Feeding colostrum or a 1:1 colostrum:whole milk mixture for 3 days after birth increases serum immunoglobulin G and apparent immunoglobulin G persistency in Holstein bulls

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ABSTRACT

Conflicting reports exist on whether prolonged IgG consumption can further increase serum IgG in neonatal calves. Given that higher serum IgG in neonates has lifelong benefits, our objective was to determine whether serum IgG can be increased by providing multiple meals containing IgG to neonatal calves. Twenty-seven Holstein bulls were all fed 1 colostrum meal (7.5% body weight; 62 g of IgG/L) at 2 h after birth and randomly assigned to be fed (5% body weight) colostrum (COL; $n = 9$), whole milk (WM; $n = 9$), or a 1:1 colostrum:whole milk mixture (MX; $n = 9$) every 12 h from 12 to 72 h. Serum IgG was measured at 1, 2, 3, 6, 9, 11, and 12 h after birth. After the 12-h meal, IgG was determined at 0.5-h intervals until 16 h and then at 1-h intervals from 16 to 24 h. Serum IgG was then measured at 27 h, then every 6 h from 30 to 60 h. From 60 to 64 h, IgG was measured every 0.5 h, then at 65 and 66 h, and then every 2 h until 72 h. Serum IgG increased rapidly between 2 and 12 h for all calves. A treatment $\times$ time interaction occurred as serum IgG began to diverge between treatments after they were fed at 12 h; the interaction was greatest over the entire period for COL compared with both MX and WM and was greater for MX than for WM. Maximum IgG concentrations ($C_{\max}$) were 30.4 ± 0.8 , 27.2 ± 0.8 , and 23.9 ± 0.8 g/L for COL, MX, and WM, respectively. Although MX $C_{\max}$ was equivalent to both COL and WM $C_{\max}$, COL $C_{\max}$ was greater than WM $C_{\max}$. Feeding COL and MX also prolonged the time to reach $C_{\max}$. Respectively, these calves achieved $C_{\max}$ at 29.5 and 27.0 ± 3.4 h, whereas WM IgG peaked at 13.4 ± 3.4 h. No differences were observed for apparent efficiency of absorption between treatments from 0 to 12 h and 0 to

24 h. Immunoglobulin G area under the curve (AUC) was the same for COL and MX calves over the entire experimental period and from when treatments were fed. The IgG AUC for 0 to 72 h for WM calves was 27.4% lesser than that for COL calves but not different from MX calves. However, the IgG AUC for 12 to 72 h for WM calves differed relative to that for both COL (30.8% less) and MX (19.6% less) calves. Serum IgG concentrations were more persistent when COL ($88.2 \pm 2.4\%$) and MX ($91.2 \pm 2.4\%$) were fed rather than WM ($75.3 \pm 2.4\%$). Prolonged IgG consumption increased serum IgG concentrations, corresponding to the mass of IgG fed, and improved apparent IgG persistency in Holstein bulls. Neonatal calves should be fed at least 62 g of IgG at 12 h after birth to further increase serum IgG concentrations.

Key words: dairy calf, neonate, immunoglobulin, colostrum, transition milk

INTRODUCTION

Serum IgG <10 g/L defines failure of passive transfer (FPT) in neonatal calves (Shivley et al., 2018). However, this threshold is dated (Robison et al., 1988; DeNise et al., 1989), and recent research has demonstrated that greater IgG concentrations are more beneficial. Calves with serum IgG concentrations ≥ 15 g/L are less susceptible to respiratory infection (Furman-Fratczak et al., 2011) and have a greater probability for survival (Urie et al., 2018). Others go further to suggest that serum IgG >20 g/L is the necessary FPT threshold to reduce mortality rates (Chigerwe et al., 2015). Currently, 12.1 to 19.2% of calves fail passive transfer (PT; Beam et al., 2009; Shivley et al., 2018) at the commonly used threshold (serum IgG <10 g/L), and we can expect on-farm FPT rates to concurrently rise with an increased FPT threshold, as evidenced by 26.7% of calves having serum IgG <15 g/L (Shivley et al., 2018). This presents an opportunity for the dairy industry to

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improve newborn calf management practices on-farm and reduce the excessive dairy calf morbidity (33.9%; Urie et al., 2018) and mortality (5.0 to 6.4%; Urie et al., 2018; Winder et al., 2018).

Neonatal calves should consume ≥ 3.78 L of high-quality colostrum (>50 g of IgG/L; Godden, 2008) within 0 to 6 h after birth (Stott et al., 1979a; Fischer et al., 2018) to successfully achieve adequate PT. In the National Animal Health Monitoring System Dairy 2014 survey, producers followed these recommendations, feeding an average of 4.4 L of high-quality colostrum (mean IgG: 75.3 g/L) at 2.9 h after birth (Shivley et al., 2018). However, 14.2% of the calves that failed PT were fed using best management practices and had no risk factors for FPT (Shivley et al., 2018), demonstrating that calf-dependent factors that are currently unaccounted for can compromise calves' capacity to either absorb immunoglobulins or maintain IgG concentrations once absorbed. Low birth weight (Urie et al., 2018) and an amplified surface area:body mass ratio (Paré et al., 1993; Mellor and Stafford, 2004; Monteiro et al., 2014), an inability to curdle first-meal colostrum within the abomasum immediately after birth (Cruywagen, 1990; Miyazaki et al., 2017), and slower abomasal emptying rate (Mokhber-Dezfooli et al., 2012) are all associated with lower serum IgG concentrations. Although the underlying mechanisms that influence IgG uptake deserve further research consideration, at present producers still need reliable strategies to overcome calf-to-calf variation.

Feeding multiple meals that contain IgG may be a promising and feasible strategy to further increase serum IgG concentrations and ensure adequate PT in calves (Morin et al., 1997; Jaster, 2005; Halleran et al., 2017). However, the efficacy of this strategy is unclear as some studies have demonstrated that prolonged IgG provision does not further increase serum IgG (Cabral et al., 2012, 2014; Conneely et al., 2014). An excessive IgG supply might saturate the intestinal uptake capacity (Besser et al., 1985; Conneely et al., 2014), thereby reducing the efficiency with which it is absorbed (Conneely et al., 2014). Transition milk (TM; milkings 2 to 6; Blum and Hammon, 2000) has a lower IgG content than colostrum, though it still contains more IgG than whole milk. As such, feeding TM as a secondary IgG source is plausibly more suited to the calf's capacity to absorb IgG after a high-IgG colostrum meal has already been fed. The objective of this experiment was to determine whether Holstein bull calves fed colostrum or a 1:1 mixture of colostrum and whole milk (to simulate TM) after the initial colostrum meal would have greater serum IgG than calves fed whole milk. It was hypothesized that additional IgG provision past 12 h

would lead to greater serum IgG in calves fed colostrum and a 1:1 colostrum:whole milk mixture (intermediate) than feeding calves whole milk.

MATERIALS AND METHODS

Experimental Design, Animal Husbandry and Measurements, and Laboratory Analysis

Experiment design and procedures used in this study were approved by the Animal Care and Use Committee (University of Alberta, AUP00001595) before the start of the experiment. Calf husbandry and feeding protocols have been previously described (Inabu et al., 2019; Pyo et al., 2020) and, as such, are described in brief here. Holstein bulls were removed from their dam immediately following parturition, bottle-fed pooled and pasteurized colostrum (62 g of IgG/L, 7.5% of BW; Saskatoon Colostrum Company Ltd., Saskatoon, SK, Canada) that had never been dehydrated at 2 h after birth, and randomly assigned to receive 1 of 3 treatment meals every 12 h beginning at 12 h until 72 h of life. Treatment DM and composition are presented in Pyo et al. (2020) and consisted of a pooled and pasteurized colostrum (COL; $n = 9$), a 1:1 colostrum:whole milk mixture (MX; $n = 9$), or pooled and pasteurized whole milk (WM; $n = 9$) fed at 5% of BW by bottle. The pooled and pasteurized whole milk fed in the MX treatment was the same as that fed for the WM treatment. By estimating variance from Fischer et al. (2018), it was determined that 9 calves were required per treatment to detect a 30% difference in serum IgG at $\beta = 0.80$ and $\alpha = 0.05$ (Berndtson, 1991).

Calves underwent jugular catheterization at 1 h after birth (Fischer et al., 2018) to facilitate blood collection during the 72-h experiment duration. Blood was collected frequently throughout the experimental period to better represent IgG absorptive kinetics during the first 3 d after birth. The first collections were performed at birth and at 1 and 2 h after birth, before the 2-h colostrum meal. Afterward, blood was sampled at 3, 6, 9, and 11 h after birth. Samples then were taken every 30 min from 12 to 16 h and every 60 min from 16 to 24 h, then at 27 and 30 h, and every 6 h from 30 to 54 h. Following that, blood was collected at 59 and 60 h, then every 30 min from 60 to 64 h, and at 65, 66, 68, 70, and 72 h after birth. All samplings that coincided with meals were performed before feeding. Sampling frequency was increased following the 12- and 60-h meals to improve measurement precision and accuracy to contrast between serum IgG concentrations following the first and last treatment meals. Blood was extracted via catheter into a 10-mL syringe, after which it was

divided equally into 2 glass vials (Becton Dickinson, Franklin Lakes, NJ). Serum was separated by centrifugation ($3,000 \times g$ at 4°C for 20 min) after clotting for 3 h at room temperature, aliquoted (1.5 mL/aliquot) into a microcentrifuge tube, and stored at -20°C until analysis of serum IgG. Serum was thawed, vortexed, centrifuged at $3,000 \times g$ for 15 min at 4°C , aliquoted to new microcentrifuge tubes, refrozen at -20°C , and then shipped overnight on ice to the Saskatoon Colostrum Company Quality Assurance Laboratory for determination of serum IgG concentrations by radial immunodiffusion analysis (Shivley et al., 2018).

Calculations and Equations

The apparent efficiency of IgG absorption (**AEA**; %) was calculated for all treatments from 0 to 12, 12 to 24, and 0 to 72 h after birth using the formula (Equation 1) described by Quigley et al. (1998). Only COL and MX calves were compared for AEA from 12 to 72 h because WM calves did not consume IgG during this time frame. Total IgG fed between 12 and 72 h to COL and MX was considered $\text{IgG}_{\text{consumed}}$, and $\text{IgG}_{\text{baseline}}$ was the concentration of IgG at 12 h. Equation 1 was used to calculate AEA from serum IgG concentrations at discrete time points (IgG_t ; g/L) and initial IgG ($\text{IgG}_{\text{baseline}}$; g/L) relative to the mass of IgG consumed ($\text{IgG}_{\text{consumed}}$; g) and corrected by the approximated plasma volume ($\text{PV} = 0.091; \text{L/kg} \times \text{birth BW (kg)}$).

$$\text{AEA (\%)} = \left[\frac{(\text{IgG}_t - \text{IgG}_{\text{baseline}}) \times \text{PV}}{\text{IgG}_{\text{consumed}}} \right] \quad [1]$$

Area under the curve (**AUC**) was calculated using the trapezoidal rule to sum the area formed between the IgG concentrations at 2 discrete time points (Equation 2; Chiou, 1978; Cardoso et al., 2011). Total IgG AUC was calculated for all calves from 0 and 12 to 72 h ($\text{AUC}_{0-72\text{h}}$ and $\text{AUC}_{12-72\text{h}}$, respectively) to represent IgG AUC ($\text{AUC}_{0-72\text{h}}$) over the total experimental period and IgG AUC following the provision of treatment meals ($\text{AUC}_{12-72\text{h}}$). Net incremental AUC (**I-AUC**) was calculated (Equation 3; Cardoso et al., 2011) from 12 to 72 h ($\text{I-AUC}_{12-72\text{h}}$) to correct for the 12-h serum IgG concentrations (baseline) established by providing all calves a primary colostrum meal at 2 h after birth.

Equation 2 was used to calculate AUC from serum IgG concentrations (IgG_1 and IgG_2) at 2 discrete time points (t_1 and t_2) using the trapezoidal rule.

$$\text{AUC (g/L} \times \text{h)} = \left[\frac{(\text{IgG}_1 + \text{IgG}_2) \times (t_2 - t_1)}{2} \right] \quad [2]$$

Equation 3 was used to calculate net I-AUC from serum IgG concentrations (IgG_1 and IgG_2) corrected for the baseline IgG concentration ($\text{IgG}_{\text{baseline}}$) at 2 discrete time points (t_1 and t_2) using the trapezoidal rule.

$$\text{I-AUC (g/L} \times \text{h)} = \left[\frac{\left[\frac{(\text{IgG}_1 - \text{IgG}_{\text{baseline}}) + (\text{IgG}_2 - \text{IgG}_{\text{baseline}})}{2} \right] \times (t_2 - t_1)}{2} \right] \quad [3]$$

The maximum IgG concentration (C_{max}) and the time to reach maximum IgG concentration (T_{max}) were calculated. In addition, we derived an equation to calculate the apparent persistency of IgG in serum following C_{max} , as shown in Equation 4.

Equation 4 was developed to quantify the apparent persistency of IgG (%) in calf serum by the end of the experimental period.

$$\text{Apparent IgG persistency (\%)} = \left[1 - \frac{(\text{IgG}_{\text{max}} - \text{IgG}_{72}) \times \frac{(\text{T}_{72} - \text{T}_{\text{max}})}{\text{T}_{\text{max}}}}{\text{IgG}_{\text{max}}} \right] \times 100 \quad [4]$$

The change in serum IgG concentration (IgG_{72}) at 72 h (T_{72}) relative to the maximal IgG concentration (IgG_{max}) was expressed proportional to IgG_{max} . The difference between T_{max} and T_{72} proportional to T_{max} was used as a correction factor within the equation to reflect the between-subject variation at which T_{max} was attained.

Statistical Analyses

All procedures were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC). All data were confirmed homoscedastic by visual appraisal of box plots, and PROC UNIVARIATE was used to test that residuals met the criteria for normality. By this, the residuals of $\text{AEA}_{0-24\text{h}}$ and C_{max} were identified (Shapiro-Wilk: $P \leq 0.025$) as having non-normal distributions. Studentized deleted residuals were generated using PROC SGPlot to identify outliers (studentized deleted residual SD > 3) within these data sets. The $\text{AEA}_{0-24\text{h}}$ and C_{max} residuals of 1 calf (COL) were identified as outliers (studentized deleted residual SD ≥ 4.5) and removed, after which $\text{AEA}_{0-24\text{h}}$ and C_{max} measurement residuals were found to be normally distributed (Shapiro-Wilk:

$P \geq 0.39$). The $T_{\max}$ distribution was also determined to be non-Gaussian as a consequence of the treatments and was log-transformed using PROC GLIMMIX with the fixed effect of treatment included in the model. The reported $T_{\max}$ values are the back-transformed logarithmic means. The remaining data were modeled with PROC MIXED using the same model as used for $T_{\max}$, as shown here:

$$Y_{ij} = \mu + \text{treatment}_i + \varepsilon_{ij},$$

where Y_{ij} = the j th observation in the i th treatment; μ = the overall mean; treatment_i = the fixed effect of the i th treatment; and ε_{ij} = the random error associated with the j th observation in the i th treatment. Time (hours after birth) and the treatment $\times$ time interaction were both modeled as fixed effects for serum IgG measurements performed repeatedly over time:

$$Y_{ijkl} = \mu + \text{treatment}_i + \text{time}_j + (\text{Trt} \times \text{T})_{ij} \\ + \text{calf}_k + \varepsilon_{ijkl},$$

where Y_{ijkl} = the l th observation of the k th calf in the i th treatment at the j th time; μ = the overall mean; treatment_i = the fixed effect of the i th treatment; time_j = the fixed effect of the j th time; $(\text{Trt} \times \text{T})_{ij}$ = the fixed effect of the interaction of the i th treatment at the j th time; calf_k = the random effect of the k th calf; and ε_{ijkl} = the random error associated with the l th observation of the k th calf in the i th treatment at the j th time. Best-fit (lowest Akaike and Bayesian information criterion) covariance structures were independently modeled to account for the autocorrelation of measurements conducted over time on one subject. Ante-dependence was found to be the best-fit covariance structure. Multiple comparisons in both the non-repeated and repeated measurement models were adjusted using Tukey's post hoc test. Treatment differences were declared when $P < 0.05$, and tendencies for treatments to differ were interpreted as $0.05 \leq P < 0.10$.

RESULTS

Calf BW did not differ ($P = 0.61$; Table 1) between treatments and, consequently, neither ($P = 0.61$) did IgG intake (COL: 188.5 ± 7.2 g of IgG; MX: 184.8 ± 7.2 g of IgG; WM: 195.2 ± 7.2 g of IgG) at 2 h when all calves received the same colostrum. From 12 to 72 h, COL and MX calves respectively consumed 125.7 and 62.1 ± 3.6 g of IgG/meal ($P < 0.001$) every 12 h, whereas WM calves no longer received IgG during feedings. Total IgG intake on d 1 was greatest ($P < 0.001$) for COL calves (314.1 ± 9.9 g of IgG) compared with

MX (246.8 ± 9.9 g of IgG) and WM (195.2 ± 9.9 g of IgG) calves. On d 1, MX calves consumed more IgG than WM calves. Total IgG intake was still increased ($P < 0.001$) for COL calves (251.3 ± 7.3 g of IgG/d) compared with MX calves (124.1 ± 7.3 g of IgG/d) on d 2 and 3, whereas WM calves consumed no more IgG.

Serum IgG concentrations were the lowest (mean: 0.8 ± 0.2 g of IgG/L; Figure 1) for all calves before consuming colostrum at 2 h after birth, after which serum IgG increased rapidly (time: $P < 0.001$) to 20.4 ± 0.7 g of IgG/L by 12 h after birth. Serum IgG began to diverge (treatment $\times$ time: $P < 0.001$; Figure 1) between COL, MX, and WM calves at 12 h. By 16 h after birth, COL serum IgG was greater than WM serum IgG, and this difference was maintained throughout the experiment. The differences in MX and WM serum IgG were not similarly pronounced early on and were only consistently detected after 48 h. On average, serum IgG was greater for MX (20.6 ± 0.8 g/L) than for WM (17.8 ± 0.8 g/L) and greatest for COL (23.7 ± 0.8 g/L) compared with both MX and WM.

Maximum serum IgG concentration was increased ($P = 0.012$) by 27.2% when COL was fed as opposed to WM; MX $C_{\max}$ did not differ from either COL or WM. Time to $C_{\max}$ was prolonged ($P < 0.001$) by feeding COL (29.5 ± 3.4 h) and MX (27.0 ± 3.4 h) compared with WM (13.4 ± 3.4 h), but $T_{\max}$ was equivalent between COL and MX calves. The IgG AUC_{0-72h} was 1.4 times greater ($P = 0.001$) when calves consumed COL rather than WM and was not different between MX and COL or MX and WM. After treatment meals were fed, the IgG AUC_{12-72h} was greater ($P < 0.001$) for COL and MX calves ($1,620.5$ and $1,395.1 \pm 71.0$ g of IgG/L $\times$ h, respectively; not different) compared with WM calves ($1,121.9 \pm 71.9$ g of IgG/L $\times$ h). Net IgG I-AUC_{12-72h} increased ($P < 0.001$) incrementally from WM (lowest) to MX (intermediate) to COL (greatest). Apparent efficiency of absorption did not differ ($P \geq 0.43$) between treatments during the intervals of 0 to 12 h and 0 to 24 h, and AEA_{12-72h} was not different ($P = 0.91$) between COL and MX calves. Over the entire experimental period, AEA_{0-72h} was lessened ($P < 0.001$) by COL and MX feeding (11.3 and $15.8 \pm 1.4\%$, respectively; not different) compared with WM feeding ($30.8 \pm 1.4\%$). Serum IgG concentrations were more ($P < 0.001$) persistent for COL and MX calves than for WM calves, but apparent IgG persistency was similar between COL and MX treatments.

DISCUSSION

It is well known that calves are born agammaglobulinemic and rely on colostrum IgG permeating the

Table 1. Body weight, colostral IgG intake per meal and day, and serum IgG characteristics of calves consuming colostrum (COL), whole milk (WM), or a 1:1 mixture of COL:WM (MX) from 12 to 72 h after an initial meal of colostrum was fed to all calves at 2 h after birth

Item ¹	Treatment			SE	P-value
	COL	MX	WM		
BW, kg	42.3	41.4	43.8	1.7	0.61
Colostral IgG intake, g/meal					
Meal 1	188.5	184.8	195.2	7.2	0.61
Meals 2–6	125.7	62.1	—	3.6	<0.001
Colostrum IgG intake, g/d					
d 1	314.1 ^a	246.8 ^b	195.2 ^c	9.9	<0.001
d 2 and 3	251.3	124.1	—	7.3	<0.001
IgG C _{max} , g/L	30.4 ^a	27.2 ^{ab}	23.9 ^b	1.3	0.012
IgG T _{max} , ² h	29.5 ^a	27.0 ^a	13.4 ^b	3.4	0.001
IgG AUC, ³ g/L × h					
0–72 h	1,781.4 ^a	1,549.3 ^{ab}	1,294.2 ^b	81.4	0.001
12–72 h	1,620.5 ^a	1,395.1 ^a	1,121.9 ^b	71.9	<0.001
IgG net I-AUC for 12–72 h ³	417.9 ^a	240.7 ^b	–179.0 ^c	47.3	<0.001
Apparent efficiency of IgG absorption, ⁴ %					
0–12 h	38.1	36.6	40.9	2.3	0.43
0–24 h	33.2	33.6	36.5	2.1	0.50
0–72 h	11.3 ^b	15.8 ^b	30.8 ^a	1.4	<0.001
12–72 h	3.2	3.4	—	1.0	0.91
Apparent IgG persistency, %	88.2 ^a	91.2 ^a	75.3 ^b	2.4	<0.001

^{a–c}Means within a row with different superscripts differ ($P < 0.05$).

¹C_{max} = maximum IgG concentration; T_{max} = time to maximum IgG concentration; AUC = area under the curve; I-AUC = incremental AUC.

²T_{max} values are back-transformed lognormal means.

³The AUC was calculated as the sum of the trapezoidal area formed between serum IgG concentrations at 2 discrete time points. Net I-AUC was similarly calculated but corrected for the concentrations of serum IgG at 12 h after birth as baseline (Cardoso et al., 2011).

⁴Calculated using the formula described in Quigley et al. (1998).

gastrointestinal tract to establish their own peripheral concentrations (Godden, 2008); thus, the rapid increase in serum IgG concentration after 2 h is not surprising. It should be noted that all calves in the current study had surpassed the defined FPT threshold (IgG >10 g/L by 24 h; Shivley et al., 2018) and a suggested FPT threshold (IgG >15 g/L by 24 h; Furman-Fratczak et al., 2011) by 6 h after birth (serum IgG: 17.5 ± 0.8 g/L). In fact, calf serum IgG rose above the more stringent threshold (>20 g of IgG/L by 24 h; Chigerwe et al., 2015) very early during the experiment (11 h after birth). Collectively, these results highlight several important notions. First, given that all calves within the current study rapidly surpassed FPT thresholds, we are confident that results within this study and companion studies (Inabu et al., 2019; Pyo et al., 2020) are not confounded by inadequate PT between treatments. Second, our data showed that serum IgG >20 g/L can be achieved early on, supporting the use of higher thresholds to determine adequate PT (Furman-Fratczak et al., 2011; Chigerwe et al., 2015). Third, the different times to achieve serum IgG >15 g/L (5 and 9 h; Desjardins-Morrisette et al., 2018; Fischer et al., 2018) between our current and past work likely reflect variations in calf-to-calf responses rather than

significant variation within our feeding protocols (≤2 h after birth, ~200 g of IgG ingested); as such, this is an interesting direction for future research. We must note, however, that Desjardins-Morrisette et al. (2018) fed calves a colostrum-derived dried colostrum replacer, and it is possible that this could account for some of the observed variation in responses (Godden et al., 2009; Priestley et al., 2013; Murphy et al., 2014). Frequent early measurements of serum IgG, as done within this study and others (Desjardins-Morrisette et al., 2018; Fischer et al., 2018), can improve our understanding of gastrointestinal IgG permeation kinetics to determine what drives between-calf variation. This may help us understand why calves often fail to achieve adequate PT (12.1 and 26.7% of calves with serum IgG <10 and 15 g/L, respectively; Shivley et al., 2018) when 67% of producers report following recommended colostrum-feeding practices (Winder et al., 2018) and 14.2% of FPT continues to occur in calves with no risk factors (Shivley et al., 2018). In particular, deducing why calf responses to colostrum feedings are so variable is critical to ensuring calf welfare and benchmarking should FPT thresholds be increased to serum IgG >15 g/L (Furman-Fratczak et al., 2011) or 20 g/L (Chigerwe et al., 2015) in the near future.

Figure 1. Serum IgG concentrations in calves fed colostrum (COL, $n = 9$), whole milk (WM, $n = 9$), or a 1:1 COL:WM mixture (MX, $n = 9$) from 12 to 72 h after birth after all calves had received an initial colostrum meal at 2 h after birth. Serum IgG concentrations began to diverge (treatment $\times$ time: $P < 0.001$) after 12 h between COL and MX calves and COL and WM calves but not MX and WM calves. The difference between COL and WM calves was maintained throughout the remaining experimental period, whereas by the end of the experiment, COL and MX no longer differed and MX serum IgG was greater than that of WM. The P -values for the main effects of treatment and time were both $P < 0.001$. Error bars represent SE.

Feeding IgG in more than 1 meal (by additional colostrum or by feeding TM) before gut closure could be a useful strategy for producers to ensure PT in their youngstock. However, research has largely demonstrated mixed results regarding whether prolonged IgG feeding can improve serum IgG in neonatal calves (Morin et al., 1997; Jaster, 2005; Conneely et al., 2014). This is most likely due to inconsistencies between studies in the total mass of IgG fed and timing of IgG consumption. We aimed to determine whether providing IgG in more than 1 meal to neonatal calves through COL or a 1:1 COL:WM mixture (representing TM) could be used to further increase serum IgG concentrations. All calves consumed equivalent masses of IgG at 2 h after birth, and from 12 to 72 h, COL and MX calves respectively consumed 125.7 and 62.1 ± 3.6 g of IgG/meal every 12 h, whereas WM calves no longer received IgG during feedings. Thus, our experimental design successfully met the condition of our objective. We observed that serum IgG began to diverge between COL, MX, and WM once treatment meals were fed at 12 h. Serum

IgG was greater for COL than for WM early on (by 16 h) and remained elevated for COL for the duration of the experiment. In contrast, the differences in MX and WM serum IgG were only consistently detected after 48 h. We propose that serum IgG became different between MX and WM after 48 h due to different apparent IgG persistencies between these treatments (discussed below). The effects of both the treatment $\times$ time interaction and the treatment on serum IgG support our hypothesis that prolonged IgG provision may be used to increase neonatal serum IgG. Our hypothesis is additionally supported by $C_{\max}$ increasing incrementally with continued IgG consumption and $T_{\max}$ being delayed by 16.1 (COL) and 13.6 (MX) h relative to WM. It is important to note that additional COL or MX feeding at 12 h did not compromise absorptive efficiency between 0 and 24 h compared with WM. As such, prolonged IgG provision during the first day after birth can be used to further increase neonatal serum IgG concentrations without sacrificing the efficiency with which IgG are utilized.

Gut closure begins between 12 and 24 h after birth (Stott et al., 1979a), and it is thought that there is little benefit from feeding additional meals containing IgG if the calf has consumed adequate quantities shortly after birth. Indeed, serum IgG did not differ between calves fed 191.4 g of IgG in 1 colostrum meal at 45 min after birth or in 2 colostrum meals (123 to 127.6 g of IgG at 45 min and 61.5 to 63.8 g of IgG at 6 h after birth; Cabral et al., 2012, 2014). Similarly, serum IgG did not increase by offering TM (IgG content not reported) as early as 3 h or as late as 20 h (56% of calves >12 h) after calves had consumed high-IgG colostrum (≥ 100.3 g of IgG/L) at 7, 8.5, and 10% of their BW (Conneely et al., 2014). Our data contrast with those of Cabral et al. (2012, 2014) and Conneely et al. (2014) but are comparable with other works that demonstrated that a second colostrum feeding can further increase serum IgG (Stott et al., 1979b; Morin et al., 1997; Jaster, 2005; Halleran et al., 2017). In particular, these studies highlight the importance of timing and total IgG ingested to elicit this response. Stott et al. (1979b) noted that a second colostrum feeding 12 h after the first continued to increase serum IgG in calves initially fed 0.5 and 1.0 L of colostrum if the first feeding occurred before 12 h after birth. Interestingly, calves fed 2.0 L of colostrum at birth did not experience a further increase in serum IgG with the subsequent feeding (Stott et al., 1979b). Morin et al. (1997) fed calves 2.0 L of low-IgG (32.9 g of IgG/L) or 2.0 or 4.0 L of high-IgG (60.1 g of IgG/L) colostrum at birth and 2.0 L of high-IgG colostrum at 12 h. These authors found that serum IgG increased in response to the 12-h feeding. The rise between treatments was more pronounced when 2.0 L of high-IgG colostrum rather than 2.0 L of low-IgG colostrum was fed at 0 and 12 h (Morin et al., 1997). Calves that consumed 4.0 and 2.0 L of high-IgG colostrum at 0 and 12 h had a lesser increase in serum IgG following the 12-h meal compared with their counterparts, although absolute serum IgG was greater for this treatment due to the greater mass they consumed early on. It could be that the intestinal capacity to absorb IgG was either saturated or exhausted after consuming a large mass of IgG at 2 h (Besser et al., 1985; Conneely et al., 2014). Although experimental design varied slightly, Jaster (2005) observed similar responses to those of Morin et al. (1997) when feeding high-IgG (IgG = 84.0 g/L) and low-IgG (IgG = 31.2 g/L) colostrum to Jersey calves. In our study, all calves received on average 3.1 L of colostrum and consumed 189.5 ± 7.2 g of IgG in their first feeding. Subsequent feedings to COL and MX calves averaged 2.0 L and, as noted above, provided 125.7 and 62.1 ± 3.6 g of IgG/meal, respectively. Our design most closely matched Morin et al. (1997) and Jaster (2005), though slight differences were present in

the total volume of colostrum and total mass of IgG fed. In addition, our second meal was fed 10 h after the first, within the time frame indicated to be appropriate by Stott et al. (1979a). These factors account for the contrast between our results and previous studies (Cabral et al., 2012, 2014; Conneely et al., 2014). Consequently, we propose that at least one more feeding of IgG in colostrum, a colostrum-whole milk mixture, or possibly TM can be used to further increase serum IgG granted that a substantial amount of IgG is fed within 12 h of the first colostrum meal.

However, our data also indicated that there is little benefit from providing additional meals of colostrum past 24 h to further increase serum IgG, as has been previously suggested (Stott et al., 1979a; Weaver et al., 2000). Following the 24-h meal, we observed that $T_{\max}$ occurred at 29.5 and 27.0 ± 3.4 h after birth for COL and MX calves, respectively, after which serum IgG concentrations remained relatively stable. There was considerable variation in the time that $C_{\max}$ was attained when IgG provision was continued, occurring between 18.0 and 62.5 h for COL calves and between 16.0 and 59.0 h for MX calves. Two MX and 3 COL calves had $C_{\max}$ occur during d 3. However, the extreme maximum serum IgG concentrations observed during d 3 with our calves does not necessarily reflect prolonged intestinal permeability. For instance, dehydration could cause falsely high serum analyte concentrations due to the reductions in plasma volume (Russell and Roussel, 2007). That said, it is interesting that no WM calves exhibited considerable delays in achieving $C_{\max}$, as timing ranged from 9.0 to 19.0 h with this treatment. We suggest that the variation in $T_{\max}$ observed with COL and MX treatments warrants further investigation as, for the present, we are limited in our ability to interpret this data. Overall, our data support that intestinal permeability ceases between 24 and 36 h when calves are fed at 2 and 12 h after birth (Stott et al., 1979a), given that COL and MX $T_{\max}$ did not occur long after 24 h. As AEA_{0-72h} was also decreased by feeding COL or MX compared with WM, feeding colostrum or TM past 24 h is an inefficient strategy for increasing serum IgG.

However, it is self-limiting to focus solely on colostrum and TM feeding as a means to establish passive immunity in the neonatal calf. Colostrum is very caloric and nutrient dense and contains supraphysiological concentrations of beneficial, non-nutritive bioactive compounds (McGrath et al., 2016). It is well suited to support the greatly elevated neonatal metabolism (Roy et al., 1957; NRC, 2001), as well as thermogenesis and growth (Vermorel et al., 1983; Le Dividich et al., 1991; Quigley and Drewry, 1998; Rauprich et al., 2000), during the early period that the calf's glucose-insulin axis is relatively immature (Hammon et al., 2012,

2013) by providing calories via its high fat content (Kehoe et al., 2007; Morrill et al., 2012; McGrath et al., 2016). In addition, the colostrum bioactive fraction is critically important in promoting gastrointestinal tract development (Bühler et al., 1998; Blättler et al., 2001; Steinhoff-Wagner et al., 2014) and possibly modulating neonatal metabolism from the absorption of hormones such as insulin (Pierce et al., 1964; Kirovski et al., 2008), leptin, or adiponectin (Kesser et al., 2015; Liermann et al., 2020). Regarding TM or part-colostrum mixtures, preliminary data indicate that these do positively affect the metabolic and hormonal profiles of neonatal calves (Inabu et al., 2019; Pyo et al., 2020). It is also very clear that TM, colostrum–milk mixtures, or prolonged colostrum feedings promote gastrointestinal development (Yang et al., 2015; Pyo et al., 2020), although the degree of gastrointestinal development with TM or colostrum–milk mixture feeding appears to be equivalent to prolonged colostrum feeding only when an initial meal of colostrum is provided (Yang et al., 2015; Pyo et al., 2020). Prolonged colostrum or TM feeding may also reduce digestive morbidity and subsequent mortality in neonatal calves (Yang et al., 2015), and colostrum supplementation in milk replacer has been associated with decreased diarrhea and antibiotic treatment in preweaned calves (Berge et al., 2009; Chamorro et al., 2017).

Within the current study, we report the novel finding that serum IgG concentrations were more persistent over 72 h when calves were fed COL or MX as opposed to WM. The improved persistency of serum IgG is further supported by WM calves having the lowest total AUC_{0-72h} , total AUC_{12-72h} , and net $I-AUC_{12-72h}$ as well as being the only treatment to have a negative net $I-AUC$ after 12 h after birth. We have derived the equation for apparent IgG persistency by expressing calf serum IgG at 72 h as a proportion of their C_{max} IgG concentrations. Given that considerable between-calf variation in C_{max} and T_{max} was present, these values were both used to standardize the equation so that IgG persistency could be comparable between calves and representative of treatments. Additionally, we are unable to account for differences in plasma volume between calves or reflect alternate IgG reserves (e.g., tears, the alveolar epithelium, or the intestinal lumen; Pedersen, 1973; Besser et al., 1988; Kim and Malik, 2003) and, as such, have termed this measure “apparent” IgG persistency. Although the purpose of our estimate is similar to that of others reporting IgG half-life (9.6 to 28.5 d; Banks, 1982; Butler, 1983; Besser et al., 1988; Murphy et al., 2014), calculating IgG half-life would not have been appropriately represented by our measurements given the short duration of this experiment. To our knowledge, we are the first to report the apparent IgG persistency

during the immediate neonatal phase and, in doing so, demonstrate that IgG concentrations are more persistent when colostrum or a combination of colostrum and whole milk is fed to neonatal calves.

We have derived referent values from prior research (Morin et al., 1997; Jaster, 2005) by simple arithmetic expression of serum IgG at 48 h as a proportion of peak serum IgG at 12 h (Jaster, 2005) or 24 h (Morin et al., 1997; Jaster, 2005). Apparent IgG persistency at 48 h in these studies ranged from 86.0 to 97.8% (Morin et al., 1997) or 85.7 to 99.6% (Jaster, 2005), which is comparable with our own values at 72 h (75.3 to 91.2%). It is interesting to note that in both studies a numerically greater apparent IgG persistency at 48 h was associated with feeding more high-quality colostrum (Morin et al., 1997; Jaster, 2005). However, this association is not confirmed statistically, and as such we cannot draw any conclusions about how prolonged IgG provision affects apparent IgG persistency in neonatal calves through comparisons of our data with those of Morin et al. (1997) and Jaster (2005).

It is unclear why feeding COL or MX increased the apparent IgG persistency in calves compared with feeding WM. Speculatively, it is possible that supplying the gastrointestinal tract with IgG from COL and MX feeding reduced the need for serological IgG to return to the gastrointestinal tract (Besser et al., 1988), thus lowering the flux rate and improving the persistence of serum IgG. Alternatively, the greater nutrient provision with COL and MX rather than WM feeding (Blum and Hammon, 2000; Pyo et al., 2020) might more closely match the high metabolic requirements during the neonatal phase (NRC, 2001), supporting immunological processes and possibly reducing the catabolism of serum IgG. As discussed above, it is unlikely that COL and MX IgG continued to permeate the gastrointestinal tract after 24 h, and we affirm that we do not consider this to be the mechanism by which serum IgG was more persistent when COL and MX were fed. However, regardless of mechanism, greater apparent IgG persistency will only be beneficial to the calf, particularly when it is sustaining the high serum IgG concentrations achieved by feeding COL and MX. Although attaining high serum IgG concentrations during the first 24 h after birth is very clearly important to reduce the incidence of morbidity and mortality (Shivley et al., 2018; Urie et al., 2018), it is also likely that maintaining high serum IgG is necessary to prevent early-life morbidity. Improving apparent IgG persistency and maintaining high serum IgG concentrations could decrease the frequency of digestive disorders during the first 2 wk after birth (Urie et al., 2018). Last, we must emphasize that COL and MX performed equivalently and with similar efficiency to improve apparent IgG persistency,

which ultimately resulted in similar total AUC_{0–72h}, total AUC_{12–72h}, and serum IgG at 72 h between these treatments, despite serum IgG being greater during the first day after birth for COL calves. Consequently, it appears that COL and MX feeding are both equally effective in increasing serum IgG and improving apparent IgG persistency.

CONCLUSIONS

All calves within the current study achieved high serum IgG concentrations early on (within 6 h after birth); however, feeding COL or MX 10 h after the initial colostrum meal further increased serum IgG concentrations without compromising the efficiency with which IgG was absorbed in that first 24 h after birth. Although IgG was not likely absorbed after 24 h after birth, it is very interesting that feeding COL or MX during this time improved the degree to which IgG persisted in serum. The reasons for this are unclear and warrant further investigation. We recommend that calves be fed at least 62 g of IgG in colostrum, a colostrum–milk mixture, or TM at 12 h after birth to increase serum IgG concentrations, granted that an initial colostrum meal (supplying a minimum of 190 g of IgG) was already provided shortly after birth. Prolonged feeding of COL or MX past 24 h may be necessary to maintain high serum IgG concentrations in neonatal calves.

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