UK-VET Livestock

Youngstock health:

a focus on *Mycoplasma bovis*, nematode control and the use of NSAIDS in scour


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Foreword

Farming is under increasing scrutiny on environmental issues (including greenhouse gas emissions, resource use, water and air quality, biodiversity and other impacts), in addition to increasing economic and social pressures. It is increasingly clear that we need to ensure that every animal has a good healthy life, while reducing losses throughout the production system.

As cattle vets, we work with cattle at every stage of the production cycle, but on many dairy farms, youngstock are still seen as being of secondary importance compared with the mature herd, suffering significant levels of disease, and sustaining high mortality. This is despite the fact that dairy replacements are, or should be, the group with the highest genetic merit on the farm and are the future of the herd.

In contrast to the dairy herd, calves from the suckler herd are the only saleable product of the cow and thus her whole production for the year is lost if the calf should die. Despite this, more could still be done on many farms to improve health and productivity of these calves allowing them to be finished faster with associated environmental benefits.

For environmental, economic and social reasons, it is no longer acceptable to cull dairy bull calves, or to ignore high levels of morbidity or mortality. An animal that has a suboptimal growth rate or dies represents a financial loss to the farmer, a welfare concern to the consumer, and an environmental impact that is not compensated for by food (milk or meat) production. If we are to serve our clients to the best of our ability and help make their businesses as sustainable as possible, we need a greater focus on youngstock.

This supplement is a good place to start with its focus on *Mycoplasma bovis*, nematode control and the use of NSAIDs in calf scour.

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The role of *Mycoplasma bovis* in cattle respiratory disease

The importance of *Mycoplasma bovis* in causing and contributing to respiratory disease in cattle has been highlighted over recent years, however, it still remains a significant challenge to UK farmers. *M. bovis* has developed genetic adaptations enabling improved survivability within the host, and its ability to produce biofilms supports survival and aids spread of the organism in the environment. As for many respiratory pathogens in cattle, early diagnosis and prompt treatment with an effective antibiotic are vital in tackling *M.bovis* infections, however, preventing the spread from infected to uninfected animals is key to tackling the disease at a herd level.

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Key words: cattle | *Mycoplasma bovis* | respiratory disease

Recent science has shown the positive impacts of a good start in a calf's life on its future productivity (Soberon, 2012). The areas of particular relevance to ensure a good start are: colostrum management, calf nutrition, environmental conditions and disease control. Unfortunately, however, 14.5% of live born UK dairy replacement calves fail to make it to their first calving (Brickell et al, 2009). One of the main causes of death in these calves is pneumonia. Nationally, respiratory disease costs the UK cattle industry around £50 million per annum (Agriculture and Horticulture Development Board (AHDB), 2018), and the estimated cost of an individual case is £43–82 per calf (Andrews, 2000). Furthermore much of the disease exists subclinically, meaning animals can have it without showing any signs, and therefore the losses associated (e.g. reduced growth rates) can often be hugely underestimated. For example, it has been calculated that a reduction in average daily weight gain to weaning of just 0.1 kg/day reduces a heifer's first lactation yield by 300 litres (Bach et al, 2008). Despite these startling statistics calf pneumonia is still a significant problem on many UK farms.

Causes of cattle respiratory disease

Respiratory disease in cattle is a multifactorial disease and a number of viruses and bacteria are commonly identified pathogens. These include:

- Viruses — respiratory syncitial virus (RSV), parainfluenza 3 virus (PI3), bovine herpesvirus type 1, infectious bovine rhinotracheitis virus (IBR), bovine viral diarrhoea virus (BVDV)
- Bacteria — *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Mycoplasma bovis*
- Parasites — *Dictyocaulus viviparous* (lungworm).

The pathogenic causes of calf pneumonia are not normally seen in isolation. Frequently multiple organisms can contribute to the disease process and there are normally other predisposing factors at play. These include:

- Environmental — poor ventilation (including inadequate air outlet or inlets), draughts (uncontrolled air speed), increased humidity, damp bedding, dust (particularly common where straw blowers are used to bed cattle), cold temperatures (especially relevant to pre-weaned calves)
- Nutritional — underfeeding (especially relevant to pre-weaned calves fed milk replacer), lack of micro nutrients (vitamins and minerals), acidosis
- Stressors — weaning, transport, castration, disbudding, concurrent disease (e.g. BVD), immunocompromised animals (e.g. persistently infected BVD calves).

Mycoplasma bovis

While most of the causes of calf pneumonia are well known to veterinary surgeons and farmers, the same cannot be said for *Mycoplasma bovis*. Mycoplasmas are very small bacteria that belong to the class Mollicutes (meaning soft skin). There are over 100 *Mycoplasma* spp. found globally, with each species tending to only infect one animal species. Around a dozen *Mycoplasma* spp. occur in cattle, with most of these non-disease causing. The most pathogenic cattle species is *Mycoplasma bovis*, which presents as pneumonia, arthritis and otitis media in calves, and mastitis, arthritis and respiratory disease in adult cattle.

Mycoplasmas are a very simple organism and need to form an intimate association with host cells to obtain the growth and nutritional factors necessary for their survival. To aid their survival they have developed mechanisms to evade the host's immune system. These include (adapted from Maunsell and Donovan, 2009): antigenic variation; variable surface proteins (VSP); and biofilm production.

Antigenic variation

Antigenic variation includes:

- Phase variation — switching on/off surface antigens

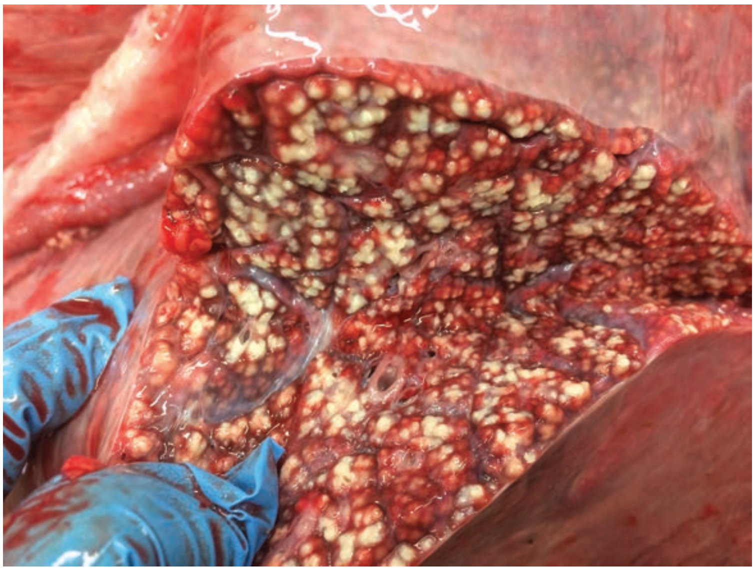

Figure 1. Microabsessation, particularly in the cranioventral lung lobes, are a common gross pathological finding with Mycoplasma bovis *infection. Photo courtesy of Ben Strugnell.*

Figure 2. A pre-weaned dairy calf with a head tilt, a common sign seen in Mycoplasma bovis *infections.*

- Size variation — changing their surface lipoproteins
- Variation of surface presentation — mask certain epitopes.

Variable surface proteins

A combination of multiple VSPs and variable lipoproteins combined with high frequency switching leads to an almost infinite number of possible variants.

Biofilm production

A biofilm is a matrix that 'hides' the bacteria from the host's immune defence and also makes it difficult for antibiotics to penetrate. The ability to produce a biofilm also enables *Mycoplasma* spp. to survive in the calf's environment and can easily be spread on shared equipment, e.g. calf tube feeders. Mycoplasmas also lack a cell wall, rendering some antibiotics that act on the bacterial cell wall to kill the bacteria, completely useless. Mycoplasmas grow slowly, which means that there are very few clinical signs in the early stages of the infection and that unfortunately by the time the infection is seen by the farmer it is well established and the prognosis for the animal is poor. All of these factors mean that *Mycoplasma* spp. infections can be hard to treat and often result in a temporary improvement in clinical signs before the calf relapses again, and death can result several weeks after the initial infection in many cases.

Disease manifestations of mycoplasmas

M. bovis can present as infections in the:

- Lungs causing calf pneumonia (colonisation alone is not always sufficient to cause disease as *M. bovis* can be isolated from the upper respiratory tract including trachea and lower respiratory tract of calves without clinical disease or gross lesions) (*Figure 1*)
- Middle ear (mainly from extension up the Eustachian tube from the oropharynx, but can also occur from an external ear infection through the tympanic membrane or from haematogenous spread) causing ear drooping and head tilt (*Figure 2*)
- Joints (from haematogenous spread) causing arthritis and joint sepsis
- Udder causing a contagious mastitis, mostly spread during milking (probably underdiagnosed, but still a rare cause of mastitis in the UK, largely associated with larger herd sized dairies).

Disease in young calves is occasionally attributed to mycoplasmas other than *M. bovis*, including *Mycoplasma dispar*, *Mycoplasma californicum*, *Mycoplasma canis*, *Mycoplasma alkalescens*, *Mycoplasma arginini*, *Mycoplasma bovirhinis*, *Mycoplasma bovigenitalium*, and *Mycoplasma bovoculi*. A variety of other species have been isolated from the middle ear or lower respiratory tract of diseased calves (Maunsel and Donovan, 2009). A number of these species are often found as part of the microbial flora of the upper respiratory tract in healthy calves, and in most reports they have been isolated in mixed infections with other known pathogens.

Mycoplasma bovis diagnosis

Traditional diagnosis using culture has required specific enrichment and extended incubation times to grow *Mycoplasma* spp. Even then distinguishing pathogenic from commensal populations requires molecular methods, such as polymerase chain reaction (PCR), PCR with denaturing gel electrophoresis (PCR/DGGE) and DNA sequencing.

Culture and PCR of bulk tank milk are both good screening tools for the presence of *M. bovis* mastitis in dairy herds. The sensitivity of milk culture for diagnosis of *Mycoplasma* spp. has been reported as being around 50% for bulk milk tank samples, and can drop to below 30% in individual cows with subclinical infections (Potter, 2019).

For respiratory disease investigation, initial PCR testing of acute cases on nasal swabs, bronchoalveolar lavages or lung tissue from post-mortem cases is recommended. Commercially available multiplex PCR panels include all the most common respiratory pathogens in cattle and have the benefits that the results are semi-quantitative. Serology testing is a useful screening tool following respiratory outbreaks to demonstrate *M. bovis* presence on the farm. Given that antibodies take 10–14 days to be produced and can persist in cattle for months, their detection on serology should be interpreted carefully. In calves 4 months old and under, maternal-derived antibodies could still be present, and while still relevant it does complicate the diagnostic picture. In calves over 4 months old a positive *M. bovis* enzyme-linked immunosorbent assay (ELISA) serum sample (<10 = negative, 10–24 = suspicious, >24 = positive) would suggest that the calf has undergone some bacterial replication rather than just colonisation, and is a significant finding. Ideally five (or more) calves should be tested per management group. To be diagnostic, paired serology demonstrating seroconversion alongside associated clinical disease is needed (*Figure 3*).

For more information about how Norbrook can support *M. bovis* investgations on farm please see details at the end of this article.

Mycoplasma spp. treatment options

As mentioned previously mycoplasmas have developed several mechanisms that aid their survival in the host. Structurally they lack the presence of a cell wall, which offers them a natural ability to resist beta-lactam antibiotics (penicillins and cephalosporins), which inhibit the cross-linking of amino acid chains in peptidoglycan synthesis in the bacterial cell wall. They are also resistant to sulphonamides, which inhibit folic acid synthesis, and those aminoglycosides that inhibit microbial respiration. Several antimicrobial classes, including oxytetracyclines, florfenicols and macrolides have efficacy against mycoplasmas (Potter, 2019), and some products within these classes have specific licensed claims against *M. bovis* in cattle.

As a result of its insidious slow growing nature, clinical presentations of *M. bovis* tend to be well established infections and successful treatment relies on early identification of infected animals, prompt intervention using antimicrobial treatment using a licensed product active against *M. bovis*, and a focused biocontainment protocol to minimise the spread within and between management groups. Poor treatment success in calf pneumonia cases, particularly when accompanied by arthritis and otits media, can be an indicator of *M. bovis* involvement on that farm (Maunsell and Donovan, 2009). Serological screening of previously affected groups can be helpful in these situations to check for the likelihood of *M. bovis* involvement.

Mycoplasma bovis prevention strategies

In commercial herds where *M. bovis* is not present, the biggest risk of infection is from purchased cows and heifers entering the herd. These animals can be asymptomatic carriers of *M. bovis* and can excrete the organism via respiratory and vaginal discharge and via the milk. Serology can again help in screening quarantined purchased animals before they enter the herd.

On farms where *M. bovis* is known to be present, the biocontainment strategy is focused on reducing the exposure of uninfected calves from infected animals.

Biocontainment strategy for *Mycoplasma bovis*

The following is a bicontainment strategy for *M. bovis* taken from Maunsell and Donovan (2009):

Reduce the level of exposure to *M. bovis*

1. Reduce exposure in milk
   a. Pasteurise whole milk
   b. Feed milk replacer
2. Reduce potential exposure in colostrum
   a. Avoid pooling
   b. Consider pasteurisation
3. Reduce potential airborne exposure
   a. Provide adequate ventilation in calf housing
   b. Consider the impact of pen design on air quality
   c. Consider ways to reduce stocking density
4. Reduce exposure to sick calves
   a. Consider segregation of calves with clinical *M. bovis*
   b. Promptly treat clinical cases
5. Prevent fomite transmission
   a. Sanitise pens, hutches, buckets, and other equipment between uses (*Figure 4*)
   b. Wear gloves when handling sick calves and change them between calves. Wear gloves when assisting calves to drink

Result interpretation (blood / indiv, milk / faeces)

Test	**Result**	**Interpretation**
Mycoplasma	<5	Negative
P13	<2	Negative
RSV	<2	Negative

Sample Material	*Mycoplasma bovis* Ab by ELISA (% positive)*	P13 Ab by ELISA (% positive)*	RSV Ab by ELISA (% positive)*
Blood	38	>100	>100
Blood	43	>100	8
Blood	42	>100	70
Blood	42	71	2
Blood	59	>100	10

Figure 3. Example of a farm where Mycoplasma bovis *was detected (laboratory interpretation <5 is negative). There is strong evidence of* M. bovis *involvement on this farm.*

Figure 4. Control measure implemented on farm with Mycoplasma bovis *— teats left soaking in hypochlorite solution between uses.*

c. Handle the youngest calves first

6. Consider 'all-in, all-out' practices, or segregate older and younger calves at the earliest possible opportunity
7. Where *M. bovis* is not already present, use biosecurity practices appropriate to the particular operation and monitor for *M. bovis.*

Maximise calf defences against *M. bovis*

1. Use nonspecific measures to maximise respiratory and immune system health
   a. Provide good air quality
   b. Control other pathogens, and, in particular, address any deficiencies in the vaccination and monitoring programmes for respiratory viruses and BVDV
   c. Provide good nutrition
   d. Address any colostrum management issues
   e. Minimise other sources of stress such as transport, heat and cold stress, and overcrowding
2. Consider metaphylactic antimicrobial use when high morbidity and mortality caused by *M. bovis* are being sustained (author's note — the evidence supporting this approach is limited and its use in this manner would not be considered responsible use of antibiotics)
3. There are insufficient data on the efficacy of currently available vaccines to recommend their use in neonatal calves at this time (author's note — there are no commercially available vaccines in the UK, although vaccines are available under special import license and autogenous vaccines can be used).

Conclusions

The nature of *M. bovis* infections means that prompt diagnosis of the presence of the pathogen is crucial in minimising the impacts of *M. bovis* on farms. Subsidised serology packages are available to support veterinary surgeons in identifying *M. bovis* infections. Once established, *M. bovis* infections require prompt treatment with an effective antibiotic to maximise cure rates and a diligent approach to biocontainment measures to reduce the spread of infection. LS

Conflict of interest: the author is veterinary advisor to Norbrook Laboratories (GB) Ltd., but all opinions and considerations are the author's own.

KEY POINTS

- Respiratory disease in young calves can have knock on consequences for the rest of its productive life.
- Mycoplasmas, particularly *Mycoplasma bovis,* play an important role in cattle respiratory disease.
- Genetic adaptations including antigenic variation, variable surface proteins and biofilm production aid host and environmental survivability of *M. bovis.*
- The slow disease manifestation in some clinical presentations and the inability of some antibiotic classes to treat *M. bovis* contribute to poor treatment outcomes.
- Prevention of *M. bovis* outbreaks involves screening all incoming animals on farms without the disease, and management protocols aimed at minimising the spread from infected to uninfected animal on farms where the organism has been detected.

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Control of nematodes in replacement heifers on spring block calving dairy herds

Gastrointestinal nematodes, *Ostertagia ostertagi* and *Cooperia onephora*, can cause economic and production losses in dairy heifers. Using grazing patterns and lifecycle, combined with treatments, it is possible to put a management plan in place for dairy heifers, which can reduce the risk of developing anthelmintic resistance, allow the development of some immunity and allow the heifers to grow and reach the required weight for service.

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Key words: nematodes | ostertagiosis | parasitic gastroenterits (pge) | anthelmintic | anthelmintic resistance | spring-calving

Gastrointestinal nematodes can cause economic and production losses in livestock, particularly intensive grazing systems (Baiak et al, 2019), which are commonly used by spring calving herds. Spring, block calving dairy herds often have very short and tight calving periods. Production losses, especially reduced growth rates in dairy heifers, can cause problems for these farms. Dairy heifers need to reach their target bulling or artificial insemination (AI) weight by 14–15 months old, to ensure calving at 2 years old and within the calving period of the herd. If they miss the weight targets, and are late reaching service or AI, they will be later in the calving period or miss it completely. To ensure the success of the block calving herd, it is essential that the replacement heifers calve within the block — but preferably early in the block.

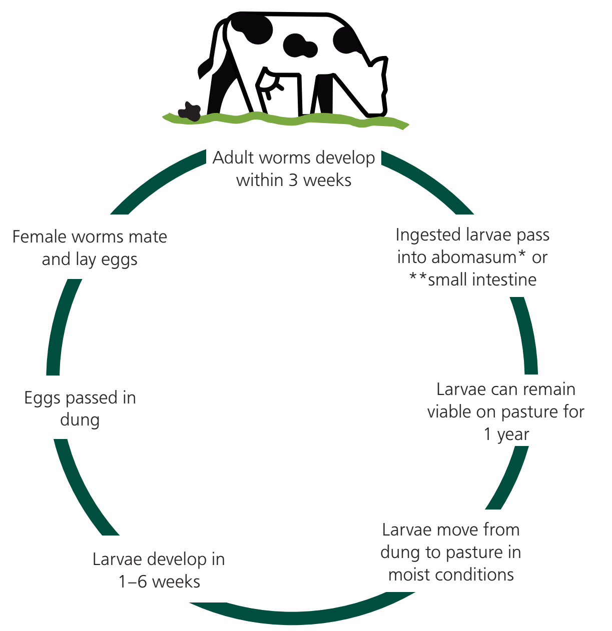
The control of nematodes is important because of the cost of anthelmintics, and gastrointestinal disorders that the heifers could suffer, leading to reduced growth rates and possible death. It is important to get the control of nematodes correct so that they do not hinder the growth of the replacement heifers.

Disease and risk

When creating a plan to control the nematodes on a farm, it is important to first consider the associated risks and the aims of any control plan. In the UK, heifer rearing farms have two nematodes of interest, *Ostertagia ostertagi* and *Cooperia oncophora* (Control of Worms Sustainably (COWS), 2020).

Both nematodes have direct (no intermediate hosts) lifecycles, with adults living within the cattle (*Figure 1*). The nematodes have two sexes and require mating. Fertile eggs are passed out with the cattle faeces and hatch in the dung. Larval development in the dung pat is dependent on temperature and moisture, taking less than a week at 15–23˚C and 3–6 weeks at 10˚C (COWS, 2020). Moisture is required for the larvae to leave the pat and climb onto herbage, leading to ingestion. Heavy rainfall will assist dispersal of the pat and larvae will be spread over a larger area. Peak levels of larvae on pastures are usually reached in late summer.

At the L3 stage, larvae are protected by an outer sheath making them more resistant to the elements and better able to survive



**Ostertagia* ***Cooperia*. Development can be inhibited in autum and resume in lare winter ir early spring

Figure 1. The lifecycle of nematodes in cattle. Courtesy of COWS – www.cattleparasites.org.uk

KEY POINTS

- Turn out of calves at 12 weeks of age can rule out the option of long-acting treatments.
- Turn out in May onto land grazed the previous season is likely to have over-wintered L3 stage larvae, which will likely lead to very high challenge in the late summer if the same pastures continue to be grazed.
- Transfer of the calves to lower risk pastures (silage fields) later in the season will reduce the challenge.
- Use of worm egg counts and growth rates to monitor the situation allows targeted or tactical treatments.
- Housing treatments should be considered for arrested larvae and reducing pasture contamination the following season.
- In the second grazing season *Ostertagia ostertagi* remains a significant risk but *Cooperia oncophera* is less of a risk.
- Continue monitoring in the second grazing season and treat as necessary.

for months. In dry weather, they can remain viable and protected within the soil. Rainfall, following a dry summer, can lead to a rapid rise in L3 on pastures. L3 numbers and challenge usually peaks from July onwards. Grazing in mid to late summer on pastures that have been used for silage earlier in the season will be lower risk, as over-wintered larvae are unlikely to survive this length of time.

Following ingestion, the *O. ostertagi* and *C. oncophora* larvae make their way to their preferred development site, the abomasal wall or small intestine respectively. At this stage, *O. ostertagi* can either continue to develop into adults and complete the lifecycle in 3 weeks (pre-patent period), or become dormant. If *O. ostertagi* continues to develop, in the spring and summer, this can lead to type I ostertagiosis. When ingested in the autumn, the *O. ostertagi* usually become dormant, stop development and remain in the gastric glands, resuming development in the late winter and early spring. If there are large numbers of larvae resuming development, this can cause type II ostertagiosis. Type II ostertagiosis often only affects a small proportion of animals, however it is usually more serious and can cause death (COWS, 2020). This arrested stage assists the nematode in surviving from one grazing season to the next.

O. ostertagi adults live within the lining of the abomasum where they damage the glandular tissues, reducing the acidity of the abomasum and disrupting protein digestion. They release appetite suppressants, which enhances weight loss (COWS, 2020). Reduction in acidity of the abomasum leads to changes in the gut bacteria, and the damage to the abomasal mucosa leads to further loss of protein, causing significant weight loss and reduced growth.

C. oncophora adults live within the small intestine and disrupt digestion and absorption. Cattle develop immunity to *C. oncophora* in the first grazing season, so cooperiosis is rarely seen in older cattle. Immunity to the nematodes is incomplete and it takes up to two grazing seasons for immunity to *O. ostertagi* to develop (COWS, 2020). Immunity is dependent on several factors including age, sex, nutrition, genetics and exposure to nematodes.

In calves, mixed infections may be present, referred to as parasitic gastroenteritis (PGE). The common clinical sign associated with PGE is diarrhoea, with loss of nutrients and fluids because of poor digestion and absorption. This also leads to weight loss, reduced body condition score and reduced growth rates, exacerbated by reduced feed intake.

Monitoring and diagnosis

Faecal worm egg counts (WEC) can be useful to show the dynamics of infection over a grazing season but it does have limitations. WEC are not always correlated with parasite burden because of the high volume of faeces and dilution. There can be a significant challenge to heifers but a relatively low WEC may be measured.

Serum pepsinogen levels can give an indication of abomasal damage caused by *O. ostertagi*. Mucosal damage caused by the larvae leads to a reduction in the transformation of pepsinogen into pepsin and accumulated pepsinogen escapes into the blood. An increase in serum pepsinogen is mainly a reflection of development and emergence of larval stages of *O. ostertagi* (Berghen, 1993), therefore levels can be used to estimate the level of challenge experienced by the heifers.

Performance monitoring, particularly growth rates, can be extremely useful to assess the challenge on the heifers. Monitoring can also help target treatment to selected heifers.

Historically, calendar-based treatments have been commonplace, and they can work because of the regular pattern of challenge faced by heifers. However, as the weather becomes more variable, and there is a move to use medicines responsibly, diagnostics and performance monitoring become more important.

Controls and treatments

A plan can be formulated by considering the lifecycle, grazing strategy, and history of nematode exposure. Consideration should be given to the farmer's targets, primarily aiming to have the heifers in calf at 15 months old. When planning control of nematodes, other parasites, including liver fluke (*Fasciola hepatica*) and lungworm (*Dictyocaulus viviparous*), should not be excluded. Any plan made should be dynamic and regularly revisited and reviewed.

Anthelmintics can be used within the control plan either strategically or therapeutically (COWS, 2020).

Strategic treatments are used to reduce faecal output of eggs and thus keep pasture contamination low. They are initiated within the first 3 weeks of grazing, and continue to minimise contamination of pasture while over-wintered L3 numbers decline. Treatments may include long-acting injectables (should not be used in cattle under 100 kg bodyweight) or boluses (should not be used in calves under 12 weeks of age or under 100 kg bodyweight), or repeated treatments. This method leads to a very high risk of developing anthelmintic resistance (COWS, 2020), and can be particularly problematic if heifers of the same age are grazing the same pastures year after year. It is also worth noting that calves at turn out could be under 12 weeks of age or under 100 kg, which can rule out the use of boluses and long-acting injections. In the author's experience, even when calves are 100 kg it can be difficult and frustrating to administer relatively large boluses.

Where there is no specific pattern of use of anthelmitics and they are used in response to clinical signs or poor performance, this is therapeutic use, this is therapeutic use. With therapeutic use of anthelmintics, there is no aim to reduce pasture contamination and the grazing heifers will be exposed to increasing risk of challenge and disease, potentially suffering PGE. Heifers must be closely monitored with regular growth rate checks and WECs. Care must be taken as challenge and worm burden can rise very quickly, within a few weeks and WECs should be performed every 14 days and heifers closely monitored. WECs do not correlate well to infection level and can still be low (compared with sheep WECs) with significant disease. Tactical treatments should be based on WECs and the performance of the animals.

Performance monitoring with new technologies allowing instant assessment of growth rates while the heifer is handled can significantly reduce reliance on anthelmintics and allow individual targeted selective treatments. As the heifer is being handled and weighed this is an opportune time to treat accurately based on her current weight and, if growing well, avoid treatment. Growth rates and WECs do not necessarily correlate, so while this may help to reduce pasture contamination by treating those with the highest burdens, there may still be significant egg output on to pastures. Avoiding treatment of all heifers, particularly those performing well, maintains a refugia of nematodes aiding in the slowing of the development of anthelmintic resistance (Merlin et al, 2017).

If housing the heifers during the winter period, this is an ideal time for strategic treatment to reduce arrested larvae and reduce pasture contamination at turn out the following spring (COWS, 2020). It is worth noting that benzimidazoles have an unpredictable activity against arrested larvae.

There are three groups of anthelmintic treatments for nematodes (*Table 1*). Macrocyclic lactones are commonly used in heifers because of the convenience of injecting, or pouring on, duration of action and ability to reduce arrested larvae during the winter (Barton et al, 2006).

Anthelmintic resistance is increasingly being observed and reported in cattle, so it would be prudent to check the efficacy of treatments used on heifers (O'Shaughnessy et al, 2019). *Table 2* details the method of anthelmintic resistance testing performed by the author.

Table 1. Nematode treatment groups

Benzimidazoles	1-BZ	Drench treatments: not easy or quick to administer Bolus treatments: longer acting but calves must be over 12 weeks of age and over 100 kg bodyweight
Levamisole	2-LV	Drench treatments only: not quick or easy to administer
Macrocyclic lactones	3-ML	Injectable treatments: either long or short acting and easy to administer. Long-acting injectables minimum bodyweight 100 kg. Topical treatments: more convenient to administer Concerns around increasing anthelmintic resistance

Table 2. Anthelmintic resistance testing or drench checking

1	Initial mob worm egg counts (WEC), ideally at least 15 heifers. The author uses the FecPakG2 system in the practice and uses 100 eggs per gram (epg) to determine whether to proceed to treatment or not
2	Treatment day, day 0: select 15 animals to be tested and treated, taking individual samples, record their identities or clearly mark them
3	Administer the chosen anthelmintic, ensuring correct dose for the weight and the equipment is working correctly
4	Day 7: collect faecal samples from the same 15 individuals if levamisole is being checked
5	Day 14: collect faecal samples from the same 15 individuals, if benzimadazoles or macrocyclic lactones are being checked
6	Following analysis of the samples calculate the efficacy of each anthelmintic: ((Mean day 0 WEC – Mean day 7/14 WEC)/Mean day 0 WEC) x 100
7	Where there is less than a 95% reduction in WEC, resistance is present

Conclusions

As part of a herd health plan it is possible to make a control plan for nematodes. Knowledge of all the above information can be combined with the farmers' priorities to make a comprehensive control plan. The control plan can be tailored to the farm, while accounting for the risks and allowing for monitoring and treatments. LS

The author declares no conflict of interest

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The role of NSAIDs in the treatment of calf scour

Neonatal calf diarrhoea is both common and important in dairy and suckler herds. A number of pathogens may cause infectious diarrhoea, but the key goals of treatment are the same regardless of cause: provision of appropriate fluid therapy to counteract dehydration and acidosis; alleviation of clinical signs; and antibiosis where sepsis is present. The use of the non-steroidal anti-inflammatory drug (NSAID) category of anti-inflammatory drugs to reduce pain, pyrexia and anorexia is appropriate and supported by the evidence. The drug meloxicam is licensed for treatment of diarrhoea in calves over 7 days old, in combination with appropriate fluid therapy, to reduce clinical signs.

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Key words: neonatal calf diarrhoea | calf rearing | oral rehydration therapy | non-steroidal anti-inflammatory drugs

Neonatal calf diarrhoea is a common and important disease. Baxter-Smith and Simpson (2020) found that, in the UK, it was experienced by 93% of dairy farmers and 72% of suckler farmers in the preceding 12 months, causing mortality in 68% of dairy units and 32% of suckler herds. 48% of UK dairy heifers, when examined weekly by a veterinary surgeon, were found to have at least one episode of calf scour by 9 weeks of age (Johnson et al, 2021).

Its importance is due not only to the poor welfare of the sick calf, but the significant impact on the economics of a farm, from direct costs such as mortality and medicines to the extremely detrimental indirect costs on growth rate, time to weaning and age at first service. Death of a calf, or a 'poor doer' not entering the breeding herd, results in loss of vital genetic input to the farm. With the recent focus on the importance of reducing unnecessary antimicrobial use, it is relevant to note that diarrhoea treatments may represent a sizeable portion of the antimicrobial use on farm.

Prevention of the disease is far better than cure, and readers are referred to Meganck et al (2014) and Heller and Chigerwe (2018) for excellent coverage of the ways in which calf scour can be both managed and prevented. However, disease incidence remains high on many farms and effective treatment protocols should be constantly sought and refined.

Oral rehydration therapy (ORT) has long been a cornerstone of diarrhoea treatment. Meganck et al (2014) provided a suitable summary of the indications and benefits of fluid therapy. The pathophysiology of diarrhoea results in dehydration, metabolic acidosis, electrolyte imbalances (particularly potassium) and hypoglycaemia (see *Figure 1*). These can all be corrected by appropriate use of isotonic alkalinising oral fluid. ORT should begin as soon as diarrhoea is seen and continue until it is resolved.

Seriously ill (collapsed) calves require intravenous fluid (and often bicarbonate) therapy which can be administered by a veterinarian in an ambulatory or hospital context. Antibiotics are used indiscriminately by many farmers and even veterinarians (44% of Scottish suckler farmers and veterinary surgeons used antibiotics in every case of calf scour in the survey by Eibl et al (2021)); however, their use is indicated only in calves with sepsis, endotoxaemia or suspected *Salmonella* spp. infection. Since many causes of diarrhoea are viral (rotavirus, coronavirus) or parasitic (*Cryptosporidium parvum*, coccidiosis), antibiotics have no direct benefit, and may in fact worsen the condition as a result of disruption of the gut microflora (Eibl et al, 2021). Specific agents for a specific pathogen, such as halofuginone for the treatment of *C. parvum* or toltrazuril for coccidiosis, may also be appropriate.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is considered beneficial in managing pain, fever and malaise associated with diarrhoea (Reader et al, 2020). A field study commissioned by the manufacturers of the first commercial meloxicam product indicated that scouring calves treated with meloxicam had improved faecal scores, demeanour scores and reduced fever compared with controls (Phillip et al, 2003). Meloxicam has since received a UK license for the treatment of diarrhoea in calves (see *Table 1*). Other NSAIDs licensed for use in cattle in the UK, principally flunixin, carprofen, ketoprofen and sodium salicylate, are not specifically licensed for use in calf diarrhoea (see *Table 2*).

Calf diarrhoea

Neonatal diarrhoea is principally infectious in cause, although nutritional and management factors may also be implicated. *Figure 1* summarises the pathophysiology of infectious diarrhoea. Destruction of intestinal villi, inflammation of the enteric mucosa and motility disturbances will cause abdominal pain and discomfort in affected calves. Some pathogens will also produce

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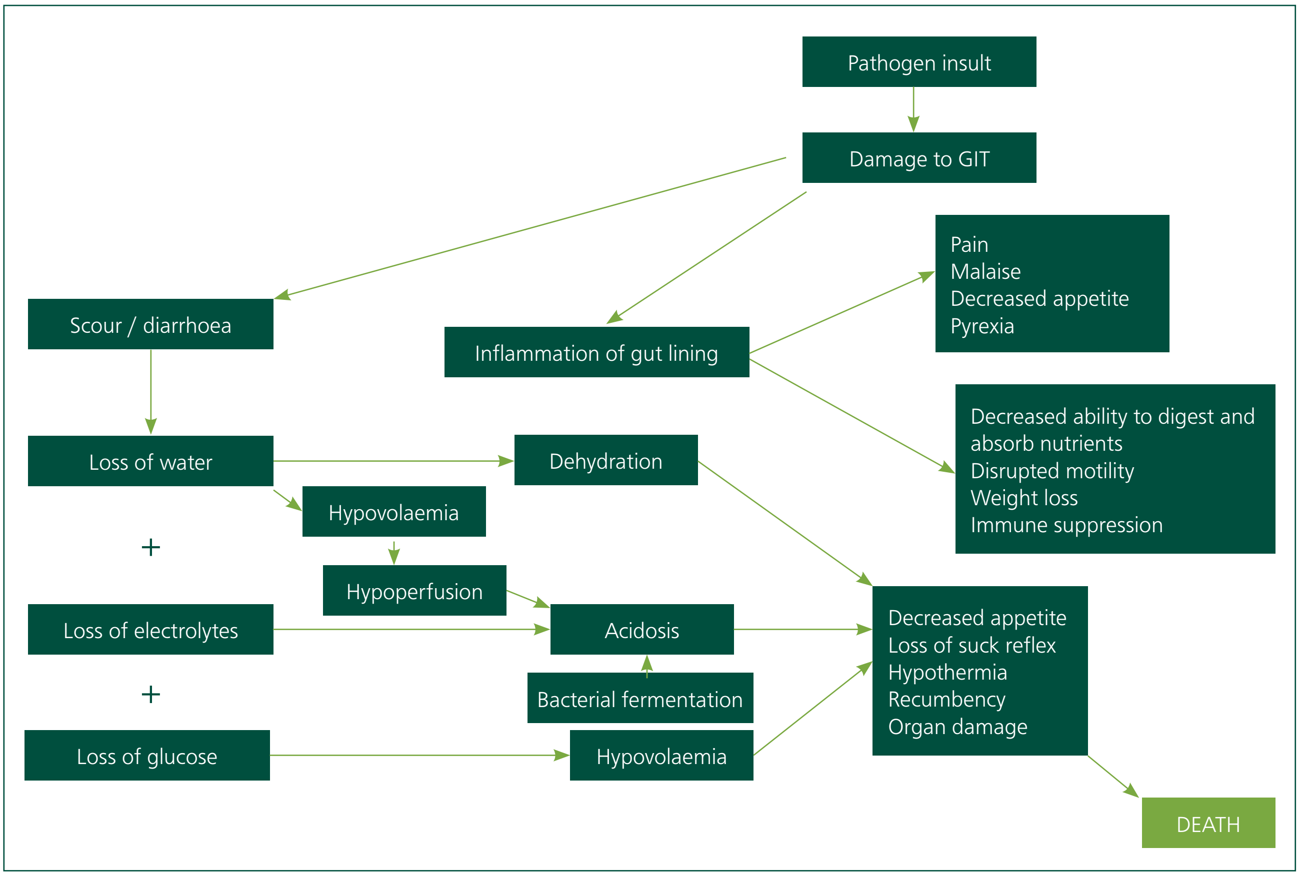

Figure 1. The pathophysiology of diarrhoea in calves. GIT = gastrointestinal tract.

Table 1. Non-steroidal anti-inflammatry drugs (NSAIDs) licensed in the UK for the treatment of calf diarrhoea

Trade name	Manufacturer	Active ingredient	Licensed for	Contraindications
Loxicom	Norbrook	Meloxicam	Diarrhoea, in combination with oral rehydration therapy, to reduce clinical signs in calves of over 1 week of age For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. For the relief of postoperative pain following dehorning in calves.	Do not use to treat diarrhoea in calves under 1 week of age Do not use in severely dehydrated, hypovolaemic or hypotensive animals
Recocam	Bimeda			
Metacam	Boehringer Ingelheim			
Rheumocam	Chanelle			
Inflacam	Virbac			
Meloxidyl	Ceva			
Meloxidolor	Dechra			

pyrexia and associated malaise, and endotoxaemia is sometimes a feature.

Although diarrhoea is the principal clinical sign, scour in calves is often accompanied by dull demeanour, reduced or absent desire to feed and reduced mobility or recumbency. These indicators help to guide assessment of the severity of the disease and are produced by a combination of dehydration, electrolyte derangements, pyrexia and pain or discomfort. While ORT can be very effective at ameliorating the first two, there is a likely role for NSAIDs in the latter two (*Figure 2*).

Non-steroidal anti-inflammatory drugs

NSAIDs exert their anti-inflammatory effect by inhibiting cyclooxygenase (COX), the enzyme that coverts arachidonic acid to prostaglandins in the inflammatory cascade (Reader et al, 2020). Inhibition of COX results in reduced prostaglandin levels and thus decreases pain (both peripheral and central), inflammation and fever (*Figure 3*). Some NSAIDs also have anti-endotoxic properties because they have been shown to inhibit production of thromboxane B2 induced by *Escherichia coli* endotoxin.

Table 2. Non-steroidal anti-inflammatory drugs (NSAIDs) licensed in cattle in the UK, but not licensed for treatment of calf diarrhoea

Active ingredient	Route of administration	Treatment regimen	Licensed for	Warnings
Flunixin meglumine	Intravenous or topical	May be repeated at 24 hour intervals for up to 5 days (injectable formulation)	Control of acute inflammation associated with respiratory disease and adjunctive therapy in treatment of clinical mastitis	Use in animals less than 6 weeks old may carry additional risk Do not use in hypovolaemic animals Do not use in animals suffering from cardiac, renal or hepatic disease
Carprofen	Subcutaneous or intravenous	Single injection	An adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis	Avoid use in dehydrated, hypovolaemic and hypotensive patients Do not use in animals suffering from cardiac, renal or hepatic disease
Ketoprofen	Intramuscular or intravenous	Daily for up to 3 days	Supportive treatment of parturient paresis Reducing pyrexia and distress associated with bacterial respiratory disease Improving recovery rate in acute clinical mastitis Reducing oedema of the udder associated with calving Reducing pain associated with lameness	Use in animals less than 6 weeks old may carry additional risk Avoid use in dehydrated, hypovolaemic and hypotensive patients Do not use in animals suffering from cardiac, renal or hepatic disease
Sodium salicylate	Orally in drinking water or milk (replacer)	40 mg sodium salicylate per kg bodyweight once daily, for 1–3 days	Supportive treatment of pyrexia in acute respiratory disease, in combination with appropriate (e.g. anti-infective) therapy if necessary	Do not use sodium salicylates in neonates or calves less than 2 weeks of age Do not administer in case of severe hypoproteinaemia, liver or kidney disorder Do not administer in case of gastrointestinal ulcerations and chronic gastrointestinal disorders Do not administer in case of malfunction of the haemopoietic system, coagulopathy, haemorrhagic diathesis, or within 7 days of elective surgery

NSAIDs have well-proven clinical effectiveness in calves: for mitigating pain during and after calf procedures (castration and dehorning); increasing post-surgery feed consumption and weight gain; and improving recovery rates for pneumonia. Their use is becoming more commonplace among UK practitioners and farmers (Laven, 2020) and would be considered routine in the treatment of a number of common presentations in adults, such as toxic mastitis/metritis and down cows. In terms of cost to the farmer, Remnant et al (2017) found that 52% of veterinary surgeons agreed with the statement 'farmers are happy to pay the costs involved with giving analgesics to cattle' up from 36% in the same questionnaire carried out 10 years earlier, which together with other positive responses suggests a change in attitudes towards the use of NSAIDs in cattle practice. Remnant et al (2017) also discussed studies finding that veterinary surgeons are more likely than producers to cite cost as a reason for not administering pain relief.

NSAIDs can be effectively used to reduce antimicrobial use on farms as Atkinson (2018) described, when using in milk sodium salicylate for 5 days in batches of newly-arrived young calves in three calf rearing units. Overall antibiotic usage reduced by 43% ($p<0.05$) without impacting calf performance.

NSAIDs must be used with care in dehydrated animals because of the potentially nephrotoxic effects associated with the regulation of renal blood flow. Therefore, in calves with diarrhoea, attention must always be paid to correcting hypovolaemia before administering NSAIDs. All the NSAID data sheets carry warnings about use in dehydrated or hypovolaemic animals.

NSAIDs should in theory be used cautiously in the youngest calves because of their immature metabolism (*Figure 4*). Therefore, they are thought to be less suitable for scouring calves under a week old and this is reflected in the licensing of meloxicam. Flunixin and ketoprofen are advised not to be used in animals under 6 weeks old. However, several studies into NSAID use in calves after dystocia have involved treatment in the first 24 hours of life with no reported side effects. A randomised control trial treating 225 beef calves with meloxicam after an assisted delivery found no detrimental side effects, compared with calves injected with placebo, when followed up to 6 weeks of age (Pearson et al, 2019). All calves that died during the study underwent a full post-mortem examination at which no detrimental effects of NSAID use were discovered. Similarly, a UK study treating 75 dairy heifers with ketoprofen at birth found no adverse impact, and quotes the manufacturers as using the product off-licence down to 3 days of age safely. The low risk of side effects is discussed, given that in most farm situations only a single dose at the recommended dose rate is given (Gladden et al, 2019). In other species it is usually long-term or high-dose treatment that results in toxicity.

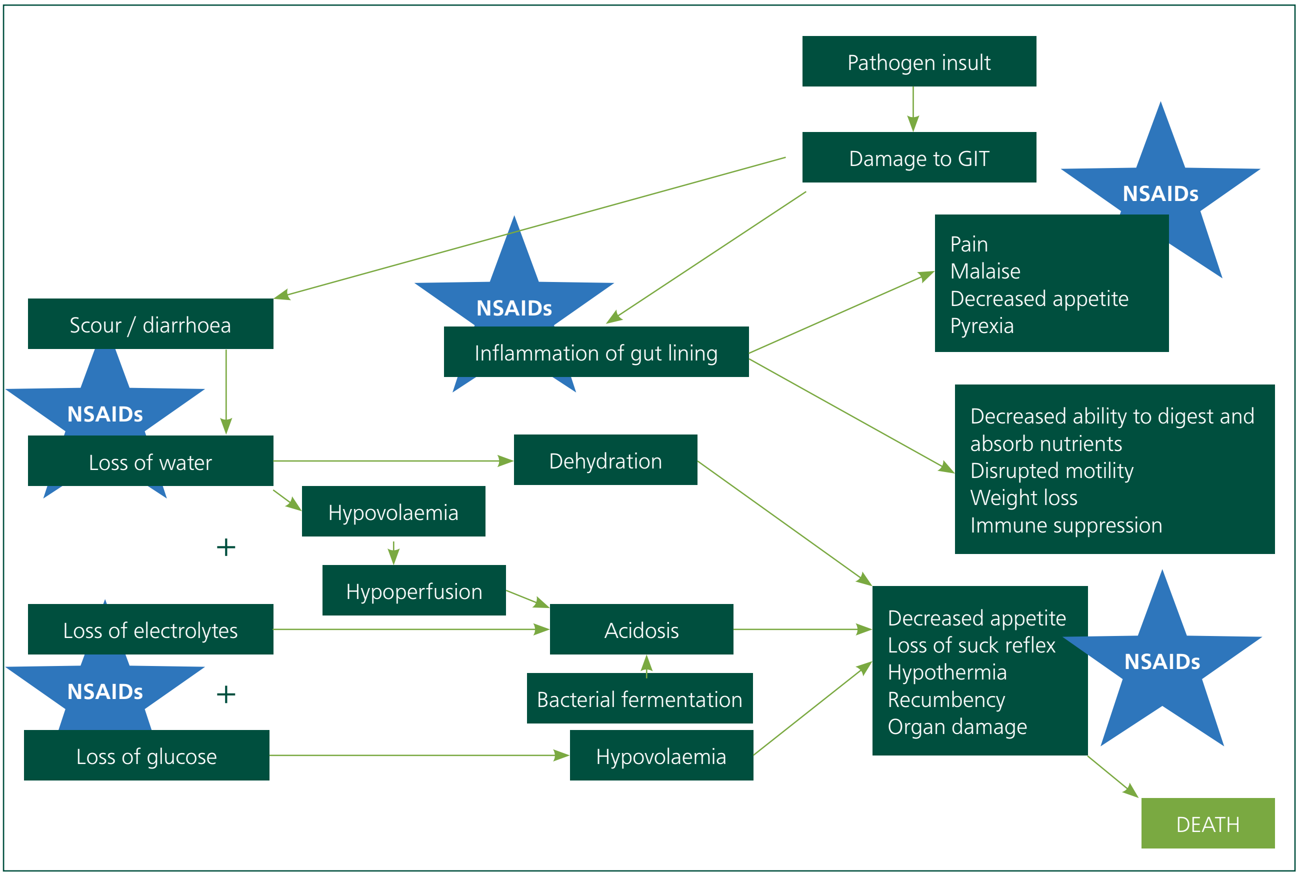

Figure 2. The action of non-steroidal anti-inflammatory drugs to treat diarrhoea in calves. GIT = gastrointestinal tract.

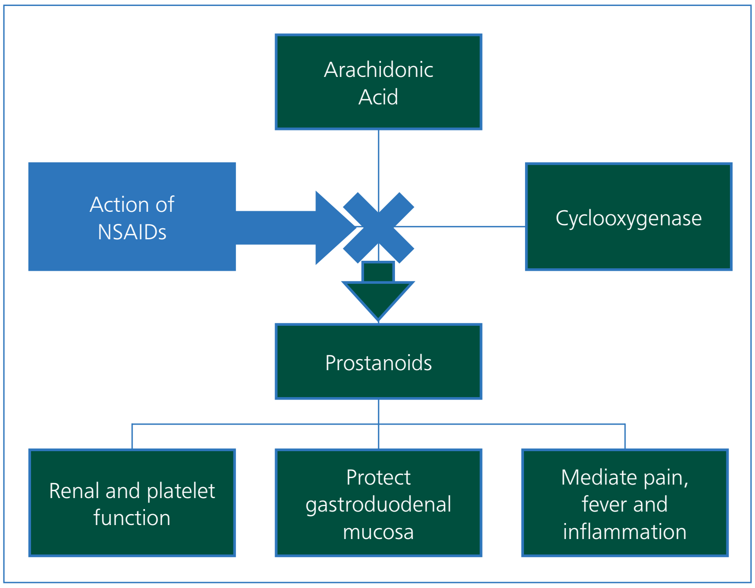

Figure 3. Schematic representation of the action of NSAIDs on the conversion of arachidonic acid in the inflammatory cascade.

Non-steroidal anti-inflammatory drugs in neonatal calf diarrhoea

A number of clinical trials have been conducted to examine the potential benefits of NSAID treatment in scouring calves. Initially, a field trial by Phillip et al (2003), commissioned by Boehringer Ingelheim, of 191 calves on 38 farms in Germany found both clinical and behavioural improvement in calves treated with one dose of meloxicam after the onset of scour. Clinical diarrhoea score (a composite of faecal consistency, dehydration and signs of visceral pain) was significantly ($p \leq 0.05$) improved, as was clinical index score (the sum of scores assessing behaviour, feed intake and fever plus clinical diarrhoea score) ($p \leq 0.05$); and rectal temperature ($p \leq 0.05$). The average age of the calves was 2 weeks at the start of the study. Calves were monitored at 6–8 hours, 24 hours and 48 hours post-treatment. All calves received ORT on days 1 and 2, with administration on day 3 optional. All calves received gentamicin on day 1, with treatment at day 2 optional. The number of repeat treatments were reduced in meloxicam treated calves ($p \leq 0.05$ for ORT but not for gentamicin). This field study provided sufficient evidence for meloxicam to be licensed for the treatment of diarrhoea in calves over 1 week old in combination with ORT, plus antibiotic therapy as indicated.

Barnett et al (2003) examined the impact of flunixin meglumine treatment on 115 US dairy calves with scour. Calves were transported to the ranch from multiple sources at 1–3 days old. A cohort of 500 calves was selected and followed for those that would develop diarrhoea between 1 and 3 weeks old. These calves were randomly allocated to receive flunixin either once or twice 24 hours apart, or a sham injection. Other treatments were given at the discretion of ranch staff, but all calves received spectinomycin on the first day of

Figure 4. Non-steroidal anti-inflammatory drugs are not licensed in calves under a week old, but may be used cautiously.

KEY POINTS

- Non-steroidal anti-inflammatory drugs (NSAIDs) are an appropriate treatment in neonatal calf diarrhoea as they act to reduce prostaglandin production and hence reduce pain, fever and inflammatory response.
- The beneficial effects are noted in three different research studies, the most recent of which focused on feed intake and found significant improvements in appetite and weight gain in treated animals.
- NSAIDs must always be used alongside appropriate fluid therapy as they are contraindicated in dehydrated or hypovolaemic animals.
- The NSAID meloxicam is licensed to be used alongside ORT in the treatment of calf diarrhoea in calves over 1 week old.

diarrhoea. Calves were followed for 30 days and monitored twice daily for demeanour score, faecal score, rectal temperature and skin elasticity (score of 0–4 for each). Any calves with a score of >1 were categorised as morbid. Calves with haemorrhagic diarrhoea had statistically significant fewer morbid days, when treated with flunixin once, than control calves. There was no effect of treatment on calves with non-haemorrhagic diarrhoea and no additional effect from two flunixin treatments. This study also measured passive transfer on arrival at the ranch and found that calves with higher IgG concentrations had fewer morbid days compared with those that had low and medium IgG concentrations.

The most recent study by Todd et al (2010), also supported by Boehringer Ingelheim, examined the effect of meloxicam treatment on feed intake and weight gain during and after an episode of diarrhoea. Of 62 male Canadian dairy calves enrolled at birth and housed in a research facility from 1–3 days old, 56 subsequently developed diarrhoea and were randomly allocated to receive treatment with meloxicam or placebo. All scouring calves were given access to ad lib ORT; and antibiotics or intravenous fluid therapy were used as appropriate. Milk replacer was provided at 2 litres per calf twice a day and ad lib starter food and water were available. All feed and water consumption was measured daily for each calf and individuals were weighed weekly and at weaning. Calves were weaned if they were greater than 28 days old and consumed more than 750 g of starter a day for 3 consecutive days.

The authors comment on the high incidence of scour in this study (>90%) and link it to both the high prevalence of *C. parvum* in Canadian dairies at the time (up to 80% of calves in a herd could be shedding *C. parvum*), and the poor colostrum management of these calves prior to their arrival at the facility (77% of calves had failure of passive transfer). *C. parvum* was found to be the most significant pathogen in this group of calves (proportionally more from calves over 10 days of age), but rotavirus and coronavirus were also isolated (proportionally more from younger calves).

Calves enrolled after 10 days old were 5.3 times more likely to consume their entire milk ration if treated with meloxicam versus control ($p<0.05$). Calves treated with meloxicam consumed starter rations on average 5 days earlier than control calves ($p<0.01$) and each consumed 12.2 kg more starter ration over the 8 week study period ($p<0.01$). Meloxicam treated calves had significantly improved water intakes ($p<0.001$), were weaned on average 6 days earlier ($p<0.05$), but with no difference in weaning weight, and each gained an additional 4.3 kg bodyweight over the period ($p<0.01$). There was no difference in faecal scores between the treated and control group.

None of the studies above make reference to the fact that NSAIDs should be used with care in dehydrated animals and in

Box 1. Possible benefits of NSAIDs in the treatment of calf scour

- Reduce pyrexia ▲• ⟶ improved demeanour ▲• and appetite •* ⟶ reduce weight loss *
- Reduce abdominal pain ▲(•) ⟶ improved demeanour ▲• and appetite ▲• ⟶ reduce weight loss *
- Reduce increased secretion as a result of inflammatory response (•) ⟶ reduce liquid faecal output ▲ and dehydration ▲•
- Reduce malabsorption as a result of inflammatory response ⟶ reduce weight loss *
- Reduce catabolic state caused by inflammatory response ⟶ reduce weight loss *
- Anti-endotoxic ⟶ disease-modifying role in endotoxaemia (•)

*Supported by Todd et al (2010); • Supported by Barnett et al (2003); ▲ Supported by Phillip et al (2003). Symbols in brackets indicate an implied but not directly proven benefit

Table 3. Author's suggestions for practical use of non-steroidal anti-inflammatory drugs (NSAIDs) in cases of calf diarrhoea

Clinical picture	Advice to client
Calf over 7 days old, scouring (any type), bright and drinking milk	• Treat with meloxicam SC 0.5 mg/kg as soon as scour is seen • Treat with appropriate ORT as soon as scour is seen and continue until scour resolves
Calf under 7 days old, scouring (any type), bright and drinking milk	• Treat with appropriate ORT as soon as scour is seen and continue until scour resolves
In contact calves	• Consider treating with meloxicam SC 0.5 mg/kg if dull, anorexic or pyrexic • Consider using flunixin pour on or sodium salicylate for ease of treating a group
Calf over 7 days old, scouring (any type), dull/ depressed and/or not drinking milk and/or pyrexic	• Treat with meloxicam SC 0.5 mg/kg as soon as scour is seen • Treat with appropriate ORT as soon as scour is seen and continue until scour resolves • Appropriate antibiosis if demeanour does not improve within 12 hours of initial treatment • Consider veterinary visit • Repeat meloxicam SC 0.5 mg/kg after 48 hours if still unwell
Calf under 7 days old, scouring (any type), dull/ depressed and/or not drinking milk and/or pyrexic	• Treat with meloxicam SC 0.5 mg/kg as soon as scour is seen • Treat with appropriate ORT as soon as scour is seen and continue until scour resolves • Appropriate antibiosis • Advise veterinary visit • Repeat meloxicam SC 0.5 mg/kg after 48 hours if still unwell
Calf over 7 days old, scouring (any type), recumbent and/or cannot hold up head and/or no suck reflex	• Do not administer oral fluids • Do not administer NSAIDs • Veterinary visit essential • Veterinary surgeon to administer IV fluids and bicarbonate, antibiosis, meloxicam 0.5 mg/kg IV
Calf under 7 days old, scouring (any type), recumbent and/or cannot hold up head and/or no suck reflex	• Do not administer oral fluids • Do not administer NSAIDs • Veterinary visit essential • Veterinary surgeon to administer IV fluids and bicarbonate, antibiosis, meloxicam 0.5 mg/kg IV

SC = subcutaneously; ORT = oral rehydration therapy; IV = intravenous. Off-licence use is highlighted in red

animals under a week old. In each study, the calves were provided with ORT and any other treatments that were required including intravenous therapy as necessary. However, it would seem wise to issue this caution, particularly as in practice many veterinary surgeons may be advising farmers remotely and may not be able to adequately assess hydration status before recommending a particular treatment. In Barnett et al (2003) calves were all over a week old at enrolment, but the other two studies treated younger calves. No adverse effects were reported as a result of using NSAIDs; in each study all deaths were followed by a post-mortem examination, and none were suggestive of NSAID toxicity or complications.

The three studies combine to confirm many of the putative benefits of NSAIDs in the treatment of neonatal calf diarrhoea (see *Box 1*). Todd et al (2010) reported increased feed and water intake and improved weight gain as a result of meloxicam administration. Barnett et al (2003) found reduced clinical signs and faster recoveries in calves with haemorrhagic diarrhoea that were treated with flunixin. The haemorrhage may represent increased intestinal damage and hence inflammation and pain; and/or the possibility of endotoxin involvement. Phillip et al (2003) described improvements in demeanour, clinical signs and faecal score when scouring calves were treated with meloxicam.

Also of interest is a study of the pharmacokinetics of oral and injectable meloxicam (Shock et al, 2020) in calves under 2 weeks old with clinical diarrhoea. Oral meloxicam is licensed in Canada where the study was carried out, funded by the manufacturer. Both oral and subcutaneous meloxicam reached appropriate therapeutic plasma levels. Oral liquid meloxicam achieved significantly higher plasma levels than when given by subcutaneous injection ($p<0.05$), although the dose rate was different (0.5 mg/kg for injectable, 1 mg/kg for oral, these are both the licensed dose). This applied equally to all oral meloxicam treatments, whether given directly into the mouth, mixed with ORT or mixed with milk replacer. Oral meloxicam given with milk replacer had a significantly longer half-life than other methods of oral treatment ($p<0.05$), and the authors caution that this may make it an unsuitable route for neonatal calves that may be more prone to NSAID toxicity if exposure is prolonged. Disease outcomes were not measured in this study.

Suggestions for practical use in first opinion cattle practice

To summarise the evidence presented here, the author suggests a number of ways in which NSAIDs might be practically used in the treatment of neonatal calf diarrhoea (*Table 3*), appreciating that veterinary surgeons will often be discussing cases with clients remotely or during health planning reviews. In all cases, clients should be advised when a medicine is used off-licence.

Conclusions

NSAIDs have a good evidence-base of effectiveness for adjunctive treatment in neonatal calf diarrhoea, and helping to ameliorate economic losses by improving feed intake and weight gain. The additional cost associated with the NSAID is therefore compensated. Calf welfare will be improved by the reduction of pain and malaise and shortening of the disease process. Studies also suggest that antimicrobial use could be reduced by the use of NSAIDs in calf scour. Meloxicam is safe, cost-effective and appropriate when used in conjunction with ORT in all calves with scour over 7 days old that do not have hypovolaemia. There are other appropriate situations where NSAIDs may be used off licence in the treatment of calf scour. LS

Conflict of interest: none.

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