Gangrenous pneumonia, ovine respiratory complex and visceral form of caseous lymphadenitis: relevance in lower respiratory tract disorders of adult sheep

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ABSTRACT

'Numerous disorders affect the lower respiratory tract of adult sheep, including Maedi Visna, ovine pulmonary adenocarcinoma and verminous pneumonias as reported elsewhere in this special issue. Herein we examine gangrenous pneumonia, ovine respiratory complex (ORC) and the visceral form of caseous lymphadenitis (CLA).

Gangrenous pneumonia is a pulmonary infection commonly caused by inhalation of foreign materials, producing inflammation and necrosis of the lung parenchyma. ORC is a complex disease process involving a range of host-pathogen-environment interactions, where host immunological and physiological mechanisms interact with multiple etiological agents including bacteria, plus environmental factors or stressors. Visceral form of CLA commonly causes lesions in mediastinal lymph nodes and lung parenchyma, producing respiratory clinical signs, particularly the coughing that is responsible for transmission of the disease by aerosol. The economic relevance, etiological, clinical and pathological findings of these diseases are reviewed.

Keywords: ovine, lower respiratory tract diseases, foreign body aspiration pneumonia, Fº Pasteurellacea, *Corynebacterium pseudotuberculosis.*

1. Introduction

Ruminants are particularly sensitive animals to the development of lung pathologies and respiratory diseases are commonly encountered in sheep flocks, affecting groups or individuals. There are several infectious diseases affecting upper and lower respiratory tract in sheep that often involve a combination of infectious causes as well as predisposing management factors, potentially leading to significant losses. Respiratory diseases have been extensively studied in lambs as these animals are usually more severely affected than adults. However, adult sheep can suffer from several relevant respiratory diseases that furthermore are some of the most frequent pathologies found in these animals (Mearns, 2009; Suárez and Busetti, 2009; Lacasta et al., 2016).

The three upper respiratory tract pathologies more frequently found in sheep in Europe have been the subject of specific articles in this special issue: oestrosis (Gracia et al., 2019); enzootic nasal adenocarcinoma (De las Heras et al., 2019) and chronic proliferative rhinitis (Rubira et al., 2019). In lambs, the most relevant disease affecting lower respiratory tract is ovine respiratory complex, widely studied in this journal (Navarro et al., 2019a; 2019b; González et al., 2019a; 2019b). However, in adults, there are several diseases affecting the lower respiratory tract, including Maedi Visna (MV), ovine pulmonary adenocarcinoma (OPA), ovine respiratory complex (ORC), gangrenous pneumonia, verminous pneumonia and the visceral form of caseous lymphadenitis (CLA). Further, the diagnostic difficulty relies on the clinical differentiation of all of them, because auscultation of the ovine chest alone does not always allow the clinician to determine the presence of all superficial lung pathology nor accurately define its distribution (Scott et al., 2010). Therefore, it will be necessary to make use of diagnostic imaging techniques, such as ultrasonography, X-rays or computed tomography that provide more accurate information regarding the nature and extent of the superficial lung lesion, or perform bronchoalveolar lavages in order to determine the etiological agent of the disease and pattern of inflammatory cells. Post-mortem examination should be encouraged to identify the diseases present on the farm as well as for the collection of samples for etiological analysis.

As Maedi Visna (Luján et al., 2019), ovine pulmonary adenocarcinoma (Ortín et al., 2019) and verminous pneumonia (Ferré and Sotiraki, 2019) have been deeply studied in this special issue only gangrenous pneumonia, ovine respiratory complex and caseous lymphadenitis will be reviewed in the article.

2. Gangrenous pneumonia associated with aspiration of foreign body

Gangrenous pneumonia is a pulmonary infection commonly caused by inhalation of foreign materials, producing inflammation and necrosis of the lung parenchyma. It is sometimes described as foreign-body pneumonia, inhalation pneumonia or aspiration pneumonia and has been diagnosed in several domestic animals (Blowey and Weaver, 2011; Scott et al., 2011; Scott, 2017; Darcy et al., 2018). The aspirated material is usually inspired into the antero-ventral lobes of the lung where it produces moderate to severe, peracute or subacute, necrotizing bronchopneumonia, depending on the composition of the inhaled material, the microorganisms involved and the host responses.

Aspiration of foreign material into the lung can be due to a range of causes, as described in the literature (Blowey and Weaver, 2011; Scott et al., 2011; Scott, 2017; Darcy et al., 2018). Aspiration of foreign material into respiratory system may come from rumen contents following bloat or during general anaesthesia. When animals are anesthetized, regurgitation of gastric contents can occur both light (active regurgitation) and deep (passive regurgitation) (Pugh and Baird, 2012). Moreover, aspiration of inappropriately administered oral antiparasitic treatments as drenches, is common and usually reflects poor drenching technique, often involving lifting of the head of the sheep when administered to sheep. In dips is also common, often involving excessive immersion of the head as the animals is swimming in the dip bath or shute (Scott, 2017).

Another possible cause of aspiration pneumonia described in the literature can be a laryngeal hemiplegia, which was referred in an 18-month-old ram with a macroscopic laryngeal asymmetry and musculature atrophy in the left side. Necropsy showed a gangrenous pneumonia accompanied by fibrinous pleuritis (Sáez et al., 2003). Aspiration pneumonia has been also found associated with oesophageal myonecrosis due to BTV infection in sheep (Antoniassi et al., 2010). Lambs with nutritional myopathy can also have difficulties of deglutition and develop inhalation pneumonia (Scott, 2017) and also milking lambs fed by bottle can suffer a choking that leads to an aspiration pneumonia. In addition, those respiratory pathologies that hinder the correct breathing, favour the inhalation of vegetable material and the appearance of these conditions. In this sense, it is common to find gangrenous pneumonia in association with other lower respiratory disorders (Lacasta et al. 2016; Lacasta et al., 2019).

Vegetable material is frequently seen at post-mortem examination and in histological sections of lung lesions of adult sheep with gangrenous pneumonia. The presence of this vegetable material can suggest that seeds or ears of cereals have been inhaled while they are eating (Figure 1) or that regurgitated vegetable material from the rumen has been inspired during rumination (Viall et al., 2018). In this sense, gangrenous pneumonia was experimentally reproduced by Biescas et al. (2009) with a fragment of wall from barley mixed in a sample of fresh ovine rumen content and introduced directly into the bronchus. However, no foreign bodies into the airways were found by Ménsua et al. (2003) in a study of AA amyloidosis in small ruminants where the 76.2% of animals had gangrenous pneumonia that triggered renal amyloidosis.

Most of the microorganisms producing gangrenous pneumonia are normal inhabitants of the nasopharynx. A range of anaerobic and aerobic bacteria, fungi and viruses have been isolated from these gangrenous lesions, indicating that most involve mixed infections (Sáez et al., 2003; Azizi et al., 2013). In a survey developed by Lacasta et al. (2019), which involved 195 culled sheep, *Trueperella pyogenes, Pasteurella multocida* and *Mycoplasma ovipneumoniae* were the most frequently isolated microorganism from gangrenous pneumonias. Pyogenic bacteria are usually isolated from these lesions, such as *Streptococcus* or *Trueperella pyogenes* which are ubiquitous inhabitants of oropharynx, upper respiratory and gastrointestinal tracts of animals (Risseti et al., 2017). *Trueperella pyogenes* has been frequently isolated from suppurative lungs or abscesses from sheep (Ribeiro et al., 2015; Risseti et al., 2017), in which *plo* gene was detected promoting haemolysis, cytolysis of immune cells and tissue damage, being considered the major virulence factor of *T. pyogenes* (Risseti et al., 2017). *Fusobacterium necrophorum* has also been isolated from pneumonic lungs of Bighorn sheep with suppurative and necrotic lesions (Shauthalingam et al., 2016).

Clinical signs often appear within a week or two following an intervention, including oral anthelmintic or dip bath treatments, although initially, an association with the intervention may not be readily apparent. Affected sheep separate from the mob, displaying inappetence, appear to be in pain, showing antalgic position and depressed. The rectal temperature can be as high as 41.5ºC (Biescas et al., 2009). Respiratory signs may include coughing, dyspnea, rales when the process progresses sufficiently, abnormal breath odour can be detected suggestive of the necrotizing exudates occurring in gangrenous pneumonia (Méndsua et al., 2003; Biescas et al., 2009; Pugh and Baird, 2012). As auscultation and clinical examination not always lead to a proper diagnosis, ancillary tests as ultrasonography or X-ray will become very useful tools. An X-ray shows a mixed pattern (alveolar and interstitial) where the lesion is located. Affected areas present loss of opacity that sometimes can be mistaken for emphysema, although usually the lesion is surrounded by clear border (Castells et al., 2019). Ultrasound images are clear, offering different hyperechogenic foci in all the affected area depending on the material inside the lesion (Castells et al., 2019).

At necropsy, necrotizing lesions usually distributed in anteroventral lung lobes and usually involving bronchi, bronchioles and occasionally causing pleuritis, are characteristic of gangrenous pneumonia. The lesions are usually accompanied by accumulation of a foul-smelling brown to grey exudate (Biescas et al., 2009). Further, gangrenous pneumonia frequently leads to AA amyloid deposition in gastrointestinal tract and kidneys triggering a renal amyloidosis easy to diagnose macroscopically (Ménsua et al., 2003; Biescas et al., 2009).

Although laboratory analyses are not normally necessary to diagnose a gangrenous pneumonia, aetiological analysis can be performed in order to know the microorganisms implicated. Bronchoalveolar lavages enable examination of exudates from live animals, assisting choice of therapy. Increases in serum gamma globulins in response to the chronic infectious process that promotes antigenic stimulation were demonstrated in experimental infections (Biescas et al., 2009). Other findings reported by these authors were the decrease in serum albumin, cholesterol and calcium levels and alterations in urinary parameters due to renal amyloidosis induced by the chronic infection (Biescas et al., 2009).

If therapy is possible, results of antibiotic susceptibility tests performed on exudate samples can guide the choice of antimicrobial agent to administer. In addition, imaging techniques (X-ray and ultrasound) may assist in determining the degree of extension of the lung lesion and, consequently, the prognosis. Equally, if it is known that a sheep has inhaled a foreign body, treatment should commence immediately, prior to the onset of respiratory signs. Therefore, in early cases, treatment should be carried out based on β-lactam antibiotics, during at least seven days, associated with nonsteroidal anti-inflammatory drugs (NSAIDs) at the first days of the therapeutic protocol to improve the breathing condition (Scott, 2017). If aspiration or regurgitation occurs during anaesthesia and before intubation of animal can be completed, a bronchodilator such as aminophylline should be administered to relieve bronchospasm (Pugh and Baird, 2012). Despite the treatments and efforts to treat this disease, the prognosis is very poor (mainly at chronic phase) and many animals die or must be euthanized, then efforts must be directed to prevention. Prevention against this disease requires that risk factors for aspiration are addressed, particularly the risks from inappropriate administration of oral therapies and antiparasitic baths.

3. Ovine Respiratory Complex in adult sheep

The major bacterial respiratory processes affecting adult sheep was traditionally described as "pasteurellosis" reflecting that bacteria from the family *Pasteurellaceae* were predominantly involved. Other names associated with this disease are enzootic pneumonia or atypical pneumonia. However, these are names related only to the pneumonic presentation, but not to the systemic form of the disease. In our opinion, similarities of adult "pasteurellosis" with the ovine respiratory complex in lambs suggests that the disease be described as well as ovine respiratory complex (ORC). As in ORC in lambs, this respiratory disorder in adults reflects a complex disease process involving a range of host-pathogen-environment interactions (HPE), where host immunological and physiological mechanisms (host), interact with multiple etiological agents including bacteria (pathogen), plus environmental factors or stressors (environment). Environmental factors have proven to be key in the development of this pathology, so the influence of climatic factors and the facilities where animals are housed has been widely reported (Lacasta et al., 2008; Navarro et al., 2019b). Although the clinical presentation and severity of the disease may differ with ORC in lambs, the distribution of lesions at necropsy are similar, reflecting common disease mechanisms. Hyperacute or peracute lesions are often characterized by hemorrhages. Acute and subacute forms are characterized by varying degrees of lung consolidation from the exudates produced, including pus causing suppurative or catharral pneumonia or fibrin causing fibrinous pneumonia. Chronic pneumonias reflect the onset of fibrous tissue, increasing the severity of consolidation. Description of the clinical presentations of ORC can be found in González et al. 2019a of this special issue.

In a survey developed at the greatest dairy sheep farm in Spain, the ovine respiratory complex was the 2nd most frequent reason of death, following by reproductive disorders, and in another study carried out in a large meat-production flock managed under the semi-extensive system ORC was the first cause of death in both adult animals and replacement (Lacasta et al., 2019).

In a study conducted on 3,673 necropsied animals (786 milking lambs, 2,730 feedlot lambs, 94 replacement animals and 63 adult sheep), differences among the groups in the type of ORC clinical presentation were observed in the analyzed animals (Figure 2). The most frequent presentation that caused the death in the youngest animals was the acute form of ORC, while adult animals primarily died of hyperacute ORC. In adults, very often, hyperacute form of ORC is the final cause of death after the animal has undergone another process. When the immune system is comprised, etiological agents of ORC can cause the rapid death of the animal. Chronic forms of the disease are responsible for an early culling of sheep. In a survey carried out on 195 culling sheep, 60% of the animals showed some pattern of lung lesion (Lacasta et al., 2019).

Clinical signs of the hyperacute form of ORC are those related to a septicemic process with sudden deaths or non-specific clinical symptoms as fever, anorexia and depression. The clinical signs in the acute form are dullness, anorexia, pyrexia and varying degrees of hyperpnoea or dyspnea with respiratory pathological sounds as rhonchus and crackles. Finally, the symptoms of the chronic form are similar to those other chronic diseases that affect the respiratory tract in adult sheep and that involve productive-like lesions such as ovine pulmonary adenocarcinoma (OPA) or gangrenous pneumonia with severe dyspnea accompanied with rhonchus, crackles and wheezing. Advanced OPA can be distinguished with the "wheelbarrow test", even sometimes, when the animal lowers the head during feeding, clear frothy fluid may flow freely from both nostrils. However, the only difference in clinical signs of ORC from gangrenous pneumonia is the presence of malodorous breath in the latter disorder. An accurate clinical diagnosis of ORC usually requires that ancillary tests including ultrasonography of the lung (Scott, 2010) or bronchoalveolar lavages to identify the microorganisms involved (Rowe et al., 2001) are performed. In an outbreak, necropsies with sample collection and microbiological analysis is required.

As in lambs, several infectious agents have been associated with ORC, the more important being: *Mannheimia haemolytica*, *Pasteurella multocida*, *Bibersteinia trehalosi* and *Mycoplasma* spp., usually, found mixed in the isolates with more than one bacteria species implicated (Miller et al., 2011). Moreover, most of these bacteria exist as commensal organisms of the nasopharynx, tonsil and lungs of healthy sheep (Glendinning et al., 2016) and under certain circumstances can produce disease. For that reason, etiological diagnosis is essential for the control of ORC.

As described, treatment of ORC can be complicated by the range of pathogens including bacterial serotypes involved, however, several treatments can be advisable on the use of β-lactams and NSAIDs (eg. Flunixin) that may play a very important role in the acute condition of avoiding death due to intense pulmonary edema resulting from inflammation. However, the treatment of chronic cases is less advisable since very long treatments would be necessary to obtain an appropriate degree of healing.

Prevention is important for controlling the disease and is based on optimal management of the animals and facilities to avoid or at least minimize the risk factors causing stress, improving animal welfare, as it has been extensively explain in other article of this special issue (González et al., 2019b). In outbreaks, vaccination plans could be implemented or at least considered for the flock at risk of ORC.

4. Pseudotuberculosis or caseous lymphadenitis (visceral form)

Caseous lymphadenitis (CLA) is caused by *Corynebacterium pseudotuberculosis* and can present as either the superficial form characterized by abscess development in superficial lymph nodes, or the visceral form affecting internal lymph nodes and organs, mostly observed in adults (Fontaine and Baird, 2008). CLA is common in sheep and distributed worldwide, causing important economic losses (Fontaine and Baird, 2008; Windsor and Bush, 2016). In countries where there is minimal vaccination, the losses may include costs of managing clinical cases, although where the clinical disease is largely controlled by vaccination, the losses mostly occur at abattoirs from carcass condemnations (Windsor, 2014). Several surveys have confirmed the importance of CLA, including a study of CLA prevalence in 485 culled sheep where the prevalence of animals with abscesses of any etiology was 36% compared to 21% for confirmed CLA (Arsenault et al., 2003). A more recent abattoir survey of over 692 sheep concluded that the prevalence of CLA, based on gross and bacteriological examination, was 32.65% (Al-Gaabary et al., 2010).

The previously report study of 485 culled sheep, found 70% of culled sheep with CLA had abscesses in the thoracic cavity, 26% in external sites (head, neck and shoulder) and 25% in the abdominal cavity (Arsenault et al., 2003). In a study by our research group of over 132 culled sheep with an average age of 5.2 years, we identified that 32% of the animals had CLA lesions, of which 70% had the visceral form of the disease, with 80.9% having lesions in the thoracic cavity. CLA was the only cause of culling in 47% of these animals. The mediastinal lymph node was the most commonly affected lymph node, identified in 57.1% of the animals although as a single lesion in 48.0% of these (Figure 3). Lesions involving the lung parenchyma resembling abscesses caused by *C. pseudotuberculosis* were observed in a 23.8% of the affected animals, with 19.0% occurring as a single lesion (Navarro et al., 2015). Consideration of the high rate of CLA lesions in the thoracic cavity, including either mediastinal lymph node and/or lung parenchyma and usually producing respiratory clinical signs, the inclusion of CLA in this review of respiratory disorders is justified (Figure 4), particularly as these lesions are the source of the aerosol that is considered of relevance to the mode of transmission of the disorder (Windsor, 2011). This respiratory route for the transmission of *C. pseudotuberculosis* infection from infected animals with pulmonary lesions presenting as the major source of exposure to naïve animals within a flock is well recognised (Pepin et al., 1999; Williamson, 2001; Fontaine and Baird, 2008). That pulmonary lesions occurring within the walls of airways may rupture resulting in local exudation and the production of an infectious aerosol is supported by the isolation of infectious organisms from the tracheas of the infected sheep (Pepin et al., 1999; Fontaine and Baird, 2008; Windsor, 2011).

The control of CLA is assisted by a confirmed diagnosis of the disease although this is still a matter of intense research (Oreiby, 2015; De la Fuente et al., 2017). Clinical lesions suggestive of the superficial form of CLA may be confirmed by microbiological analysis. Visceral lesions are more difficult to detect clinically, unless the animal with respiratory lesions is coughing. Progressive weight loss and chronic recurrent ruminal tympanism may also accompany visceral CLA lesions (Oreiby, 2015). Microbiological confirmation of the visceral form in live animals is challenging, although isolation of *C. pseudotuberculosis* from respiratory exudates and/or urine are indicative of respiratory or renal lesions, respectively (Ferrer et al., 2009). However, respiratory clinical signs associated with CLA are often not readily recognized, particularly if only dyspnoea is detected without audible sounds of thoracic cavity pathology, as occurs when the content of abscesses is encapsulated. Diagnostic imaging techniques assist confirmation of the visceral form of the disease, with isolation of *C. pseudotuberculosis* at necropsies enhancing diagnostic investigations. Although the etiological diagnosis of the disease would be advisable, absence of a confirmed bacteriological diagnosis should not preclude implementation of strategic control by vaccination where the pathological evidence is considered sufficiently diagnostic.

In countries where CLA vaccination is not available, control of the disease may require identification of the infected animals to prevent their contact with the uninfected ones, which usually means that serologic testing is required (Windsor, 2011), although autologous vaccines can be considered. Serological tests, particularly those detecting humoral responses, have specificity and/or sensitivity deficiencies and consequently, repetitive serological monitoring is a preferred option than applying a single testing policy for diagnosis and control of CLA in sheep and goat flocks (Oreiby, 2015). Moreover, CLA can be diagnosed by blood and milk gamma interferon assay (Oreiby and Hegazi, 2016).

The preferred strategy to control CLA is routine and persistent vaccination of healthy sheep in a population, coupled with culling of infected animals (Windsor, 2011). As with many vaccination programs, the currently licensed vaccines suppress the disease rather than conferring complete protection of immunized animals, so CLA will persists despite routine vaccinations (Lacasta et al., 2015; Windsor and Bush, 2016). However, vaccination schedules should be implemented to reduce the numbers of infected animals and the prevalence of the disease into the flock, with efficacy of the vaccination plan dependent on the vaccination programme used (Windsor, 2011; Windsor, 2014).

4. Concluding remarks

The lower respiratory tract pathology in sheep is very common and has great diagnostic difficulty due to the high number of pathological processes that settle at this level, all causing a very similar clinical symptomatology. ORC and gangrenous pneumonia are both disorders that have to be included in the differential diagnosis of productive processes, along with the ovine pulmonary adenocarcinoma. However, caseous lymphadenitis, as it does not produce productive clinical signs, should be added to the differential diagnosis of non-productive processes, such as interstitial pneumonia associated with Maedi Visna virus.

Conflict of interest statement

The authors have nothing to disclose.

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Figure legends

Figure 1. Vegetable material causing gangrenous pneumonia is shown inside the lesion. The lesions comprised foci of pulmonary necrosis with accumulation of a foul-smelling exudate with an associated pleuritis.

Figure 2. Hyperacute, acute and chronic clinical presentation of ovine respiratory complex in 3,673 necropsied animals: lactation, feedlot, replacement and adults. (Original research without publishing).

Figure 3. Location of the lesions in the visceral form of caseous lymphadenitis in 485 culled sheep (multiorgan presentation, mesenteric lymphnode, mediastinal lymphnode and lung parenchyma).

Figure 4. Gross view of a sheep lung. (A) Mediastinal lymph node affected by caseous lymphadenitis. (B) CLA pyogranuloma within the parenchyma.

*Manuscript (latest version with changes highlighted)

Gangrenous pneumonia, ovine respiratory complex and visceral form of caseous lymphadenitis: relevance in lower respiratory tract disorders of adult sheep

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ABSTRACT

'Numerous disorders affect the lower respiratory tract of adult sheep, including Maedi Visna, ovine pulmonary adenocarcinoma and verminous pneumonias as reported elsewhere in this special issue. Herein we examine gangrenous pneumonia, ovine respiratory complex (ORC) and the visceral form of caseous lymphadenitis (CLA). Gangrenous pneumonia is a pulmonary infection commonly caused by inhalation of foreign materials, producing inflammation and necrosis of the lung parenchyma. ORC is a complex disease process involving a range of host-pathogen-environment interactions, where host immunological and physiological mechanisms interact with multiple etiological agents including bacteria, plus environmental factors or stressors. Visceral form of CLA commonly causes lesions in mediastinal lymph nodes and lung parenchyma, producing respiratory clinical signs, particularly the coughing that is responsible for transmission of the disease by aerosol. The economic relevance, etiological, clinical and pathological findings of these diseases are reviewed.

Keywords: ovine, lower respiratory tract diseases, foreign body aspiration pneumonia, Fº Pasteurellacea, *Corynebacterium pseudotuberculosis.*

1. Introduction

Ruminants are particularly sensitive animals to the development of lung pathologies and respiratory diseases are commonly encountered in sheep flocks, affecting groups or individuals. There are several infectious diseases affecting upper and lower respiratory tract in sheep that often involve a combination of infectious causes as well as predisposing management factors, potentially leading to significant losses. Respiratory diseases have been extensively studied in lambs as these animals are usually more severely affected than adults. However, adult sheep can suffer from several relevant respiratory diseases that furthermore are some of the most frequent pathologies found in these animals (Mearns, 2009; Suárez and Busetti, 2009; Lacasta et al., 2016).

The three upper respiratory tract pathologies more frequently found in sheep in Europe have been the subject of specific articles in this special issue: oestrosis (Gracia et al., 2019); enzootic nasal adenocarcinoma (De las Heras et al., 2019) and chronic proliferative rhinitis (Rubira et al., 2019). In lambs, the most relevant disease affecting lower respiratory tract is ovine respiratory complex, widely studied in this journal (Navarro et al., 2019a; 2019b; González et al., 2019a; 2019b). However, in adults, there are several diseases affecting the lower respiratory tract, including Maedi Visna (MV), ovine pulmonary adenocarcinoma (OPA), ovine respiratory complex (ORC), gangrenous pneumonia, verminous pneumonia and the visceral form of caseous lymphadenitis (CLA). Further, the diagnostic difficulty relies on the clinical differentiation of all of them, because auscultation of the ovine chest alone does not always allow the clinician to determine the presence of all superficial lung pathology nor accurately define its distribution (Scott et al., 2010). Therefore, it will be necessary to make use of diagnostic imaging techniques, such as ultrasonography, X-rays or computed tomography that provide more accurate information regarding the nature and extent of the superficial lung lesion, or perform bronchoalveolar lavages in order to determine the etiological agent of the disease and pattern of inflammatory cells. Post-mortem examination should be encouraged to identify the diseases present on the farm as well as for the collection of samples for etiological analysis.

As Maedi Visna (Luján et al., 2019), ovine pulmonary adenocarcinoma (Ortín et al., 2019) and verminous pneumonia (Ferré and Sotiraki, 2019) have been deeply studied in this special issue only gangrenous pneumonia, ovine respiratory complex and caseous lymphadenitis will be reviewed in the article.

2. Gangrenous pneumonia associated with aspiration of foreign body

Gangrenous pneumonia is a pulmonary infection commonly caused by inhalation of foreign materials, producing inflammation and necrosis of the lung parenchyma. It is sometimes described as foreign-body pneumonia, inhalation pneumonia or aspiration pneumonia and has been diagnosed in several domestic animals (Blowey and Weaver, 2011; Scott et al., 2011; Scott, 2017; Darcy et al., 2018). The aspirated material is usually inspired into the antero-ventral lobes of the lung where it produces moderate to severe, peracute or subacute, necrotizing bronchopneumonia, depending on the composition of the inhaled material, the microorganisms involved and the host responses.

Aspiration of foreign material into the lung can be due to a range of causes, as described in the literature (Blowey and Weaver, 2011; Scott et al., 2011; Scott, 2017; Darcy et al., 2018). Aspiration of foreign material into respiratory system may come from rumen contents following bloat or during general anaesthesia. When animals are anesthetized, regurgitation of gastric contents can occur both light (active regurgitation) and deep (passive regurgitation) (Pugh and Baird, 2012). Moreover, aspiration of inappropriately administered oral antiparasitic treatments as drenches, is common and usually reflects poor drenching technique, often involving lifting of the head of the sheep when administered to sheep. In dips is also common, often involving excessive immersion of the head as the animals is swimming in the dip bath or shute (Scott, 2017).

Another possible cause of aspiration pneumonia described in the literature can be a laryngeal hemiplegia, which was referred in an 18-month-old ram with a macroscopic laryngeal asymmetry and musculature atrophy in the left side. Necropsy showed a gangrenous pneumonia accompanied by fibrinous pleuritis (Sáez et al., 2003). Aspiration pneumonia has been also found associated with oesophageal myonecrosis due to BTV infection in sheep (Antoniassi et al., 2010). Lambs with nutritional myopathy can also have difficulties of deglutition and develop inhalation pneumonia (Scott, 2017) and also milking lambs fed by bottle can suffer a choking that leads to an aspiration pneumonia. In addition, those respiratory pathologies that hinder the correct breathing, favour the inhalation of vegetable material and the appearance of these conditions. In this sense, it is common to find gangrenous pneumonia in association with other lower respiratory disorders (Lacasta et al. 2016; Lacasta et al., 2019).

Vegetable material is frequently seen at post-mortem examination and in histological sections of lung lesions of adult sheep with gangrenous pneumonia. The presence of this vegetable material can suggest that seeds or ears of cereals have been inhaled while they are eating (Figure 1) or that regurgitated vegetable material from the rumen has been inspired during rumination (Viall et al., 2018). In this sense, gangrenous pneumonia was experimentally reproduced by Biescas et al. (2009) with a fragment of wall from barley mixed in a sample of fresh ovine rumen content and introduced directly into the bronchus. However, no foreign bodies into the airways were found by Ménsua et al. (2003) in a study of AA amyloidosis in small ruminants where the 76.2% of animals had gangrenous pneumonia that triggered renal amyloidosis.

Most of the microorganisms producing gangrenous pneumonia are normal inhabitants of the nasopharynx. A range of anaerobic and aerobic bacteria, fungi and viruses have been isolated from these gangrenous lesions, indicating that most involve mixed infections (Sáez et al., 2003; Azizi et al., 2013). In a survey developed by Lacasta et al. (2019), which involved 195 culled sheep, *Trueperella pyogenes, Pasteurella multocida* and *Mycoplasma ovipneumoniae* were the most frequently isolated microorganism from gangrenous pneumonias. Pyogenic bacteria are usually isolated from these lesions, such as *Streptococcus* or *Trueperella pyogenes* which are ubiquitous inhabitants of oropharynx, upper respiratory and gastrointestinal tracts of animals (Risseti et al., 2017). *Trueperella pyogenes* has been frequently isolated from suppurative lungs or abscesses from sheep (Ribeiro et al., 2015; Risseti et al., 2017), in which *plo* gene was detected promoting haemolysis, cytolysis of immune cells and tissue damage, being considered the major virulence factor of *T. pyogenes* (Risseti et al., 2017). *Fusobacterium necrophorum* has also been isolated from pneumonic lungs of Bighorn sheep with suppurative and necrotic lesions (Shauthalingam et al., 2016).

Clinical signs often appear within a week or two following an intervention, including oral anthelmintic or dip bath treatments, although initially, an association with the intervention may not be readily apparent. Affected sheep separate from the mob, displaying inappetence, appear to be in pain, showing antalgic position and depressed. The rectal temperature can be as high as 41.5ºC (Biescas et al., 2009). Respiratory signs may include coughing, dyspnea, rales when the process progresses sufficiently, abnormal breath odour can be detected suggestive of the necrotizing exudates occurring in gangrenous pneumonia (Ménsua et al., 2003; Biescas et al., 2009; Pugh and Baird, 2012). As auscultation and clinical examination not always lead to a proper diagnosis, ancillary tests as ultrasonography or X-ray will become very useful tools. An X-ray shows a mixed pattern (alveolar and interstitial) where the lesion is located. Affected areas present loss of opacity that sometimes can be mistaken for emphysema, although usually the lesion is surrounded by clear border (Castells et al., 2019). Ultrasound images are clear, offering different hyperechogenic foci in all the affected area depending on the material inside the lesion (Castells et al., 2019).

At necropsy, necrotizing lesions usually distributed in anteroventral lung lobes and usually involving bronchi, bronchioles and occasionally causing pleuritis, are characteristic of gangrenous pneumonia. The lesions are usually accompanied by accumulation of a foul-smelling brown to grey exudate (Biescas et al., 2009). Further, gangrenous pneumonia frequently leads to AA amyloid deposition in gastrointestinal tract and kidneys triggering a renal amyloidosis easy to diagnose macroscopically (Ménsua et al., 2003; Biescas et al., 2009).

Although laboratory analyses are not normally necessary to diagnose a gangrenous pneumonia, aetiological analysis can be performed in order to know the microorganisms implicated. Bronchoalveolar lavages enable examination of exudates from live animals, assisting choice of therapy. Increases in serum gamma globulins in response to the chronic infectious process that promotes antigenic stimulation were demonstrated in experimental infections (Biescas et al., 2009). Other findings reported by these authors were the decrease in serum albumin, cholesterol and calcium levels and alterations in urinary parameters due to renal amyloidosis induced by the chronic infection (Biescas et al., 2009).

If therapy is possible, results of antibiotic susceptibility tests performed on exudate samples can guide the choice of antimicrobial agent to administer. In addition, imaging techniques (X-ray and ultrasound) may assist in determining the degree of extension of the lung lesion and, consequently, the prognosis. Equally, if it is known that a sheep has inhaled a foreign body, treatment should commence immediately, prior to the onset of respiratory signs. Therefore, in early cases, treatment should be carried out based on β-lactam antibiotics, during at least seven days, associated with nonsteroidal anti-inflammatory drugs (NSAIDs) at the first days of the therapeutic protocol to improve the breathing condition (Scott, 2017). If aspiration or regurgitation occurs during anaesthesia and before intubation of animal can be completed, a bronchodilator such as aminophylline should be administered to relieve bronchospasm (Pugh and Baird, 2012). Despite the treatments and efforts to treat this disease, the prognosis is very poor (mainly at chronic phase) and many animals die or must be euthanized, then efforts must be directed to prevention. Prevention against this disease requires that risk factors for aspiration are addressed, particularly the risks from inappropriate administration of oral therapies and antiparasitic baths.

3. Ovine Respiratory Complex in adult sheep

The major bacterial respiratory processes affecting adult sheep was traditionally described as "pasteurellosis" reflecting that bacteria from the family *Pasteurellaceae* were predominantly involved. Other names associated with this disease are enzootic pneumonia or atypical pneumonia. However, these are names related only to the pneumonic presentation, but not to the systemic form of the disease. In our opinion, similarities of adult "pasteurellosis" with the ovine respiratory complex in lambs suggests that the disease be described as well as ovine respiratory complex (ORC). As in ORC in lambs, this respiratory disorder in adults reflects a complex disease process involving a range of host-pathogen-environment interactions (HPE), where host immunological and physiological mechanisms (host), interact with multiple etiological agents including bacteria (pathogen), plus environmental factors or stressors (environment). Environmental factors have proven to be key in the development of this pathology, so the influence of climatic factors and the facilities where animals are housed has been widely reported (Lacasta et al., 2008; Navarro et al., 2019b). Although the clinical presentation and severity of the disease may differ with ORC in lambs, the distribution of lesions at necropsy are similar, reflecting common disease mechanisms. Hyperacute or peracute lesions are often characterized by hemorrhages. Acute and subacute forms are characterized by varying degrees of lung consolidation from the exudates produced, including pus causing suppurative or catharral pneumonia or fibrin causing fibrinous pneumonia. Chronic pneumonias reflect the onset of fibrous tissue, increasing the severity of consolidation. Description of the clinical presentations of ORC can be found in González et al. 2019a of this special issue.

In a survey developed at the greatest dairy sheep farm in Spain, the ovine respiratory complex was the 2nd most frequent reason of death, following by reproductive disorders, and in another study carried out in a large meat-production flock managed under the semi-extensive system ORC was the first cause of death in both adult animals and replacement (Lacasta et al., 2019).

In a study conducted on 3,673 necropsied animals (786 milking lambs, 2,730 feedlot lambs, 94 replacement animals and 63 adult sheep), differences among the groups in the type of ORC clinical presentation were observed in the analyzed animals (Figure 2). The most frequent presentation that caused the death in the youngest animals was the acute form of ORC, while adult animals primarily died of hyperacute ORC. In adults, very often, hyperacute form of ORC is the final cause of death after the animal has undergone another process. When the immune system is comprised, etiological agents of ORC can cause the rapid death of the animal. Chronic forms of the disease are responsible for an early culling of sheep. In a survey carried out on 195 culling sheep, 60% of the animals showed some pattern of lung lesion (Lacasta et al., 2019).

Clinical signs of the hyperacute form of ORC are those related to a septicemic process with sudden deaths or non-specific clinical symptoms as fever, anorexia and depression. The clinical signs in the acute form are dullness, anorexia, pyrexia and varying degrees of hyperpnoea or dyspnea with respiratory pathological sounds as rhonchus and crackles. Finally, the symptoms of the chronic form are similar to those other chronic diseases that affect the respiratory tract in adult sheep and that involve productive-like lesions such as ovine pulmonary adenocarcinoma (OPA) or gangrenous pneumonia with severe dyspnea accompanied with rhonchus, crackles and wheezing. Advanced OPA can be distinguished with the "wheelbarrow test", even sometimes, when the animal lowers the head during feeding, clear frothy fluid may flow freely from both nostrils. However, the only difference in clinical signs of ORC from gangrenous pneumonia is the presence of malodorous breath in the latter disorder. An accurate clinical diagnosis of ORC usually requires that ancillary tests including ultrasonography of the lung (Scott, 2010) or bronchoalveolar lavages to identify the microorganisms involved (Rowe et al., 2001) are performed. In an outbreak, necropsies with sample collection and microbiological analysis is required.

As in lambs, several infectious agents have been associated with ORC, the more important being: *Mannheimia haemolytica*, *Pasteurella multocida*, *Bibersteinia trehalosi* and *Mycoplasma* spp., usually, found mixed in the isolates with more than one bacteria species implicated (Miller et al., 2011). Moreover, most of these bacteria exist as commensal organisms of the nasopharynx, tonsil and lungs of healthy sheep (Glendinning et al., 2016) and under certain circumstances can produce disease. For that reason, etiological diagnosis is essential for the control of ORC.

As described, treatment of ORC can be complicated by the range of pathogens including bacterial serotypes involved, however, several treatments can be advisable on the use of β-lactams and NSAIDs (eg. Flunixin) that may play a very important role in the acute condition of avoiding death due to intense pulmonary edema resulting from inflammation. However, the treatment of chronic cases is less advisable since very long treatments would be necessary to obtain an appropriate degree of healing.

Prevention is important for controlling the disease and is based on optimal management of the animals and facilities to avoid or at least minimize the risk factors causing stress, improving animal welfare, as it has been extensively explain in other article of this special issue (González et al., 2019b). In outbreaks, vaccination plans could be implemented or at least considered for the flock at risk of ORC.

4. Pseudotuberculosis or caseous lymphadenitis (visceral form)

Caseous lymphadenitis (CLA) is caused by *Corynebacterium pseudotuberculosis* and can present as either the superficial form characterized by abscess development in superficial lymph nodes, or the visceral form affecting internal lymph nodes and organs, mostly observed in adults (Fontaine and Baird, 2008). CLA is common in sheep and distributed worldwide, causing important economic losses (Fontaine and Baird, 2008; Windsor and Bush, 2016). In countries where there is minimal vaccination, the losses may include costs of managing clinical cases, although where the clinical disease is largely controlled by vaccination, the losses mostly occur at abattoirs from carcass condemnations (Windsor, 2014). Several surveys have confirmed the importance of CLA, including a study of CLA prevalence in 485 culled sheep where the prevalence of animals with abscesses of any etiology was 36% compared to 21% for confirmed CLA (Arsenault et al., 2003). A more recent abattoir survey of over 692 sheep concluded that the prevalence of CLA, based on gross and bacteriological examination, was 32.65% (Al-Gaabary et al., 2010).

The previously report study of 485 culled sheep, found 70% of culled sheep with CLA had abscesses in the thoracic cavity, 26% in external sites (head, neck and shoulder) and 25% in the abdominal cavity (Arsenault et al., 2003). In a study by our research group of over 132 culled sheep with an average age of 5.2 years, we identified that 32% of the animals had CLA lesions, of which 70% had the visceral form of the disease, with 80.9% having lesions in the thoracic cavity. CLA was the only cause of culling in 47% of these animals. The mediastinal lymph node was the most commonly affected lymph node, identified in 57.1% of the animals although as a single lesion in 48.0% of these (Figure 3). Lesions involving the lung parenchyma resembling abscesses caused by *C. pseudotuberculosis* were observed in a 23.8% of the affected animals, with 19.0% occurring as a single lesion (Navarro et al., 2015). Consideration of the high rate of CLA lesions in the thoracic cavity, including either mediastinal lymph node and/or lung parenchyma and usually producing respiratory clinical signs, the inclusion of CLA in this review of respiratory disorders is justified (Figure 4), particularly as these lesions are the source of the aerosol that is considered of relevance to the mode of transmission of the disorder (Windsor, 2011). This respiratory route for the transmission of *C. pseudotuberculosis* infection from infected animals with pulmonary lesions presenting as the major source of exposure to naïve animals within a flock is well recognised (Pepin et al., 1999; Williamson, 2001; Fontaine and Baird, 2008). That pulmonary lesions occurring within the walls of airways may rupture resulting in local exudation and the production of an infectious aerosol is supported by the isolation of infectious organisms from the tracheas of the infected sheep (Pepin et al., 1999; Fontaine and Baird, 2008; Windsor, 2011).

The control of CLA is assisted by a confirmed diagnosis of the disease although this is still a matter of intense research (Oreiby, 2015; De la Fuente et al., 2017). Clinical lesions suggestive of the superficial form of CLA may be confirmed by microbiological analysis. Visceral lesions are more difficult to detect clinically, unless the animal with respiratory lesions is coughing. Progressive weight loss and chronic recurrent ruminal tympanism may also accompany visceral CLA lesions (Oreiby, 2015). Microbiological confirmation of the visceral form in live animals is challenging, although isolation of *C. pseudotuberculosis* from respiratory exudates and/or urine are indicative of respiratory or renal lesions, respectively (Ferrer et al., 2009). However, respiratory clinical signs associated with CLA are often not readily recognized, particularly if only dyspnoea is detected without audible sounds of thoracic cavity pathology, as occurs when the content of abscesses is encapsulated. Diagnostic imaging techniques assist confirmation of the visceral form of the disease, with isolation of *C. pseudotuberculosis* at necropsies enhancing diagnostic investigations. Although the etiological diagnosis of the disease would be advisable, absence of a confirmed bacteriological diagnosis should not preclude implementation of strategic control by vaccination where the pathological evidence is considered sufficiently diagnostic.

In countries where CLA vaccination is not available, control of the disease may require identification of the infected animals to prevent their contact with the uninfected ones, which usually means that serologic testing is required (Windsor, 2011), although autologous vaccines can be considered. Serological tests, particularly those detecting humoral responses, have specificity and/or sensitivity deficiencies and consequently, repetitive serological monitoring is a preferred option than applying a single testing policy for diagnosis and control of CLA in sheep and goat flocks (Oreiby, 2015). Moreover, CLA can be diagnosed by blood and milk gamma interferon assay (Oreiby and Hegazi, 2016).

The preferred strategy to control CLA is routine and persistent vaccination of healthy sheep in a population, coupled with culling of infected animals (Windsor, 2011). As with many vaccination programs, the currently licensed vaccines suppress the disease rather than conferring complete protection of immunized animals, so CLA will persists despite routine vaccinations (Lacasta et al., 2015; Windsor and Bush, 2016). However, vaccination schedules should be implemented to reduce the numbers of infected animals and the prevalence of the disease into the flock, with efficacy of the vaccination plan dependent on the vaccination programme used (Windsor, 2011; Windsor, 2014).

4. Concluding remarks

The lower respiratory tract pathology in sheep is very common and has great diagnostic difficulty due to the high number of pathological processes that settle at this level, all causing a very similar clinical symptomatology. ORC and gangrenous pneumonia are both disorders that have to be included in the differential diagnosis of productive processes, along with the ovine pulmonary adenocarcinoma. However, caseous lymphadenitis, as it does not produce productive clinical signs, should be added to the differential diagnosis of non-productive processes, such as interstitial pneumonia associated with Maedi Visna virus.

Conflict of interest statement

The authors have nothing to disclose.

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Figure legends

Figure 1. Vegetable material causing gangrenous pneumonia is shown inside the lesion. The lesions comprised foci of pulmonary necrosis with accumulation of a foul-smelling exudate with an associated pleuritis.

Figure 2. Hyperacute, acute and chronic clinical presentation of ovine respiratory complex in 3,673 necropsied animals: lactation, feedlot, replacement and adults. (Original research without publishing).

Figure 3. Location of the lesions in the visceral form of caseous lymphadenitis in 485 culled sheep (multiorgan presentation, mesenteric lymphnode, mediastinal lymphnode and lung parenchyma).

Figure 4. Gross view of a sheep lung. (A) Mediastinal lymph node affected by caseous lymphadenitis. (B) CLA pyogranuloma within the parenchyma.

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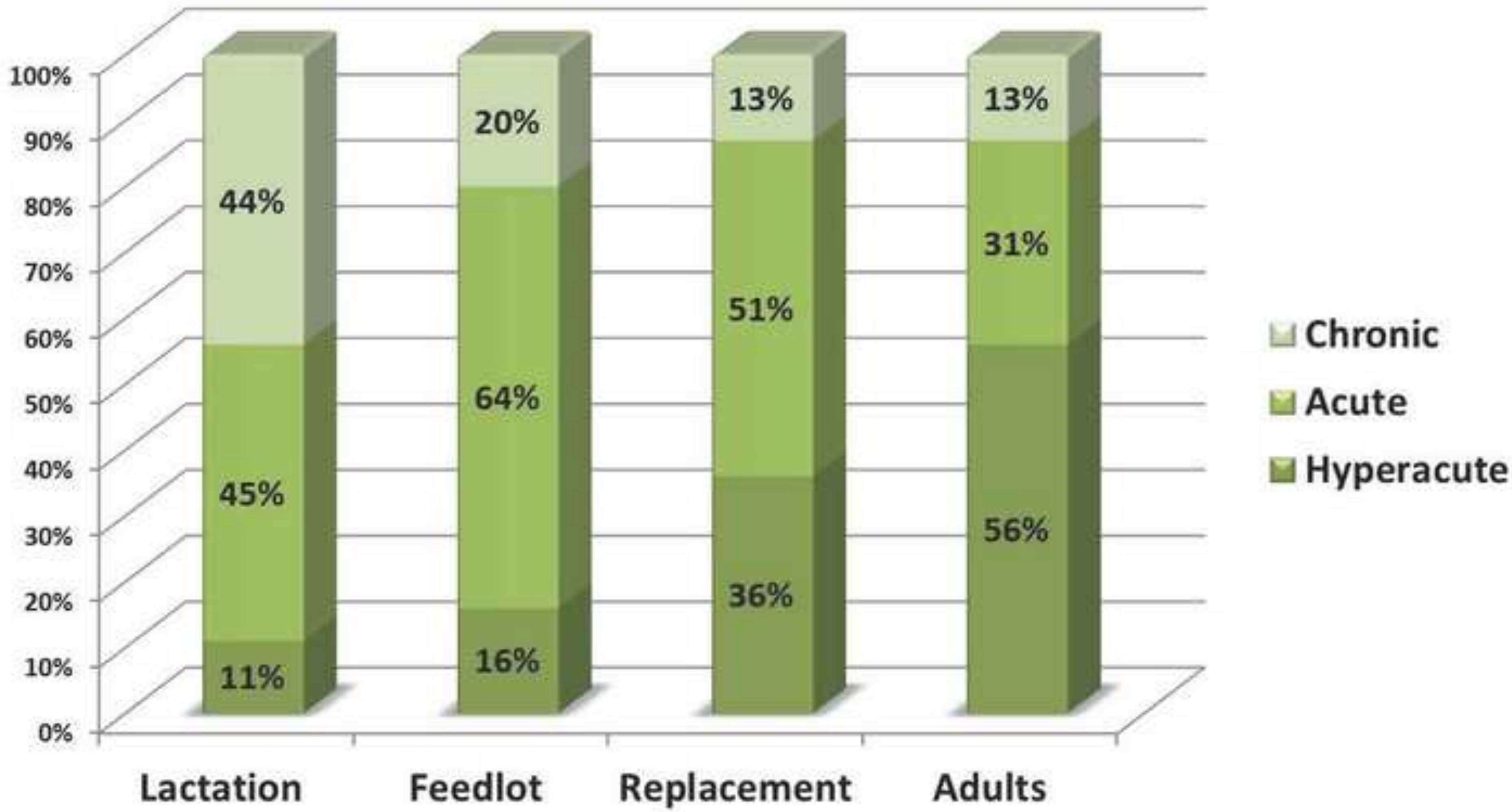

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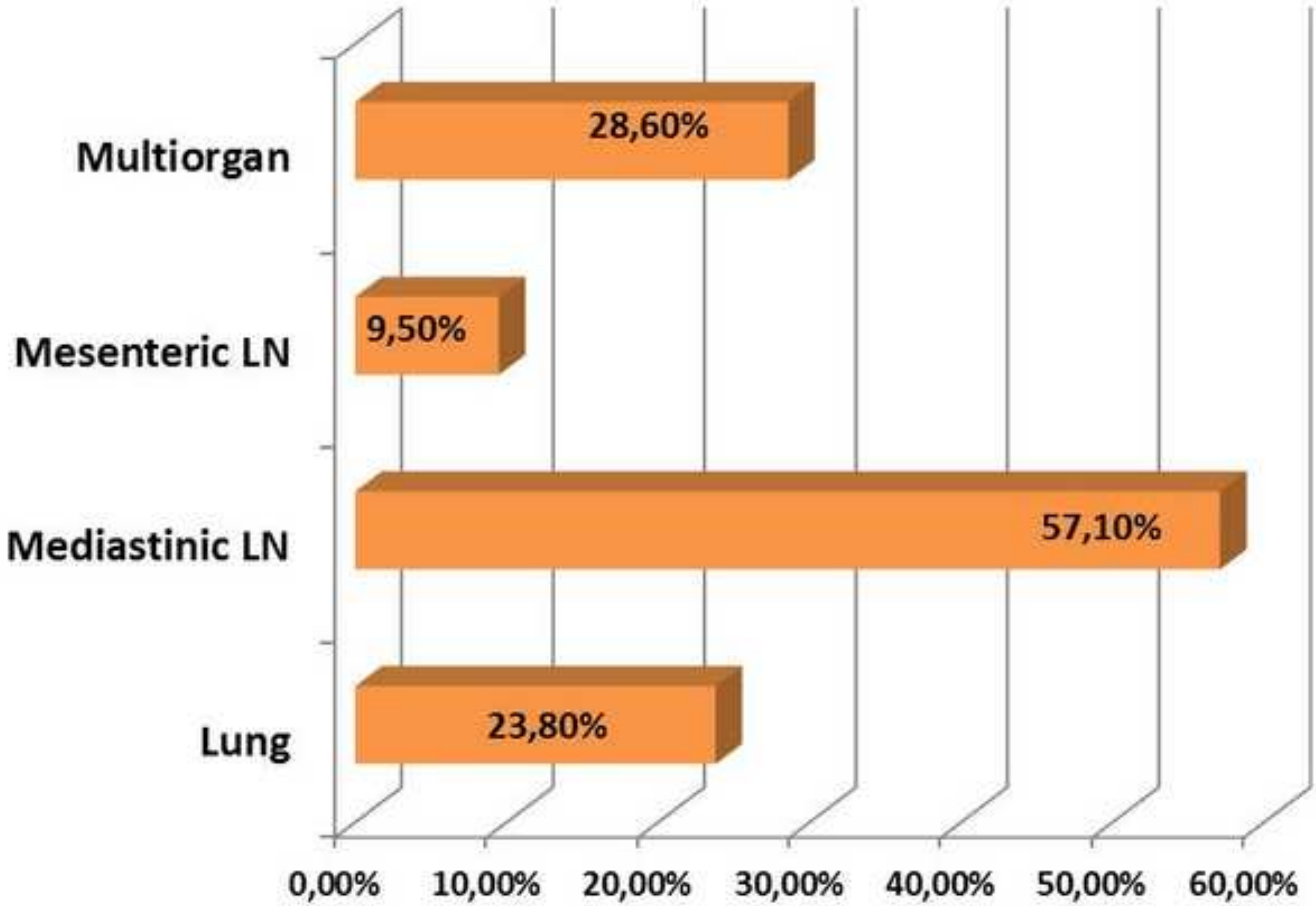

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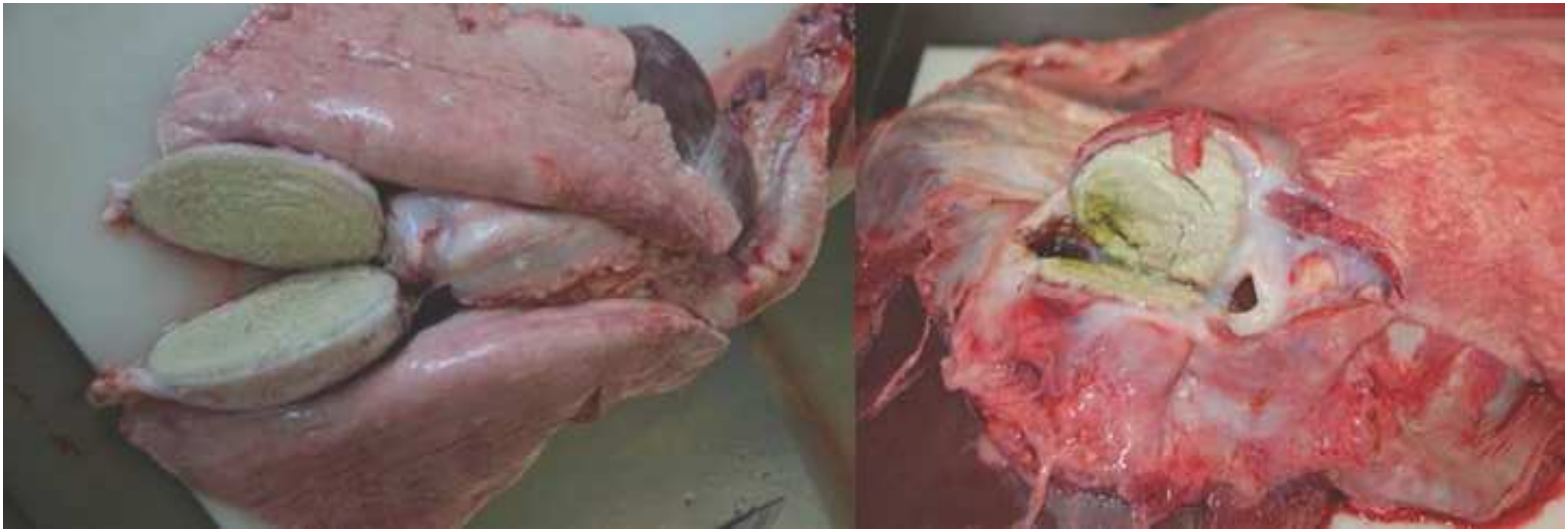

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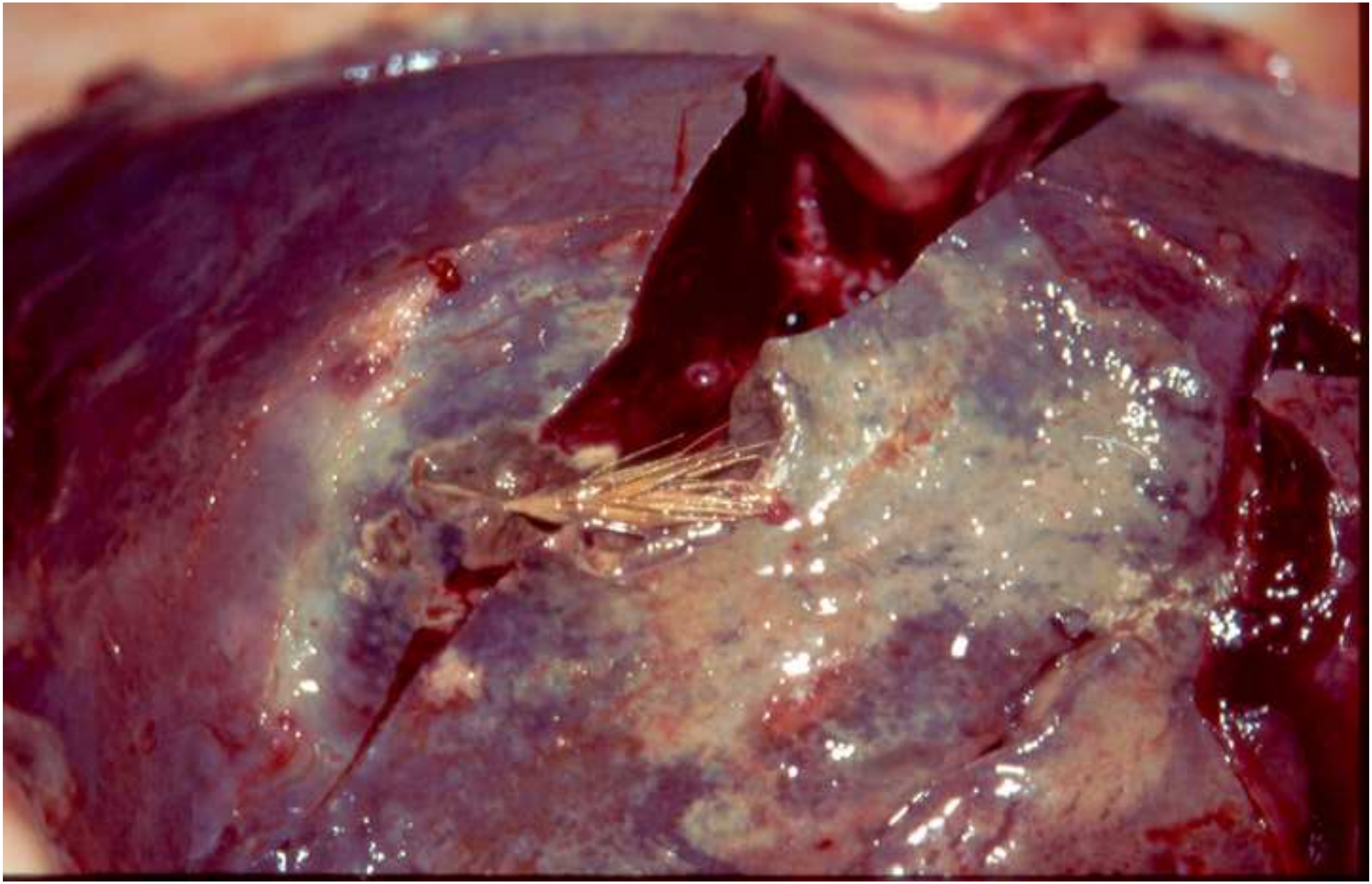

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Conflict of interest statement

The authors have nothing to disclose.

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