In Practice

Caseous Lymphadenitis (CLA) in Sheep: An Update

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Caseous lymphadentitis (CLA) caused by the Gram Positive bacteria *Corynebacterium pseudotuberculosis* has been present in the UK since the 1980s and is now considered endemic. CLA is considered to be an iceberg disease i.e. production limiting disease, characterised by slow insidious onset, and production limiting effects in a larger proportion of the flock than that exhibiting clinical signs at any given point in time. The disease was previously reviewed in *InPractice* by Baird (2003) so we will consider updates in our understanding of the pathology, risk factors for flocks and the challenges of initiating control where the cost of the disease is still relatively unquantified.

Pathogenesis

Animals become infected by either inhalation or via skin abrasions where the bacteria releases the exotoxin phospholipase D (PLD) and mycolic acid resulting in surface necrosis; increased vascular permeability, resulting in infection of phagocytes. Phospholipase D is a chemotaxonomic factor which impairs chemotaxis of neutrophils (Baird and Fontaine, 2007). Whilst these lesions may be confined to superficial lesions, migration of infected phagocytes to regional lymph nodes can result in lymph node destruction and further infection of phagocytes. CLA infection results in chronic granulomatous lesions known commonly as “cheesy gland” due to accumulation of infected phagocytes, eosinophils and cellular debris forming distinct abscesses with multi-centric layers (see figure 1).

Figure 1: A mesenteric lymph node with CLA showing concentric rings (source Delia Lacasta, University of Faculty of Veterinary Medicine, University of Zaragoza)

Lesions fistulate permitting bacterial dissemination i.e. through the skin allowing abscesses to drain or mediastinal abscesses fistulating into the bronchi to permit aerosolisation.

Both visceral and superficial lymph nodes can be affected with the anatomical location apparently linked to the geographical location of the animals. UK lesions tend to be associated with superficial lymph nodes around the head and neck with Australian lesions more commonly linked with the torso, popliteal, prescapular and prefemoral lymph nodes (Binns, Bailey and Green, 2002; Baird, 2007). Additional locations described include the udder, upper respiratory tract (see figure 2) and kidneys (Ferrer et al., 2009) (see figure 3). Remnants of superficial lesions which have healed may be visible as scarring (figure 4).

Figure 2: A mediastinal lymph node with CLA (source Delia Lacasta, University of Faculty of Veterinary Medicine, University of Zaragoza)

Figure 3: Renal invasion with CLA (source Delia Lacasta, University of Faculty of Veterinary Medicine, University of Zaragoza)

Figure 4: A ewe with evidence of old CLA lesions i.e. scarring over lymph node site

Risk factors for transmission

Spread of the infection can be direct i.e. close contact with neighbouring animals or indirect contact via fomites. There is evidence that risk of abscess development is likely to be proportional to the inoculating dose and that some animals will clear infections but still be seropositive on screening (Batey, 1986).

Risk factors for spread are largely related to the large volumes of infectious material yielded from ruptured abscesses and inhalation as a consequence of aerosolisation of internal lesions.

Baird (2000) found that rams were significantly more likely to be seropositive than ewes in the same flock and it has been suggested that this may reflect behaviour within ram mobs i.e. fighting leading to ruptured abscesses and infection spread. With regards to fomites, *Corynebacterium pseudotuberculosis* has been reported to survive in the environment for 55 days in organic materials and that low environmental temperatures favour survival. Furthermore Windsor (2011) demonstrated the pathogen can survive in sheep dip for 2 hours post inoculation. Shearing sheep with abscesses or plunge dipping of sheep with draining tracts along with non-infected flock mates are known to be risk factors.

77 Clearly, buying in infected animals with an unknown status is a risk factor for introducing
78 CLA into naïve flocks and given the stratified system of flocks within the UK, movements are
79 a significant risk factor for the UK. The work from Baird et al., (2004) suggests that rams
80 therefore have an important role as sentinels for appraising flock health status and
81 screening rams at purchase is important for reducing the risk of introducing infected
82 animals.

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84 *Corynebacterium pseudotuberculosis* infections have been reported in humans where there
85 is a high exposure to infected sheep or they are employed in high risk occupations such as
86 livestock workers and butchers (Peel et al., 1997, Bregenzer et al., 1997) but these are often
87 isolated incidents.

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89

90 **Prevalence**

91 At a national level VIDA (Veterinary Investigation Diagnosis Analysis) data based on
92 diagnoses is available (See figure 5), but this is likely to be an underestimate of the national
93 situation. Small studies have been published which provide an indication of prevalence.
94 Baird et al., (2004) looked at terminal sire flocks and found that >18% of flocks had at least
95 one seropositive ram on screening. The overall population prevalence was found to be
96 9.93% prevalence (95% CI 8.76-11.1 per cent) (Baird et al., 2004) with 18% of flocks having
97 at least one positive animal and 36% flocks of these having more than one positive animal.

98

More recent work in the UK suggested a flock prevalence of 4% based upon the identification of macroscopic CLA lesions (superficial and visceral) detected during post-mortem examination and confirmed by culture (P Davies, *unpublished data*). The sampling frame from which this data was derived involved a convenience sample of 56 flocks from England, Scotland and Wales. Each flock supplied between 12- 25 cull ewes for post-mortem examination by Farm Animal Post Mortems Ltd. The flocks represented a wide variety of breeds with a bias towards lowland breeds and were distributed throughout the high sheep density areas of the mainland UK. However, the Davies et al data required farmer cooperation in the participation and submission of cull ewes. Therefore, this data cannot be regarded necessarily as a representative sample of UK flocks. Furthermore, the diagnosis of CLA was based upon presence of lesions visible to the pathologist conducting the examination. This contrasts with the serological approach adopted by previous studies. This contracting methodology would be expected to be less sensitive but more specific than serological studies. This complements data collected in a fallen stock survey which found <1% of carcasses positive for CLA lesions on gross post-mortem (Lovatt and Strugnell., 2013). However, when uncontrolled in flocks, 60% of adults can become seropositive (Binns et al., 2002). To date in the UK, no CLA prevalence study has been conducted using a truly randomised sampling frame.

Figure 5: Graph to show VIDA diagnoses submitted through APHA

Productivity losses

CLA is often listed as an “iceberg disease” along with Maedi Visna and Ovine Pulmonary Adenomatosis causing prematurely thin ewe syndrome i.e. emaciation in absence of other pathology and with normal nutrition. The iceberg nature i.e. clinical cases being an indicator of many more subclinical cases, makes identification and eradication of subclinical infected animals important for disease management on farm. Thin ewes with CLA are more commonly associated with the visceral form of CLA. Arsenault et al., (2003) showed that 38.5% of animals with superficial lesions had visceral lesions on post-mortem inspection at the abattoir in Canada.

Where CLA is endemic in flocks, economic costs are associated with premature culling, reduced milk yields, and documented reductions in wool yields. Whilst all the of work done looking at reduced wool crops is Australian, the reductions of 0.2-0.25kg per head and overall reduction by 4-7% (Windsor, 2011) of clean fleece are likely to indicate the physiological impact of CLA on individual sheep that may well be correlated with reduced production in other areas such as milk yield and fecundity. More research is required to understand the significance of these physiological impacts in the context of the UK sheep sector.

CLA is a challenge for the processing sector as documented in Canada and Australia (Arsenault et al., 2003, Windsor and Bush, 2016) with lesions at risk of rupturing whilst on

142 the line resulting in carcass contamination in addition to trimming due to the presence of a
143 lesion.

144

145 At the low prevalence suspected in the UK, the economic impact of CLA is poorly
146 understood. However, CLA infection within a flock and particularly the presence of CLA
147 lesions is detrimental to profitability of pedigree flocks due to the inability to sell affected
148 animals through public sales. It will restrict export opportunities in some cases.

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150 **Differential diagnoses**

151 When approaching individuals with a suspected abscess in the region of lymph nodes, other
152 differential diagnoses should be considered. Investigation should be with care given the
153 highly infectious nature of the purulent materials i.e. lesions should not be lanced to
154 minimise the risk of spreading CLA. Fine needle aspiration of lesions is recommended before
155 draining. Key differentials could include the following:

156

157 Actinobacillosis i.e. granulomatous lesions infected with *Actinobacillus lignieresii* that results
158 in a suppurative adenitis in the regional lymph nodes. This gram negative bacteria would be
159 differentiable on fine needle aspirate and gram stain.

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Salivary mucocoele are less common in sheep but may be an important differential in goats. The contents of these cysts will initially mimic saliva and be sterile but may become inspissated over time (Linklater and Smith, 1993).

Actinomyces pyogenes: Lumpy jaw secondary to primary dental lesions or drench gun injuries may result in mandibular swelling with regional lymph node involvement. The involvement of the bone in the mandible or maxilla would move this up the differential list (see figure 6).

Figure 6: *Actinomyces pyogenes* infection of the jaw.

Morel's disease: *Staphylococcus aureus subsp. Anaerobius* has been found to produce similar abscesses to CLA on the head and neck of goats and be reported at high prevalences within flocks. However, in contrast to CLA, Morel's typically affects young goats, has a shorter incubation periods (<3 weeks) and lesions are not always located near lymph nodes (Szaluś-Jordanow et al., 2010) (see figure 7)).

Figure 7: Morel's disease in a goat (source Jaroslaw Kaba, Faculty of Veterinary Medicine, Warsaw University of Live Sciences).

Other differentials could include trauma, haematoma, healing fractures, granulomas or dermal cysts.

Diagnosis

There are a range of ways in which CLA can be diagnosed. Lesions can be identified on clinical examination or post-mortem examination and bacteriology with isolation of the bacteria is considered gold standard. However, this proves challenging where internal abscesses are of concern or in live animals where lesions may take up to 6 months to appear. Furthermore, direct microscopy can be limited especially when sampling old and calcified lesions. Haematology changes were described by Scott et al., (1997) in affected animals i.e. neutrophilia and lymphocytosis but these are non-specific changes.

Serology

The most common test currently used in the live animal is the ELISA, however clear communication of sensitivities and specificities to the farmer prior to tests being conducted is important. CLA stimulates both the humoral and cellular immunities and therefore IgG or IFN-γ can be measured as indicators of each respectively. Serology against exotoxin phospholipase D is the most commonly used test because of its cost efficacy and acceptable test performance (Sn 87%, Sp 98%, Voigt et al., 2012, ELLITEST CLA Hyphen, France). The low sensitivity is likely to be a reflection of the intracellular nature of the bacteria. The low specificity will reflect the potential confusion with other Corynebacterium and potentially vaccination (Oreiby, 2015). It is also recommended that only lambs over 6 months old should be tested using serology (Williamson, 2001). Furthermore, serological tests are not able to distinguish animals who have cleared infections and those with active lesions. Western Blot testing is often used as a confirmatory test to improve the specificity of results

found. Currently the only available vaccination (Glanvac; Zoetis) cannot be differentiated from natural infection on serology.

Bulk milk tank testing has been developed for goats in Norway (Nagel-Alne et al., 2015) with sensitivity of 72.7% and specificity of 88.6% with respect to identified prevalences >2%.

Interferon Gamma Testing

Interferon Gamma testing is in development (Sunil et al., 2008) with early sensitivities of 91% and specificities of 98% demonstrated *in vivo.* A major advantage of IFN- γ testing is the increased sensitivity and being unaffected by the vaccinal status of the sheep. In addition, it has early diagnostic capability being able to detect animals 5 days post infection (in comparison with between 6-11 days post infection with the ELISA Paule et al., 2003). There is no correlation between the severity of lesion and either the level of sero-positivity or the level of IFN- γ positivity

Box 1: An approach to CLA diagnosis in a commercial flock

Flocks may trigger screening for multiple reasons. Flocks may be interested in pursuing high health status, may have been requested to demonstrate freedom from CLA pre-sale of animals or may be concerned after finding evidence of suspicious lesions.

Gold standard diagnosis of CLA on farm would be isolation and culture of *Corynebacterium pseudotuberculosis* from lesions of affected animals. Abscesses should be conservatively aspirated to avoid further spread whilst diagnosis pending, an impression smear made, and the bacteria submitted on a plain swab. This approach can be applied to both live animal and post-mortem samples

When lesions are largely resolved i.e. scarred or where calcified serology should be considered. The ELISA with Western Blot to confirm infection in animals with a positive ELISA result for the identification of CLA positive animals.

Cull ewe screening

When trying to establish status for a flock with no history of lesions a cull animal screen with both physical and serological examination could be considered as is common practice with the other iceberg diseases. However we know that rams are valuable sentinels for flock and therefore annual tup screening could also be considered.

Screening suspect clinical cases

For all flocks, recommending isolation of any animals with suspicious lesions prior to sampling for culture is prudent. Ewes are most likely to be examined for CLA as single/small groups of incidental animals i.e. in an outbreak situation or as part of thin ewe screens post-weaning at culling.

Screening at introduction and biosecurity

Where there is an absence of a history of CLA on farm and where a farm wants to preclude its introduction into a flock, screening on new animals on arrival and whilst in isolation is recommended. Due to the delays in seroconversion, repeat testing at a 12 week interval and whilst in isolation should be considered. A single sample may miss recently infected animals. Vaccination status should be established prior to sampling as false positives may occur where there has been a history of vaccination.

Whilst movement of animals is the most obvious risk factor, fomites and persons should not be forgotten. Shearing equipment, shared handling facilities or handling infected animals and then clean ones subsequently may spread CLA. Where CLA is present in a flock, shearing older animals or those with lesions later on may reduce the risk of "nicking" abscesses and spreading infection to younger animals. All equipment including that of contractors should be thoroughly cleaned prior to use on all flocks.

Crucially, abscesses should not be lanced as they release highly infectious material contaminating the environment and potentially increasing the risk of further cases.

End of Box 1

Treatment

Given the highly infectious nature of CLA, the risk of multi-systemic involvement and the inability to entirely eradicate infection, animals are not conventionally treated. Whilst in the literature there are references to the relatively high susceptibility of *Corynebacterium pseudotuberculosis* to antibiotics including penicillin, the thick nature of the abscess wall make treatment prohibitive Senturk and Temizel, 2006, Washburn et al., 2009, Selera et al., 2016).

Senturk and Temizel, (2006) attempted to treat animals with draining abscesses with Rifamycin and Oxytetracyline. Whilst the 10 day combined courses resolved gross lesions, bacteriological cure was not demonstrated and we must be mindful that it is not appropriate to use Rifamyin as it is not licensed in the UK and it is listed as a critically important antibiotic given its role in treating *Mycobacterium tuberculosis* and leprosy.

Selera et al., (2016) attempted photodynamic therapy post-operatively after surgical draining of lymph nodes. There was no evidence of recurrence within the treated lymph nodes within 6 months of the procedure. Whilst this does not involve antibiotic therapy, this treatment by definition will not access internal abscesses.

Given the good efficacy of vaccination for CLA compared to the very poor efficacy of antibiotic treatment, the authors do not consider it justifiable or prudent antibiotic stewardship to treat cases with antibiotics and would encourage an emphasis of flock level control and prevention measures.

Management

Following initial diagnosis and investigation (see box 1), there are two main strategies described for management of CLA in commercial flocks: vaccination and test-and-cull.

The vaccine available is a formalin inactivated exotoxin vaccine for PLD Glanvac 6 (Zoetis, Australia) with field trial results showing rates of protection from 25-90%. The vaccination is also a clostridial vaccination requiring annual boosting pre-lambing. It can be imported into the UK under license via the Veterinary Medicines Directorate as it is not commercially available in the UK. Vaccination has resulted in the near elimination of overt clinical signs associated with CLA in flocks using the vaccine correctly in Australia (Windsor, 2014).

The advantages of using vaccination include that it reduces the number of animals with lung and skin lesions thus reducing challenge in the flock and rate of new infections. It will therefore reduce spread in a flock but is not able to eradicate disease entirely. Sustained vaccination is therefore required to reduce bacterial load within the flock i.e. protecting younger animals whilst older infected animals are progressively culled. However, we need to mindful and communicate the limitations of our understanding of the efficacy of *Glanvac* programmes in the absence of epidemiological trials conducted under UK management conditions, pathogen strain, host genetic susceptibility and transmission dynamics/infection pressure. It should also be clearly communicated to flocks that at the moment there is no

DIVA vaccine available. Whilst this may be of little importance in commercial flocks, this may be of imperative significance in those considering future export and informed consent should be sought. Vaccination can be used in adult animals to reduce infection burden permitting the serological screening of young animals pre-sale and may be most appropriate for flocks with confirmed disease wishing to reduce infectious load within the flock with an aspiration to sell either pre-vaccinated or pre-screened animals for sale.

The protocol for vaccination is two doses, 4 weeks apart with an annual booster at least a month before lambing or shearing. Strategies for application of vaccination are described in box 2. The vaccination experience in Australia has been that prior to vaccination introduction, flock prevalence was as high as 97% flocks (New South Wales) with the flock level prevalence 29% in 1995. Abattoir screening and recording was subsequently introduced and found to be as low as 17% of consignments had at least one lesion positive animal and 1.3% of all animals were lesion positive (Windsor, 2011). These results have been achieved despite a further piece of work demonstrated that just 12% of flocks used the vaccines as recommended (Paton et al., 2003). The prevalence was demonstrated to be lower when vaccines were used correctly.

'Test and cull' has been used for control in commercial suckler sheep flocks using individual antibody ELISA (Baird and Malone (2010), Voigt et al., (2012)) and coupled with bulk milk tank serology in goat herds in Norway (Nagel-Alne et al (2015). This requires repeated serological testing of the adult flock with subsequent removal of any positive animals.

Voigt et al., (2012) demonstrated that they achieved flock sero-positivity reduction from 10% to 0.4% within two years by blood sampling every three months and culling any seropositive or culture positive animals.

However, there is a huge cost associated with this strategy (see table 1) (Baird and Malone (2010). There may be a premium obtainable for CLA negative flocks, however, in the absence of an accreditation scheme in the UK, there is no formal recognition, standardisation or quality control available. The test characteristics needs to be clearly explained as it is highly likely that false negatives will occur, prolonging the testing period and extending time to eradication and furthermore false positives will be taken which in itself may have consequences for the economic value of the flock. Additionally, as prevalence reduces, the relative proportion of false positives increased (which may be equally detrimental for flocks with high value individuals). We must also remember that prevalence is not static, and animals with false negative results or those only recently infected may propagate infection during the testing interval. CLA common in inguinal & scrotal lymph nodes of rams at breeding soundness exam but semen quality was normal & no organism excreted in semen (Gouletsou & Fthenakis, 2010) so CLA positive animals could be considered for semen collection or embryo flushing.

Table 1: Examples of costs for a 300 ewe flock, with 60 replacements and 5 rams testing and removing after sequential rounds of testing. We have made the assumption that the starting

prevalence of CLA is 10% before the onset of testing and that given the sensitivity some animals will be missed at each round of testing.

Testing round >12 weeks intervals	**Blood sampling cost** (£5.80 per sample, SAC 2018, >40 samples)	**Time to bleed animals** (£100 per hour)	**Animals identified** (87%) sensitivity (98% specificity)	**CLA positive animals remaining in the flock** 10% starting prevalence
0				37 animals
1	£2117	£500	32 animals true positive, 1 false positive	5 animals
2	As above	As above	4 animal true positive, <1 false positive	1 animal
3	As above	As above	87% chance of finding the remaining 1 animal	
Total	£6351	£1500		
Total	£7851			

Box 2: Application of vaccination in sheep flocks

Glanvac 6 (Zoetis, Australia) is a multi-valent vaccine licensed for the use in flocks for control of caseous lymphadentitis in addition to clostridial management. The protocol requires 1ml of vaccine injected under the skin near the neck. The primary course is completed with a second vaccine four weeks later with recommended annual booster doses to control CLA. Injection site reactions are not uncommon with the vaccine.

How the vaccine is applied within flocks requires clear communication and informed decision making between vets and farmers.

- Whole flock vaccination with initial vaccination when replacements recruited to the flock
- Rams have been shown to be high risk for becoming and propagating infection. Therefore some commercial flocks may choose to vaccinate rams to reduce propagation within ram mobs and reduce infection risk to the ewe mob. This will not limit the impact of CLA within the ewe flock
- Flocks wishing to control CLA but sell stock which could be demonstrated to be free from disease may choose to vaccinate the adult flocks and retained replacements, leaving for young-stock for sale unvaccinated in the absence of a DIVA vaccination. These animals should be in strict isolation and ideally blood sampled twice 12 weeks apart as per the former SAC health scheme. This may

Implications for flocks

Although the suspected UK flock-level prevalence is low and the economic implications for CLA infection are not fully understood, sheep movements between infected and non-infected flocks means that the spread of CLA is very likely.The impact of this is described in Norwegian literature where test and cull had to begin after an outbreak of CLA in a “ram breeding circle” (Hektoen et al., 2012).

A positive diagnosis of CLA on a farm may preclude the premises from exporting and furthermore preclude them from sales where “clear” animals are required. Formerly, there was an accreditation scheme available in the UK through the Scottish Agricultural College. The scheme was abandoned due to low uptake and difficulties in isolating new animals for long periods post-purchase to complete quarantine testing and the cost of two veterinary visits, 12 weeks apart to accredit a small number of rams.

There are limitations with all strategies of management for CLA. Whilst vaccination has been highly efficacious in the Australian situation, this has not been repeated in the UK and for those flocks who may require sero-negative status to permit export or because this is required from their customers, the lack of DIVA vaccine available may preclude this option. Test and cull may be a costly strategy given the sensitivity of the test and even after apparent "clearance of reactors" positive animals may still be found. The lack of a strategy which is practical with clear cost benefit is compounded by the apparent inertness of CLA in the UK commercial market in contrast with MV, OPA, infectious lameness, resistance parasites etc and the difficulty in defining the cost of the disease. Whilst motivators in the UK have not been studies with regards to attitudes towards CLA, in the authors' experiences, desire to sell "clean" stock, the visual nature of the disease in prized stock, avoiding comeback, protecting the breed brand and pride in the stock they sell are motivators for implementing any strategy. For some farmers the emotional/reputational cost of this disease may drive their decision making above the cost benefit.

Summary

Further work is needed to understand the economic impact and prevalence of CLA in the UK sheep flock and goat herd but initial work suggests that the prevalence of infected flocks is much lower than observed in Australia. Vaccination has been demonstrated to be highly efficacious in reducing prevalence of disease within infected flocks but this requires a period of sustained vaccination, client compliance and clear communication. If a declared 'CLA-free status' is the aim, other routes such as test and cull should be considered. The relatively low sensitivity of serological testing presents its own challenges and informed consent should be

sought before commencing whole flock testing as this may be a long and costly process. Whilst we suspect the national prevalence is low, there is also evidence that prevalence is high among ram breeders and terminal sire flocks in particular and therefore the role of rams in the spread of CLA should not be underestimated. Discussions can be initially triggered by vets at cull ewe screens or of rams at point of purchase but as described, the next step for flocks as to investigation and implementation of control can be a tricky decision. Often there are bigger, clearer threats to production but for businesses built on a reputation of higher health, elite stock, this may be just as damaging to their business. Ultimately in the absence of clear cost-benefit analysis based on observational data from the UK, CLA management should be a clearly communicated undertaking with defined, costed outcomes.

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