Johne's disease in sheep: is it different from cattle?

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ABSTRACT

Sheep are not just a smaller version of a cow. They are affected by specific diseases and their management and economics might be quite different from cattle enterprises. However, they often share pastures and sometimes accommodation, and might also share aetiological agents, which makes them an important matter to consider regarding disease management and control. In the case of Johne's disease, although many similarities exist, there are also some fundamental differences. The lack of the typical watery diarrhoea seen in cattle, the even lower sensitivity of the diagnostic tests in subclinical cases and the availability of a licenced vaccine, combined with the differences in farm economics, should all be considered when dealing with this disease in sheep. This review article provides an overview of Johne's disease in sheep, covering clinical signs, diagnostic testing and management of the disease, focusing on the main differences between cattle and sheep and the rationale behind them, to avoid assumption that what is valid for cattle will necessarily apply directly to sheep.

KEYWORDS: Johne's, sheep, paratubercolosis, MAP

JOHNE'S DISEASE IN SHEEP

Ovine Johne's disease (OJD) or paratubercolosis in sheep is caused by the same aetiological agent as cattle, *Mycobacterium avium* subsp. *paratubercolosis* (MAP). It is a disease of all farmed ruminants, reported worldwide and included in the OIE-listed disease (OIE 2018) and a notifiable disease in Scandinavian countries (Ulvund 2012). It was first described in 1895 by Johne (hence the name) and Frothingham (Johne and Frothingham 1895) and the very first case reported in sheep was in Bosnia in 1908 (Bruère and West 2009). There seem to be major limitations in assessing the reliable prevalence of MAP within countries, due mainly to the low accuracy of the tests available for screening and because of the lack of consistency in study design (Nielsen and Toft 2009). Based on data available, a guess estimate of a European flock level prevalence above 20% has been made. Recent reported prevalence of OJD in Europe show that 65% of flocks in Germany (Stau and others 2012), 73.7% of dairy flocks in Italy (Attili and others 2011) and 46.7% of flocks in Portugal (Coelho and others 2007) are infected. In the UK, in a fallen stock survey, 6% of sheep examined were diagnosed with Johne's (Lovatt and Strugnell 2013), while according to the APHA surveillance data, OJD is the 11th most commonly diagnosed disease with 620 cases reported between 2012 and 2018 (SRUC 2018).

OJD is defined as an "iceberg disease", which means clinical signs are usually seen only in a small proportion of cases. Production losses due to subclinical disease have, therefore, a much higher impact than losses from culling or death of symptomatic animals. In particular, subclinical disease seems to have a negative impact on live weight (McGregor and others 2015), number of lambs born per ewe and wool production (Morris and others 2006). Mortality attributed to OJD in affected farms varies from 4 up to 12% (Bush and others 2006), compared to an average of 1-2% in healthy, well-managed flocks. On the other side, once Johne's has been diagnosed in a flock, farmers might attribute all cases of ill-thrift or poor production to it, where in fact OJD is only contributing to other management issues or infectious disease present on farm (Bruère and West 2009).

CLINICAL SIGNS

As in cattle, OJD causes a chronic enteropathy which leads to intestinal malabsorption and protein loss through compromised villi. One of the major differences with cattle is probably the lack of profuse watery diarrhoea. This is likely due to the ability of sheep to reabsorb a high quantity of water in the distal colon (McKie and others 1991), which is also why they produce pelleted faeces. Sometimes diarrhoea is found, but it is intermittent and mostly associated with concurrent diseases. The major clinical signs of Johne's in sheep is therefore severe weight loss (Figure 1), which makes this disease almost impossible to diagnose on clinical signs alone (Nielsen and Toft 2009). Other signs include submandibular oedema (bottle jaw) due to hypoprotenemia and wool break. There is usually normal or even increased appetite and

Figure 1. A 4 year old, female, Texel X, with a history of loss of condition over the previous 2-3 months. At clinical examination there was low body condition score (1.5 out of 5), the animal was bright, alert and responsive and with normal appetite. Significant hypoalbuminemia (14g/l – reference range 24-31), low worm egg count (50epg) and absence of liver fluke eggs were detected.

a reduction in general immunity, which might predispose to other diseases (mainly bacterial infection or high parasite burden).

Susceptibility to MAP infection decreases with age, which means the chances of acquiring and developing the disease are very high in the first months of life (Begg and others 2005), to decrease as the animal becomes older. However, clinical signs are not usually seen until later on, usually adult sheep over 2 years of age, because of the long incubation period. Typically, appearance of clinical signs will be triggered by stressful events, such as lambing, lactation, nutritional deficiency or transport. There is no evidence for sex predisposition, while some breed of sheep, like fine wool Merino, seem to be more affected than others (Lugton 2004). The main route of infection is faecal-oral (Gilmour and others 1977), followed by mammary secretions (Nebbia and others 2006) and evidence of intra-uterine (Lambeth and others 2008) and venereal transmission (Eppleston and Whittington 2001), although these last two represent a less important pathogenic route.

Due to the lack of specific clinical signs, differentials should include all causes of ill-thrift in adult animals, like nutritional deficiency, parasitic gastro-enteritis, chronic liver fluke, periodontitis, ovine pulmonary adenocarcinoma (OPA or Jaagsiekte), Maedi Visna, caseous lymphadenitis (CLA or pseudotuberculosis), intestinal adenocarcinoma and other chronic infection (*e.g.* pneumonia and mastitis).

Cross-infection and relationship with other diseases

Are sheep a potential source of Johne's disease for cattle? There are cattle (C or "type II") strains and sheep (S or "type I and III") strains. Although sheep strains tend to be almost species-specific, cross infection to cattle can occur, but at a very low-risk (Moloney and Whittington 2008). Sheep are primarily infected by S strains. Although experimentally sheep can also be infected by cattle strains, it also seems they have the ability to recover from it (Fernández and others 2014), which leaves cross-infection between cattle and sheep under natural exposure still up to debate. It is worth mentioning the Icelandic example, where it is suspected that eradication of the disease in the sheep population was unsuccessful due to infected cattle remaining on the farms (Fridriksdottir and others 2000). Goats are, on the contrary, easily infected with both strains (Stewart and others 2006). Depending on the pathogenicity of the MAP strain, the dose and frequency of exposure (Begg and others 2005), the host immune response and susceptibility (Gillan and others 2010), animals exposed to MAP might either develop resistance to infection, become infected and shed the bacteria but remain asymptomatic or develop clinical disease.

It has also been demonstrated that protective immunity against mycobacterial infection can be dysregulated by co-infection with helminth parasites and also postulated that co-infection with *Fasciola hepatica* could result in accelerated development of Johne's disease (Naranjo Lucena and others 2017). Since both fascioliasis and parasitic gastro enteritis are very common in sheep, this poses the question of the role of controlling for these diseases in regard to OJD control.

Finally, the possible association between Johne's in food-producing animals and Crohn's disease in humans must be kept in mind (Collins 2011). Although MAP has been isolated among patients with Crohn's disease (Abubakar and others 2008), this does not necessarily mean it is involved in the pathogenesis of the disease, which makes the association, at present, still controversial and inconclusive. Regardless of the potential issue with MAP being a zoonotic pathogen, it is worth remembering that meat and milk from infected animals are usually contaminated (Nebbia and others 2006, Eltholth and others 2009) and as

major contributors to public health, reducing human exposure to this infectious agent should be considered one of our priorities.

DIAGNOSIS

Due to the lack of specific clinical signs, diagnosis based exclusively on clinical examination is not possible, therefore ancillary testing are required. At serum biochemistry, there is consistency of low albumin, even before obvious clinical signs of wasting are detected, although this is usually in the advanced pathological stages of the disease (McGregor and others 2015). While decreased circulating albumin is not specific for OJD, it could be a useful indicator to include this disease in the differential lists for ill-thriven adult animals, especially when associated with low total protein (Jones and Kay 1996).

Serum ELISA is a low-cost, highly specific (usually around 94-99%) and rapid turn-around test. It has, however, very low sensitivity (14-21%) in sub-clinical cases (Mathevon and others 2017), which means we can trust a positive result, but not a negative one in clinically healthy sheep. Interestingly, sample handling seems to affect results (Alinovi and others 2009): storage for one week and temperature of -20°C were associated with lower MAP scores, increasing the chances of false negative results. The suggestion would therefore be to be particularly careful when interpreting results from animals due to enter the flock or in cases of freedom from disease. The use of colostrum instead of blood for ELISA testing has also been suggested to improve the sensitivity of the test (Jenvey and others 2015).

Faecal culture is regarded as the gold standard method for detection of infected animals as well as potentially identifying those shedding the highest doses of MAP (Bastida and Juste 2011). It is, however, very expensive, with prolonged turn round time and potentially false positive due to passive shedding of MAP, especially evident in highly contaminated farm or where super-shedders are present. Sheep strains are also more difficult and even slower to grow than cattle strains (de Juan and others 2006), which further reduces the use of this test in sheep. An alternative is faecal PCR. This has better sensitivity than ELISA in sub-clinical cases (30-60%), but higher cost and it is more rapid and sensitive than faecal culture (Bauman and others 2016). In this case too, there could be potential false positives due to few environmental mycobacteria yielding positive results (Cousins and others 1999). Due to the economic constrains in sheep farming, it might be worth considering the use of pooled samples for both techniques. Pool size (number of animals sampled per pool) and number of pools depend on both the flock prevalence and the dose of shedding within individual animals, but a recommendation would be for at least 6-7 faecal pools per flock (if prevalence is >5%) and at least 50 animals per pool (Dhand and others 2010).

At post mortem examination, infected animals might have a range of lesions, from nothing grossly visible to some striking and pathognomonic pathological changes. If present, gross changes are similar to those in cattle, with thickening, corrugation (Figure 2A) and reddening of the small intestinal mucosa, enlarged mesenteric lymph nodes and draining lymphatic ducts (Figure 2B), usually more severe in the terminal ileum and ileo-ceacal valve (Clarke 1997). A peculiarity of OJD is the occurrence of an orange-yellow pigmentation of the intestinal mucosa (Figure 3), caused by pigmented strains of MAP (Stamp and Watt 1954), which, however, occurs only in a minority of cases (Lovatt and Strugnell 2013). Other gross changes include serous atrophy of fat (Figure 2C), submandibular oedema, ascites and hydropericardium. Following post mortem examination, samples to collect for the diagnosis of OJD would ideally be: a blood sample (for serology), samples for histology (tissue from the terminal ileum and a mesenteric lymph node, submitted into a 1:10 ratio of 10% formalin) and a faecal sample (for culture and PCR). Something to bear in mind, compare to cattle, is the frequency in which asymptomatic/subclinical cases might not present with any pathological lesions, either grossly or histologically (Gillan and others 2010), which further complicates diagnosis in this species.

More studies are also looking at alternative solutions to improve diagnosis, for example by using MAP specific recombinant proteins (Hughes and others 2013), or alternative culture media (de Juan and others 2006). Furthermore, the recent growing interest in new technologies for point-of-care testing (Busin and others 2016) has also been applied to the diagnosis of OJD, by using nanoparticles on lateral flow devices (Karthik and others 2013). The possibility of diagnosing OJD on farm would be particularly useful when selecting culling ewes or deciding to provide supplementary feeding to ill-thriven animals.

CONTROL

As usual, the most important things to determine before any control option is put in place are the goal of the farmer and the disease status.

One option is obviously eradication. This

Figure 2. A) A section of the jejunum showing diffuse and severe thickening and corrugation of the intestinal mucosa. B) Thickened and easily visible lymphatic vessels on the intestinal serosa. C) Severe serous atrophy (gelatinous appearance) of mesenteric fat.

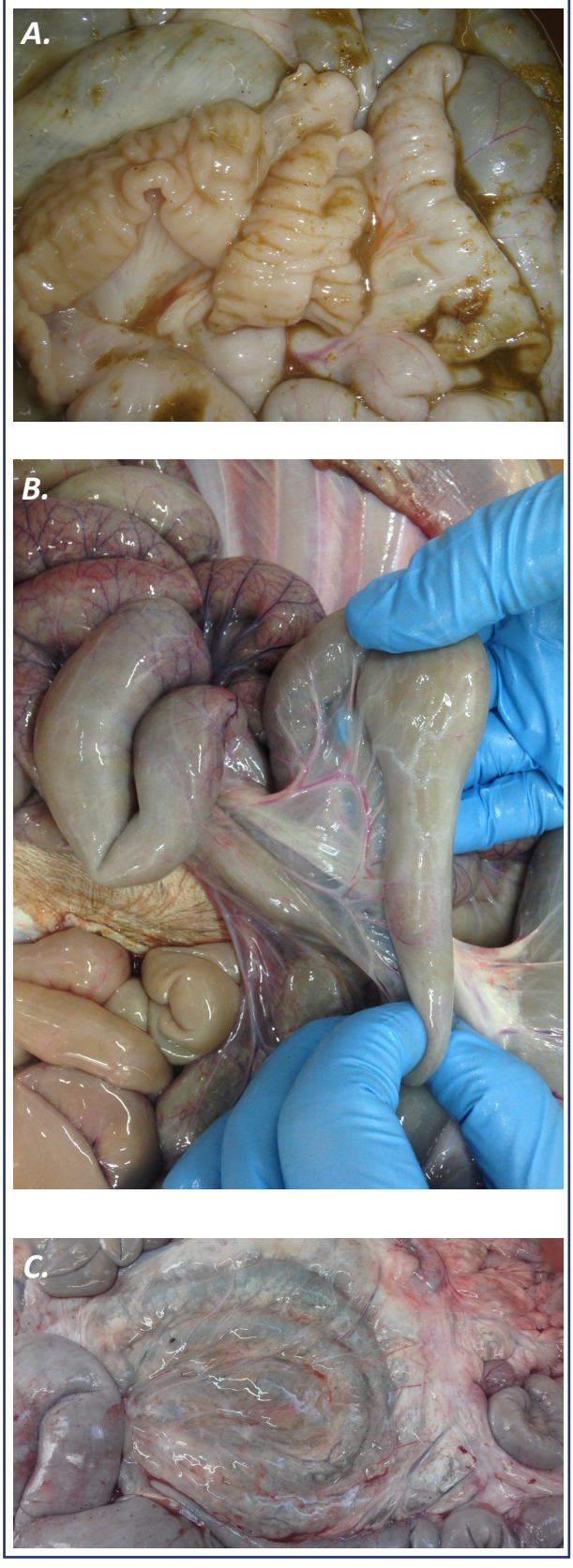

Figure 3. A pigmented strain of MAP giving the intestinal mucosa a yellow-orange discoloration.

has been attempted in some parts of Australia (Hood and Seedsman 2004) through a model of destocking and pasture resting for 18 months (two summers), and restocking with free from diseased animals. In our current situation, with the unknown true prevalence and the high economic cost of eradication, control is a more cost-efficient solution for most flocks (Juste and Casal 1993). In this case, the standard systematic approach to control of infectious diseases applies: identification and elimination of infected animals to reduce the prevalence, appropriate changes to hygiene and husbandry to reduce the spreading and biosecurity to prevent introduction.

Identification: the most likely time to come across clinical disease is around lambing time. However, this is the busiest time of the year for farmers and it might not be productive to cull ewes at this stage. Suggestion would be to isolate the infected animal(s) and to avoid breeding any replacement from them (if traceable, this applies to previous offspring too). A good time to identify affected animals (through body condition score and testing) is before mating, when ewes going to the ram are selected. Routine body condition of animals and sampling/post mortem of ill-thriven sheep is a very cost-effective tool to diagnose and monitor OJD. Routine testing of pooled faecal samples to assess the presence or the prevalence of the disease is another sensible option.

Regarding hygiene and husbandry, since the main route of transmission is faecal-oral, the focus is on reducing faecal contamination. In a temperate climate, given the right amount of moisture and shade, the lack of vegetation or soil, MAP can persist in the environment for up to a year (Whittington and others 2004). Therefore, environmental contamination could be reduced by improving general farm hygiene (increase cleaning of facilities, design feed and water

troughs to reduce faecal contamination) and reducing contamination (reduce loose faeces due concomitant diseases such as parasite and nutrition). Based on the age-related predisposition for infection, avoiding feeding pooled colostrum, heat-treatment (60°C for 60 minutes) of colostrum and milk (Godden and others 2006), sourcing replacement from non-infected animals and avoiding manure spreading of fields grazed by young stock are all possible solutions. Interestingly, mortality from OJD is not related to higher stocking density farms, therefore reducing the stocking density might not have any effect on the manifestation of OJD (Lugton 2004).

BIOSECURITY

The most likely route of entry of OJD in a flock is by introduction of diseased animal(s). Quarantine and testing of new and returning animals is therefore the best option, as well as sourcing of animals from reputable, free-from-disease sources. It is worth remembering that, in general, quarantine is not just to prevent introduction of the disease in the first place, but to reduce the addition of diseased animals (and therefore maintain a low prevalence) or the introduction of a more pathogenic strains.

VACCINATION

The inactivated vaccine licensed for use in small ruminant in the UK has shown to prevent clinical signs and reduce mortality in vaccinated flocks, however it does not prevent infection and might not reduce bacterial shedding significantly. Although this last point depends largely on management practice and therefore should be more farm specific (Windsor 2013), it is still an important consideration in case of vaccinated animals been moved to low risk areas. This also suggests that if vaccination was to be stopped, re-emergence of the disease will be very likely. The vaccination schedule recommended by the manufacturer is for a single subcutaneous administration between 4 weeks and 6 months of age for all replacement animals. In practical terms, young animals are usually vaccinated at weaning, when a decision is made on which animals will be kept for breeding. In countries like New Zealand (de Lisle 2002), Australia (Reddacliff and others 2006) and Iceland (Fridriksdottir and others 2000), vaccination campaigns have proven very successful in controlling the disease.

OJD vaccination is known to cause interference with the tuberculosis testing. There is a chance of false positive reaction at the single intradermal tuberculin test up to 12 months post-vaccine, while by using the comparative (avian and mammalian) tuberculin test or the blood-based interferon gamma this could be avoided (Roy and others 2018). Since sheep are not routinely screened for tuberculosis, this issue does not actually interfere with its utilisation in this species. Something worth mentioning, is the associated injection site lesion, caused by the oil-based adjuvant used. These lesions (and lymph nodes if involved) will require trimming at slaughter (Eppleston and Windsor 2007) and the granulomatous lesion within the lymph nodes might resemble caseous lymphadenitis or tuberculosis.

CONCLUSIONS

Although some fundamental differences exist between cattle and sheep in terms of clinical signs (lack of watery diarrhoea), MAP strains (sheep are primarily infected with the S-strain with very little cross-infection between cattle and sheep) and diagnostic testing (the lack of pathological changes in asymptomatic animals, the use of pooled faecal PCR and the really cost-effective and practical option of post mortem ill-thriven animals), control measures and management issues arising from the disease are very similar and our approach should follow the same methodology that is applied to cattle and to other infectious diseases.

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