Ancillary Therapy for Infectious Disease in Cattle

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In this session we will take an evidence-based medicine approach to ancillary therapy of bovine respiratory disease, bovine toxic mastitis, bovine neonatal enteric disease, and retained placenta/metritis. The literature reviewed here is not presented as being all-inclusive, but rather as a summary of many commonly cited articles on these subjects. The citations are primarily peer reviewed, but some are from freedom of information (FOI) summaries and a few are proceedings papers or abstracts.

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You should evaluate the entire article when deciding whether a publication will have an influence on your therapeutic regimens.
Bovine Respiratory Disease

No published data could be found to support the use of Vitamin B or C, vaccines (at the time of therapy), antihistamines, anthelmintics, probiotics, or oral electrolytes in the ancillary therapy of bovine respiratory disease. For the purposes of this presentation, we will examine the published data concerning the use of steroidal and non-steroidal anti-inflammatory drugs as ancillary therapy for respiratory disease.

Glucocorticosteroids

Decades after publication of the study described here, there is still only one published clinical trial addressing the use of steroids for ancillary therapy of BRD as you would encounter it clinically in the United States.

Efficacy of corticosteroids as supportive therapy for bronchial pneumonia in yearling feedlot cattle

One of two treatments was administered to animals identified as displaying clinical signs of BRD. Common drugs for the two treatment groups included IV oxytetracycline (5 mg/lb) and IM pyrilamine (250 mg total dose) on a daily basis for 3 days. Treatment group 1 also received 20 mg dexamethasone every day while treatment group 2 received a 10 ml placebo injection. The same treatments for each group were continued through day 9, as needed, for non-responders. Response was significantly different at \( P \leq 0.05 \) and relapse rate was significantly different at \( P \leq 0.01 \).

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<tr>
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<tr>
<td>Number treated</td>
<td>1113</td>
<td>1071</td>
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<tr>
<td>Number responding</td>
<td>913 (82%)</td>
<td>916 (85.5%)</td>
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<tr>
<td>Death loss</td>
<td>77 (6.9%)</td>
<td>61 (5.7%)</td>
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<tr>
<td>Relapses</td>
<td>265 (23.8%)</td>
<td>193 (18%)</td>
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These findings aren’t that surprising since dexamethasone, at 0.04 mg/kg daily (0.9 ml/100 lbs of a 2 mg/ml solution) for 3 days, is used as a research model to suppress neutrophil function in cattle.\(^2\) This model was utilized in small Holstein calves in conjunction with induced \textit{Haemophilus somnus} pneumonia to demonstrate that this dexamethasone regimen increased lung lesions.\(^3\) An IBR latency model in rabbits demonstrated that a single high-dose injection of dexamethasone (2.8 mg/kg) could bring about reactivation of latent BHV-1.\(^4\) Other studies have failed to show significant differences in treatment response using prednisone acetate, methyl
prednisolone, or methyl-prednisolone-succinate in natural and induced respiratory disease.5,6

What does one vs 3 doses of dexamethasone do to neutrophil function in cattle? Effects of dexamethasone treatment and respiratory vaccination on rectal temperature, complete blood count, and functional capacities of neutrophils in beef steers.7 The 0.5 mg/kg dexamethasone dose used in this study is about 11 cc/100# of the 2 mg/ml alcohol solution dexamethasone which is commonly used, so quite a bit higher than the common 1 cc/100# dose.

The objective of this research was to examine the effects of dexamethasone (DEX) treatment on various aspects of immunity following administration of a multivalent respiratory vaccine, using a model intended to mimic acute versus chronic stress. Angus × Hereford steers (n = 32; 209 ± 8 kg) were stratified by BW and randomly assigned to 1 of 3 treatments: 1) acute stress (ACU), in which 0.5 mg/kg BW DEX was intravenously administered at 1000 h only on d 0; 2) chronic stress (CHR), in which 0.5 mg/kg BW DEX was intravenously administered at 1000 h on d -3 to 0; or 3) control (CON), in which no DEX was administered. Steers were fitted with indwelling jugular catheters and rectal temperature (RT) recording devices on d -4 relative to vaccination and placed in individual stanchions in an environmentally controlled facility. Blood samples were collected and serum was isolated at -74, -50, and -26 h; at 0.5-h intervals from -4 to 6 h; and at 12, 24, 36, 48, and 72 h relative to multivalent respiratory vaccination at 1200 h on d 0. Additional blood samples were used to analyze complete blood cell count (CBC) and functional capacities of neutrophils. There was a treatment × time interaction (p < 0.01) for RT such that DEX treatment in CHR and ACU steers decreased RT on d -3 and 0, respectively. A treatment × time interaction (p < 0.01) was observed for total white blood cells (WBC), neutrophils, lymphocytes, and monocytes. Specifically, DEX increased WBC and neutrophils in CHR and ACU steers (p < 0.001) yet decreased lymphocytes in CHR steers (p = 0.02) compared with CON steers. Neutrophil concentration increased rapidly, within 2 h of the DEX infusion, in ACU steers. Monocytes transiently increased (p < 0.001) in response to DEX treatment in CHR and ACU steers. In contrast, eosinophils were greater (p < 0.01) in CON steers than in ACU and CHR steers. A treatment × time interaction (p = 0.004) was observed for interferon-γ, with CON cattle exhibiting greater concentrations than the ACU and CHR cattle at 5 h after vaccination, through d 3. Treatment also influenced (p ≤ 0.001) the expression of L-selectin on the surface of neutrophils. The percentage of neutrophils engaging in phagocytosis and the oxidative burst were suppressed (p ≤ 0.001) among only the CHR steers, whereas the intensity of the oxidative burst was suppressed (p ≤ 0.001) for both ACU and CHR steers. These data suggest that our model induced acute and chronic immunosuppression and defined the acute response to a multivalent vaccine in CON steers.
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

The NSAID currently labeled specifically for BRD in the United States is Flunixin meglumine (Banamine® Injectable Solution, Schering-Plough Animal Health). The label includes indications for the control of pyrexia associated with bovine respiratory disease, acute bovine mastitis, and endotoxemia. The inflammation indication on the label is for the control of inflammation in endotoxemia. Flunixin meglumine is considered an effective analgesic, anti-inflammatory, and antipyretic. The mechanism of action is cyclooxygenase inhibition.

The outlines below summarize published studies and the Freedom of Information (FOI) summaries of flunixin meglumine effects on respiratory disease outcome.

Flunixin BRD study 1: Evaluation of the efficacy of flunixin meglumine using four different experimentally induced bovine respiratory disorders.8

12 week old dairy calves, induced Pasteurella haemolytica pneumonia
4 treatment groups - no treatment, oxytetracycline (10 mg/kg IM SID for 3 days), flunixin meglumine (2.2 mg/kg IV SID for 3 days), and both oxytetracycline and flunixin meglumine. Results:
• OTC alone reduced the number of calves with fevers and tachypnea and reduced the extent and severity of fibrinous pneumonia as compared to the controls (no mortality)
• Flunixin alone had no antipyretic effect and no reduction in severity of Pasteurella pneumonia compared to the control calves although fewer calves were noted with tachypnea. (1 dead out of 8)
• OTC and flunixin combined had no evident macroscopic consolidation in the lungs, rectal temperature dropped more quickly than in any of the other three groups. (no mortality)

Flunixin BRD study 2: Effect of anti-prostaglandin therapy in experimental parainfluenza type 3 pneumonia in weaned, conventional calves.9

12-week-old calves, PI3 virus administered into the upper airways
2 treatment groups: Flunixin meglumine (2.2 mg/kg IV SID for 3 days) and controls. Results: Flunixin reduced the number of calves coughing, the number of calves with fever (> 39.7° C), and the number of calves with tachypnea as compared to untreated controls. There was a marked decrease in pulmonary consolidation in the treated group.
Flunixin BRD study 3: Field study of undifferentiated respiratory disease in housed beef calves.¹⁰

Calves receiving 3 methylindole (3MI) intratracheally
2 treatment groups: flunixin meglumine (2.2 mg/kg) on the mornings of days 1, 2, and 3 when they started displaying respiratory rates twice that of baseline, and negative controls. Results: Respiratory rates of the treated calves did not significantly differ from that of environmental controls which did not receive the 3MI, while the untreated calves which received 3MI had significantly elevated respiratory rates. Flunixin calves had much less pronounced alveolar epithelial hyperplasia as compared to controls.

Flunixin BRD study 4: Field study of undifferentiated respiratory disease in housed beef calves.¹¹

Housed beef calves, undifferentiated respiratory disease (a rectal temperature > 39.5°C, respiratory rate > 30/minute, and an increased respiratory effort). Further treatment based on a rectal temperature of 39.5°C on day 4.
2 treatment groups: Tilmicosin phosphate (10 mg/kg SC, once) vs. therapy with tilmicosin phosphate (10 mg/kg SC, once) combined with flunixin meglumine (2.2 mg/kg IV, once).
Results: 17/51 tilmicosin calves (27.9%) required further therapy while 9/58 tilmicosin/flunixin calves (15.5%) were treated again. This difference was not significant. No mortalities occurred.

Flunixin BRD study 5: Freedom of Information Summary 101-479¹²

Freedom of Information Summary study. 363 calves (heifers, steers, and bulls) 6-12 months old (mean weight 420 lbs.) at 3 locations. Naturally occurring respiratory disease.
2 treatment groups: OTC injectable solution administered for 3 consecutive days at 10 mg/kg (4.5 mg/lb.) IM, as compared to OTC injectable solution (as above) plus flunixin meglumine at 2.2 mg/kg SID for 1-3 days (administered again on days 2 and 3 if temp. not below 104.0°F). Duration of study: 10 days, treatment failure was defined as developing severe recurrent respiratory disease (score of 3 or more on scale of 0=normal, 1=slightly ill, 2=moderately ill, 3=very ill, and 4-moribund) from the end of the 3 days of treatment to the end of the study.

Results:

- Mortality – 15/182 dead in OTC alone, 8/181 died in OTC/flunixin group. (One site had 1 mortality in the OTC group, one site had one dead in the OTC/flunixin group, and one site had a concurrent BVD outbreak with 14
dead in the OTC group and 7 dead in the OTC/flunixin group. Not statistically significant

- Character of respiration – No significant difference at pretreatment (day 0) and on day 1. OTC/f group was better on days 2 and 4. On day 9, 99/144 (69%) of the OTC/f calves had normal respiration compared to 70/139 (50%) in the OTC group.
- Illness index scores – More OTC/f animals scored normal on days 1-9. Statistically significant?
- Rectal temperature – Statistically significant difference in temperature decrease on day 1, with OTC/f group having a greater decrease. No significant differences on other study days.
- Depression – Fewer depressed animals in OTC/f group.
- Treatment success/failure – 47/179 (26%) failures in OTC group, 40/181 (22%) in OTC/f group. Not statistically significant.
- Lung pathology – Little or no difference in lung pathology between groups
- Weight gain and daily feed intake – OTC group numerically superior to OTC/f group (16.5 lbs. Vs. 10.6 lbs. respectively) but this was not significantly significant.

Flunixin BRD study 6: Freedom of Information Summary 101-479

81 male Holstein calves (3-4 months, mean 82.3 kg) with naturally occurring BRD (acute clinical signs of pneumonia with elevated rectal temp ≥104.0 °F and respiratory rate ≥40/minute). 2 treatments: OTC injectable solution administered for 3 consecutive days at 10 mg/kg (4.5 mg/lb.) IM, as compared to OTC injectable solution (as above) plus flunixin meglumine at 2.2 mg/kg SID for 1-3 days (administered again on days 2 and 3 if temp. not below 104.0° F).

Results:

- Number of flunixin treatments – 58.1% of OTC/f calves required one flunixin meglumine injection, 34.9% required a second, 7% required a third.
- Mortality – No deaths during the study
- Character of respiration – For days 2-7, more animals in OTC/f group had normal respiration than did the OTC group. Statistically significant?
- Illness index scores – More normal animals in OTC/f group on days 2 and 3. Statistically significant.
- Rectal temperature – Statistically significant advantage to OTC/f group on days 1, 2, and 3.
- Depression – Improved demeanor in OTC/f group on days 2-7. Statistically significant?
- Treatment success/failure – 40% treatment failures in OTC/f group, 47% treatment failures in OTC group. 44% of the OTC treatment group occurred on day 3, while 24% of the OTC/f treatment failures occurred on day 3.
- Weight gain – 4.6 kg for OTC/f, 4.0 KG for OTC. Not statistically significant.

**Flunixin BRD study 7: Flunixin meglumine as adjunct therapy for bovine respiratory disease in stocker cattle.**

Ninety-six Arkansas salebarn calves were purchased and placed in stocker grass catches in Arkansas (6 calves per lot). BRD cases were treated with tilmicosin phosphate at 10 mg/kg SC, with one of the groups also receiving flunixin meglumine at 2.2 mg/kg IV. Treatment successes were higher in the flunixin group (88% vs. 61%, P = 0.06) when evaluated at 48 hours after treatment. Treatment success required abatement of clinical signs as well as reduction of the rectal temperature to ≤ 103.5° F.

Combined treatment failures and relapses were also less in the flunixin group (11% vs. 38%, P = 0.02). There was some confusion in the paper as the combined treatment failures and relapses for the flunixin group were reported as 5% in the text and 11% in the paper. The split of treatment failures and relapses (3 total for the flunixin group, and 10 total for the non-flunixin group) was not given in the paper, making it unclear as to the relationship of failures at 48 hours to relapses after initially being declared a clinical success. It is also unclear how a chi-square analysis of treatment success and failures/relapses (as one group) would come up with differing P values.

Treatment cost was also numerically less for the flunixin group $14.66 vs. $18.66, P = 0.10). Average daily gain during the 35 day period was not statistically different (2.2 lb/day for the flunixin group vs. 2.4 lbs/day without flunixin, P = 0.51).

**Flunixin BRD study 8: Flunixin meglumine as adjunct therapy with florfenicol in calves affected with bovine respiratory disease.**

The aim of the study was to evaluate the effect of a combined use of a long-acting antibiotic with a non-steroidal anti-inflammatory drug (NSAID) as an adjunctive therapy in calves suffering from bovine respiratory disease (BRD) on their clinical status and alterations of cellular immune indices in comparison with the antibiotic alone. The calves were treated either with a new combined antibacterial therapeutic agent (Resflor; MSD Animal Health, Boxmeer, Netherlands) consisting of both an antibiotic (florfenicol) and a NSAID (flunixin meglumine) in group I and antibiotic only (florfenicol) in the control group (group II). During the experiment the following parameters were measured: calf clinical status as so-called Clinical Illness Index Score (CIIS) together with selected cellular immune parameters i.e. white blood cell count (WBC), number and percentage of polymorphonuclear leukocytes (PMNL),...
mid-size leukocytes (MID), monocytes (CD14+/CD45⁺) and total peripheral lymphocytes (LYM). The lymphocyte population was also subdivided into their subsets: CD2⁺ (T-lymphocytes), CD4⁺ (Th-lymhocytes), CD8⁺ (Tc/s-lymphocytes) and WC4⁺ (B-lymphocytes). The results obtained showed that the mean values of the WBC, PMNL, MID and monocytes decreased markedly in the both groups of calves after treatment. However, in the same animals the total number of lymphocytes and their subpopulations (CD2⁺, CD4⁺, CD8⁺, WC4⁺ cells) increased as a consequence of the treatment. In calves from group I most of the immune changes were statistically significant (p<0.05) compared with the control group or their initial values, which was indicated by a more rapid normalisation of the physiological ranges. In the same group of calves the more rapid recovery process which was observed was manifested by the lower values of CIIS. The study showed that the therapy based on using a new combined therapeutic agent (Resflor) was more effective and had a more protective effect in the calves affected with BRD both with regard to the improvement of their clinical status as well as the intensity and normalisation of the cellular immune response compared with the animals treated with the antibiotic alone.

Flunixin BRD study 9: Treatment of naturally occurring bovine respiratory disease in juvenile calves with a single administration of a florfenicol plus flunixin meglumine formulation.

The efficacy and safety of a florfenicol plus flunixin meglumine formulation in the treatment of respiratory disease was evaluated in calves less than six weeks of age, compared with a positive control group treated with a well-established florfenicol formulation. A total of 210 calves, selected from nine sites in Belgium, France and Spain, showing severe signs of respiratory disease, were randomly assigned to treatment with either florfenicol plus flunixin meglumine (Resflor; MSD Animal Health) or florfenicol (Nuflor; MSD Animal Health), both administered subcutaneously once. Animals were clinically observed daily for 10 days following treatment initiation. The predominant respiratory pathogens were Pasteurella multocida, Mycoplasma bovis, Mannheimia haemolytica and Histophilus somni. All isolates were subject to in vitro sensitivity testing and found susceptible to florfenicol. In both groups, rectal temperature dropped and clinical index (depression and respiratory signs) significantly improved after treatment. Specifically, for the change in rectal temperature from pretreatment to six hours post-treatment, the florfenicol-flunixin formulation was found significantly superior to florfenicol. Moreover, the florfenicol-flunixin formulation alleviated the clinical signs of disease more rapidly, and was demonstrated to be non-inferior to florfenicol on days 4 and 10. The use of the product combining florfenicol and flunixin in calves is safe and efficacious in the treatment of outbreaks of bovine respiratory disease.
Flunixin BRD study 10: Resflor Gold FOI summary.\textsuperscript{16}

“RESFLOR GOLD was non-inferior to NUFLOR GOLD Injectable Solution for the treatment of BRD, with a one-sided 95% lower confidence bound for the difference between the two treatments equal to -13.2%, within the specified 15% margin of non-inferiority.” Clinical success values for the two treatment regimens have not been released.

Additional studies including flunixin are included in the multiple NSAID studies below.

What about other NSAIDs for ancillary therapy of BRD?

If there is published evidence that \textbf{phenylbutazone} or \textbf{aspirin} change therapeutic outcome in BRD therapy, I have not been able to find it. The pharmacokinetics, published anti-inflammatory effects in cattle, and dosing strategies of these compounds in cattle have been previously summarized.\textsuperscript{17} Practitioners should be aware that the residue potential of phenylbutazone in cattle is coming under increased scrutiny.

\textbf{Meloxicam} is a member of the oxicam class of NSAID’s. The elimination half time is 24 to 26 hours which has resulted in a “long-acting” label claim in the European Union. A recent report evaluating Meloxicam has provided, to our knowledge, the first evidence of a demonstrated economic benefit to using a NSAID in the treatment of respiratory disease in feedlot cattle.

\textbf{Pharmaco-economic benefit of Meloxicam (Metacam) in the treatment of respiratory disease in feedlot cattle.}\textsuperscript{18}

Animals with clinical symptoms of BRD received 20mg/kg oxytetracycline with either 0.5mg/kg meloxicam or 0.9% isotonic saline. To assess performance, animals were weighed at 0, 7, 35, 70 and 105 days and finally before slaughter. Approximately 200 cattle with a mean body weight of 232kg were evaluated. Mean body weight was significantly higher for the meloxicam treated cattle from Day 70 (p<0.05) until slaughter (p<0.01). The mean average daily gain until slaughter was significantly higher with 1.23 kg in the treated group compared with 1.12kg in the control group (p<0.01). The mean carcass weight of the meloxicam treated group was significantly greater than the control group (P<0.05; 282.1kg vs 269.8 kg). It was concluded that a single injection of meloxicam as adjunct therapy in BRD in feedlot cattle resulted in a substantial pharmaco-economic benefit.

Clinical efficacy of meloxicam (Metacam) and flunixin (Finadyne) as adjuncts to antibacterial treatment of respiratory disease in fattening cattle.\textsuperscript{19}

The clinical efficacy of two non-steroidal anti-inflammatory drugs (NSAIDs), meloxicam (Metacam 20 mg/ml) and flunixin meglumine (Finadyne), as adjuncts to
antibacterial therapy in the treatment of acute febrile respiratory disease in cattle was compared. The randomized blind, positive controlled study was conducted under feedlot conditions in Mexico. Overall, 201 female cattle (weighing 220-250 kg) diagnosed with bronchopneumonia at the feedlot were recruited into the study. On Day 0 all animals were treated with 20 mg oxytetracycline/kg body-weight (Bivatop 200) by subcutaneous injection, in conjunction with either meloxicam (0.5 mg/kg subcutaneously, Metacam 20 mg/ml, n = 100), or flunixin meglumine (2.2 mg/kg intravenously, Finadyne, n = 101). According to label instructions, meloxicam was administered as a single dose, whereas flunixin meglumine could be administered daily for up to 3 consecutive days depending on the rectal temperature (with re-administration, if rectal temperature > or = 40.0 degrees C). Rectal temperature, respiratory rate, appetite, dyspnoea, coughing, nasal discharge and general condition were recorded on Days 0 (prior to treatment), 1, 2, 3 and 7 using a weighted numerical score. Scores were summed to generate a 'Clinical Sum Score' (CSS, range 7 to 24 points). Individual animal body weights were measured on Days 0 and 7. Nasal swabs were collected from 10 animals per treatment group on Day 0 for microbiological culture. Clinical parameters and the mean CSS showed no significant differences between treatment groups with mean CSS on Days 0 and 7 of 16.18 and 10.55 in the meloxicam group and 16.41 and 10.88 in the flunixin meglumine group. However, a significantly lower mean rectal temperature was measured in the meloxicam group on Day 2 (p < or = 0.01). No significant differences in mean body weights were found between groups. Repeated administration of flunixin meglumine was performed in 45% of the animals. No suspected adverse drug events related to treatments were reported. It is concluded that a single subcutaneous dose of meloxicam was as clinically effective as up to 3 consecutive daily intravenous doses of flunixin meglumine when used as an adjunctive therapy to antibacterial therapy in the treatment of acute febrile respiratory disease in feedlot cattle.

In 2009, Meloxicam was approved in Canada for “…an aid in improving appetite and weight gains when administered at the onset of diarrhea, in combination with oral rehydration therapy, in calves over one week of age.” Also “for relief of pain following de-budding of horn buds in calves less than 3 months of age”.20

**Carprofen** is a propionic acid derivative that demonstrates weak COX binding. This compound demonstrates age dependent pharmacokinetics with significantly longer elimination times in younger cattle. In Europe, the manufacturer claims that a single injection provides relief for up to 3 days in calves less than 12 months of age.

**Clinical efficacy of carprofen as an adjunct to the antibacterial treatment of bovine respiratory disease.**21

A clinical trial was undertaken to investigate the efficacy of a single dose of carprofen (CPF) in the treatment of bovine respiratory disease in cattle. Tilmicosin was used as a basal treatment in all animals. Six hours after dosing, body
temperature and respiratory rates in animals treated with CPF-tilmicosin had decreased and were significantly lower than in the animals treated with tilmicosin alone (P < 0.05). Over the period of clinical observation, CPF-tilmicosin treatment produced a clinical resolution of the pneumonia similar to treatment with tilmicosin alone.

A study comparing treatment of naturally occurring respiratory disease treated with ceftiofur alone or in combination with carprofen, flunixin meglumine or ketoprofen has been published.\textsuperscript{22}

Sixty-six mixed-breed beef cattle weighing on average 197 kg met the inclusion criteria of pyrexia of at least 400°C, an illness score indicating at least moderate illness and at least moderate dyspnoea. They were allocated randomly to four treatment groups. All the groups received ceftiofur for three days at a dose rate of 1.1 mg/kg by intramuscular injection, and three groups received, in addition, a single dose of either flunixin (2.2 mg/kg by intravenous injection) or ketoprofen (3 mg/kg by intravenous injection) or carprofen (1.4 mg/kg by subcutaneous injection). During the first 24 hours of the study, the pyrexia of the three groups treated with a NSAID was reduced significantly more than the pyrexia of the group treated with ceftiofur alone, and two and four hours after treatment the reduction in pyrexia was significantly greater in the groups treated with flunixin and ketoprofen than in the group treated with carprofen. There were no statistically significant differences between the four groups with respect to depression, illness scores, dyspnoea or coughing. There was less lung consolidation in the three groups treated with a NSAID than in the animals treated with ceftiofur alone, but the difference was significant only in the group treated with flunixin.

A study in comparison of carprofen and flunixin meglumine as adjunctive therapy in bovine respiratory disease.\textsuperscript{23}

In an open, controlled, multi-centre clinical field trial, 7 outbreaks of acute febrile (rectal temperature ≥39.5°C) respiratory disease in housed calves were treated with a single antimicrobial agent, and either the non-steroidal anti-inflammatory drug (NSAID) carprofen (95 calves) or flunixin meglumine (92 calves) on an alternate basis. Carprofen was administered as a single s.c. injection at a mean dosage of 1.4 mg/kg (range 1.2 to 1.9 mg/kg) body weight on the first day and flunixin meglumine by i.v. injection at a mean dosage of 2.0 mg/kg (range 1.2 to 2.6 mg/kg) on the first 3 days. All calves were examined clinically immediately before initial treatment and on 3 occasions up to 1 week after the end of treatment. There were no significant differences between NSAID groups in reduction of clinical parameters between examinations, or in overall efficacy. It is concluded that a single dose of carprofen was equally effective as 3 daily doses of flunixin meglumine as adjunctive therapy to antimicrobial treatment in acute respiratory disease in calves.
A study evaluating diclofenac and flunixin as adjuncts to BRD therapy.\textsuperscript{24}

**OBJECTIVE:** To compare the efficacy of the non-steroidal antiinflammatory drugs, diclofenac sodium and flunixin meglumine as adjuncts to the antibiotic treatment of bovine respiratory disease (BRD).

**PROCEDURE:** We randomly allocated 80 Holstein calves with BRD to three groups. All the calves received a dose of 2.5 mg/kg tulathromycin by single subcutaneous injection and two of the groups received, in addition, either 2.5 mg/kg diclofenac sodium as a single intramuscular injection (diclofenac group, \( n = 30 \)) or 2.2 mg/kg flunixin meglumine as an intravenous injection on the first three consecutive days after tulathromycin administration (flunixin group, \( n = 30 \)). All calves were given a clinical score prior to initial treatment (day 0) and after treatment (days 1, 2, 3, 7 and 14) by observing appetite, demeanour, rectal temperature, the rate and type of respiration, presence or absence of coughing, and nasal discharge.

**RESULTS:** During the first 48 h, improvement of adverse signs of respiratory disease, such as pyrexia and elevated respiratory rate, and of a high clinical index score was significant in the two adjunct groups compared with the calves receiving antibiotic alone. The reduction in pyrexia was greatest in the diclofenac group. There were no statically significant differences between treatment groups with regard to eventual perceived recovery from respiratory disease in 14 days.

**CONCLUSION:** In this trial, a single intramuscular dose of diclofenac sodium was equally effective as three intravenous injections of flunixin meglumine given on consecutive days as adjunctive therapy for BRD.

**Studies Evaluating Multiple Ancillary Therapies**

Evaluation of multiple ancillary therapies used in combination with an antimicrobial in newly received high-risk calves treated for bovine respiratory disease.\textsuperscript{25} (Flunixin, Vitamin C, intranasal vaccine)

Ancillary therapy (ANC) is commonly provided in conjunction with an antimicrobial when treating calves for suspected bovine respiratory disease (BRD) in an attempt to improve the response to a suspected BRD challenge. The first experiment evaluated the effects of 3 ANC in combination with an antimicrobial in high-risk calves treated for BRD during a 56-d receiving period. Newly received crossbred steers (\( n = 516 \); initial BW = 217 ± 20 kg) were monitored by trained personnel for clinical signs of BRD. Calves that met antimicrobial treatment criteria (\( n = 320 \)) were then randomly assigned to experimental ANC treatment (80 steers/experimental ANC treatment): intravenous flunixin meglumine injection (NSAID), intranasal viral vaccination (VACC), intramuscular vitamin C injection (VITC), or no ANC (NOAC). Animal served as the experimental unit for all variables except DMI and G:F (pen served as the experimental unit for DMI and G:F). Within calves treated 3 times for BRD, those receiving NOAC had lower (\( P < 0.01 \)) clinical severity scores (severity scores ranged...
from 0 to 4 on the basis of observed clinical signs and severity) and heavier (P = 0.01) BW than those receiving NSAID, VACC, or VITC at the time of third treatment. Between the second and third BRD treatments, calves receiving NOAC had decreased (P < 0.01) daily BW loss (−0.13 kg ADG) compared with those receiving NSAID, VACC, or VITC (−1.30, −1.90, and −1.41 kg ADG, respectively). There were no differences in rectal temperature, combined mortalities and removals, or overall performance among the experimental ANC treatments. Overall, morbidity and mortality attributed to BRD across treatments were 66.5% and 13.2%, respectively. After the receiving period, a subset of calves (n = 126) were allocated to finishing pens to evaluate the effects ANC administration on finishing performance, carcass characteristics, and lung scores at harvest. Ultrasound estimates, BW, and visual appraisal were used to target a common physiological end point for each pen of calves. There were no differences among the experimental ANC observed during the finishing period (P ≥ 0.11). In summary, the use of NSAID, VACC, and VITC do not appear to positively impact clinical health and could potentially be detrimental to performance during the receiving period in high-risk calves receiving antimicrobial treatment for suspected BRD.
Toxic Mastitis

Steroid study summaries

Mastitis steroid study 1: Effect of dexamethasone on experimental E. coli mastitis in the cow.  

30mg Dexamethasone IM to cows immediately following Induction of E. coli into the mammary gland.

Results: Reduced mammary gland swelling. Maintained rumen motility. Higher rectal temperatures when compared with untreated controls. Higher milk production when compared with untreated controls (reduced losses).

Mastitis steroid study 2: Anti-inflammatory therapy in acute endotoxin-induced bovine mastitis.  

One dose of 0.44mg/kg dexamethasone (220 mg/ 500 kg cow) 2 HOURS FOLLOWING introduction of purified endotoxin into the mammary gland. Mammary gland swelling was evident at treatment but no other systemic signs were evident.

Results: Dexamethasone treatment resulted in lower rectal temperatures when compared with controls and lower milk production (increased losses). Dexamethasone also significantly increased blood leukocytes but there was no difference in somatic cell count.

Anti-inflammatory therapy (both dexamethasone and flunixin meglumine) reduced rectal and mammary gland surface temperatures.

This study also evaluated the effect of flunixin meglumine at two doses of 1.1 mg/kg IV, 8 hours apart. Flunixin did not alter milk production or blood or milk leukocyte counts.

Mastitis steroid study 3: Effects of two anti-inflammatory drugs on physiologic variables and milk production in cows with endotoxin-induced mastitis.  

20mg isoflupredone acetate IV administered after the development of clinical signs of mastitis induced by intramammary infusion of endotoxin.

Results: No measurable differences in heart rate, rectal temperature, rumen motility or mammary gland surface area in 14 hours following endotoxin infusion. No difference in milk production between treated and untreated cows.
Flunixin Meglumine study summaries

Mastitis NSAID study 1: FOI Summary: Multi-site field trial in dairy cows with acute bovine mastitis.\(^{29}\)

Design: 117 adult lactating dairy cows, mainly Holsteins divided into 2 treatment groups. 58 cows received flunixin at 2.2 mg/kg and 59 cows received saline IV.

Inclusion criteria: ≥ 104 degrees F and showing at least 2 clinical signs of udder inflammation, swelling, pain or firmness

Test duration: 4 hours

Primary Variables: Treatment success if body temperature decreased by ≥ 2º F or a decrease to normal (101.5 ºF) 4 Hours after administration. Udder inflammation was assessed on a 4 tier scale (normal, mild, moderate, severe)

Results: Forty cows in the analysis. Statistically significant (p < 0.0001) reduction in pyrexia at 4 hours after administration (No assessment of fever at any other time points). No statistically significant difference in success rates for inflammation (p = 0.0632). The only conclusion we can draw from this study is that Banamine reduces fever 4 hours after administration. We can draw no inferences from this in terms of reduced production losses or increased survival.

Mastitis NSAID study 2: Effects of two anti-inflammatory drugs on physiologic variables and milk production in cows with endotoxin-induced mastitis (same reference as #3 under steroids above).\(^3\)

Objective: To determine the effects of 2 anti-inflammatory drugs in lactating Holstein cows with endotoxin-induced mastitis.

Animals: 30 multiparous Holstein cows that had been lactating for 30 to 60 days.

Procedure: Bacterial culture of milk samples and physical examinations established that study cows were in good health and free of mastitis. Mastitis was induced in 1 front mammary gland by intramammary administration of purified bacterial endotoxin. Cows were allocated into 1 of 3 treatment groups: untreated endotoxic mastitis (n = 9), endotoxic mastitis plus flunixin meglumine (9), and endotoxic mastitis plus isoflupredone acetate (10). Heart rate, rectal temperature, mammary surface area, and rumen motility were recorded hourly for 14 hours following endotoxin administration. Flunixin meglumine or isoflupredone acetate was administered after mammary swelling and rectal temperature > or = 40 degrees C had developed. Milk production was evaluated from 5 days before to 10 days after induction of mastitis.
Results: Neither drug ameliorated loss of milk production or swelling of the affected mammary gland. Both drugs reduced mean heart rate during the 14 hours following endotoxin administration, compared with untreated control cows. Cows treated with flunixin meglumine had increased rumen motility and decreased rectal temperature during the same period, compared with all other cows.

Conclusions: Neither drug enhanced recovery of milk production following endotoxin-induced mastitis. Flunixin meglumine decreased rectal temperature, whereas isoflupredone did not; however, it has not been established that reduction of fever is beneficial to cows with naturally occurring mastitis.

Mastitis NSAID study 3: Comparison of fluid and flunixin meglumine therapy in combination and individually in the treatment of toxic mastitis.\textsuperscript{30}

During a three-year study, 54 cows with toxic mastitis were allocated randomly to one of three treatment groups (A, B and C). Each cow was re-examined within 24 hours of the initial examination, and, during this time, group A received fluid therapy (45 liters of intravenous isotonic electrolyte solution) and flunixin meglumine (2000 mg), group B received fluid therapy only, and group C received flunixin meglumine only. In addition all the cases were treated with parenteral and intramammary tetracyclines, oxytocin and calcium borogluconate. There was no significant difference in the rate of survival between the treatment groups and 29 of the cows (53.7 per cent, 95 per cent confidence interval of 39 to 67 per cent) survived.

Mastitis NSAID study 4: Effect of phenylbutazone and flunixin meglumine on acute toxic mastitis.\textsuperscript{29}

A double-blinded randomized prospective clinical trial was designed to evaluate the effectiveness of flunixin meglumine and phenylbutazone for treatment of acute toxic mastitis in dairy cows. All cows were treated 4 times at 12-hour intervals by intramammary infusion of gentamicin (150 mg). A total of 45 dairy cows with toxic mastitis were randomly assigned to 1 of 3 treatment groups: group 1 (control), saline solution, IV; group 2, 1 g of flunixin meglumine, IV; or group 3, 4 g of phenylbutazone, IV. Physical examination and udder variables were assessed at initial examination and 24 hours later. Milk production was recorded at regular intervals from 1 week before until 10 weeks after development of mastitis. Rear quarters (34/45) were more commonly affected than front quarters. Thirty-five cows returned to the herd, 9 cows were culled, and 1 cow died. There were no significant differences among treatment groups in the need for further treatment or outcome. Klebsiella spp (18/45) and Escherichia coli (16/45) were the most common pathogens isolated by culture of milk from affected quarters. The overall bacteriologic cure rate on days 7 and 14 was 64 and 75%, respectively. At the time of initial examination, cows of the control group had higher rectal temperature than
did cows of the flunixin group. At the examination 24 hours later, the rectal
temperature of cows in all treatment groups was lower than the temperature at
initial examination; at that time (24 hours), however, there were no significant
differences in temperature among the treatment groups.

**Mastitis NSAID study 5: The effects of experimentally induced *Escherichia coli* mastitis
and flunixin meglumine administration on activity measures, feed intake, and milk
parameters.**³⁰

The use of flunixin meglumine (FM), a nonsteroidal antiinflammatory drug, during
experimentally induced *Escherichia coli* mastitis was evaluated. Twenty-four
primiparous and multiparous lactating dairy cows were challenged with 1×10⁵ cfu
of *E. coli* 727 in 1 uninfected quarter. Of the 24 *E. coli*-challenged animals, 12 were
administered FM [ECF; 100mg (2cc)/45.5kg of body weight] at the onset of clinical
mastitis signs. The remaining 12 challenged cows were untreated (EC). An additional
11 cows were infused with 1mL of sterile phosphate-buffered saline and served as
the nonchallenged control (CTL) group. Activity measures, dry matter intake (DMI),
milk production, milk bacterial counts from challenged mammary glands, and
somatic cell score (SCS) were collected on all animals. Activity measurements were
collected using both a behavior-monitoring system and data loggers. Activity was
summarized by day (behavior-monitoring system) and in 3-h time periods (data
loggers). An examination of animal activity indicated that EC and ECF cows stood
more and lay less as compared with the CTL animals in the first 6h after FM
administration. When DMI was analyzed, CTL and ECF animals had greater DMI than
the EC animals on d 1 postchallenge. However, by d 2 postchallenge, DMI for ECF
and EC cows was significantly less than for the CTL cows. The ECF cows had greater
milk yield than did EC animals by d 3 and 4 postchallenge, and no significant
difference in yield was observed between the ECF and CTL animals. No differences in
SCS were observed between the parity groups. Yet, bacterial counts in milk were
greater in multiparous animals compared with the primiparous cows. Therefore, it
can be concluded that *E. coli* mastitis does alter animal activity and may have a
negative effect on animal well-being. However, the improvement in DMI and milk
production for ECF animals provides evidence for using a nonsteroidal
antiinflammatory drug as supportive therapy in alleviating the adverse effects
associated with *E. coli* mastitis.

**Mastitis NSAID study 6: The effect of NSAID, antioxidants or an immunomodulator on
results of intramammary antibiotic treatment of acute mastitis in dairy cows.**³¹

The aim of this study was to examine the effect of an additional drug which is
injectable for the treatment of mastitis. Field trials were conducted on three farms
on 161 cows with acute form of mastitis (221 inflamed quarters). After clinical
examination of the cow and its udder as well as screening of their milk the cows
were grouped into four. Group 1 (N=50) served as control, Group 2 (N=35) treated
with the recommended antibiotics plus 2.2 mg/kg b. w. of flunixin meglumine, Group 3 (N=46) same antibiotic treatment as group 2 plus 0.01 mg/kg vitamin C, 0.4 mg/kg beta-carotene and 1 mg/kg of vitamin E, combined with selenium, and Group 4 (N=30) same antibiotic as groups 2 and 3 plus 0.02 lysozyme dimer (0.02 mg/kg). Results after treatment showed that mastitis was controlled at the following rates: 51.0% for group 1, 54.2%, 65.2% and 66.6% for groups 2 to 4 respectively. Therefore, efficacy of the antibiotic treatment was enhanced using lysozyme dimer (group 4) for the control of udder inflammations caused by Escherichia coli, Streptococcus, and Staphylococcus aureus.

**Mastitis NSAID study 7: The effect of acute mastitis treatment methods on fertility indices in dairy cows.**

The aim of this study was to examine the effect of a parenteral injection of Non-Steroidal anti-inflammatory agents (NSAID), antioxidants or an immunomodulator to the intramammary glands of the treated cows with reference to fertility indices. Cows with acute mastitis were subjected to the following treatment: group 1 (control, N=60), group 2- antibiotic treatment only (N=44), group 3- antibiotic plus flunixin meglumine (N=25), group 4- plus antioxidants; vitamin C, beta-carotene, vitamin E and selenium (N=35), and group 5- plus lysozyme dimer (N=25). Recovery after treatment were 52%, 54.2%, 65.2% and 66.6% from groups 2-5 respectively. Results after treatment of mastitic cows showed that an injection of antioxidants or flunixin meglumine or lysozyme dimer to cows with clinical infections not only recovered but improves its fertility indices namely: calving to first artificial insemination, pregnancy rate, and days calving to conception.

**What about other NSAIDs for ancillary therapy of acute mastitis?**

Aspirin, flunixin meglumine, phenylbutazone, carprofen, ibuprofen, and ketoprofen have been studied as treatments of experimental coliform mastitis or endotoxin-induced mastitis. Meloxicam has been evaluated in naturally occurring mastitis.

**Mastitis NSAID study 8: Efficacy of oral and Parenteral ketoprofen in lactating cows with endotoxin-induced acute mastitis.**

One hind quarter of 27 healthy lactating cows was infused with 100 μg *Escherichia coli* endotoxin. Two hours later, nine of the cows were given physiological saline by intramuscular injection, nine were given 4 mg/kg ketoprofen orally, and nine were given 3 mg/kg ketoprofen by intramuscular injection. Ketoprofen administered either orally or parenterally significantly reduced the effect of the endotoxin on rectal temperature, ruminal contractions and respiratory rate. The size of the udder, the signs of pain and the concentrations of thromboxane B2, especially in plasma, were also reduced, and the appearance of their milk was almost normal.
response of cows to the oral treatment was as rapid as it was to intramuscular treatment.

Mastitis NSAID study 9: Effect of caprofen treatment following experimentally induced Escherichia coli mastitis in primiparous cows.³⁴

Acute Escherichia coli mastitis is one of the major sources of economic loss in the dairy industry due to reduced milk production, treatment costs, discarded milk, and occasional fatal disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as adjunctive therapy to antibiotics. The objective of the current study was to evaluate the effect of carprofen treatment following infusion of Escherichia coli into the mammary glands of primiparous cows during the periparturient period. Severity of mastitis was scored based on the average milk production in the uninfected quarters on d+2 postinoculation and a clinical severity score. Carprofen was administered intravenously at 9 h postchallenge, when clinical signs of mastitis appeared. In previous work, efficacy of NSAIDs was mainly evaluated using clinical symptoms. In the present study, the effect of carprofen on innate immune response was also assessed by quantification of inflammatory mediators. All primiparous cows reacted as moderate responders throughout the experimental period. Primiparous cows were intramammarily inoculated with $1 \times 10^4$ cfu of E. coli P4:O32 in 2 left quarters. Analysis of blood and milk parameters, including IL-8, complement component C5a, lipopolysaccharide-binding protein (LBP), soluble CD14, prostaglandin E₂, and thromboxane B₂ was performed from d 0 to d+6 relative to intramammary inoculation. Rectal temperature in carprofen-treated animals was lower than in control animals at 3 and 6 h posttreatment. Treatment also restored the decreased reticulorumen motility that occurs during E. coli mastitis to preinfection levels faster than in control animals. Carprofen treatment resulted in an earlier normalization of the clinical severity score. Eicosanoid (prostaglandin E₂ and thromboxane B₂ production in milk tended to be inhibited by carprofen. No significant differences in the kinetic patterns of somatic cell count, IL-8, complement component C5a, LBP, and soluble CD14 were observed. In conclusion, carprofen treatment improved general clinical condition by effective antipyrexia and restoration of reticulorumen motility but did not significantly inhibit eicosanoid production. Carprofen treatment did not result in a significant decrease of chemotactic inflammatory mediators, IL-8 and C5a, and early innate immune molecules, sCD14 and LBP. Therefore, major modulatory effects from NSAID administration were not observed in this mastitis model, although a larger study might confirm some apparent trends obtained in the present results.

Mastitis NSAID study 10: The anti-inflammatory drugs phenylbutazone and dipyrone in the treatment of field cases of bovine mastitis.³⁵
The efficacy of the non-steroidal anti-inflammatory drugs (NSAID), phenylbutazone and dipyrone, for the treatment of acute clinical mastitis were compared in a clinical trial. All cows were treated with 20 g sulfadiazine and 4 g trimethoprim i.m. upon diagnosis and half dosage once daily thereafter. In addition, the NSAID-treated cows received once daily either 4 g phenylbutazone or 20 g dipyrone i.m. for the duration of the antimicrobial therapy. In all treatment groups the main pathogens were coliforms. Recovery rates for the controls, the phenylbutazone and dipyrone treatment groups were 81.1, 89.4 and 86.6%, respectively. Recovery was evaluated by the logistic regression analysis, the odds ratio (OR) and 95% confidence interval (CI) of treatment success for phenylbutazone and dipyrone treatments relative to the control treatment. Odds ratio of recovery was high for phenylbutazone (OR=2.42; CI=0.98-5.96; P=0.054) and for dipyrone (OR=1.71; CI=0.98-3.00; P=0.060), showing a strong trend towards improved recovery in NSAID groups. The odds of treatment failure for the phenylbutazone group relative to the dipyrone group was 0.71 with 95% CI of 0.28-1.78. Clearly no significant difference could be identified between phenylbutazone and dipyrone in this field trial.

Mastitis NSAID study 11: Effect of treatment with the nonsteroidal antiinflammatory meloxicam on milk production, somatic cell count, probability of re-treatment, and culling of dairy cows with mild clinical mastitis.  

It was hypothesized that treatment of clinical mastitis with a combination of a nonsteroidal antiinflammatory treatment (meloxicam) and a parenteral antibiotic (penethamate hydriodide) would result in lower somatic cell counts (SCC), reduced milk yield losses, improved clinical outcomes, and reduced culling rates compared with antibiotic therapy alone. Cows in 15 herds with clinical mastitis during the first 200 d of lactation (median = 13 d) were treated with 5 g of penethamate hydriodide daily for 3 d, and one-half these cows were treated with 250 mg of the nonsteroidal antiinflammatory drug meloxicam (n = 361 cows), whereas the other half (n = 366 cows) were treated with the vehicle (control group). Milk samples for bacteriology were collected from clinically affected glands before treatment, and samples were collected at 7 (+/-3), 14 (+/-3), and 21 (+/-3) d after commencement of treatment for SCC determination. Additionally, the rectal temperature, udder edema score, California Mastitis Test score, and milk clot score were determined before treatment and daily milk yield data were collected across the lactation. There were no differences between the treatment groups in calving date, days in milk, age, breed, rectal temperature, California Mastitis Test score, clot score, udder edema score, or bacterial pathogens isolated before treatment. There was no difference between treatment groups in the number of cows that were defined as treatment failures (i.e., re-treated within 24 d of initial treatment, died, or the treated gland stopped producing milk); 79 (21.9%) vs. 92 (25.1%) cows in the meloxicam and control groups failed, respectively. The SCC was lower in the meloxicam-treated group compared with the control group after treatment [550 +/- 48 vs. 711 +/- 62 geometric mean]
(x1,000/mL) +/- standard error of the mean SCC for quarters after treatment with meloxicam vs. control, respectively]. There was no difference in milk yield for the cows treated with meloxicam compared with the control cows within 28 or 200 d after treatment. Fewer meloxicam-treated than control cows were removed (culled) from the herds [39/237 (16.4%) vs. 67/237 (28.2%) for meloxicam vs. control cows, respectively; odds ratio = 0.42, 95% confidence interval = 0.26 to 0.68]. It was concluded that treatment of cows with clinical mastitis with a combination of meloxicam and penethamate resulted in a lower SCC and a reduced risk of removal from the herd (culling) compared with treatment with penethamate alone.

**Mastitis NSAID study 12: The effect of meloxicam on pain sensitivity, rumination time, and clinical signs in dairy cows with endotoxin-induced clinical mastitis.**

The objectives of this study were to (1) evaluate the use of a pressure algometer and an automated rumination monitoring system to assess changes in pain sensitivity and rumination time in response to endotoxin-induced clinical mastitis and (2) evaluate the effect of the nonsteroidal antiinflammatory drug meloxicam on pain sensitivity and rumination time, as well as other clinical signs, in dairy cattle with endotoxin-induced clinical mastitis. Clinical mastitis was induced in 12 primiparous and 12 multiparous lactating dairy cows by intramammary infusion of 25 g of *Escherichia coli* lipopolysaccharide (LPS) into 1 uninfected quarter. Immediately after, half the cows were injected subcutaneously with meloxicam (treated group) and half with the same volume of a placebo solution (control group). Pain sensitivity was assessed by measuring the difference in pressure required to elicit a response on the control and challenged quarter using an algometer 3 d before, immediately before, and at 3, 6, 12, and 24 h after LPS infusion and either meloxicam or placebo injection. Rumination was continuously monitored from 2 d before to 3 d after LPS infusion using rumination loggers. Udder edema, body temperature, somatic cell score, and dry matter intake were also monitored to evaluate the occurrence and the duration of the inflammation after LPS infusion. In control animals, the difference in the pressure applied to the control and challenged quarter (control - challenged quarter) increased by 1.10.4 kg of force 6 h after LPS infusion compared with the baseline, suggesting an increase in pain sensitivity in the challenged quarter. Neither the LPS infusion nor the meloxicam treatment had an effect on daily rumination time. However, the rumination diurnal pattern on the day of LPS infusion showed an overall deviation from the baseline pattern. Cows spent less time ruminating in the hours following LPS infusion and more time ruminating later in the day. Meloxicam did not alter somatic cell score or dry matter intake. However, meloxicam-treated animals had less udder edema and a lower body temperature in the hours following LPS infusion compared with control animals. In conclusion, pressure algometers and rumination loggers show promise as tools to detect mastitis and monitor recovery on farm. Further, meloxicam has a beneficial effect in relieving pain and decreasing udder edema and body temperature in LPS-induced clinical mastitis.
Orally administered aspirin should be used with caution as a treatment of acute mastitis because many of these cases develop severe rumen atony. When used, FARAD recommends a milk and slaughter withdrawal interval of 24 hours to reduce the risk of Reye’s syndrome in children. Phenylbutazone has also been studied and widely used as treatment of acute mastitis; however the FDA-CVM has strongly discouraged its use in food animals. The tolerance level for phenylbutazone is zero and detection of any concentration is an illegal residue. The use of phenylbutazone in dairy cattle greater than 20 months of age has been prohibited by the Food and Drug Administration Center for Veterinary Medicine.

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**Metritis**

Treatment of acute puerperal metritis with flunixin meglumine in addition to antibiotic treatment.

The objective of this field trial was to evaluate effects of a single administration of 2.2 mg/kg of body weight (BW) of flunixin meglumine (FM) in addition to a systemic antibiotic treatment in cows with acute puerperal metritis (APM). Outcome variables tested were proportion of cows with a fever, prevalence of chronic endometritis 18 to 22 and 32 to 35 d in milk (DIM), and reproductive performance measures in the current lactation. In addition, serum concentrations of haptoglobin and fibrinogen were analyzed. Daily milk yield within 6 d after the first treatment was recorded. Cows were examined 4 to 5 DIM by rectal palpation and vaginoscopy, and rectal temperature was measured. Fetid vulvar discharge and a body temperature ≥ 39.5 degrees C were signs of APM. Cows with APM were treated in the reference group with 1.0 mg/kg of BW of ceftiofur on 3 to 5 consecutive days (CEF, n = 119). In the study group, cows received the same antibiotic treatment as in CEF and 2.2 mg/kg of BW of FM on treatment d 1 (CEF + FM, n = 119). Blood samples were collected 4, 6, and 10 DIM and analyzed for concentrations of haptoglobin and fibrinogen. A group of cows without APM remained untreated and served as controls (n = 9). There were no significant differences between CEF and CEF + FM in the proportion of cows with fever 1 d after the first treatment (33.6 vs. 46.2%), milk yield per milking 10 DIM (7.5 +/- 0.3 vs. 7.6 +/- 0.3 kg in primiparous, 9.6 +/- 0.4 vs. 10.6 +/- 0.4 kg in multiparous cows), prevalence of chronic endometritis 32 to 35 DIM (64.3 vs. 52.2%), and in reproductive performance (31.5 vs. 34.3% conception to first AI, 58.0 vs. 54.6% pregnancy rate, 107.8 +/- 36.9 vs. 101.6 +/- 41.4 d open). Compared with the control, CEF and CEF + FM had significantly greater concentrations of haptoglobin (1.1 +/- 0.28 vs. 1.9 +/- 0.06 and 1.8 +/- 0.07 mg/mL at 4 DIM; 0.3 +/- 0.15 vs. 1.1 +/- 0.06 and 1.2 +/- 0.07 mg/mL at 10 DIM) and fibrinogen (2.2 +/- 0.17 vs. 3.9 +/- 0.14 and 3.7 +/- 0.13 g/L at 4 DIM; 1.9 +/- 0.1 vs.
2.6 +/- 0.1 and 3.0 +/- 0.13 g/L, respectively, at 10 DIM) on all test days. The additional treatment with FM had no effect on these acute phase proteins. In conclusion, the single administration of 2.2 mg/kg of BW of FM in addition to a systemic antibiotic treatment of cows having APM did not result in beneficial effects on clinical cure, milk yield within 6 d after the first treatment, or reproductive performance.

### Neonatal Enteric Disease

**Evaluation of flunixin meglumine as an adjunct treatment for diarrhea in dairy calves.**

One hundred fifteen Holstein bull calves, 1-21 days old, randomized, no identifying marks as to treatment. Treatments were standard antimicrobial (spectinomycin orally 10 mg/kg) then flunixin meglumine 2.2 mg/kg IM, once (treatment 1), same flunixin dose but administered on days 1 and 2 (treatment 2), or no treatment in addition to antibiotic (control). Additional treatment was on an empirical basis by crew. When split into calves with and without fecal blood, calves with fecal blood and treated with a single dose of flunixin meglumine received fewer antimicrobial treatments and had fewer morbid days as opposed to controls. Calves receiving 2 doses of flunixin in 24 hours were not significantly different from the controls, but had numerically lower morbidity days. Calves with no fecal blood had no difference between treatments. Calves that did not recover or died by day 30 were censored from the morbid day analysis above; these were 13, 10, and 11 calves for treatments 1, 2, and controls respectively. Although not significantly different, death loss during the study was 10% (4/38) for treatment one, 8% (3/37) for treatment 2, and 2% (1/40) for the controls. The lack of significance in death loss figures may be due to the relatively small numbers in the study and dilution of power attributable to 3 rather than 2 treatment groups.

**Flunixin in an induced endotoxin model of calf enteric disease**

In a study to evaluate the effect of flunixin meglumine on secretory diarrhea, 11 calves were assigned to 3 groups: group 1 (n = 3) served as controls, group-2 calves (n = 4) were given 2.2 mg of flunixin meglumine/kg, IM at 7 AM and 3 PM, and group-3 calves (n = 4) were given 2.2 mg of flunixin meglumine/kg, IM at 7 AM, 11 AM, and 3 PM. All calves were given approximately 200 micrograms of heat-stable Escherichia coli enterotoxin (STa) orally at 8 AM. Mean cumulative fecal output for groups 1, 2, and 3 was 1,331.0 +/- 317.2 g, 1,544.3 +/- 154.4 g, and 785.5 +/- 276.5 g, respectively. There was a significant (P less than 0.05) reduction in mean fecal output in group-3 calves, compared with that in groups 1 and 2. Calves in group 2 tended to have a delay, but not a reduction, in their fecal output. At 12 hours,
hemoconcentration was significantly (P less than 0.05) greater in group-1 calves than in group-2 or group-3 calves.
Anti-inflammatory drug therapy for neonatal calf diarrhea complex: Effects on calf performance.\(^{42}\)

The aim of this study was to examine the efficacy of meloxicam (MEL) as supportive therapy for calves with neonatal calf diarrhea complex. For this double-blind controlled trial, 62 Holstein male calves were purchased at birth and transported to a research facility. At the naturally occurring onset of diarrhea, defined as the first occurrence of a fecal score greater than 2 on a 4-point scale, calves were enrolled in the study. Each calf with diarrhea was randomly assigned to receive a single subcutaneous injection of MEL at a rate of 0.5 mg/kg of BW or an equal volume of placebo (PLA) solution. Milk, starter ration, and water intakes were determined daily for each calf from arrival until 56 d of age. The calves were weighed on arrival and each week thereafter. Time to weaning and weaning weight were recorded for each calf. Crude associations between treatment and each outcome variable were examined using t-tests and Pearson chi-squared tests. Subsequently, multivariable regression models were constructed to examine the impact of MEL therapy on meaningful outcome variables. The primary experimental unit in all analyses was the individual calf. In total, 56 calves presented with clinical signs of diarrhea and were enrolled in the study. Two PLA-treated calves died after being enrolled in the study, and there was no calf mortality among the MEL-treated calves. For calves that developed diarrhea after 10 d of age, MEL-treated calves were more likely to consume their entire daily milk allowance (P < 0.05) as compared with PLA-treated calves. Meloxicam-treated calves began consuming starter ration earlier (P < 0.01) and at a greater rate (P < 0.001), and consumed more water (P < 0.001) compared with PLA-treated animals. Over the study period, calves treated with MEL gained BW at a faster rate (P < 0.01) than calves treated with PLA. There was no difference in weaning weight (P > 0.05), but MEL-treated calves tended to wean earlier (P = 0.11) than PLA-treated calves. These results demonstrate that calves receiving a single injection of MEL at the onset of diarrhea had improved appetite and performance compared with PLA-treated calves. Thus, MEL is an effective supportive therapy for neonatal calf diarrhea complex.

Impact of dexamethasone-induced immunosuppression on the duration and level of shedding of Escherichia coli O157:H7 in calves.\(^{43}\)

The goal of this study was to determine whether immunosuppression plays a role in the level and duration of fecal shedding of Escherichia coli O157. Immunosuppression was induced in calves by administering dexamethasone. Six 1-week-old Holstein bull calves were injected intramuscularly with dexamethasone and orally inoculated with \(10^9\) CFU of a mixture of three nalidixic-acid resistant strains of E. coli O157:H7. Five 1-week-old Holstein bull calves that were given the same oral inoculation of E. coli O157:H7, but not the dexamethasone injections, served as controls. All calves were examined daily and fecal samples were collected
three times a week for detection and enumeration of the nalidixic-acid resistant E. coli O157. Four weeks after the last calf stopped shedding, all calves were necropsied and samples from the gastrointestinal tract were taken for the detection of the nalidixic-acid resistant E. coli O157. Dexamethasone-injected calves shed at higher levels ($P = 0.04$) on days 4 and 7 postinoculation, but not thereafter. None of the samples collected at necropsy were positive for E. coli O157. Data from this study suggest that there may be a time-dependent relationship between dexamethasone immunosuppression and the fecal concentration of E. coli O157 but that transient immunosuppression does not appear to prolong shedding of E. coli O157.

Retained Placenta, Mastitis

**Effect of flunixin meglumine treatment following parturition on cow health and milk production.**

Blinded, 2 site, randomized clinical trial, 148 cows in Ontario and 1,174 cows in Michigan. Treatment consisted of negative controls or 1.1 to 2.2 mg/kg IV (fixed volume of 25 ml for cows and 12 ml for heifers) given approximately 2 hours post calving and repeated approximately 24 hours later. No significant effect of treatment was identified related to milk fever, abomasal displacement, clinical ketosis, or mastitis. However, flunixin treated cows were 2.5 times more likely to have a retained placenta and 1.5 times more likely to be diagnosed with metritis. Milk yield was not significantly different.

**The effects of periparturient administration of flunixin meglumine on the health and production of dairy cattle.**

Research on the assessment and management of pain in cows following difficult or assisted calving is still limited, especially on the effects of analgesics intended to mitigate this pain. The purpose of this study was to assess the effects of flunixin meglumine on the health and production of Holstein cows after calving. In total, 34 flunixin-treated and 38 placebo-treated animals were enrolled in a precalving treatment trial. A total of 633 animals given flunixin and 632 animals administered a placebo were enrolled in a postcalving treatment trial. In both cases, animals were randomly assigned to treatment, and researchers were blind to treatment condition until after analysis. A total of 1,265 animal records were analyzed for milk production for the first 14d in milk and health outcomes for the first 30d in milk. Animals treated with flunixin meglumine before calving had a significantly increased risk of stillbirth. Animals treated immediately after calving had increased odds of having a retained placenta and, in turn, increased risk of a high temperature, decreased milk production, and an increased risk of developing metritis.
administration of flunixin meglumine within 24h of parturition is not recommended in dairy cattle.

Clinical and Bacteriological Aspects on the Use of Oxytetracycline and Flunixin in Primiparous Cows with Induced Retained Placenta and Post-partal Endometritis.46

Retention of the fetal membranes and post-partal endometritis (RFM) are common problems in dairy cows. Treatment often includes manual removal of the placenta in combination with antibiotic treatment. Earlier studies have shown that cows with endometritis post-partum have a strong tendency to recover spontaneously. The present study focused on treatments of post-partal endometritis with the prostaglandin synthesis inhibitor, Flunixin (F) either alone or combined with oxytetracycline (T). The study was conducted in two experiments, using 12 primiparous cows in each. As a model for RFM, premature parturition was induced in late pregnant heifers by injecting PGF2α (25 mg i.m.) twice with a 24 h interval. In each experiment the cows were set into four groups and treated with either T (10 mg/kg BW i.m. once daily), F (2.2 mg/kg BW p.o. twice daily), a combination of T and F (dosage, as above) or conservatively (group 0, no drugs). The treatment periods lasted from days 11±14 post-partum in experiment 1 (groups T1, F1, TF1 and 0) and from days 3±6 post-partum in experiment 2 (groups T2, F2, TF2 and 0). Jugular vein blood samples were collected for analyses of flunixin and total white blood cells. Uterine biopsies were collected twice weekly for investigation of endometrial microbiology. Rectal palpation and ultrasonographic examinations were performed three times weekly for investigations of uterine involution and ovarian activity. No attempts were made to remove the placentas manually. The experiment lasted until day 56 post-partum. The induction of parturition was successful in all heifers and 22 of 24 animals had RFM. All RFM cows had bacterial endometritis. The predominant bacteria were Escherichia coli α-haemolytic streptococci, Fusobacterium necrophorum, Arcanobacterium (Actinomyces) pyogenes, Bacteroides spp., Pasteurella spp. and Proteus spp. Fusobacterium necrophorum and A. pyogenes could be isolated for 3±5 weeks post-partum and E. coli, Pasteurella and Proteus could be isolated for 2±3 weeks post-partum. Animals treated with tetracycline after placental shedding (T1 and TF1) had a more rapid recovery from infections with A. pyogenes and F. necrophorum than animals that were not treated with tetracycline. No other genera were affected. Antibiotic treatment before placental shedding (T2 and TF2) did not shorten the uterine infection but altered the bacterial flora, seen as an overgrowth of Proteus spp. (p < 0.05) and increased frequency of Pasteurella (p < 0.05). The α-haemolytic streptococci were less common in T2 and TF2 than in other groups (NS). Antibiotic treatment of cows before placental shedding (T2 or TF2, n.6) postponed detachment of placenta compared to cows were no antibiotics were administered before placental shedding (T1, TF1, F1, F2 and 0, n.16, 9.8 days pp (median) versus 11.8, p<0.004). Neither treatment shortened uterine involution. Flunixin treatments did
not seem to influence recovery from infection or uterine involution. It was concluded that early oxytetracycline treatment of retained fetal membranes in the cow did not shorten the uterine involution or uterine infection but it did slow down the detachment process of the retained placenta. Oxytetracycline treatment after placental shedding might shorten the uterine infection but otherwise did not affect the clinical results. Flunixin treatment had no influence on the clinical outcome of the disease.

Future Prospects

A number of NSAIDs have recently been approved for use in food animals in the European Union. It is conceivable that many of these products might become available in the United States in due course. Some of these compounds, such as ketoprofen (Ketofen, Merial) are already approved in the U.S for use in horses. Other compounds such as carprofen (Rimadyl, Pfizer) and meloxicam (Metacam, Boehringer Ingelheim) have been available for use in small animals in the U.S for many years.

A recent breakthrough was the first approval of a compound for pain in cattle in the United States. Topical flunixin meglumine (Banamine Transdermal) was approved in the United States in 2017 for control of pain associated with foot rot and the control of pyrexia (fever) associated with bovine respiratory disease.


http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM203309.pdf: Food and drug Administration Center for Veterinary Medicine, 2009.


20. Ingelheim B. Metacam® Canadian Label. *20 mg/ml solution for injection.*

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