A new old parasite – liver fluke

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Abstract

Fasciola hepatica, the common liver fluke, has been known to cause ill health in livestock for over 100 years in the United States, yet it remains a parasite of importance in the Gulf Coast and Pacific Northwest. One of its major effects is to cause anemia, however, its presence may not immediately be considered, especially in the southeastern United States, because of the highly pathogenic and ubiquitous barber pole worm, *Haemonchus contortus*. Little research has been conducted on *F. hepatica* in the United States in recent years, and goats appear to have been much less studied than sheep and cattle. Alternative, complementary diagnostics to conventional fecal examination (normally using sedimentation techniques) would be useful, as would new anthelmintics. However, in the absence of both, control of liver flukes must be given careful consideration in terms of maintaining animal health and welfare and preserving the efficacy of existing flukicides. Testing for efficacy of anthelmintics currently used in practice would contribute towards making recommendations regarding their rational use.

Key words: anthelmintic resistance, diagnostics, *Fasciola hepatica*, goats, *Haemonchus contortus*, North America, sheep

Background

In the United States, infection with the digenean trematode, *Fasciola hepatica*, the common liver fluke, has been known to be a cause of poor profitability in sheep and cattle farming since at least the late 1800s.[1] Lower birth rates, inefficient feed conversion, slower growth, poor quality milk and meat, and rough and brittle hair and wool in sheep and cattle were all described.[1] In the early 1900s, liver fluke infections spread rapidly from the West Coast and Rocky Mountain states eastward and northward and caused significant losses for sheep and cattle ranchers.[1] In North America today, liver fluke infections remain endemic in the Gulf Coast states, the Pacific Northwest, the Caribbean, and eastern Canada, and continue to be problematic,[2] yet there is little ongoing research into the prevalence of liver fluke, the effectiveness of available treatments, or the management of the disease, particularly in goats.

Life cycle

The geographical regions noted previously contain habitats that are favorable for the survival of the snails that *F. hepatica* requires to continue its life cycle. Indeed, the key to the presence of *F. hepatica* in an area is the existence of certain species of mud snails of the lymnaeid family.[3] For an excellent video depicting the life cycle stages of *F. hepatica*, refer to the video by Bennett and Barlow.[4] The adult hermaphroditic parasites live in the bile ducts. They release eggs which move into the common bile duct and intestinal tract and are then passed out in the feces. Following development of the fertilized egg in a watery environment, the ciliated miracidium emerges and swims to try to find the foot of a suitable snail host which it must enter within 24 hours.[3] Here the miracidium undergoes several stages of asexual reproduction (miracidium → sporocyst → redia → daughter rediae → cercariae) before the long-tailed cercariae emerge from the snail. The cercariae encyst on vegetation as metacercariae, which are the infective stage. Following ingestion of the metacercariae, the immature flukes penetrate the intestinal wall and migrate across the peritoneum to the liver, where they bore through the parenchyma for several weeks. Eventually, the young flukes enter the bile ducts and mature to adults. The prepatent period is 60 days.[3] Hence the snail not only serves as a source of protection for the developing cercariae, but it also serves to help propagate the parasite.

The snails that support the development of *F. hepatica* require neutral soils that remain reasonably moist throughout the year and environments with milder winters such that the eggs and juvenile stages are not destroyed.[3] In Louisiana, transmission occurs between February and July, while summer drought tends to interrupt the life cycle by causing snail mortality and promoting aestivation of snails.[5] Peak transmission occurs in mid and late spring.[5] In Texas, peak transmission appears to occur earlier, in January to February.[6] In a recent retrospective study of 15 cases with *F. hepatica* infection (confirmed by fecal sedimentation or necropsy) presenting to the Louisiana State University Veterinary Teaching Hospital from 2012 to 2022, 67% of the cases presented during February to July.[7] In the northwestern states, transmission gradually increases through the summer and fall grazing seasons to reach a peak during November, with winter cold tending to interrupt the life cycle in these areas.[8]

Fasciola hepatica coinfection with Haemonchus contortus

Liver fluke disease may manifest in acute or chronic forms.[3] The acute form is caused by the invasion of the liver by the immature flukes and, in heavy infections, this condition may be fatal.[3] However, even in light infections, the disease may also be rapidly fatal if clostridial organisms enter the body and multiply in damaged and poorly oxygenated tissues.[3] The chronic form of fasciolosis is caused by the presence of the adult flukes in the bile ducts.[3] Signs include progressive loss of condition, weakness, anemia, and hypoproteinemia manifesting as dependent edema ("bottlejaw").[3] At the Louisiana State University Veterinary Teaching Hospital, the diagnosis of fasciolosis is frequently complicated because of co-infection with *Haemonchus contortus*, the barber pole worm,[7] which is the major cause of anemia in sheep and goats in the southeastern United States and is especially common during the summer months.[9]

Unfortunately, the distribution of *F. hepatica* and *H. contortus* overlap throughout Louisiana, Mississippi, Arkansas and parts of eastern Texas and Oklahoma, as well as Florida. In these states, while the highest on the list of differential diagnoses for anemia will be haemonchosis, it is important to remember that chronic infection with *F. hepatica* may be contributing to

the anemia. This may be of particular concern for producers who are examining the conjunctival mucous membranes using the FAMACHA© system,[9] and treating animals accordingly, but are not mindful of the possible co-infection with liver fluke. The definitive underlying cause can only be confirmed by fecal examination by sedimentation (*F. hepatica*) and coproculture or lectin staining of trichostrongyle eggs (*H. contortus*),[10] especially if there is a history of both parasites being present on a particular property.

Diagnostics

Fecal examination for *F. hepatica* eggs is currently the only diagnostic method available in the United States and the FLUKEFINDER®[a] diagnostic system is commonly employed as the sedimentation method of choice. Recently, the Mini FLOTAC has been shown to be reliable for the detection of trematode eggs where zinc sulphate is used as the flotation solution.[11] In Europe, a copro-antigen enzyme-linked immunosorbent assay (ELISA) is available commercially for the diagnosis of *F. hepatica* infections in cattle and sheep[b]. The copro-antigen ELISA is able to detect infection 6 to 8 weeks after infection compared with 8 to 10 weeks for fecal examination[b]. Commercial ELISAs are also available in Europe, which may be used to detect antibodies in bovine and ovine sera or bovine milk.[12] Unfortunately, no flukicides are currently available for the treatment of immature flukes in the United States.

Predictions regarding the risk of exposure to liver fluke infections may be made based on climate (for example, rainfall and specifically the number of days with rainfall above certain levels) and environmental factors (for example, soil type) and models have been developed to refine the predictions by examining the relationship between the climatic and environmental factors and actual exposure to *F. hepatica* based on the presence of antibodies in bulk bovine milk tank samples.[13] There is ongoing work to develop and refine sentinel screening using serology at the start of expected periods of exposure, with the aim of alerting farmers about possible impending threats so that treatments may be administered.[14] Since antibodies may be detected as early as 2 to 4 weeks post infection,[12] this should theoretically allow for the treatment of the immature stages, which may be particularly pathogenic in sheep, in countries where drugs are available that are effective against those stages (for example, triclabendazole). Alas, such programs are not currently available in the United States.

Treatment

While strategies to fence off pastures, or areas within pastures, known to be heavily contaminated with the infective metacercariae may be possible on some farms, generally this is challenging, especially in areas of the Gulf Coast where snail habitats are widespread but may also be temporary in nature, with areas of standing water advancing and receding within pastures with seasonal fluctuations in soil moisture content.[5,12] If pasture rotation is possible, pastures that are known to be more heavily contaminated may be avoided during periods of high transmission. Given the challenges of avoiding snail habitats for grazing, anthelmintics will remain the most important measure to assist in the control of the parasites.

Only albendazole, a benzimidazole, and clorsulon, a sulfonamide, are available in the United States for the treatment of *F. hepatica*. Albendazole oral suspension[c] is labeled for the treatment of adult *F. hepatica* in sheep and nonlactating goats. The label dosages differ between sheep (3.4 mg/lb; 7.5 mg/kg) and goats (4.54 mg/lb; 10 mg/kg). Clorsulon is marketed as an injectable in combination with ivermectin for use in cattle[d] and its use would be off label in sheep and goats. The combination product has a label indication for adult *F. hepatica* only. The author does not know of any studies demonstrating the effectiveness of the off-label use of the combination product in sheep and goats. A product containing clorsulon as the only active ingredient was available for oral use in cattle[e], but no longer appears to be marketed. One study tested this oral product for efficacy against the adult stages of *F. hepatica* in goats and determined that a dosage of 3.18 mg/lb (7 mg/kg) was 98% effective in removing adult flukes and dosages of 5 mg/lb (11 mg/kg) and 6.82 mg/lb (15 mg/kg) were 99% and 100% effective, respectively.[15] The salicylanilide, closantel, is licensed in Canada for the treatment of *Haemonchus contortus* infection in sheep[f], however, closantel is known to have flukicidal activity and will kill flukes 7 to 8 weeks or older.[12] The author is not familiar with the legal requirements for off-label use of pharmaceuticals in Canada, but in cases of suspected resistance, closantel could, in theory, be used for the treatment of albendazole-resistant *F. hepatica*.

Anthelmintic resistance

There have been no reports of anthelmintic resistance in *F. hepatica* in the United States, but to the author's knowledge, no surveys have been done. In countries outside the United States, resistance to flukicides has been documented, including to albendazole[16] and triclabendazole.[17] Resistance may be suspected when a producer has livers condemned at slaughter despite treatment of the animals with a flukicide, or when fecal egg counts remain positive following treatment with albendazole. While no standardized method has been established for the detection of anthelmintic resistance on farm, flukicide efficacy has been evaluated by determining the reduction in fecal egg count following treatment or through copro-antigen ELISA testing following treatment.[16,17] Where the anthelmintics used are not effective against immature flukes, results may be inaccurate because of the maturation of immature flukes in the interim between treatment and repeat testing. In such cases, an egg hatch test for albendazole has been found to be useful when conducted in parallel with the on-farm testing.[16,18]

The recommended practice has been to treat approximately 2 months after the last expected snail activity which allows for immature flukes to develop to adulthood so that the flukes are susceptible to treatment with the available anthelmintics. This translates to treatment being recommended in the late summer and fall in the southern United States and in the late autumn and winter in the northern United States.[12] While such strategies are likely to provide the best control as they target all the fluke population in the animal when the infective stages are at their lowest levels on the vegetation, the strategy of deworming all the individuals at any one time, at a time when the parasites in refugia are at their lowest has been linked to strong selection for resistance in gastrointestinal nematodes[19] and this finding may be extrapolated to be the case for liver flukes.

Any anthelmintic-resistant flukes remaining in the animals after treatment will survive in the host during the period when conditions are unfavorable for the life cycle to continue in the environment and their eggs will contaminate the pastures when conditions improve, increasing the relative proportion of resistant alleles in the population of offspring that will eventually reinfect the host.[20] Over time, the proportion of parasites

carrying resistant alleles will increase to levels where a lack of efficacy will be clinically evident.

An additional consideration when using a product such as albendazole for the treatment of liver fluke is that it will also have an effect against *H. contortus*, at least on farms where the drug is still effective against barber pole worm. This may be more of concern in the Pacific Northwest than the southeastern United States, because in the latter region, it will be difficult, if not impossible, to find a property where benzimidazole resistance is not present.[21,22] Nevertheless, treatment of all the animals in a flock or herd will not only select for anthelmintic resistance in *F. hepatica* but also in the gastrointestinal nematodes present in the host and should be avoided.

Conclusions and recommendations

Infection of sheep and goats with *F. hepatica* should always be considered in areas where liver flukes are known to be endemic (and even on farms in areas adjacent to known endemic areas, as the parasites do spread). Sheep and goats presenting with anemia where haemonchosis is the most likely cause should nevertheless be screened for liver fluke, where possible. In the absence of surveillance for resistance, treatments should not be assumed to be effective. Because albendazole is not effective against immature stages, which will continue to develop after albendazole treatment, it is difficult to recommend a period following treatment at which repeat fecal egg counts (by sedimentation) should be done, but counts done at 7, 14 and 21 days after treatment may provide some evidence of efficacy or lack thereof, both for *H. contortus* and *F. hepatica*. Avoid treating the whole herd or flock at any one time, especially during periods when transmission is expected to be lower. Instead, leave those individuals who appear to be less affected by the flukes (those that are not anemic or not losing condition, for example) untreated.[23] Obviously, any individuals showing overt clinical signs such as severe anemia or bottle jaw should be treated immediately (and possibly transfused) to prevent further deterioration or death of the animal.

Endnotes

[a] FLUKEFINDER®, Soda Springs, ID; **www.flukefinder.com**

[b] Monoscreen AgELISA *Fasciola hepatica*, Bio-X Diagnostics S.A., Rochefort, Belgium

[c] Valbazen® Suspension, Zoetis, Parsippany, NJ

[d] ivomec® Plus, Boehringer-Ingelheim, Duluth, GA

[e] Curatrem®, Merck Sharp & Dohme Research Laboratories, Division of Merck & Co. Inc., Rahway, NJ

[f] Flukiver®, Elanco Canada Limited, Mississauga, Ontario, Canada

References

1. Liver flukes. In: *USDA's Contribution to Veterinary Parasitology. Parasites, Diseases, and Control Measures.* National Agricultural Library, USDA. Accessed September 6, 2023. **https://www.nal.usda.gov/exhibits/speccoll/exhibits/show/parasitic-diseases-with-econom/parasitic-diseases-with-econom/liver-flukes**

2. Navarre CB. Epidemiology and control of gastrointestinal nematodes of cattle in southern climates. *Vet Clin North Am Food Anim Pract* 2020;36(2020):45–57. **https://doi.org/10.1016/j.cvfa.2019.11.006**

3. Bowman DD. Helminths. In: Bowman DD, ed. *Georgis' Parasitology for Veterinarians,* 11th ed. Elsevier; 2021:135–260.

4. Bennett C, Barlow D. Life cycle of the liver fluke: *Fasciola hepatica*. YouTube. Accessed September 4, 2023. **https://www.youtube.com/watch?v=CV5liUm5it4**

5. Malone JB, Loyacano AF, Hugh-Jones ME, Corkum KC. A three-year study on seasonal transmission and control of *Fasciola hepatica* of cattle in Louisiana. *Prev Vet Med* 1984;3(1984/85):131–141.

6. Craig TM, Bell RR. Seasonal transmission of liver flukes to cattle in the Texas Gulf coast. *J Am Vet Med Assoc* 1978;173(1):104–107.

7. Freeman B, Scully CM, Liu CC, et al. A retrospective study on the detrimental effects of liver flukes on small ruminants. Abstract presented at: National Veterinary Scholars Symposium; 2022; St. Paul, MN

8. Hoover RC, Lincoln SD, Hall RF, Wescott R. Seasonal transmission of *Fasciola hepatica* to cattle in northwestern United States. *J Am Vet Med Assoc* 1984;184(6):695–698.

9. Kaplan RM, Burke JM, Terrill TH, Miller JE, Getz WR, Mobini S, et al. Validation of the FAMACHA© eye color chart for detecting clinical anemia in sheep and goats on farms in the southern United States. *Vet Parasitol* 2004;123(1/2):105–120. **https://doi.org/10.1016/j.vetpar.2004.06.005**

10. Palmer DG, McCombe IL. Lectin staining of trichostrongylid nematode eggs of sheep: rapid identification of *Haemonchus contortus* eggs with peanut agglutinin. *Int J Parasitol* 1996;26(4):447–450.

11. Bosco A, Ciuca L, Maurelli MP, et al. Comparison of Mini-FLOTAC, Flukefinder® and sedimentation techniques for detection and quantification of *Fasciola hepatica* and *Calicophoron daubneyi* eggs using spiked and naturally infected bovine faecal samples. *Parasit Vectors*. 2023;16:260. **https://doi.org/10.1186/s13071-023-05890-2**

12. Howell AK, Williams DJL. The epidemiology and control of liver flukes in cattle and sheep. *Vet Clin North Am Food Anim Pract* 2020;36(2020):109–123. **https://doi.org/10.1016/j.cvfa.2019.12.002**

13. Selemetas N, De Waal T. Detection of major climatic and environmental predictors of liver fluke exposure risk in Ireland using spatial cluster analysis. *Vet Parasitol* 2015;209(2015):242–253. **http://dx.doi.org/10.1016/j.vetpar.2015.02.029**

14. McEvoy et al. The use of Cathepsin L1 (FhCL1) blood-test ELISA in sentinel screening for liver fluke on sheep farms. Abstract presented at: 29th Conference of the World Association for the Advancement of Veterinary Parasitology; 2023; Chennai, India

15. Sundlof SF, Bliss EL, Greiner EC, Tran TQ, Wertenberger MA. Efficacy of clorsulon for the treatment of experimentally induced infections of *Fasciola hepatica* in goats. *Am J Vet Res* 1991;52(1):111–114

16. Novobilský A, Solis NA, Skarin M, Höglund J. Assessment of flukicide efficacy against *Fasciola hepatica* in sheep in Sweden in the absence of a standardized test. *Int J Parasitol: Drugs Drug Resist* 2016;6(2016):141–147. **http://dx.doi.org/10.1016/j.ijpddr.2016.06.004**

17. Brockwell YM, Elliott TP, Anderson GR, Stanton R, Spithill TW, Sangster NC. Confirmation of *Fasciola hepatica* resistance to triclabendazole in naturally infected Australian beef and dairy cattle. *Int J Parasitol: Drugs Drug Resist* 2014;4(2014):48–54. **http://dx.doi.org/10.1016/j.ijpddr.2013.11.005**

18. Robles-Pérez D, Martínez-Pérez JM, Rojo-Vázquez FA, Martínez-Valladares M. Development of an egg hatch assay for the detection of anthelmintic resistance to albendazole in *Fasciola hepatica* isolated from sheep. *Vet Parasitol* 2014;203(2014):217–221. **http://dx.doi.org/10.1016/j.vetpar.2013.11.020**

19. Van Wyk JA. Refugia – overlooked as perhaps the most potent factor concerning the development of anthelmintic resistance. *Onderstepoort J Vet Res* 2001;68(1):55–67

20. Kaplan RM. Biology, epidemiology, diagnosis, and management of anthelmintic resistance in gastrointestinal nematodes of livestock. *Vet Clin North Am Food Anim Pract* 2020;36(2020):17–30. **https://doi.org/10.1016/j.cvfa.2019.12.001**

21. Howell SB, Burke JM, Miller JE, Terrill TH, Valencia E, Williams MJ, Williamson LH, Zajac AM, Kaplan RM. Anthelmintic resistance on sheep and goat farms in the southeastern United States. *J Am Vet Med Assoc* 2008;233(12):1913–1919. **https://doi.org/10.2460/javma.233.12.1913**

22. Howell SB, Park BW, Vidyashankar AN, Storey BE, Collins JB, Kaplan RM. A 16-year retrospective analysis of anthelmintic resistance in *Haemonchus contortus* on small ruminant farms in the United States. Abstract presented at: 27th Conference of the World Association for the Advancement of Veterinary Parasitology; 2019; Madison, WI

23. Greer AW, Van Wyk JA, Hamie JC, Byaruhanga C, Kenyon F. Refugia-based strategies for parasite control in livestock. *Vet Clin North Am Food Anim Pract* 2020;36(2020):31–43. **https://doi.org/10.1016/j.cvfa.2019.11.003**

