Failure of Passive Transfer: Risk Factors and Effects on Lifetime Performance

Louis J. Perino, *DVM, PhD*
Great Plains Veterinary Educational Center
University of Nebraska - Lincoln
Clay Center, Nebraska 68933

Thomas E. Wittum, *PhD*
Department of Veterinary Preventive Medicine
The Ohio State University
Columbus Ohio 43210

Gary S. Ross, *DVM*
Roman L. Hruska U.S. Meat Animal Research Center
United States Department of Agriculture - Agricultural Research Service
Clay Center, NE 68933

R. J. Sutherland, *BVSc*
Vet Path Services
North Ryde NSW 2113
Australia

Neal E. Woollen, *DVM, PhD*
Pathology Division
U.S. Army Medical Research Institute of Infectious Diseases
Ft. Detrick
Fredrick, MD 21702

Abstract

Blood samples were collected from the first calves of 48 four-breed composite cows and postpartum hours 0 and 24 (group 1) and heparinized blood samples were collected from the 263 calves born to 203 cows at postpartum hours 10 (±2) and 24 (±2) (group 2). For group 1, at birth, the mean serum concentrations of IgG and protein were 131 mg/dl and 3.9 g/dl, respectively, and serum activity of GGT was 28 IU/L. After 24 hours, these values had increased to 1,400 mg/dl, 5.0 g/dl, and 734 IU/L, respectively. The calves with failure of passive transfer (FPT) had a 9.5 times greater risk of becoming classified as sick prior to weaning compared with calves with partial FPT and normal passive transfer ($P=0.0004$). The retrospective sensitivity and specificity of a cut-off value of 200 IU of GGT/L of serum for diagnosing FPT were 80 and 97%, respectively. The retrospective sensitivity and specificity of a cut-off value of 4.2 g of protein/dl of serum for diagnosing FPT were 80 and 100%, respectively. The Kappa values for diagnosis of FPT using serum concentrations of IgG vs serum activity of GGT, IgG vs protein, and GGT vs protein were 0.72, 0.86, and 0.79, respectively. For group 2, the prospective sensitivity and specificity of a cut-off value of 4.8 g of protein/dl of plasma, measured at 10 hours, for diagnosing FPT at 10 hours were 78 and 94%, and for diagnosing FPT at 24 hours were 88 and 73%, respectively. Colostrum supplement administered to calves with low PP concentration at 10 hours had no effect on PP or IgG values at 24 hours or on preweaning morbidity and mortality. Total PP and IgG concentrations were similar for single and twin calves at 10 hours, but IgG values at 24 hours were higher ($P < 0.01$) in twin calves. Calves born to dams that had dystocia had consistently lower mean PP and IgG values. However, observed differences were small, and after adjustment for other important factors, these differences were not significant. Calves of dams diagnosed with mastitis had lower mean PP and IgG values at 10 ($P < 0.05$) and 24 ($P < 0.01$) hours. Results of logistic regression analysis indicated that IgG concentration at 24 hours was associated with morbidity and mortality outcomes prior to weaning. Calves classified as having inadequate IgG concentration at 24 hours were at greater risk of mortality from birth to weaning (odds ratio [OR] = 5.4), morbidity in the first 28 days of life (OR = 6.4), and morbidity from birth to weaning (OR = 3.2), compared with calves classified as having adequate IgG concentration at 24 hours. Calves classified as having marginal IgG concentration at 24 hours also had a greater risk of preweaning morbidity (OR = 3.6), compared with calves that had adequate IgG concentration. Calf PP concentration at 24 hours was associated with morbidity in the feedlot. Calves classified as having inadequate PP concentration were at greater risk of feedlot morbidity (OR = 3.0) and feedlot respiratory tract morbidity (OR = 3.1). The lowest calf weaning weights were observed among calves classified as having inadequate IgG or PP concentration at 24 hours. However, multivariable modeling indicated that the effect of passive transfer on weaning weight was indirect through its effect on neonatal morbidity. Morbidity during the first 28 days of life resulted in a 16-kg lower expected weaning weight. Similar to weaning weight, passive immune status at 24 hours was not directly associated with feedlot growth rate. There was, however, an indirect association through the effect of PP concentration at 24 hours on morbidity in the feedlot. Adjusted mean MDG for calves with respiratory tract morbidity while in the feedlot was 0.04 kg less than that for noncases. The magnitude of the effects

of passive immune status on the health and growth performance of calves in this study emphasize the importance of producer management strategies to identify calves at risk of failing to acquire passive immunity and to provide appropriate intervention.

Introduction

It has been well established that the passive transfer of immunoglobulin (Ig) in colostrum is the most important source of immunologic protection available to neonatal calves. Inadequate intake and absorption of maternal antibody has been associated with increased risk of disease and death in neonatal calves.[1,2,3,4,5] However, much of the work investigating these relations has involved intensively managed dairy calves. Dairy calves are generally reared in an environment considerably different from that experienced by most beef calves raised in range production environments. The different management systems might well result in differences in the degree of pathogen challenge, opportunity for exposure to pathogens, and relative importance of specific infective agents. As a result, observed associations between passive immune status and health events may not be of the same magnitude for beef and dairy calves. Reports of passive immunity and subsequent health in beef calves exist,[4] but are far from comprehensive.

In addition, relations between passive immunity and subsequent growth and production of dairy heifers have been reported.[5,6] However, little has been reported about the relations between passive immune status and growth rates of beef calves.

Several methods of detecting failure of passive transfer (FPT) have been described.[7] Direct measurement of serum concentrations of IgG usually is accomplished using single radial immunodiffusion. Other indirect indicators of serum Ig concentration include zinc sulfate turbidity, glutaraldehyde clumping, sodium sulfite turbidity, and refractometry. Previous studies have indicated that protein concentration in serum or plasma is correlated to serum Ig concentration in neonatal calves.[8,9] Although subject to artifacts, plasma or serum protein concentration can be determined quickly and inexpensively.

Activity of γ- glutamyltransferase (GGT) in colostrum has been reported to be high in human beings, cattle,[11,12] and sheep.[13] In cattle,[11,12] sheep,[13] and dogs,[14] but not horses,[15] serum activity of GGT is high in neonates that consumed colostrum.

Increasing calf survivability through reducing FPT is accomplished by identifying and minimizing factors contributing to FPT and inexpensively identifying calves with FPT early in life, then treating them to lessen the effect of FPT. Colostrum substitutes and supplements are available for use in calves. There are few reports of clinical efficacy in refereed literature.

The objectives of the studies reported here were (1) to characterize the activity of serum GGT in newborn calves before and after suckling and to explore the usefulness of serum GGT and serum or plasma protein (PP) as indicators of FPT in calves; (2) to identify important predictors of calf PP and IgG concentrations at 10 and 24 hours; (3) to determine the effects of a colostrum supplement, administered at 10 hours, on calves with low PP concentration; (4) to quantify the effect of passive immune status at 24 hours, as measured by PP or serum IgG concentration, on pre- and postweaning health and growth performance of calves raised in a typical beef-calf production environment.

Materials and Methods

Animals

Group 1: Blood samples were collected from the first calves of 48 four-breed composite cows (one-fourth Red Poll, one-fourth Hereford, one-fourth Pinzgauer, one-fourth Angus) at the time of birth and at 1 day of age. Serum was harvested from the blood, frozen, and stored for later assay.

At birth, all calves were given rotavirus and coronavirus vaccines orally, and their navels were treated with iodine. At approximately 60 days of age, and 3 weeks before weaning (approximately 5 months of age), the calves were vaccinated with multivalent clostridial and leptospiral vaccines. A modified-live virus vaccine containing infectious bovine rhinotracheitis and bovine virus diarrhea viruses also was given 3 weeks before weaning.

Group 2: Heparinized blood samples were collected from the 263 calves born to 203 cows. The crossbred dams and calves represented multiple beef and dairy breeds and were part of a herd selected for a high rate of multiple births. The dairy breed influence in this population is greater than commonly seen in beef herds. Cows were managed in a beef production setting. Cows in this herd are bred to have their first calf at the age of 2.5 years. All cows having twins, and any cow or calf that had perinatal complications, were moved to a barn for care and observation. Any birth that required assistance was considered to be a dystocia. Dam body condition score (BCS) at calving was recorded, using an ordinal scale of 1 to 9, as described.[16] Development of clinical mastitis was determined by routine examination of cow, udder, and calf appearance by trained animal caretakers and was confirmed by a positive California mastitis test result. Additionally, if any cow was restrained to assist the calf in suckling, the udder and milk were examined. Development of clinical mastitis in the dam at any time during lactation was considered to represent subclinical infection present at parturition.

All calves were identified, weighed, and vaccinated orally against rotavirus and coronavirus infections at birth. All twin calves were reared by their dam. Calves were maintained in an extensively managed range-production environment until they were weaned at a mean age of 163 days. At weaning, the calves went directly into a feedlot. At approximately 3 weeks prior to weaning, and again at feedlot entry, the calves were vaccinated (modified-live virus) against infectious bovine rhinotracheitis virus and bovine viral diarrhea virus infections. Most male calves in the study population were nonsurgically castrated at approximately 200 days of age.

Blood samples were collected at postpartum hours 10 (±2) and 24 (±2). The 10-hour samples were used to identify calves with low PP concentration prior to gastrointestinal tract closure. Blood was collected at 24 hours to evaluate the final status of passive Ig transfer.

Plasma was immediately harvested from the 10-hour blood sample and protein content was determined by refractometry (temperature corrected clinical refractometer, protein scale 0 to 12 g/dl). Calves with less than 4.8 g of protein/dl of plasma were considered to be at risk for FPT and were assigned to either a treatment or control group, using a previously determined random order. Treatment consisted of 1 dose (454 g) of a commercial colostrum supplement (Colostrix, Fisons Animal Health, Minneapolis, Minnesota), containing 30 g of bovine IgG, prepared according to label directions and administered by esophageal feeder. Plasma was harvested from the 10- and 24-hour blood samples, frozen, and stored for later assay.

Immunoglobulin, protein, and GGT determinations

Concentration of IgG was determined by use of a commercial radial immunodiffusion kit (RID Kits, VMRD, Pullman, Washington). The upper and lower limits of detection were 3,300 and 412 mg/dl, respectively. Serum total protein value was assessed with a refractometer (temperature corrected clinical refractometer, protein scale 0 to 12 g/dl). Activity of GGT in serum was measured by automated spectrophotometry, using a commercially available kit (GGT reagent 44074, Ciba Corning Diagnostics Corp, Oberlin, Ohio). Serum IgG concentration at 24 hours was classified as adequate (> 1,600 mg/dl), marginal (800 to 1,600 mg/dl), or inadequate (< 800 mg/dl). Plasma protein values were determined, using a refractometer. Calf PP concentration at 24 hours was classified as adequate (≥ 4.8 g/dl) or inadequate (< 4.8 g/dl).

Health Performance

Morbidity and mortality events in the study population were observed and recorded by experienced field personnel under veterinary supervision. Specific outcomes of interest included morbidity during the first 28 days of life (neonatal morbidity) or at any time from birth to weaning (preweaning morbidity). Preweaning mortality included any calf death prior to weaning. Feedlot morbidity included any morbidity observed during the postweaning feeding period, whereas feedlot respiratory morbidity included only calves diagnosed with respiratory tract disease. These were identified by experienced pen riders on the basis of subjective criteria. Calf mortality was zero in the study population while they were in the feedlot. Cases of traumatic injury were assumed to be random events and were not included as cases for any of the outcomes.

Growth Performance

In group 2, weaning weight was used as the measure of calf growth performance prior to weaning. Actual data were used to adjust weaning weights for the effects of calf age, sex, and age of dam. Mean daily gain (MDG), from weaning to a mean 242 days on feed, was used to assess postweaning calf growth. Attrition attributable to preweaning death loss and exit from the study population early in the feeding period resulted in 234 observations available for the feedlot health and performance outcomes.

Statistics

For the Ig, protein, and GGT values of group 1, correlation coefficient, means, percentages, and standard deviation were generated with a commercial microcomputer spreadsheet program (Lotus Development Corp, Cambridge, Massachusetts). Mantel-Haenszel χ^2, relative risk, and Kappa values were calculated using a public-domain microcomputer epidemiologic statistic program (USD Inc, Stone Mountain, Georgia).

For group 2, individual animal factors investigated for their association with PP and IgG concentrations included calf gender, birth date, birth weight, type of birth (single or twin), age of the dam, dam BCS at calving, and mastitis in the dam. Independent variables were initially examined for unadjusted bivariate associations with PP and IgG concentrations using ANOVA and simple linear regression procedures. Variables found to be associated ($P < 0.10$) with at least 1 of the outcomes were included in a final analysis of covariance model to identify their adjusted effects. Potential interactions were tested and removed from the final model if found to be nonsignificant. Pairwise comparisons were accomplished using the Tukey-Kramer method. Mean serum IgG and PP concentrations among cases and noncases were compared, using Student's t-test. The adjusted effects of serum IgG and PP values at 24 hours on morbidity and mortality outcomes were determined, using the multiple logistic regression model.[17] Models were developed by entering independent variables into

the model in stepwise manner. Criteria to enter or leave the model were set at $P = 0.05$ assessed using the maximal likelihood ratio χ^2 statistic. Potential two-way interaction was assessed at each step of the model building process. A similar model building procedure was used to develop ANOVA models of calf growth performance outcomes.

Results

For group 1, paired serum samples were obtained from 48 calves. At birth, the mean serum concentrations of IgG and protein were 131 mg/dl and 3.9 g/dl, respectively, and serum activity of GGT was 28 IU/L. After 24 hours, these values had increased to 1,400 mg/dl, 5.0 g/dl, and 734 IU/L, respectively. For IgG, averages at birth and 24 hours include 14 and 8 calves, respectively, with serum IgG concentrations < 412 mg/dl for which 411 mg/dl was used to determine the mean. Serum IgG concentrations, serum protein concentrations, and serum activity of GGT were related. The correlation coefficient between IgG and GGT was 0.41. The correlation coefficient between IgG and protein was 0.77.

Calves were classified as having FPT, partial FPT, and normal passive transfer, on the basis of concentration of serum IgG detected by radial immunodiffusion.[7] Twenty-one percent of calves had FPT (Table 1). Significant differences were detected in the morbidity between calves classified as having FPT, partial FPT, and normal passive transfer (Table 2). The calves with FPT had a 9.5 times greater risk of becoming classified as sick prior to weaning compared with calves with partial FPT and normal passive transfer ($P=0.0004$). The causes of morbidity were variable (Table 2).

Table 1. Number of calves and mean (±SD) serum IgG, γ- glutamyltransferase (GGT), and total protein (TSP) values at 24 hours after birth for calves classified as having failure of passive transfer (FPT), partial failure of passive transfer (PFPT), and normal passive transfer of immunity.

Variables	FPT*	PFPT†	Normal‡
No. calves	10	18	20
Mean (±SD) IgG mg/dl	449.0§ (91.0)	1,272.0 (226.0)	1,990.0 (214.0)
Mean (±SD) GGT IU/L	154.0 (186.0)	706.0 (466.0)	1,049.0 (641.0)
Mean (±SD) TSP g/dl	4.0 (0.4)	5.0 (0.4)	5.5 (0.4)

* < 800 mg IgG/dl; † = 800-1600 mg IgG/dl; ‡ > 1600 mg IgG/dl.
§ Includes 8 calves with IgG concentrations < 412 mg/dl for which 411 mg/dl was used to determine the mean.

The retrospective sensitivity and specificity of a cut-off value of 200 IU of GGT/L of serum for diagnosing FPT were 80 and 97%, respectively. The retrospective sensitivity and specificity of a cut-off value of 4.2 g of protein/dl of serum for diagnosing FPT were 80 and 100%, respectively. The Kappa values for diagnosis of FPT using serum concentrations of IgG vs serum activity of GGT, IgG vs protein, and GGT vs protein were 0.72, 0.86, and 0.79, respectively.

Table 2. Clinical diagnoses in sick calves classified as having failure of passive transfer (FPT), partial failure of passive transfer (PFPT), and normal passive transfer of immunity at 24 hours after birth.

DIAGNOSIS	FPT	PFPT	Normal
Diarrhea	2	0	1
Keratoconjunctivitis	1	0	0
Arthritis	1	0	0
Pneumonia	1	0	0
Omphalophlebitis	0	0	1
TOTAL SICK	5	0	2
TOTAL AT RISK	10	18	20

See Table 1 for key.

For group 2, mean PP and IgG concentrations at 10 and 24 hours (Table 3), along with additional descriptive statistics for the study population were determined (Table 4). When results of the bivariate analysis were evaluated, calf gender, dam BCS, and calf birth weight were not associated with PP or IgG concentration and were not considered in the multivariable analysis. Analysis of variance results and least square means for the remaining variables were summarized (Table 5).

Table 3. Descriptive statistics for plasma protein (PP; g/dl), IgG (mg/dl), day born in calving season, and birth weight (kg).

Variable	Mean	SD	Minimum	Maximum
PP (10 h)	5.2	1.0	2.9	7.9
PP (24 h)	6.0	1.2	3.6	8.9
IgG (10 h*)	1,350	1,189	0	3,871
IgG (24 h*)	2,148	1,153	0	3,297
Birth date†	21	14.1	1	63
Birth weight	45	7.5	26	68

* Samples with IgG < the lowest standard concentration (412 mg/dl) were assigned a value of 411 mg/dl.
† Birth date relative to beginning of calving season for the study population.

Total PP and IgG concentrations were similar for single and twin calves at 10 hours, but IgG values at 24 hours were higher ($P < 0.01$) in twin calves. Calves born to dams that had dystocia had consistently lower mean PP and IgG values (Table 4). However, observed differences were small, and after adjustment for other important factors, these differences were not significant (Table 5). Calves of dams diagnosed with mastitis had lower mean PP and IgG values at 10 ($P < 0.05$) and 24

Table 4. Unadjusted means (SD) for PP (g/dl), and IgG (mg/dl) at 10 and 24 hours.

Variable	N	PP (10 h)	PP (24 h)	IgG (10 h)	IgG (24 h)
Type of birth					
Single	143	5.2[a] (1.1)	5.8[a] (1.2)	1,340[a] (1230)	1,870[a] (1224)
Twin	120	5.2[a] (1.0)	6.2[b] (1.1)	1,368[a] (1149)	2,471[b] (978)
Parturition type					
Unassisted	177	5.3[a] (1.0)	6.0[a] (1.2)	1,421[a] (1217)	2,226[a] (1149)
Assisted	86	5.0[b] (1.0)	5.8[a] (1.2)	1,203[a] (1106)	2,014[a] (1135)
Mastitis in dam					
No	240	5.3[a] (1.0)	6.1[a] (1.1)	1,425[a] (1198)	2,253[a] (1115)
Yes	23	4.6[b] (0.7)	5.0[b] (0.9)	553[b] (716)	1,044[b] (962)
Calf gender					
Bull	140	5.1[a] (1.0)	6.0[a] (1.1)	1,223[a] (1183)	2,145[a] (1149)
Heifer	123	5.3[a] (1.0)	6.0[a] (1.2)	1,499[a] (1176)	2,170[a] (1150)
Age of dam					
2.5/3 yr	66	5.0[a] (0.9)	5.8[a] (1.1)	1,334[a] (1210)	1,924[a] (1115)
3.5/4 yr	73	5.2[a] (1.0)	6.0[a] (1.2)	1,434[a] (1124)	2,304[a] (1138)
4.5/5 yr	60	5.5[a] (1.1)	6.3[a] (1.1)	1,540[a] (1210)	2,396[a] (1062)
5.5/6 yr	21	5.4[a] (1.2)	6.0[a] (1.3)	1,426[a] (1402)	1,986[a] (1278)
6.5/7 yr	23	4.9[a] (1.0)	5.8[a] (1.3)	966[a] (1149)	2,211[a] (1157)
7.5/8+ yr	20	5.1[a] (0.9)	5.8[a] (1.4)	913[a] (992)	1,670[a] (1285)
Dam BCS at calving					
4	5	4.9[a] (0.7)	5.6[a] (1.0)	638[a] (1210)	1,926[a] (1202)
5	20	5.5[a] (1.1)	6.4[a] (1.2)	1,693[a] (1095)	2,289[a] (1050)
6	133	5.2[a] (1.0)	6.0[a] (1.2)	1,390[a] (1193)	2,194[a] (1125)
7	100	5.2[a] (1.0)	5.9[a] (1.1)	1,271[a] (1192)	2,096[a] (1212)
Colostrum supplement (calves < 4.8 PP at 10 h)					
Treatment	52	4.3[a] (0.4)	5.0[a] (0.6)	353[a] (502)	1,178[a] (900)
Control	49	4.3[a] (0.6)	5.2[a] (1.0)	403[a] (644)	1,444[a] (1244)

[a,b] Means lacking a common superscript letter differ ($P < 0.05$).
BCS = body condition score.

Table 5. Analysis of variance F statistics and least square means for PP (g/dl), and IgG (mg/dl).

Variable	PP (10 h)	PP (24 h)	IgG (10 h)	IgG (24 h)
ANOVA				
Type of birth	1.7	1.1	0.3	10.4*
Parturition type	2.8‡	0.4	2.4	1.7
Mastitis in dam	6.2†	9.7	8.1	14.3*
Age of dam	2.6†	1.1	2.0‡	1.2
Birth date	3.6‡	7.1	2.3	3.1‡
Least squares means				
Type of birth				
Single	5.0	5.5	914	1,470
Twin	4.8	5.7	829	1,935
Parturition type				
Unassisted	5.0	5.7	993	1,799
Assisted	4.8	5.6	751	1,606
Mastitis in dam				
No	5.2	6.0	1,246	2,166
Yes	4.6	5.2	498	1,239
Age of dam				
2.5/3 yr	4.7	5.5	972	1,679
3.5/4 yr	4.9	5.6	1,050	1,808
4.5/5 yr	5.2	5.9	1,220	1,913
5.5/6 yr	5.1	5.7	947	1,743
6.5/7 yr	4.5	5.5	478	1,800
7.5/8+ yr	4.9	5.5	563	1,273

* $P < 0.01$, † $P < 0.05$, ‡ $P < 0.10$

($P < 0.01$) hours. Nine percent of dams had clinical mastitis; however, breed or type predilection was not apparent. Age of dam was associated with PP ($P < 0.05$) and IgG ($P < 0.10$) values at 10 hours, but had no effect at 24 hours. Plasma protein and IgG concentrations decreased as calves were born later in the calving season, although the association of birth date with IgG concentration at 24 hours was marginal ($P = 0.07$). The prospective sensitivity and specificity of a cut-off value of 4.8 g of protein/dl of plasma, measured at 10 hours, for diagnosing FPT at 10 hours were 78 and 94%, and for diagnosing FPT at 24 hours were 88 and 73%, respectively. Colostrum supplement administered to calves with low PP concentration at 10 hours had no effect on PP or IgG values at 24 hours or on preweaning morbidity and mortality (Table 6).

Table 6. Effect of colostrum supplement on mean (SD) PP (g/dl), and IgG (mg/dl) concentrations and preweaning morbidity and mortality outcomes.

Variable	Colostrum supplement	No colostrum supplement	P Value
n	52	49	--
PP at 10 h	4.3 (.4)	4.3 (.6)	0.52
PP at 24 h	5.0 (.6)	5.2 (1.0)	0.31
IgG at 10 h	353 (502)	403 (644)	0.66
IgG at 24 h	1,178 (890)	1,444 (1244)	0.23
Preweaning mortality	4%	8%	0.43
Neonatal morbidity	21%	18%	0.73
Preweaning morbidity	35%	31%	0.67

Observed rates of the morbidity and mortality outcomes in the study population were: preweaning mortality, 3%; neonatal morbidity, 9.9%; preweaning morbidity, 19.8%; feedlot morbidity, 52.6%; and feedlot respiratory tract morbidity, 46.6%. Mean serum IgG and PP concentrations at 24 hours among cases and noncases for each of the morbidity and mortality outcomes were compared (Table 7). Concentrations of serum IgG and PP were lower for cases than for noncases of preweaning mortality ($P < 0.05$), and for neonatal and preweaning morbidity ($P < 0.01$). Feedlot morbidity and respiratory morbidity cases had lower ($P < 0.01$) PP values at 24 hours than did noncases, but similar IgG values ($P = 0.11$ and $P = 0.08$, respectively).

Twenty-five percent of calves classified as having inadequate IgG concentration at 24 hours subsequently became morbidity cases during the neonatal period, whereas, only 5% of calves with adequate IgG concentration were observed to be ill during the same period. Rates among IgG and PP classification groups for all morbidity and mortality outcomes were determined (Table 8). The lowest rates were observed among the adequate classification group for each of the morbidity

Table 7. Mean (SD) serum immunoglobulin and plasma protein concentrations at 24 hours for cases and noncases of morbidity and nortality outcomes among 263 calves.

Variable* of calves	No.	Plasma protein (g/dl)	Serum IgG (mg/dl)
Preweaning mortality			
Cases	8	5.0(1.0)†	1,116(1,136)‡
Noncases	255	6.0(1.2)	2,181(1,284)
Neonatal morbidity			
Cases	26	5.1(0.8)‡	1,181(1,050)‡
Noncases	237	6.1(1.2)	2,254(1,118)
Preweaning morbidity			
Cases	52	5.5(1.0)‡	1,593(1,170)‡
Noncases	211	6.1(1.2)	2,285(1,109)
Feedlot morbidity			
Cases	123	5.8(1.2)‡	2,038(1,180)
Noncases	111	6.2(1.1)	2,266(1,115)
Feedlot respiratory morbidity			
Cases	109	5.8(1.2)‡	2,011(1,180)
Noncases	125	6.2(1.1)	2,265(1,120)

* Cases are calves with clinical signs of infectious disease as determined by Animal Research Technicians under veterinary supervision.

† $P < 0.05$, ‡ $P < 0.01$.

Table 8. Rates of morbidity and mortality outcomes by passive transfer status as determined by serum immunoglobulin or plasma protein values among 263 calves.

	Serum IgG status at 24 hours*			Plasma protein status at 24 hours†	
Classification	Inadequate	Marginal	Adequate	Inadequate	Adequate
No. of calves	60	20	183	49	214
Preweaning mortality					
Cases	5	0	3	3	5
Rate (%)	8.3	0	1.6	6.1	2.3
Neonatal morbidity					
Cases	15	2	9	10	16
Rate (%)	25.0	10.0	4.9	20.4	7.5
Preweaning morbidity					
Cases	20	7	25	15	37
Rate (%)	33.3	35.0	13.7	30.6	17.3
Feedlot morbidity					
Cases	36	14	86	34	102
Rate (%)	60.0	70.0	47.0	69.4	47.7
Feedlot respiratory morbidity					
Cases	33	12	76	31	90
Rate (%)	55.0	60.0	41.5	63.3	42.1

* Inadequate, < 800 mg/dl; marginal, 800 to 1,600 mg/dl; and adequate, > 1,600 mg/dl.
† Inadequate, < 4.8 g/dl and adequate, > 4.8 g/dl.

outcomes. As in group 1, the observed causes of preweaning morbidity were variable (data not shown).

Results of logistic regression analysis indicated that IgG concentration at 24 hours was associated with each of the morbidity and mortality outcomes prior to weaning (Table 9). Calves classified as having inadequate IgG concentration at 24 hours were at greater risk of preweaning mortality (odds ratio [OR] = 5.4), neonatal morbidity (OR = 6.4), and preweaning morbidity (OR = 3.2), compared with calves classified as having adequate IgG concentration at 24 hours. Calves classified as having marginal IgG concentration at 24 hours also had a greater risk of preweaning morbidity (OR = 3.6), compared with calves that had adequate IgG concentration. No calves classified as marginal IgG died during the study, and therefore, none were included in the analysis of preweaning mortality.

Table 9. Final models for estimating adjusted odds ratios for morbidity and mortality outcomes among 263 calves, using multiple logistic regression.

Model	Variables in final model	Adjusted odds ratio	95% CI OR*
Preweaning mortality			
	IgG value at 24 hours:		
	Adequate	1.0	
	Marginal	----†	
	Inadequate	5.4‡	1.3 to 23.5
Neonatal morbidity			
	IgG value at 24 hours:		
	Adequate	1.0	
	Marginal	2.1	0.4 to 10.7
	Inadequate	6.4§	2.6 to 15.7
Preweaning morbidity			
	IgG value at 24 hours:		
	Adequate	1.0	
	Marginal	3.6‡	1.3 to 10.0
	Inadequate	3.2§	1.6 to 6.4
	Calf sex:		
	Female	1.0	
	Male	2.2‡	1.1 to 4.2
Feedlot morbidity			
	Plasma protein value at 24 hours:		
	Adequate	1.0	
	Inadequate	3.0§	1.4 to 6.3
	Calf sex		
	Female	1.0	
	Male	3.0§	1.7 to 5.2
Feedlot respiratory morbidity			
	Plasma protein value at 24 hours:		
	Adequate	1.0	
	Inadequate	3.1§	1.5 to 6.5
	Calf sex:		
	Female	1.0	
	Male	3.2§	1.9 to 5.6

* 95% confidence interval for the odds ratio.
† There were no cases of preweaning mortality among calves classified as partial failure of passive transfer, and, thus, none were included in the analysis of this outcome.
‡ $P < 0.05$, § $P < 0.01$.

Calf PP concentration at 24 hours was associated with morbidity in the feedlot. Calves classified as having inadequate PP concentration were at greater risk of feedlot morbidity (OR = 3.0) and feedlot respiratory tract morbidity (OR = 3.1).

The lowest calf weaning weights were observed among calves classified as having inadequate IgG or PP concentration at 24 hours (Table 10). However, multivariable modeling indicated that the effect of passive transfer on weaning weight was indirect through its effect on neonatal morbidity. Morbidity during the first 28 days of life resulted in a 16-kg lower expected weaning weight (Table 11). Preweaning morbidity was not associated with calf weaning weight when neonatal morbidity remained in the model.

Table 10. Unadjusted calf growth performance means (SD) by passive transfer status and morbidity outcomes among 263 calves.

Classification	N	Weaning weight (kg)	N	Feedlot mean daily gain* (kg)
All calves	254	223(31)	234	1.01(0.27)
Plasma protein at 24 hours				
Adequate	208	225(29)	191	1.00(0.27)
Inadequate	46	213(36)	43	1.03(0.28)
Serum IgG at 24 hours				
Adequate	179	225(27)	165	1.00(0.27)
Marginal	20	225(29)	18	1.01(0.27)
Inadequate	55	214(40)	51	1.04(0.29)
Neonatal morbidity				
Cases	21	200(38)	21	1.02(0.32)
Noncases	233	225(29)	213	1.01(0.27)
Preweaning morbidity				
Cases	44	221(37)	42	1.09(0.30)
Noncases	210	223(30)	192	0.99(0.27)
Feedlot morbidity				
Cases	123	227(32)	123	1.05(0.26)
Noncases	111	219(30)	111	0.96(0.29)
Feedlot respiratory morbidity				
Cases	109	228(32)	109	1.06(0.26)
Noncases	125	220(30)	125	0.96(0.28)

* Mean 242 days of feed.

Similar to weaning weight, passive immune status at 24 hours was not directly associated with feedlot growth rate. There was, however, an indirect association through the effect of PP concentration at 24 hours on morbidity in the feedlot. Adjusted mean MDG for calves with respiratory tract morbidity while in the feedlot was 0.04 kg less than that for noncases (Table 11).

Discussion

The least expensive and most rapid indicator of passive immune status in this study was determination of concentration of serum total protein. However, refractometric total serum protein can be misleading because other plasma analytes such as glucose, urea, and creatinine contribute to the refractive index. Thus, sick and/or dehydrated calves can render spuriously high total serum protein values. Serum activity of GGT also gave reliable indications of concentration of passive immunity, but such determinations were more costly and time consuming to determine than those used for serum protein. Serum activity of GGT is not susceptible to changes in other serum analytes and is less susceptible to artifacts caused by dehydration. Serum activity of GGT is high in 24-hour-old calves that have consumed colostrum; therefore, the diagnostic value of GGT for determinations of hepatic lesions is limited during the first week of life for a calf that has received an adequate amount of colostrum.

Determination of either GGT serum activity or protein serum concentrations was less expensive and gave results sooner than single radial immunodiffusion for IgG. Determination of both would be useful in evaluating the success or failure of colostral management in groups of bovine neonates. The value in applying these tests lies in evaluation of groups of calves. Failure of passive transfer is a management problem and the prevalence of subsequent infection depends largely on the success of the colostral management. The role for

Table 11. Summary of final models for estimating growth performance among 263 calves, using ANOVA

Model	Variables in final model	df	F	Beta*	LS means
Weaning weight (kg)					
	Birth weight	1	95§	0.8	
	Age at weaning	1	203§	1.2	
	Calf sex:	1	29§		
	Female				208
	Male				222
	Type of birth:	1	7§		
	Single				218
	Twin				212
	Neonatal morbidity:	1	14§		
	Cases				207
	Noncases				223
Feedlot ADG† (kg)					
	Birth weight	1	36§	0.003	
	Weaning weight	1	5‡	-0.0003	
	Calf sex:	1	717§		
	Female				0.81
	Male				1.29
	Mastitis in dam:	1	10§		
	No				1.01
	Yes				1.10
	Feedlot respiratory morbidity:	1	8§		
	Cases			1.03	
	Noncases				1.07

* Regression coefficients for continuous variables.
† Mean 242 days on feed.
‡ $P < 0.05$, § $P < 0.01$.

these tests is in testing a sample of healthy 1- to 7-day-old calves to assess the efficacy of colostral management strategies.

Mastitis in the dam is a risk factor for development of FPT in beef calves. The observed higher IgG concentration in twin calves suggests that appropriate management can overcome biologic risk factors for FPT. Despite our ability to identify calves with FPT at 10 hours with reasonable accuracy using refractometry, our attempts to intervene by giving a commercial colostrum supplement were ineffective at significantly affecting plasma protein or IgG concentration at 24 hours, morbidity or mortality. While some of the outcomes measured, for example preweaning mortality, may have lacked statistical power, the large p-values and the fact that the numeric differences for the various outcomes were both positive and negative, suggest that supplementation had neither a beneficial nor detrimental effect.

Our results indicate that inadequate transfer of passive immunity is directly associated with a greater risk of health problems before and after weaning, and indirectly associated with preweaning and feedlot growth performance through its effect on morbidity.

In group 1, calves classified as FPT at 24 hours were at greater risk (relative risk = 9.5) of being ill prior to weaning, compared with calves classified as having adequate Ig concentrations or partial FPT. In group 2, the risk of morbidity among calves classified as having inadequate IgG concentration at 24 hours, compared with calves with adequate IgG values, was over 6 times greater during the neonatal period, and over 3 times greater during the entire preweaning period. Calves classified as having marginal IgG values at 24 hours experienced a similar increase in the risk of morbidity for the entire preweaning period, although increased risk during the neonatal period was not observed.

In group 2, the risk of death prior to weaning was over 5 times greater for calves classified as having inadequate passive transfer, compared with calves having adequate passive transfer. No calves classified as marginal passive transfer died prior to weaning.

Calves with inadequate passive transfer had a larger increase in the risk of morbidity during the neonatal period than during the time that all preweaning morbidity was considered. In contrast, calves with marginal passive transfer did not have increased risk of morbidity during the neonatal period. When all preweaning morbidity was considered, however, calves with marginal passive transfer had an increase in risk of similar magnitude to that in calves classified as having inadequate passive transfer. Thus, calves with inadequate passive transfer had the greatest risk of morbidity early in life, whereas, the increased risk for calves with marginal passive transfer was delayed until later in the preweaning period. This suggests that calves with marginal passive transfer obtained sufficient amounts of Ig to provide protection during the neonatal period. The lower initial concentrations of the maternal antibody may have rapidly decreased to values inadequate for protection, resulting in increased risk of disease, but at a later date. However, at this older age, the calves are likely to be able to provide a better active immune response, which may explain the observed lack of preweaning mortality in calves with marginal passive transfer.

Factors that have been previously reported to be associated with the risk of preweaning morbidity, (including dystocia, twin birth, and age of the dam) were not associated in these data after adjustment for passive immune status. It is likely that these reported relations may simply be indicators of risk of FPT. These factors were associated with passively acquired serum Ig concentration in this population. **This supports the hypothesis that acquisition of maternal immunity is the single most important factor influencing the risk of infectious morbidity and mortality prior to weaning.**

Passive immune status at 24 hours was associated with morbidity and respiratory tract morbidity in the feedlot, but the logistic regression model selected PP rather than serum IgG classification as the better predictor of these outcomes. It is difficult to explain biologic reasons that passive immune status at 24 hours would be associated with disease at over 6 months of age when calves should be well capable of mounting an active immune response to infectious challenge. It has been postulated that adequate maternal immunity might allow controlled development of a competent active immune system, whereas, similar immune system development in calves with inadequate passive antibody concentrations might be overwhelmed by a large infectious challenge.[3] The observed result also suggests the possibility that nonIg factors in colostrum may contribute to optimal development of the immune system. Potentially relevant nonIg factors include WBC[b] and interferon.[15] The PP status of a calf in this study might also simply represent some other unmeasured or unmeasurable factors and, thus, have no direct biologic relation to health in the feedlot.

In both groups of calves, the variety of observed causes of morbidity in calves prior to weaning suggests generalized immunodeficiency resulting from failure to obtain adequate passive immunity. The association between passive immune status and morbidity after weaning would seem to support the same hypothesis. Thus, we might postulate that colostrum derived immunity consists of important factors other than just pathogen-specific maternal antibody. Others have suggested similar hypotheses.[3,6,19]

Passive immune status at 24 hours did not directly

affect calf weaning weight. Rather, the association was indirect through the effect of neonatal morbidity on weaning weight. Passive immune status has previously been associated with growth rates of young dairy calves.[5,20] A correlation ($\underline{r}$ = 0.32) between 24-hour IgG concentration and weaning weight of beef calves has been reported, with the hypothesis that the observed relation might reflect increased resistance to disease and, therefore, improved growth.[8] The observed reduction in weaning weight for calves experiencing neonatal morbidity is similar to the value previously reported for beef calves that become ill during the first 45 days of life.[21] Preweaning morbidity was not associated with weaning weight when neonatal morbidity remained in the model. Thus, it was morbidity early in life, when maternal antibody appeared to have the greatest role, that influenced growth of calves. Previous work also suggests that calves that were ill early in life were not able to compensate completely by weaning for any associated weight loss.[21]

Others have reported that dairy heifer growth to 180 days was associated with serum Ig concentrations at 24 to 48 hours.[5] In addition, it has been reported that serum Ig concentration at 24 hours was related to first-lactation milk and fat production in dairy heifers.[6] An association between passive immune status and MDG of feedlot cattle would, therefore, not be unexpected. We found, however, that feedlot MDG was not directly associated with passive immune status at 24 hours, but was indirectly influenced through the association between 24-hour PP values and feedlot respiratory tract morbidity. Reports of reduced rate of gain among feedlot cattle treated for respiratory tract disease are not uncommon.[22,23]

The magnitude of the effects of passive immune status on the health and growth performance of calves in this study emphasize the importance of producer management strategies to identify calves at risk of failing to acquire passive immunity and to provide appropriate intervention. The principal factors that influence the passive transfer of the maternal antibody in colostrum to calves are the total mass of Ig ingested[24,25] and the age of the calf at colostral ingestion.[26] Other factors that have been associated with acquisition of maternal immunity by the neonatal calf include the presence of the dam,[27] the method of colostral feeding,[27] season,[5,28] age of the dam,[5] and environmental conditions experienced by the neonate.[29,30] Producers and veterinarians must be aware of these and other potential risk factors, and be prepared to intervene in a timely manner when required.

In conclusion, our data provide additional evidence that acquisition of maternal immunity is one of the most important factors determining health of neonatal calves. In addition, passive immunity may have an important role in the long-term health and growth of calves reared in a production environment typical for beef calves in the United States. Using PP, we identified calves with FPT at 10 hours with reasonable accuracy using refractometry. The observed higher IgG concentration in twin calves suggests that appropriate management can overcome biologic risk factors for FPT. Our attempts to intervene by giving a commercial colostrum supplement were ineffective. **Colostral management strategies should, therefore, receive appropriate attention by producers and veterinarians attempting to improve health and performance of calves raised in this environment.**

References

1. Boyd JW. The relationship between serum immune globulin deficiency and disease in calves: A farm survey. *Vet Rec* 1972;90:645-649. 2. Boyd JW, Baker JR, Leyland A. Neonatal diarrhea in calves. *Vet Rec* 1974;95:310-313. 3. Williams MR, Spooner RL, Thomas LH. Quantitative studies on bovine immunoglobulins. *Vet Rec* 1975;96:81-84. 4. McGuiire TC, Pfeiffer NE, Weikel JM, *et al.* Failure of colostral immunoglobulin transfer in calves dying from infectious disease. *J Am Vet Med Assoc* 1976;169:713-718. 5. Robison JD, Stott GH, DeNise SK. Effects of passive immunity on growth and survival in the dairy heifer. *J Dairy Sci* 1988;71:1283-1287. 6. DeNise SK, Robison JD, Stott GH, *et al.* Effects of passive immunity on subsequent production in dairy heifers. *J. Dairy Sci* 1989;72:552-554. 7. Banks KL, McGuire TC. Neonatal immunology. In: Halliwell REW, Gorman NT, eds. *Veterinary Clinical Immunology.* Philadelphia: WB Saunders Co, 1989;193-204. 8. Odde KG. Survival of the neonatal calf. *Vet Clin North Am: Food Anim Pract* 1988;4:501-508. 9. Donoval GA, Shearer JK, Braun RK. Total serum protein levels in dairy calves, in *Proceedings*. Soc for Theriogenol Annu Meet, 1988;127-134. 10. Sobiech KA, Wieczorek E. γ-Glutamyl transpeptidase activity in human colostrum. *Enzyme* 1981;26:153-155. 11 Thompson JC, Pauli JV. Colostral transfer of gamma glutamyl transpeptidase in calves. *N Z Vet J* 1981;29:223-226 12. Bouda J, Dvorak V, Minksova E, *et al.* The activities of GOT, gamma-GT, alkaline phosphatase in blood plasma of cows and their calves fed from buckets. *Acta Vet (Brno)* 1980;49:193-198. 13. Pauli JV. Colostral transfer of gamma glutamyl transferase in lambs. *N Z Vet J* 1983;31:150-151. 14. Center SA, Randolph JF, ManWarren T, *et al.* Effect of colostrum ingestion on gamma-glutamyltransferase and alkaline phosphatase activities in neonatal pups. *Am J Vet Res* 1991;52:499-504. 15. Patterson WH, Brown CM. Increase of serum γ-glutamyltransferase in neonatal Standardbred foals. *Am J Vet Res* 1986;47:2461-2463. 16. Richards MW, Spitzer JC, Warner MB. Effect of varying levels of postpartum nutrition and body condition at calving on subsequent reproductive performance of beef cattle. *J Anim Sci* 1986;62:300-306. 17. Hosmer DW, Lemeshow S. *Applied logistic regression.* New York: John Wiley and Sons, 1989. 18. Wittum TE, Salman MD, King ME, *et al.* Individual animal and maternal risk factors for morbidity and mortality of neonatal beef calves in Colorado, U.S.A. *Prev Vet Med* 1994;19:1-14. 19. Thomas LH, Swann RG. Influence of colostrum on the incidence of calf pneumonia. *Vet Rec* 1973;92:454-455. 20. Nocek JE, Braund DG, Warner RG. Influence of neonatal colostrum administration, immunoglobulin, and continued feeding of colostrum on calf gain, health, and serum protein. *J Dairy Sci* 1984;67:319-333. 21. Wittum TE, Salman MD, King ME, *et al.* The influence of neonatal health on weaning weight of Colorado, USA beef calves. *Prev Vet Med* 1994;19:15-26. 22. Martin SW, Bateman KG, Shewen PE, *et al.* The frequency, distribution and effects of antibodies, to seven putative respiratory pathogens, on respiratory disease and weight gain in feedlot calves in Ontario. *Can J Vet*

Res 1988;53:355-362. 23. Morck DW, Merrill JK, Thorlakson BE, *et al.* Prophylactic efficacy of tilmicosin for bovine respiratory tract disease. *J Am Vet Med Assoc* 1993;202:273-277. 24. Bush LJ, Aguilera MA, Adams GD, *et al.* Aborption of colostral immunoglobilins by newborn dairy calves. *J Dairy Sci* 1971;54:1547-1549. 25. Stott GH, Marx DB, Menefee BE, *et al.* colostral immunoglobulin transfer in calves. III. Amount of absorption. *J Dairy Sci* 1979;62:1902-1907. 26. Kruse V. Absorption of immunoglobulin from colostrum in newborn calves. *Anim Prod* 1970;12:627-638. 27. Selman IE, McEwan AD, Fisher EW. Absorption of immune lactoglobulin by newborn dairy calves. Attempts to produce consistent immune globulin absorptions in newborn dairy calves using standardized methods of colostral feeding and management. *Res Vet Sci* 1971;12:205-210. 28. Gay CC, McGuire TC, Parish SM. Seasonal variation in passive transfer of immunoglobulin G1 to newborn calves. *J Am Vet Med Assoc* 1983;183:566-568. 29. Stott GH, Wiersma BE, Menefee BE, *et al.* Influence of environment on passive immunity in calves. *J Dairy Sci* 1976;59:1306-1311. 30. Olson DP, Papasian CJ, Ritter RC. The effects of cold stress on neonatal calves. II. Absorption of colostral immunoglobulins. *Can J Comp Med* 1980;44:19-23.

CVM UPDATE Center for Veterinary Medicine

Update on BST

October 12, 1995

FDA approved Monsanto Company's recombinant bovine somatotropin (rbST) product in November 1993 after a comprehensive review of the product's safety and efficacy, including human food safety. Monsanto's product, known as Postilac®, is the only rbST product approved for increasing milk production in dairy cattle. The product has been commercially available since February 4, 1994.

In a March 14, 1995 FDA Talk Paper, the Agency stated that during the first year of commercial use a total of 806 adverse effects to the drug were reported to Monsanto and submitted to FDA. The following is an update of the adverse experiences to Posilac® reported to FDA during the next seven months of commercial use; from February 1, 1995 through August 25, 1995. During this period, FDA received 509 adverse experience reports (see table below). It is important to note that a report of an adverse effect in relation to a drug does not itself establish that the effect was caused by the drug. FDA believes that 392 of the 509 reports were **possibly** associated with the use of Posilac®, and that the other 117 reports were not related to treatment with Posilac®. Also, **all of the reported clinical manifestations are known to occur in dairy cattle not supplemented with Posilac®.**

Of the 392 reports possibly related to the use of Posilac®, 100 included reproductive disorders, 77 involved digestive disorders, 69 included mastitis, 62 included injection site reactions, 54 included swelling of the udder or abnormal milk, 53 included foot or leg problems, and 44 involved increased somatic cell counts. In some cases, one report contained more than one condition.

The number and severity of the reported conditions raise no new animal health concerns about the safety of Posilac®. The numbers and types of reactions are similar to those found during clinical trials and indicated on the label. Also, there is no indication that the drug is any less effective than labeled. In addition, FDA and the States have found no indication of a change in the incidence of violative drug residues in milk since Posilac® has been in commercial use.

Based on theses reports of adverse reactions to Posilac®, FDA does not find any cause for concern. However, it is important for dairy farmers to continue to report all adverse reactions associated with the use of rbST. They may report such reactions to Monsanto, to FDA through their veterinarian, or directly to FDA's Center for Veterinary Medicine. CVM accepts collect calls during working hours, and an answering machine is available to record after-hours calls. The telephone numbers are (301) 594-1751 for collect calls during working hours, and (301) 594-0797 to leave a message on evenings and weekends.