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Bovine Postparturient Hemoglobinuria: A Review of the Literature

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SUMMARY

Predisposing causes of bovine postparturient hemoglobinuria are summarized along with suspected pathogeneses, clinical signs, laboratory findings, clinical management and early experimentation.

RÉSUMÉ

Une revue de la littérature relative à l'hémoglobinurie puerpérale bovine

Les auteurs présentent un résumé des causes prédisposantes, de la pathogénèse probable, des signes cliniques, des résultats d'épreuves de laboratoire, de l'approche clinique et des premières expériences concernant l'hémoglobinurie puerpérale bovine.

HISTORY

In the latter half of the nineteenth century, hemoglobinuria was reported in Scottish cattle following parturition (1). Similar descriptions from Africa, Asia, Australia, Europe and North America followed under a variety of different names. Parturient hemoglobinemia or hemoglobinuria (2), red water (3) and nutritional hemoglobinuria (4) have been used synonymously with postparturient hemoglobinuria (PPH) which is the designation favored in many publications (5).

INCIDENCE AND OCCURRENCE

As described in North America, postparturient hemoglobinuria is a sporadic disease of multiparous, high producing dairy cattle characterized by intravascular hemolysis, hemoglobinuria and anemia. The incidence of the disease in the total cattle population is very low with a case fatality rate ranging from 10 to 50% (2). Occasionally, farms with a particularly high incidence may be encountered but usually only one or two cases are clinically apparent at one time (6,7). In 39 cases of PPH, an interval of 11 to 42 days was reported between parturition and the onset of clinical signs (2). Similarly, 19 of 27 cases documented in Australia occurred within 30 days of calving (8). The occurrence of this syndrome in bulls, antepartum cows, heifers less than two years old, or beef cows is unusual but has been reported (6,9). A disease with many similarities has been described in sheep (10), Egyptian and Indian buffaloes (11,12) and a goat (13).

The disease is usually seen in adult dairy cattle during their third to sixth lactation (5,14). Postparturient hemoglobinuria tends to occur during the winter months, especially when preceded by a dry growing season (15,16).

ETIOLOGY AND PATHOGENESIS

The pathogenesis of erythrocyte destruction leading to anemia and hemoglobinuria in PPH is unknown. In part, this is probably due to the number and diversity of etiological factors associated with the disease. Early investigators searched for bacterial hemolysins or blood parasites such as *Babesia* spp. as etiological agents (16). Animal transmission studies using blood, urine and intestinal filtrates have been unsuccessful. Subsequent papers concluded that PPH was neither infectious nor contagious based on negative serological and bacteriological evidence for pathogenic bacteria and failure to identify erythrocyte parasites (2,5,7,11,17,18).

A disease in Ontario known as "red water" was associated with several predisposing factors which included: a) recent parturition, b) heavy milk production, c) dietary phosphorus deficiency and d) consumption of turnips, rape, kale, green alfalfa and sugar beet pulp (3,9,19). In addition, many cows were hypophosphatemic (2,20,21).

Since the 1930's, the list of feeds associated with PPH (Table I) has expanded to include: a) sugar beet roots (mangels) and leaves, b) field crops such as green oats, perennial ryegrass, Egyptian clover and alfalfa and c) members of the genus *Brassica*, often referred to as cruciferous plants. In addition to their low phosphorus content ($< 0.4\%$ dry matter) or high calcium to phosphorus ratio ($> 2:1$), some feeds (e.g. rape and kale) in Table I contain hemolytic substances

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(31,32). Hemolytic saponins from sugar beets or alfalfa may interact with a low serum phosphorus concentration to produce PPH (6). It has also been postulated that phosphorus deficiency was a "necessary predisposing factor" and that feeding cruciferous plants precipitated the hemolytic crisis (17).

Copper deficiency has been suggested as a possible etiology of PPH by workers in New Zealand. Cattle from dairy farms with a high incidence of PPH had low levels of copper in serum and liver (33). A recent application of lime or molybdate fertilizer to grazing land was a feature common to these farms. Analysis of pasture samples revealed high concentrations of molybdenum and low levels of copper, especially during the months of highest disease incidence (July, August, September and October). Since molybdenum may interfere with copper absorption from the gut, the copper-deficient status of the cattle may have been induced by the application of excessive molybdenum to pastures (34,35). Parenteral administration of copper has been effectual in dairy herds with prior histories of PPH (36,37). The incidence of PPH was significantly lower (5.18% versus 25.51%; $P \leq 0.01$) in cows treated with copper prior to calving. Futhermore, a top dressing of copper sulfate to pastures four months prior to calving was followed by an increase in pasture, blood and liver concentrations of copper and a marked decrease in the incidence of PPH. In New Zealand, hypophosphatemia was not a consistent finding in PPH.

CLINICAL SIGNS, DIAGNOSIS AND TREATMENT

Hemoglobinuria is often the premonitory clinical sign before anemia, depression, inappetence, or decreased milk production are observed (2). As the anemia develops, mucous membranes become pale and may become icteric. As the heart rate increases (80-130 beats/min), breathing becomes rapid and shallow. Affected cows are weak and often recumbent. Forced exercise at this time can be fatal. The feces may be firm, dry and bile-stained, or fetid and diarrheic. An elevated body temperature (up to 40° C) in the early stages and intense thirst are variable features.

TABLE I
CALCIUM AND PHOSPHORUS CONTENT OF FEEDS (22) ASSOCIATED WITH PPH

Feed	Ca[a]	P[a]	Reference(s)
Alfalfa (*Medicago sativa*)			2,9,6
aerial part, fresh	2.01	0.28	
Brussels Sprouts (*Brassica oleracea germmifera*)			23
heads, fresh	0.27	0.54	
Cabbage (*Brassica oleracea capitata*)			13,23
leaves, fresh	0.63	0.21	
whole, fresh	0.66	0.39	
Clover, Egyptian (*Trifolium alexandrium*)			11,18,27,28
aerial part, fresh	3.56	0.32	
Kale (*Brassica oleracea acephala*)			1,9,10,23
aerial part, fresh	1.61	0.51	
Oats (*Avena sativa*)			17,30
aerial part, fresh	0.28	0.31	
Rape (*Brassica* spp.)			9,10,18
aerial part, fresh	1.47	0.43	
Ryegrass, Perennial (*Lolium perenne*)			29
aerial part, fresh	0.53	0.37	
Sugar Beet (*Beta saccharifera*)			2,5,6,9,16,25,26
pulp, dehydrated	0.75	0.10	
aerial part, fresh	1.01	0.22	
roots (mangels)	0.24	0.24	
Turnip (*Brassica rapa*)			9,24
roots, fresh	0.56	0.28	
aerial part, fresh	2.92	0.51	

[a] Expressed as percent dry matter.

The acute disease (three to five days) can terminate in death or be followed by prolonged convalescence (two to eight weeks). Ketonuria and a depraved appetite may occur during recovery (14). Gangrene and sloughing of the extremities (digits, tail, ears and teats) are reported sequelae. Recovered animals regain their former body condition and milk production slowly.

The recommended treatment for PPH in North America includes: a) intravenous infusion of sodium acid-phosphate (60 g in 300 mL of water), b) 100 g of bone meal administered as a drench twice a day, c) transfusion of fresh blood as indicated and d) intravenous fluids to maintain hydration (2,14,38). Correction of any phosphorus deficiency or imbalance in the ration along with removal of incriminated feeds (Table I) may prevent additional cases. Because of inconsistent results with phosphate therapy and the copper-deficient status of affected cows, workers in New Zealand suggest parenteral copper (120 mg available copper per cow) as the preferred treatment (34).

LABORATORY FINDINGS

Hematologically, PPH has the features of an acute intravascular hemolytic anemia. The packed cell volume falls rapidly to its lowest level four to nine days after the onset of hemoglobinuria (2). The plasma, initially hemoglobinemic, becomes icteric as the destruction of erythrocytes progresses. Morphologically, the anemia is characterized by evidence of intensified erythrogenesis. Polychromasia, anisocytosis, macrocytosis, basophilic stippling, reticulocytosis and increased numbers of metarubricytes are commonly seen on stained blood films. Swollen erythrocytes with dimpled centers and thorn-apple shaped erythrocytes were described in 1940 (39) and may be comparable to echinocytes in the current nomenclature. Results for erythrocyte osmotic fragility have been conflicting. A period of increased erythrocyte osmotic fragility was reported immediately after parturition in a cow which subsequently developed PPH (40). Others have found normal erythrocyte osmotic fragility (8,19,35). A neutrophilic leukocytosis is often observed during the hemolytic crisis.

In addition to studies implicating a copper-molybdenum imbalance, Heinz bodies have been found consistently in the erythrocytes of New Zealand cattle with PPH. Surveys indicate that: a) the incidence of Heinz bodies is greater in PPH affected herds (29), b) the prevalence of Heinz body anemia is greater than the incidence of clinical hemoglobinuria (34) and c) the severity of Heinz body anemia seems to correlate with the degree of hypocupremia (35). Mechanisms for Heinz body formation as a result of copper deficiency are speculative. Heinz bodies are formed when irreversible oxidation causes precipitation of denatured hemoglobin. Superoxide dismutase, a copper metalloenzyme, is part of the erythrocyte's protective mechanism against oxidant stress. A copper deficiency would likely depress superoxide dismutase activity, compromise the erythrocyte's potential to withstand oxidative injury and cause Heinz body formation (38).

Urinalysis can be helpful in the diagnosis of PPH. Hemoglobinuria is the most remarkable clinical sign of PPH. Microscopic examination of the urine sediment is imperative to differentiate hematuria from hemoglobinuria. Ketones, bilirubin and protein can be expected in the urine depending on the course of the disease.

Most authors have reported very low levels of serum phosphorus (0.4-1.5 mg/dL) during the hemolytic crisis. In affected herds, lactating but clinically normal cows have been moderately hypophosphatemic (2-3 mg/dL); nonlactating cows usually have normal serum phosphorus concentrations (14). Serum calcium concentration is usually normal and total bilirubin levels parallel the intensity of clinical icterus (2,19).

EXPERIMENTATION

Attempts to reproduce the disease under experimental conditions have been successful. Hemoglobinuria was observed in three of ten cows fed an exclusive diet of rape over a period of two to four weeks (9). One of the affected animals was hypophosphatemic. Hemoglobinuria did not occur in a second experiment in which four cows were fed turnips. A diet of alfalfa hay and dried beet pulp fed to one cow for 32 months (three pregnancies) produced clinical signs of PPH 19 days after the third calving (40). Signs of phosphorus deficiency such as stiff gait, creaking joints and chewing on foreign objects were noted during the last 18 months of the study. A decreased erythrocyte count and hypophosphatemia were reported in four cows which were fed a ration of sugar beet leaves (6). Signs consistent with PPH were observed in three of the four cows. While able to duplicate the clinical signs of PPH, these investigators were unable to make definite conclusions because the number of test animals was inadequate and control animals were not included.

CONCLUSIONS

The papers from New Zealand are the most recently published material on PPH. The features of the disease in New Zealand present a definite contrast to the syndrome observed in North America (Table II). Postparturient hemoglobinuria in New Zealand is a herd problem usually affecting younger cows. Copper deficiency and Heinz body anemia, as features of PPH, have not been reported elsewhere. It is possible that the Heinz bodies and the copper-deficient status of affected cows have been overlooked by other investigators. However, it is also possible that the syndrome in New Zealand represents a separate disease entity.

In summary, PPH in North America is typified by acute intravascular hemolysis, hemoglobinuria, anemia, and hypophosphatemia. Postpartum, high-producing dairy cows in their third to sixth lactation are most commonly affected. Dietary phosphorus deficiency and/or rations containing cruciferous plants or beet products are suspected etiologies. The diagnosis of PPH can be made on the basis of the history, clinical and laboratory findings and after eliminating other causes of intravascular hemolysis. The pathogenesis of red cell destruction is unknown. Recent reports in human beings and laboratory animals associating severe hypophosphatemia with hemolytic anemia and with abnormalities in red cell metabolism suggest that a similar mechanism may be involved in PPH (41).

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TABLE II
COMPARATIVE FEATURES OF PPH IN NORTH AMERICA AND NEW ZEALAND

	North America	New Zealand
Incidence	sporadic	herd problem: up to 40% incidence
	mortality: 10-50%	mortality: occasional
Occurrence	high-producing, adult cows	younger cows
	3rd-6th lactation	1st and 2nd lactation
	2-4 weeks postpartum	2-4 weeks postpartum
	winter housing	ryegrass pasture
Suspected Etiology	phosphorus deficiency	copper deficiency
	cruciferous plants or beet products	induced by excessive molybdenum fertilization
Pathogenesis	unknown	diminished capacity of RBC to withstand oxidant stress
Clinical Signs	---------- Similar ----------	
Laboratory Findings	regenerative anemia	regenerative anemia
	hemoglobinuria	hemoglobinuria
	serum phosphorus: low	serum phosphorus: usually normal
		Heinz bodies
		low levels of serum and liver copper
Treatment	phosphate therapy	parenteral copper

REFERENCES

1. PENNY RHC. Post-parturient haemoglobinuria (haemoglobinaemia) in cattle. Vet Rec 1956; 68: 238-241.
2. MADSEN DE, NIELSEN HM. Parturient hemoglobinemia of dairy cows. J Am Vet Med Assoc 1939; 94: 577-586.
3. SCHOFIELD FW. Bovine hemoglobinuria associated with an intestinal infection caused by the *Cl. welchii*. In: Rep Ont Vet Coll 1933: 42-61.
4. HUNGERFORD TG. Diseases of livestock. Sidney: Angus and Robertson, 1970: 274.
5. FARQUHARSON J, SMITH KW. Post-parturient hemoglobinuria of cattle. J Am Vet Med Assoc 1938; 93: 37-39.
6. FREUDENBERG F. Untersuchungen uber die puerperale hamoglobinurie des rindes. DTW 1955; 62: 422-429.
7. UDALL DH. The practice of veterinary medicine. 6th ed. Ithaca: Udall DH, 1954: 287-289.
8. MULLINS JC, RAMSAY WR. Haemoglobinuria and anaemia associated with aphosphorosis. Aust Vet J 1959; 35: 140-147.
9. SCHOFIELD FW. Nonspecific hemoglobinuria and acute pulmonary emphysema of cattle as essential enterotoxemias. J Am Vet Med Assoc 1941; 96: 28-32.
10. STAMP JT, STEWART J. Haemolytic anaemia with jaundice in sheep. J Comp Pathol 1953; 63: 48-52.
11. AWAD FI, EL-LATIF K. The first record of a disease condition in Egyptian Buffalo simulating post-parturient haemoglobinuria. Vet Rec 1963; 75: 298-300.
12. NAGPAL M, GAUTAM OP, GULATI RL. Haemoglobinuria in buffaloes. Indian Vet J 1968; 45: 1048-1959.
13. SETTY D, NARAYANA K. A case of non-febrile haemoglobinuria in a she goat. Indian Vet J 1975; 52: 149.
14. BLOOD DC, HENDERSON JA, RADOSTITS OM. Veterinary medicine. 5th ed. Philadelphia: Lea & Febiger, 1979: 862-863.
15. TARR A. A note on the occurrence of puerperal haemoglobinaemia of cattle in South Africa. J S Afr Vet Assoc 1947; 188: 167-168.
16. HJARRE A. Die puerperale hamoglobinamie des rindes. Acta Pathol Microbiol Scand 130; (Suppl) 7.
17. PARKINSON B, SUTHERLAND AK. Post-parturient haemoglobinuria of dairy cows. Aust Vet J 1954; 30: 232-236.
18. MALIK K, GAUTAM OP. Haemoglobinuria in buffaloes. J Res HAU 1971; 1: 109-113.
19. SCHOFIELD FW. Further studies in bovine hemoglobinuria (red water), In: Rep Ont Vet Coll 1938: 35-39.
20. SJOBERG K. Blodets Kemiska sammansattning. II. Vid puerperal hamoglobinemi hos not. Svenk Vet Tidskr 1938; 43: 335-345.
21. MADSEN DE, NIELSEN HM. The relationship of parturient hemoglobinemia of dairy cows to aphosphorosis. N Am Vet 1940; 21: 81-89.
22. NATIONAL ACADEMY OF SCIENCES —National Research Council. Atlas of nutritional data on United States and Canadian feeds. Washington DC, 1971.
23. CLEGG FG, EVANS RK. Haemoglobinaemia of cattle associated with the feeding of Brassicae species. Vet Rec 1962; 74: 1169-1176.
24. WALLACE WR. Parturient hemoglobinuria of bovines. Vet Rec 1926; 6: 1035-1038.
25. GLAWISCHNIG E. Zur behandlung der peurperalen hamoglobinurie des rindes. Wien Tieraerztl Mschr 1961; 48: 589-594.
26. BARRIERE G. Puerperal haemoglobinaemia in cows. Encycl Vet Period 1964; 21: 374-376.
27. EL-LATIF K, AWAD FI. Haemoglobinuria of buffaloes associated with excessive feeding of *Tripholium alexandrinum* (berseem). J Vet Sci UAR 1964; 1: 69-74.
28. DHILLON KS, SINGH J, BAJWA R. Treatment of haemoglobinuria due to molybdenum-induced phosphorus deficiency in buffaloes: A note. Indian J Anim Sci 1972; 42: 996-998.
29. MARTINOVICH D, WOODHOUSE DA. Post-parturient haemoglobinuria in cattle: A Heinz body haemolytic anaemia. N Z Vet J 1971; 19: 259-263.
30. RAINEY JW. An acute case of parturient haemoglobinuria. Aust Vet J 1945; 21: 73-74.
31. CHASE LE. Mineral supplementation of various roughage diets for milking cows. In: Proc Cornell Nutr Conf Feed Manufacturers 1976: 34-39.
32. SMITH RH. S-methylcysteine sulphoxide, the Brassica anaemia factor. Vet Sci Comm 1978; 2: 47-61.
33. SMITH B, COUP MR. Hypocuprosis: A clinical investigation of dairy herds in Northland. N Z Vet J 1973; 21: 252-258.
34. SMITH B. Copper and molybdenum imbalance in relationship to post-paturient haemoglobinuria in cattle. N Z Vet J 1973; 21: 240.
35. GARDNER DE, MARTINOVICH D, WOODHOUSE DA. Haematological and biochemical findings in bovine post-parturient haemoglobinuria and the accompanying Heinz-body anaemia. N Z Vet J 1976; 24: 117-122.
36. SMITH B. The effects of copper supplementation on stock health and production. 1. Field investigations into the effects of copper supplementation on stock health in dairy herds with a history of post-parturient haemoglobinuria. N Z Vet J 1975; 23: 73-77.
37. SMITH B, WOODHOUSE DA, FRASER AJ. The effects of copper supplementation on stock health and production. 2. The effect of parenteral copper on incidence of disease, haematological changes and blood copper levels in a dairy herd with hypocuprosis. N Z Vet J 1975; 23: 109-112.
38. CAPLE IW. Post-parturient hemoglobinuria. In: Howard JL, ed. Current veterinary therapy, food animal practice. Philadelphia: WB Saunders, 1981: 355-357.
39. GEERTSEMA G. Een toxische haemoglobinaemie en haemoglobinurie bij het rund in Drenthe. Tijdschr Diergeneesk 1940; 64: 176-185.
40. MADSEN DE, NIELSEN HM. The production of parturient hemoglobinemia by low phosphorus intake. J Am Vet Med Assoc 1944; 105: 22-25.
41. KNOCHEL JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 1977; 137: 203-220.