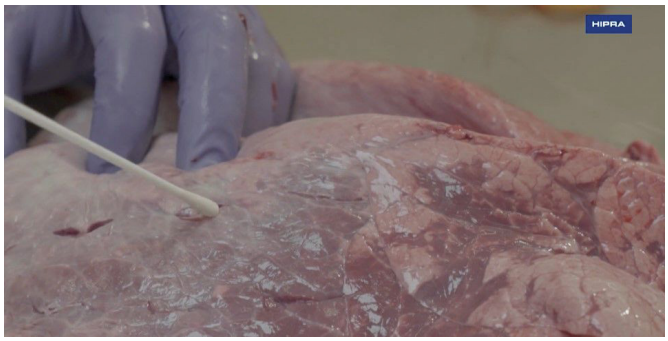

Image 3: Sample collection with swabs from lung parenchyma for PCR testing

The answer is dependent on the host-pathogen relationship.

- On the one hand, there are evidence that some **virus strains** are better able to elicit a severe inflammation. One small peptide was identified for BRSV to be one of the key players of the biased reaction: the virokinin[8].. It has proven to be able to attract eosinophils (pivotal cells in Th2 reaction) and to contract smooth muscles of the bronchi. This last effect is probably the explanation of the severe emphysema that is characteristic of BRSV induced pulmonary lesions.
- On the other hand, in the pathogeny of the BRVS, the role of the **host** is not secondary. At field level, clinical BRSV outbreaks highlight the importance of the host. Indeed, unlike many other pathogens, which induce the most aggressive diseases in the weakest animals, BRSV often kills the healthiest animals. In beef farms, as an example, it is frequently seen that "the most beautiful" calves die first. This simple observation reflects the fact that a special configuration of the host's organism has

to be present to trigger the disease and not just a "classical" weakness.

Chronic evolution

The chronic consequences of the infection are far less obvious than the acute morbidity and mortality and are often underestimated.

Medium term consequences

The above-mentioned acute lesions reflect the action of the virus on the epithelial cells of bronchioles and alveoli. But, BRSV has also severe repercussions on the **tracheal epithelial** cells. The ciliated epithelium of the trachea, together with the goblet cells, form one of the most efficient innate defences of the respiratory system: the **mucociliary escalator**. In physiological conditions, the mucociliary escalator is a mechanical fence that prevent the colonization of the respiratory tract by *Pasteurellacea*, the main pathogenic bacterial family in cattle. Experimentations show that in healthy calves, 90% of the *Pasteurella multocida* experimentally introduced in the trachea are cleared within 4 hours. However, other studies point out that BRSV can decrease the mucociliary clearance by 50%[9]. In those conditions, the fence is a lot easier to cross for the nasopharyngeal pathogenic microflora. Moreover, the increased attraction of neutrophils[10] during BRSV infection is thought to increase the effect of the Leukotoxin of *Mannheimia haemolytica* (the main virulence factor). By its detrimental action on the tracheal epithelium, BRSV **greatly promotes bacterial infections** of the lungs.

Long term consequences

Because of the high level of exudation and tissue damage, the chronic long-term consequences of a bacterial infection are straightforward. For viral infections, the usual vision is an acute phase, that can be life-threatening, followed, if the animal survives, by a full recovery. This conception is not true with BRSV. The best illustration of that is the case described by Klem and colleagues[11]. The authors measured the long-term effects of an outbreak of BRSV in an artificial insemination test centre. Because of the available zootechnic data in the centre, the imperceptible consequences of the infection became visible. Compared to the "non clinical/non treated" group, the bulls that showed symptoms had a constantly lower (4-10%) weight/age-ratio during the 8 month period of the study. But, more surprisingly, when the "non clinical/non treated" group was compared with a comparable group of the following year, this "healthy" group had a reduced daily gain of 111g/day. This study shows how harmful is a clinical outbreak of BRSV for the productivity of the young herd. Even in asymptomatic animals, a virulent strain of BRSV can induce long-term lesions that will reduce cattle performances.

The origin of these long-term alterations is a lesion called **bronchiolitis obliterans**[12]. This is an unspecific lesion of the bronchioles which can be induced by BRSV in a very large number. It consists in small fibrous polypoid nodules that bulge in the lumen of the bronchioles causing a large obstruction. The functional consequence is a drop in the gas exchanges efficiency in the lungs.

Conclusion

Evidences of long-lasting deleterious consequences of BRSV outbreaks in naive animals (in addition to the obvious losses associated with the calves that die of the disease) are the reasons for which **prevention is the only effective way** to deal with this issue.

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Dr Calixte graduated in Veterinary Medicine from the University of Liège (Belgium) in 2006. After spending a few years as a field veterinarian practicing a mixed practice (2006-2009), he started to work as a assistant in the Pathology and Autopsy Department (2009-2019) in the University of Liège. In 2019, Calixte completed his PhD in the same university where he is first assistant in the Production Animal Clinical Department: clinic for individual cases referred, herd audits and reproduction monitoring.

He is author of numerous scientific publications in different cattle diseases, having also a wide teaching experience in cattle udder health and analysis of reproductive parameters at the herd level. He has performed trainings to veterinary practitioners on respiratory diseases and calf nutrition and delivered also popular presentations for other professions or the general public such as on bovine respiratory syncytial virus for livestock farmers.

References available on request