

# Survival of dairy cattle presumptively suffering from idiopathic pericardial hemorrhage using parenteral dexamethasone or isofluprednone acetate

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## Abstract

A total of 81 female dairy cows were treated with corticosteroids for presumed hemorrhagic idiopathic pericardial effusion over a 34-month period on a 2,200 cow dairy in southern Wisconsin. Individual cattle were treated with either dexamethasone or isofluprednone acetate based upon pregnancy status. The median age and days-in-milk at the time of diagnosis was 49 months and 181 days for those receiving dexamethasone (n = 51), and 47 months and 316 days for those receiving isofluprednone acetate (n = 30), respectively. Mean survival time from time of diagnosis for the non-pregnant group was 131 days +/- 101 days, which did not differ significantly from the slightly shorter mean survival time of 114 days +/- 111 days in the pregnant cow group. Mean mature equivalent milk production for the lactation at the time of diagnosis also did not differ between groups (27,792 ± 6,096 lb [12,633 ± 2,771 kg] in the group receiving dexamethasone, compared to 30,970 ± 4,325 lb [14,077 ± 1,966 kg] in the group receiving isofluprednone). Previous accounts of this condition have documented extended survival times following hospital-based treatment that has typically included pericardial drainage. However, our findings underscore the possibility that commercial cattle can be treated on-farm with corticosteroids without the need for drainage, and that extended survival times, reproductive, and lactational performance can still be achieved.

**Key words:** pericardial hemorrhage, dexamethasone, isofluprednone, heart failure

## Résumé

On a traité 81 vaches laitières avec des corticostéroïdes pour ce que l'on croyait être un épanchement péricardique hémorragique idiopathique sur une péri-

ode de 34 mois dans une ferme laitière de 2200 vaches dans le sud du Wisconsin. Les bovins étaient traités avec soit de la dexaméthasone ou soit avec de l'acétate d'isofluprednone selon le statut de gestation. L'âge médian et le nombre de jours en lactation au moment du diagnostic étaient respectivement de 49 mois et de 181 jours pour les bovins recevant la dexaméthasone (n=51) et de 47 mois et 316 jours pour ceux recevant l'acétate d'isofluprednone (n=30). Le temps moyen de survie depuis le diagnostic était de 131 jours +/- 101 jours dans le groupe non-gestant, une valeur qui ne différait pas significativement de celui un peu plus court dans le groupe gestant (114 jours +/- 111). La production moyenne de lait en équivalent adulte pour la lactation en cours au moment du diagnostic ne différait pas entre le groupe recevant la dexaméthasone (27792 ± 6096 lb [12633 ± 2771 kg]) et le groupe recevant l'acétate d'isofluprednone (30970 ± 4325 lb [14077 ± 1966 kg]). Un prolongement du temps de survie suite à un traitement hospitalier a été décrit dans des cas précédents qui impliquaient un drainage péricardique. Toutefois, nos résultats soulignent la possibilité de traiter des bovins en élevage avec des corticostéroïdes à la ferme sans drainage permettant un prolongement du temps de survie et une augmentation de la performance de reproduction et de lactation.

## Introduction

The list of differential diagnoses for adult dairy cattle presenting with clinical signs of congestive heart failure is quite short and, in most cases, such individuals are perceived as having a poor prognosis and are culled. Traumatic pericarditis, vegetative endocarditis, cardiac lymphosarcoma, cor pulmonale associated with altitude disease, chronic pneumonia, and possibly ionophore or gossypol toxicity would represent the most likely differentials for overt signs of congestive heart failure with tachycardia, peripheral edema, and distended jugular

and mammary veins.<sup>2</sup> Muffled heart sounds are most commonly associated with clinically significant pericardial effusion, for which the most likely diagnoses are traumatic pericarditis or cardiac lymphosarcoma.<sup>2,5</sup>

In recent years there have been a few individual case reports and small retrospectives describing a condition of idiopathic pericardial effusion in dairy cattle.<sup>1,3,4,6</sup> Affected cattle present acutely with signs of cardiac failure, including tamponade with distended and poorly compressible jugular and mammary veins, edema, muffled heart sounds, and a sudden drop in milk production and appetite. In contrast to other forms of cardiac disease, idiopathic pericardial effusion appears to carry a more favorable prognosis in terms of longevity, reproductive, and lactational productivity.<sup>3,4,6</sup> Retrospective case studies have sometimes documented extended survival times up to several years in individually valuable cattle that were referred to university teaching hospitals for diagnostic work-up and treatment.<sup>1,3,4,6</sup> Principal amongst the treatments associated with successful therapy has been pericardiocentesis with fluid drainage, a procedure with limited practical applicability on-farm. Anecdotally, the condition has been observed more frequently in the last few years and, although there are practical challenges in reaching a definitive ultrasonographic and cytologic diagnosis on-farm, we document our experiences with this condition on a large dairy, with the hypothesis that anti-inflammatory medical treatment alone would be a more practical and conservative approach to treatment success.

This report describes experiences with this condition on 1 large dairy for nearly 3 years, including a prospective comparison of the effect of different treatments on production and survival.

### Materials and Methods

Affected cows were housed on a 2,200-cow, sand-bedded, free-stall dairy in southern Wisconsin with a rolling herd average of 29,000 lb (13,181 kg) of milk production, a mean somatic cell count of 220,000, and a 21% conception rate during the time of the study. Idiopathic pericardial effusion cases were presumptively diagnosed, and cases were monitored from March 2011 to January 2014. The herd had been closed to new cattle purchases since 2007.

Cattle were presumptively diagnosed with pericardial effusion based on clinical signs of cardiac tamponade including muffled heart sounds, distended jugular veins, distended and poorly compressible mammary veins, tachycardia, and neck and brisket edema. Prior to beginning the prospective treatment study we had confirmed the condition in 5 consecutive animals from this farm by ultrasound and cytologic evaluation of fluid obtained by pericardiocentesis. During the study, we

further confirmed large-volume pericardial effusion by transthoracic ultrasound in 6 animals that were undergoing treatment with 1 of the 2 protocols described below.

Not all animals diagnosed with idiopathic pericardial hemorrhage were treated. Some, based upon production and health histories, were sold or culled without treatment. The remaining cases were treated based on pregnancy status with 1 of the 2 following medical protocols: 1) cattle confirmed to be more than 75 days pregnant were administered 24 mg of isofluprednone acetate<sup>a</sup> intramuscularly once daily for 4 days, combined with 125 g of potassium chloride orally (PO) once daily each day; 2) cattle that were not pregnant or less than approximately 75 days gestation were administered 60 mg of dexamethasone intramuscularly once daily for 4 days, 60 mg of dexamethasone IM every other day for 2 treatments, followed by 30 mg dexamethasone every other day for 2 more treatments.

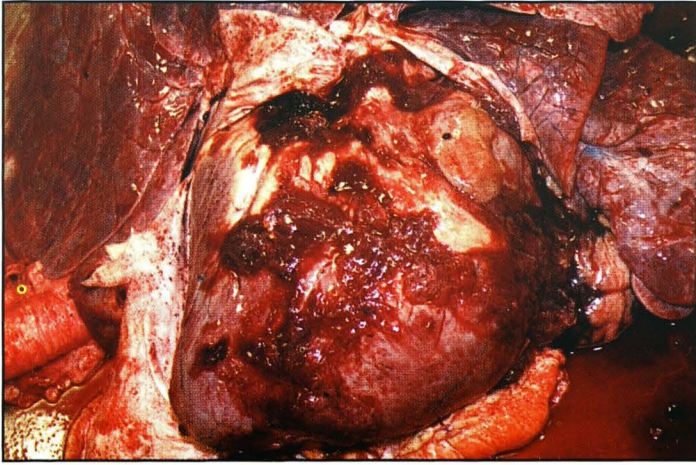
Comparisons between treatment groups were made using DC 305 data and appropriate non-Gaussian and Gaussian statistical analyses depending on data set distributions with significance set at  $P \leq 0.05$ . Specific comparisons were made regarding survival in the herd after diagnosis and mature equivalent (ME) 305-day lactational yield between the 2 treatment groups. Furthermore, production and survival statistics were compared between the 2 treatment groups and age-matched herd-mates by using the population of cattle that had become 48 months of age during the calendar year 2012 ( $n = 749$ ), and that had not been treated for presumptive idiopathic pericardial effusion.

### Results

A total of 125 cows were presumptively diagnosed with idiopathic hemorrhagic pericardial effusion based upon clinical signs over the 34-month period in question. Of this total, 44 individuals were either sold ( $n = 38$ ) on the basis of culling criteria or died ( $n = 6$ ) without treatment, but 81 cows were treated with 1 of the 2 therapeutic protocols described. The 6 cattle that died without treatment underwent either field necropsy examination or full necropsy at the University of Wisconsin School of Veterinary Medicine, where examinations confirmed the characteristic appearance of an enlarged heart with extensive, diffuse proliferative epicarditis (Figure 1). In the 1 animal that underwent a complete gross and histopathologic postmortem examination, there was evidence of lymphoblastic infiltration of the proliferative fibrovascular epicardial tissue consistent with a diagnosis of lymphosarcoma.

A total of 51 non-pregnant cattle received dexamethasone (median age 49 months), and 30 pregnant or possibly pregnant individuals ( $\geq 75$  days gestation) received isofluprednone acetate (median age 47 months).





**Figure 1.** Opened pericardial sac from first-lactation cow necropsied following death associated with idiopathic pericardial effusion. Specimen shows typical gross findings of proliferative epicardial fibrosis admixed with fibrin and hemorrhage that is firmly adherent to the heart surface. Histopathologic examination of the heart demonstrated the presence of atypical neoplastic lymphoblasts within the epicardial tissue.

Median days-in-milk (DIM) for all cattle in the 2 groups at the time of diagnosis was 262 days (181 days for non-pregnant cattle, 316 days for pregnant cattle). Mean ME305 for cattle receiving dexamethasone was  $27,792 \pm 6,096$  lb ( $12,633 \pm 2,771$  kg), compared to  $30,970 \pm 4,325$  lb ( $14,077 \pm 1,966$  kg) in the group receiving isofluprednone, for the lactation at the time of diagnosis. For age-matched controls in the herd that had not been presumptively diagnosed with idiopathic pericardial effusion, mean ME305 was  $31,643$  lb ( $14,383$  kg) for pregnant cattle, and  $28,127$  lb ( $12,785$  kg) for non-pregnant cattle. Of the non-pregnant cattle treated with dexamethasone, 6 were still alive at the time of manuscript preparation, 3 died spontaneously, and 42 were sold/culled; 39 died during the lactation at the time of diagnosis and 3 in the subsequent lactation. Mean survival in the herd following diagnosis was  $131 \pm 201$  days in this group. Of cattle treated with isofluprednone acetate, 1 was still alive in the herd at the time of manuscript preparation, having calved once since; 9 calved once more and were sold in the next lactation; and 20 cows were sold/culled during that current lactation. Mean survival in the herd after diagnosis was  $114 \pm 111$  days in this group. For the age-matched controls without a presumptive diagnosis of pericardial idiopathic hemorrhage in 2012, 220 of 428 non-pregnant cattle and 259 of 321 pregnant cattle are still in the herd as of August 2014. There were no significant differences in survival to the end of the current lactation following diagnosis

in the 2 treatment groups, nor in ME305 values for either group in the lactation at diagnosis. A comparison of culling rates between the dexamethasone-treated group and the isofluprednone-treated group for either the 12-month or 24-month periods following diagnosis showed no statistically significant differences. Although there was no difference in lactation yield between the 2 treatment groups and the age-matched controls, survival rates were significantly longer ( $P < 0.001$ ) for cattle without a diagnosis of idiopathic pericardial hemorrhage.

## Discussion

These data suggest that idiopathic pericardial effusion can be treated on-farm without the need for pericardial drainage. In sharp contrast to other forms of cardiac disease in cattle, and despite being associated with clinical signs of congestive heart failure at the time of diagnosis, our findings suggest that treatment with steroids may confer some short-term survival benefit. Affected individuals treated with either isofluprednone acetate or dexamethasone may survive to the end of the current lactation or, in some cases, beyond. There does not appear to be a significant difference in outcome variables, specifically survival times and lactation yield during the lactation in question, between the 2 treatment groups in the present study. However, with particular reference to milk production, it is important to point out that the 2 treatment groups were not directly comparable, as the isofluprednone-treated group were later in lactation (median DIM 316) compared to the dexamethasone-treated group (median DIM 181). As a result, it is possible that the impact on production could have been more deleterious to overall lactation yield for the dexamethasone-treated group, but there was no significant difference in ME 305 values between the 2 groups.

Mechanistic explanation for benefits of corticosteroids in the treatment of this condition is somewhat hypothetical because the condition is idiopathic. However, it is reasonable to suggest that in the event of neoplastic epicardial involvement, as has been previously reported,<sup>3,4,6</sup> a chemotherapeutic benefit might be anticipated. Furthermore, histopathologic description of the epicardial surface of non-neoplastic cases describes a fibrodysplastic lymphoproliferative infiltrate<sup>6</sup> that would likely benefit from conventional anti-inflammatory therapy. In the authors' experience, treating hospitalized patients with this condition with non-steroidal anti-inflammatory drugs, rather than corticosteroids, has been disappointing when medical treatment was not combined with pericardial drainage; this is what led us to steroidal anti-inflammatory therapy on-farm.

Veterinarians should understand that although both dexamethasone and isofluprednone acetate are ap-



proved drugs in dairy cattle, they were used extralabel in this study. Such treatment decisions carry with them the legal responsibility to ensure residue avoidance on-farm without reliance on product insert recommendations for milk and meat withholds.

The statistical comparisons of milk yield and survival between cattle treated for presumptive idiopathic pericardial effusion and age-matched herd mates without the diagnosis revealed interesting but conflicting results. Although milk yield for the lactation in question neither differed between the 2 treatment groups nor between them and cattle without the diagnosis, there were significant differences in survival time. Greater than half of the age-matched cohort (220/428 non-pregnant and 259/321 pregnant) were alive 24 months later, compared to only 6 of 51 (non-pregnant) and 1 of 30 (pregnant) in the 2 treatment groups. Such a difference between production and survival data might suggest that conscious culling decisions were being made based upon the presumptive diagnosis of idiopathic pericardial effusion in the medium and long term, but that short-term production can still be maintained with the condition.

Based upon results of treatment of cattle pregnant at the time of diagnosis, it is also possible that affected cattle can successfully carry a fetus to term if isofluprednone acetate is the chosen steroid. Recognizing that the diagnosis of idiopathic pericardial effusion in most cattle in the current study is presumptive based on clinical signs and not on ultrasonographic findings or cytologic analysis, clinician experience, along with ultrasound examination and necropsy confirmation in some cattle, provided reassurance in the accuracy of diagnosis and gave confidence that animals in the prospective treatment study did indeed have this form of heart disease.

It is, of course, noteworthy that the present study did not include a true negative control group, specifically cattle with signs of cardiac tamponade suggestive of idiopathic pericardial hemorrhage that were allowed to progress to either death or culling, to which we could compare to treatment groups. Negative control groups are difficult to establish and maintain on commercial dairies, but the lack of a control group undoubtedly lessens the scientific impact of our conclusions. Prior experience on the farm by the investigators led to the decision to either treat with corticosteroids or cull; our empiric opinion was that if untreated, affected cows would have productive survival times measured in only a few days. We have no experience of spontaneous recovery in untreated cases, but cannot rule it out. On the study farm there was a group of cattle (n = 38) that were culled without any attempted treatment. The reason for culling was not driven by the perceived severity of cardiac disease, but instead by more common culling influences such as stage of lactation, Johne's status, and other prior

medical history (e.g., lameness, mastitis). The absence of these cows from either treatment group could have affected the measured outcome variables. Specifically, one would anticipate that concurrent illness or negative health influences could have reduced the potential benefit of corticosteroid treatment in these cows.

It is interesting that this herd has such a large number of cows with a condition previously documented only sporadically in herds. These authors are currently investigating a possible association between idiopathic pericardial effusion and bovine leucosis virus (BLV) infection in this herd, a possible etiologic link cited in the literature.<sup>3,6</sup> Management practices have already been implemented to limit possible spread of the retrovirus, but the impact of these measures is not known at this time. As our understanding of this condition develops, it will be important to better elucidate the possible link between both BLV status and cardiac lymphosarcoma, particularly if the association with neoplasia turns out to be strong, perhaps even rising to the level of cause and effect. If the latter is proven, it would place a rather different ethical perspective on culling decisions for cattle with idiopathic pericardial effusion since it would be known that the cow was suffering from lymphosarcoma.

Previous reports on this condition have emphasized treatment by pericardial drainage and medical therapy. The impetus for the present study was the observation that response to treatment with steroids alone seemed profound in several cows treated for idiopathic pericardial effusion at the University of Wisconsin School of Veterinary Medicine Teaching Hospital. Because pericardial drainage is extremely unlikely to be utilized as an on-farm treatment procedure, and because it is commonplace for cows with fulminant signs of cardiac disease to be culled or sold, prospective or retrospective studies examining production or survival data in dairy cattle diagnosed with other forms of cardiac disease, such as endocarditis, traumatic pericarditis or lymphosarcoma, are not readily available in the peer-reviewed literature.

## Conclusions

Based on this study, we conclude that treatment of idiopathic pericardial effusion can be successful with corticosteroid therapy alone. The treatment approach adopted on this dairy is practical, affordable, and carries only short-lived residue implications for cows that deteriorate or respond poorly.

## Endnote

<sup>a</sup>Predef 2X Sterile Aqueous Suspension, Zoetis Animal Health, New York, NY

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