**An Update on Liver fluke in Sheep**

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INTRODUCTION

*Fasciola hepatica,* the common liver fluke,is a ubiquitous parasite affecting the health and welfare of grazing animals worldwide. It is also an important human pathogen, affecting up to 17 million people in lower and middle-income countries. Liver fluke infection has a significant economic cost to the UK agriculture industry through mortalities in sheep, losses in production in sheep and cattle and losses to processors at the abattoir. The true cost of liver fluke to UK farming is not fully understood but the Agriculture and Horticulture Development Board suggests that infection may have an annual cost of at least £3-5 per ewe in lost productivity (https://beefandlamb.ahdb.org.uk/wp-content/uploads/2013/06/Leaflet-Reducing-liver-fluke.pdf). Evidence from various sources shows that the prevalence of liver fluke infection has increased in recent years due to a combination of factors including our changing climate, changing farming practices and increased animal movements (Beesley et al 2017a). Triclabendazole (TCBZ) resistance is a major issue in many parts of the country and the switch to other products has raised fears that resistance may also start to develop to other drug classes on the market. As our climate warms, UK winters become milder and summer weather less predictable, it is likely that liver fluke will become even more problematic, particularly for sheep farmers. This review highlights some current issues and tries to offer new insights into how fasciolosis can be better managed.

DISEASE

Mature *F. hepatica* are large, leaf-shaped trematodes; about 3 to 5cm in length and 1cm in width. They are hermaphrodite, i.e. each parasite has both female and male sex organs and, although self-fertilization can occur, cross-fertilization is more frequent (Beesley et al 2015). Both the juvenile and the adult stages of the parasite feed by secreting enzymes, most notably cysteine proteases, which break down blood and liver tissue. The parasites are covered in microscopic spines, and as the adult fluke move around in the bile ducts, the irritation causes hyperplasia of the bile duct epithelium.

Sheep are highly susceptible to fluke infection; on ingestion of large numbers of metacercariae, the resulting juvenile fluke migrating through the liver cause acute disease associated with extensive liver damage and blood loss, often leading to sudden death. Acute fasciolosis is typically seen in the early autumn, particularly following a wet summer. Chronic fasciolosis occurs in winter and spring after ingestion of smaller numbers of metacercariae the previous autumn; it is caused by blood-feeding adult fluke in the bile ducts. Typical clinical signs are weight loss and anaemia. Sub-acute disease occurs when there are both immature and mature fluke present in the liver and manifests as sudden weight loss and anaemia. Even low fluke burdens can affect weight gain and fertility and there is little evidence that sheep develop protective immunity, hence they can be repeatedly infected.

*FASCIOLA HEPATICA* LIFE-CYCLE AND TRANSMISSION

*F. hepatica* are able to parasitize a range of animals. Sheep and cattle are the main hosts in UK, but deer, rabbits, hares and horses can also be infected. *F. hepatica* are genetically heterogeneous and recent findings suggest that *F. hepatica* in sheep, cattle and horses are drawn from the same population and imply that anthelmintic resistance genes can flow rapidly through *F. hepatica* populations (Beesley et al 2017b; Howell et al 2019).

Liver fluke have an indirect life-cycle involving a snail intermediate host (Figure 1). In the UK, the principal species is *Galba truncatula,* the dwarf pond snail (Figure 2). Undifferentiated fluke eggs are passed out in the faeces of infected animals and once washed out of the faeces, the eggs start to develop. Development is temperature dependent, in a typical British summer, eggs may take 2-4 weeks to mature. A fully developed egg is stimulated to hatch by exposure to light and an increase in temperature and the short-lived miracidium is released. Miracidia seek and find *G. truncatula* then burrow through the foot and into the body cavity. The parasites grow, multiply and, after about 6 weeks, cercariae are released. A snail infected with a single miracidium can produce several thousand genetically identical cercariae, which are released over a period of time, probably several days (Hodgkinson et al 2018). The cercariae encyst on the vegetation to form infective metacercariae (cysts). When a grazing animal eats contaminated herbage, the metacercariae hatch in the gut, the newly excysted juveniles burrow through the gut wall and migrate into the liver. In sheep it takes about 10 weeks for flukes to reach the bile ducts, mature and produce eggs that can be detected in faeces.

For the fluke life-cycle to occur, normally *G. truncatula* must be present. Other species of snail such as *Radix* spp can support parasite development, and may replace *G. truncatula* in upland, peaty environments (Relf et al 2009). Snails feed on algae on the surface of mud, hence, they prefer slow moving bodies of water and a neutral pH. They also need calcium and other minerals for good shell growth. During the winter months, snails go into hibernation and the development of any stages of the parasite that are still in the snail at the start of winter will be arrested. In spring as the weather warms up, snails come out of hibernation and the parasite life-cycle resumes. When winters are mild, fewer snails will perish and more will be present in the spring, ready to become infected as eggs develop and hatch. The rate of egg development is dependent on temperature; above 10oC, development takes two to four weeks and the warmer the weather, the more rapid the development. Little development occurs in the winter when temperatures fall below 10oC, but undifferentiated eggs can survive on pasture for several months, even if temperatures drop below freezing (Smith, 2016).

Traditionally fasciolosis is considered a seasonal disease in the UK; most of the development of the free-living and intramolluscan stages occurs between May to October and if the weather conditions are ideal over the summer months, large numbers of metacercariae are released from snails onto the pasture in August, September and October. Acute fasciolosis is common in sheep that consume large numbers of metacercariae in the autumn, often following a wet summer.

If weather conditions are less favourable, for example if the summer is hot and dry as in 2018, then development of both snail and parasite is slower and fewer metacercariae are released on pasture in the autumn. Evidence from winter 2018/2019, which was mild in many parts of the country and followed a very hot, dry summer, suggested that the appearance of metacercariae was delayed and farmers, vets and diagnostic companies were reporting chronic disease in April, despite a pre-tupping dose of a flukicidal product (<https://www.scops.org.uk/news/2804/livestock-farmers-urged-to-test-sheep-and-cattle-for-liver-fluke-before-treating-this-spring/>)

Whilst typically there is a peak in the number of infective cysts on pasture from the late summer into autumn, low numbers of metacercariae are likely to be present on pasture all year round as they can survive on pasture for months given the right conditions. Also it is thought that snails that have carried the infection over the winter can release metacercariae onto the pasture when they come out of hibernation in the spring. Sheep grazing at-risk pasture, even early in the season, can pick up infection. This may not lead to clinical disease but these animals pass eggs that will develop and infect snails, perpetuating the infection on the pasture.

Metacercariae of *F. hepatica* remain viable on the pasture for several months, particularly in cool, damp conditions, for example over winter in UK. Laboratory studies suggest that metacercariae survive for up to a year at temperatures between 0oC and 20oC but at temperatures above 20oC they lose infectivity rapidly. Similarly, metacercariae survived freezing between 0oC and -20oC and survived diurnal freezing and thawing (Boray and Enigk, 1964). Recent work from the University of Liverpool has shown that metacercariae do not survive in silage made under anaerobic conditions (John et al 2018; John & Hodgkinson, unpublished observations).

The UK’s climate is changing; the 10 hottest years in the UK since 1884 have happened in the last 17 years and extreme global weather events tripled between 1980 and 2017 (https://www.metoffice.gov.uk/weather/learn-about/climate-and-climate-change/climate-change/index). Two studies have been published using the Ollerenshaw forecasting model, that predict the risk of fasciolosis over the next 50-70 years, using a range of climate change predictions from the Intergovernmental Panel on Climate Change (Fox et al 2011; Caminade et al 2015). The consensus from these studies is that prevalence of fasciolosis is likely to increase and timing of outbreaks become less predictable. It is therefore imperative that we develop new ways to prevent disease whilst relying less on blanket drug treatment.

DIAGNOSIS

Whilst abattoir reports are useful to indicate if fluke is present on a farm, specific diagnosis is important to establish if fluke is the cause of disease or production loss and to guide treatment. Traditionally, post-mortem examinations are used in severe cases to confirm chronic and acute fasciolosis. To prevent disease, few farmers in heavy fluke endemic areas attempt to diagnose infection in sheep and prefer instead to treat in the absence of a diagnosis, at traditional times of year. However, this approach can be risky if the summer is unusually hot, or extremely wet, as in 2012, or the winter unusually mild as we found early in 2019.

The timing and severity of fluke challenge varies from year to year, depending on weather over the summer season but it is also influenced by historical weather patterns (McCann et al 2010). SCOPS, COWS and NADIS all provide useful monthly updates on fluke risk for regions of UK but it is important to bear in mind that risk will vary between individual farms within an area depending on the farm environment and management practices.

Faecal egg counts (FEC) are a valuable tool to demonstrate the presence of infection in a flock and can be used both on individual faecal samples and also composite samples (Daniel et al 2012; Graham-Brown et al 2019). FEC do have limitations however; they can only diagnose the presence of adult fluke and it takes at least nine weeks for fluke to mature and shed eggs after infection. Hence FEC cannot be used to diagnose early infection and acute disease.

A coproantigen detection ELISA, based on a monoclonal antibody to fluke cathepsins (Mezo et al 2004) is offered by several diagnostic labs. Validation studies in naturally infected sheep suggest the coproantigen ELISA detects infection at a similar time to faecal egg counts (Gordon et al 2012) and, importantly, there is no evidence that it cross reacts with *Calicophoron daubneyi,* the rumen fluke, which is increasingly common in sheep and cattle in the UK (Kajugu et al 2015). The coproantigen ELISA can be used for individual sheep but there are few data to support its use for composite samples (Flanagan et al 2011).

Serum antibody detection ELISAs are a valuable tool in monitoring exposure in first season lambs if samples are collected monthly from late summer until sero-conversion, from 10-20 lambs per management group. Lambs seroconvert 2-4 weeks post infection, meaning a positive antibody test in first season grazing lambs is useful to target treatment at the right time. Serum antibodies persist following treatment, so testing serum from older sheep is less informative for planning treatment regimes.

FLUKICIDE RESISTANCE

Resistance to triclabendazole was first reported in Australia in 1995 (Overend and Bowen 1995). Since then resistance has been reported worldwide, the first report in the UK was in a Scottish sheep flock in 1998 (Mitchell, Maris and Bonniwell, 1998). Triclabendazole is unique in targeting all stages of fluke in sheep, from 2 days old to adults. For this reason it has been widely used to prevent acute fasciolosis. The lack of cheap, rapid diagnostic tests for early fluke infection has meant that sheep are often dosed repeatedly in the autumn with triclabendazole. A recent prevalence study showed that triclabendazole resistance was present in North West, North East and South West England and in Wales (Kamaludeen et al 2019). It is important that farmers test their flocks for the presence of triclabendazole resistant fluke to enable them to manage disease effectively. A fully validated composite faecal egg count reduction test has been published and can be used to detect evidence of resistance (Daniel et al 2012) and the coproantigen ELISA has also been validated in individual experimentally infected sheep to detect resistance (Flanagan et al 2011).

There are several other flukicides that are licensed for use against *F. hepatica* in sheep, namely, closantel, nitroxynil, benzimidazoles (albendazole, ricobendazole, mebendazole) and oxyclozanide, details are available on the SCOPS website ( https://www.scops.org.uk/). To our knowledge there have been no cases of confirmed resistance to any of these products in the UK as of 2019 (Hanna et al 2015). However loss of efficacy of both closantel and albendazole has been reported in Sweden and Spain respectively (Alvarez-Sanchez et al 2006; Novobilsky et al 2012).

The switch away from triclabendazole-containing products, particularly to closantel and nitroxynil, has led to fears that resistance will develop to these products too. With no prospect of either vaccines or new drugs entering the market in the near future, it is imperative that these products are used in a way that minimises selection for resistance genes. The concept of *refugia* is well established for control of gastrointestinal nematodes in sheep, but is much less certain for fluke. Targeted selective treatment strategies for *Teladorsagia circumcincta,* in the UK,focus on treating only a proportion of a flock, leaving some untreated and hence preserving a population of worms *in refugia*. However because *F. hepatica* is such a pathogenic parasite, the prospect of leaving some animals untreated is risky, without solid research to support such a strategy (Hodgkinson et al 2019).

There are numerous commercial preparations for the treatment of *F. hepatica* on the market in the UK, but the number of pharmaceuticals is limited to the active ingredients listed above. Given the different formulations and anthelmintic combinations, it is not surprising that farmers are often confused about which active they are dosing their sheep with. In our experience, there is also confusion about what product should be used at specific times of year to target the different stages of fluke in the animal. Table 1 summarises the active ingredients, the stage of fluke they target and the most appropriate time of year for their use.

Table 1: Pharmaceutical products licensed to treat *Fasciola hepatica* in sheep in the UK

|  |  |  |
| --- | --- | --- |
|  | Age of fluke | Optimum time of year to use  |
| Flukicide | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12+ |
| Albendazole |  |  |  |  |  |  |  |  |  | 50-70% | 80-99% | Spring/Summer |
| Oxyclozanide |  |  |  |  |  |  |  |  |  | 50-70% | 80-99% | Spring/Summer |
| Nitroxynil |  |  |  |  |  |  | 50-90% | 91-99% | Late Autumn/Winter |
| Closantel |  |  | 23-73% | 91% | 91-95% | 97-100% | Autumn |
| Rafoxanide\* |  |  |  | 45-98% | 85-99% | 99-100% | Not available in UK |
| Triclabendazole\*\* | 90-99% | 99.0-99.9% | Autumn |

\* Not available in UK. \*\* Assuming a fully susceptible population.

Table modified from SCOPS; Fairweather and Boray, 1999; NOAH.

Rafoxanide is no longer available in the UK although it is on the market in Ireland. Together with closantel, it belongs to the halogenated salicylanilide group of anthelmintics and there is evidence of cross-resistance between these two compounds (reviewed in Swan, 1999). At a standard dose rate, rafoxanide has a similar spectrum of activity against both mature and immature fluke as closantel, although there is some suggestion that it is more efficacious in sheep than in cattle against fluke of a similar age (Table 1).

CONTROL

Control of fasciolosis depends on the type of enterprise, the history of the farm and the level of challenge, which will vary from year to year depending on the prevailing weather conditions. Each control program should be tailored to a particular farm and the whole farm considered, including other stock that may be present, bearing in mind that wildlife can also act as reservoirs of infection. Control usually depends on a combination of strategic drug treatment to reduce contamination of pasture with eggs, grazing strategies that avoid heavily contaminated pasture particularly in the autumn, together with prophylactic treatment when there is a threat of disease. In an ideal world, diagnosing infection in specific groups of sheep prior to treatment is good practice, but practicalities often preclude this. It is also important to remember that none of the flukicides have a persistent activity so if treated stock remain on infected pasture then they will immediately become reinfected.

The presence of *F. hepatica* is dependent on the presence of *G. truncatula.* In our experience, we rarely find snails on improved/reseeded pasture.  *G. truncatula* habitat is often diverse, diffuse and can be widely distributed over an area of pasture, making it hard to avoid potentially contaminated grazing using measures such as fencing. *G. truncatula* are found in habitats with damp, bare mud, little or no vegetation cover and no shade (Figure 3). Such areas include:

* Depressions caused by tractor tyre ruts, poaching, natural landscape features
* Cleared drainage ditches
* Banks on the sides of streams or ponds
* Soft ground around leaking water taps or pipes

For many sheep farms, especially those that have entry level or higher level stewardship schemes and other conservation arrangements, it is almost impossible to do anything to control snail habitat. With this in mind, controlling fluke is difficult and complicated, but relying solely on repeated whole flock drug treatments is not a sustainable strategy. Hence, control plans need to be devised that are specific to each individual farm. Veterinary input into these control plans is essential, given the complexity of the problem.

Bespoke control plans could include a combination of the following:

1. Establish the triclabendazole resistance status of the farm.
2. Test, using a composite faecal egg count, and treat sheep in the spring with flukicides that target adult parasites. This aims to reduce egg shedding onto pasture and subsequent infection in snails.
3. Use groups of sentinel lambs (e.g. replacement breeders) and blood sample monthly from late summer until lambs sero-convert, to assess autumn challenge.
4. In the autumn, use a flukicide that targets immature fluke, such as triclabendazole (if populations of fluke are susceptible, see (1)) or closantel.
5. In winter, especially if ewes are housed, use a product such as nitroxynil that targets late immatures and adults.
6. Avoid heavily contaminated pasture in autumn; it may be necessary to consider autumn housing to avoid infection in bad years.
7. Diagnose and treat other stock, for example cattle at housing (note that very few flukicides are licensed for use in dairy cattle).
8. Quarantine test and treat bought in stock to prevent introduction of triclabendazole resistant parasites.
9. Ensure that farmers follow the 5Rs when dosing their stock (Figure 4).

CONCLUSIONS

Liver fluke is a common parasite that affects the productivity, health and welfare of sheep. Control is confounded by the lack of cheap, accurate, animal-side diagnostics, anthelmintic resistance and difficulties in avoiding heavily contaminated pasture on many farms. It is likely that changes to the UK’s climate will significantly alter the epidemiology and transmission of the parasite over the coming decades making outbreaks of fasciolosis more frequent and less predictable. Research is needed urgently into improved diagnostics, a better understanding of the mechanisms of triclabendazole resistance, identification of new drug targets and production of an effective vaccine. The availability of an annotated, whole genome map of *F. hepatica* (Cwiklinski et al 2015) is greatly accelerating developments in these areas, but in the meantime, vets must be involved in providing up to date advice on sustainable use of existing flukicides and bespoke management options to control fasciolosis at the farm level.

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Figure 1. Life-cycle of Fasciola hepatica involves an intermediate host – *Galba truncatula* (credit: Bethan John, University of Liverpool)

Figure 2. *Galba truncatula*, the dwarf pond snail, the principal intermediate host for *Fasciola hepatica* in the UK (credit: Veterinary Parasitology Research Group, University of Liverpool).

Figure 3. Extensive *Galba truncatula* habitat, marked by the presence of rushes and other water loving plants (Credit: Dr John Graham-Brown, University of Liverpool).

Figure 4. The COWS five R’s best practice for dosing sheep and cattle with anthelmintics (credit: COWS [www.cattleparasites.org.uk](http://www.cattleparasites.org.uk))