Effects of colostrum management on transfer of passive immunity and the potential role of colostrum bioactive components on neonatal calf development and metabolism

A.J. Fischer-Tlustos, A. Lopez, K.S. Hare, K.M. Wood, and M.A. Steele

Abstract: Neonatal dairy and beef calves are required to ingest adequate volumes of high-quality colostrum during their first hours of life to acquire transfer of passive immunity (TPI). As such, immunoglobulin G (IgG) has largely been the focus of colostrum research over recent decades. Yet, little is known about the additional bioactive compounds in colostrum that potentially influence newborn calf development and metabolism. The purpose of this narrative review is to synthesize research regarding the effects of colostrum management practices on TPI, as well as to address the potential role of additional colostrum bioactive molecules, including oligosaccharides, fatty acids, insulin, and insulin-like growth factor-I, in promoting calf development and metabolism. Due to the importance of IgG in ensuring calf immunity and health, we review past research describing the process of colostrogenesis and dam factors influencing the concentrations of IgG in an effort to maximize TPI. We also address the transfer of additional bioactive compounds in colostrum and prepartum management and dam factors that influence their concentrations. Finally, we highlight key areas of future research for the scientific community to pursue to ultimately improve the health and welfare of neonatal dairy calves.

Key words: immunoglobulin G, colostrogenesis, bioactive compounds, oligosaccharides, fatty acids.

Résumé : Les veaux laitiers et de boucherie nouveau-nés nécessitent la consommation d'un volume adéquat de colostrum de grande qualité au cours des premières heures de vie afin qu'il y ait transfert d'immunité passive. Par conséquent, l'immunoglobuline G (IgG) a grandement été l'objet des recherches sur le colostrum dans les décennies récentes. Par contre, il y a très peu de connaissances au sujet des autres composés bioactifs dans le colostrum qui pourraient potentiellement influencer le développement et le métabolisme du veau nouveau-né. Le but de cette revue narrative est de synthétiser la recherche sur les effets des pratiques de gestion du colostrum sur le transfert de l'immunité passive, ainsi que d'aborder le rôle potentiel des molécules additionnelles bioactives du colostrum, incluant les oligosaccharides, les acides gras, l'insuline et le facteur de croissance I qui s'apparente à l'insuline, dans la promotion du développement et du métabolisme des veaux. Vu l'importance des IgG pour assurer l'immunité et la santé des veaux, nous passons en revue les recherches passées qui décrivent le processus de colostrogénèse et les facteurs de la mère qui influencent les concentrations d'IgG dans un effort pour maximiser le transfert de l'immunité passive. Nous abordons aussi le transfert de composés bioactifs additionnels dans la gestion du colostrum et la gestion de fin de gestation, ainsi que les facteurs reliés à la mère qui influencent leurs concentrations. Finalement, nous soulignons les domaines clés de la recherche future que la communauté scientifique peut poursuivre afin d'arriver à améliorer la santé et le bien-être des veaux laitiers nouveau-nés. [Traduit par la Rédaction]

Mots-clés : immunoglobuline G, colostrogénèse, composés bioactifs, oligosaccharides, acides gras.

Introduction

Neonatal ruminants, including beef and dairy calves, can only acquire passive immunity through the

absorption of immunoglobulins, specifically immunoglobulin G (IgG; [Davis and Drackely 1998](#)). The bovine cotyledonary synepithelial placenta is composed of three

Received 14 September 2020. Accepted 3 December 2020.

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maternal and three fetal layers, preventing the passive transfer of immunoglobulins to the calf in utero (Arthur 1996). As a result, the neonatal calf is born with a naïve immune system and depends on the feeding of adequate volumes [$\sim 10\%$ of body weight (BW), 3–4 L] of high-quality colostrum containing ≥ 50 g of IgG·L⁻¹ and low bacterial ($<100\,000$ cfu·mL⁻¹) and coliform ($<10\,000$ cfu·mL⁻¹) counts within the first 2 h of life (Weaver et al. 2000; Godden et al. 2019) to ensure successful transfer of passive immunity (TPI). In contrast, TPI in beef calves relies on timely voluntary consumption of colostrum. Beef calves typically voluntarily consume approximately half of what a dairy calf would consume at first colostrum feeding (McGee and Earley 2019), and therefore, the greater IgG concentration in beef colostrum may be required to achieve successful TPI.

It is well known that TPI is crucial in preventing and reducing calf mortality and morbidity (Wells et al. 1996; Raboisson et al. 2016; Urie et al. 2018a) and promoting calf growth (Robison et al. 1988). Despite the importance of achieving TPI, failure of transfer of passive immunity (FTPI) remains relatively common on dairy farms. A recent cross-sectional study demonstrated that FTPI — defined using the traditional serum total protein (STP) cut-point of <5.2 g·dL⁻¹ (Buczinski et al. 2018) — occurred in 24% of calves on Ontario dairy farms (Renaud et al. 2020). In addition, research in beef herds has demonstrated that approximately 16.1% and 19% of calves from western (Waldner and Rosengren 2009) and eastern (Filteau et al. 2003) Canada, respectively, experienced FTPI as classified using a FPTI threshold of 16 g·L⁻¹ (Waldner and Rosengren 2009) and the traditional dairy FPTI threshold of 10 g of IgG per L (Filteau et al. 2003).

As highlighted above, TPI in dairy cattle has been traditionally defined as serum IgG concentrations ≥ 10 g of IgG per L or a STP value ≥ 5.2 g·dL⁻¹ (Gay 1983; Tyler et al. 1996; Buczinski et al. 2018), whereas, in beef cattle production systems, thresholds for TPI are less described and have historically relied upon recommendations from dairy calves. Recent work in dairy calves (Furman-Fratczak et al. 2011; Chigerwe et al. 2015) and a multitude of past research in beef calves (Dewell et al. 2006; Waldner and Rosengren 2009; Todd et al. 2018) have demonstrated that the traditional thresholds may not be adequate in defining TPI as a protective effect of serum IgG has been found at cut-points of 15 g·L⁻¹ or greater. This suggests that FPTI, and its associated increased risk of morbidity and mortality, may affect a greater amount of dairy and beef calves than previously reported. Upon recent evaluation of the efficacy of current FPTI cut-off points, researchers demonstrated that no differences in mortality existed between calves with serum IgG concentrations <10 g·L⁻¹ versus 10.0–17.9 g·L⁻¹, further demonstrating that the current dichotomous standard for FPTI is ineffective at predicting mortality risk (Lombard et al. 2020). As such, Lombard et al. (2020) proposed the following serum IgG

cut-point categories: excellent TPI (>25.0 g·L⁻¹), good TPI (18.0–24.9 g·L⁻¹), fair TPI (10.0–17.9 g·L⁻¹), and poor TPI (<10.0 g·L⁻¹) with the expectation that $>40\%$, $\sim 30\%$, $\sim 20\%$, and $<10\%$ of calves within each category, respectively, meet these standards at the herd level (Lombard et al. 2020). However, only 33 out of 103 US dairy herds met these recommendations from 2014 to 2015 (Lombard et al. 2020). Therefore, there will continue to be a further need to improve colostrum and newborn calf management to achieve or surpass the “good” cut-point category to meet new herd-level standards.

In addition to improving colostrum management in the dairy and beef sectors, there is a significant opportunity to improve colostrum quality itself. As previously mentioned, colostrum containing ≥ 50 g·L⁻¹ of IgG is considered high quality (as reviewed by Godden 2008). Yet, colostral IgG content can widely vary, with colostrum collected from US dairy farms ranging from 7.1 to 159 g·L⁻¹ and 16% of samples containing less than 50 g·L⁻¹ (Quigley et al. 2013). Although beef cattle colostrum contains approximately 1.5-fold greater concentrations of IgG than dairy cattle, there is also a tremendous variation in quality (approximately 50– >200 g·L⁻¹) and quantity (<1 L to about 6 L; McGee and Earley 2019). There are various factors that affect colostral IgG concentrations in dairy cattle and beef cattle; which are further discussed. However, research pertaining to the influence of specific prepartum dam factors on colostrogenesis — the process of colostrum formation — and ultimately the concentration of IgG in colostrum, is scarce.

Although colostrum and colostrogenesis research has largely focused on IgG, the benefits of colostrum feeding can also be attributed to bioactive factors that promote calf growth and development (Blum and Hammon 2000). In terms of macronutrients, fat accounts for the largest source of energy in colostrum, providing an estimated 63% of the digestible energy supply, whereas protein supplies an estimated 25% (K. Hare et al. unpublished data). Fat is essential in fueling the metabolism and mitigating thermoregulation of the newborn calf (Roy 1990; Quigley and Drewry 1998), and specific fatty acids (FA) that are elevated in colostrum (Contarini et al. 2014; O’Callaghan et al. 2020) can confer benefits on antioxidant status and immune response during initial weeks of life (Opgenorth et al. 2020b). Apart from the lipid fraction, colostrum contains up to 72× more oligosaccharides (OS) than whole milk (WM) (Fischer-Tlustos et al. 2020a). Bovine colostrum OS may accelerate the establishment of a healthy gut microbiome in newborn calves (Fischer et al. 2018a) and have been hypothesized to play a role in assisting in the intestinal uptake of IgG (Gill et al. 1999; Feeney et al. 2019). Furthermore, colostrum contains elevated levels of hormones, such as insulin (Blum and Hammon 2000) and insulin-like growth factor-I (IGF-I; Bühler et al. 1998; Jehle et al. 1999), both of which have positive effects on gastrointestinal cell proliferation and intestinal growth as discussed herein.

Table 1. Levels of bioactive molecules in colostrum (milking 1) compared with whole milk^a and their proposed functions.

Bioactive compound	Colostrum	Whole milk	Proposed function
IgG (g·L ⁻¹)	94.1	1.2	Passive immunity
Neu5Ac-glycosylated IgG (μM)	~1150	~210	Facilitating intestinal uptake of IgG
Fat (%)	5.7	4.3	Energy, thermoregulation
Fat (g·kg ⁻¹)	62.9	41.8	Energy, thermoregulation
ω-3 FA (%)	0.63	0.35	Immune modulation, antioxidant capacity
IGF-I (μg·L ⁻¹)	310	<2	Intestinal development
Insulin (μg·L ⁻¹)	65	1	Promote postnatal growth, gut development
3'SL (μg·mL ⁻¹)	592.4	41.2	Prebiotic, immune modulation, pathogen inhibition
Nucleotides (μmol·dL ⁻¹)	258.7	15.6	Immune function, gastrointestinal development
5'UMP (μmol·dL ⁻¹)	18.63	2.92	Modulation of immune function
miRNA (total No.)	102	53	Gastrointestinal development, immune modulation

Note: Neu5Ac, 5-N-acetylneuraminic acid; FA, fatty acid; IGF-I, insulin-like growth factor-I; 3'SL, 3'sialyllactose; 5'UMP, uridine 5'monophosphate; miRNA, microRNA.

^aIgG, fat (%) and g·kg⁻¹), and 3'SL are reported in [Fischer-Tlustos et al. \(2020a\)](#); Neu5Ac-glycosylated IgG is reported in [Takimori et al. \(2011\)](#); ω-3 FA % is reported in [Hare et al. \(2019a\)](#); IGF-I and insulin concentrations are reported in [Blum and Hammon \(2000\)](#); nucleotide concentrations are reported in [Gill et al. \(2011\)](#); total number of miRNA is reported in [Izumi et al. \(2012\)](#).

Research elucidating the effects of colostrum nutritive and bioactive factors, beyond IgG, on newborn calf development and health, and the prepartum dam factors that influence their transfer and (or) production in the bovine mammary gland, is scarce. For this reason, this narrative review will encompass a summary of the current literature describing the process of colostrogenesis, pertaining to IgG, and colostrum management practices that ensure TPI, as well as the effects of nutritional and bioactive compounds in colostrum on the neonatal calf and dam factors that may influence their transfer to and (or) synthesis in the bovine mammary gland.

Immunoglobulin G

Colostrogenesis: immunoglobulin G transfer into colostrum

Colostrogenesis is the process of colostrum formation in the mammary gland ([Baumrucker and Bruckmaier 2014](#)). It has also been stated that colostrogenesis is the process where immunoglobulins, specifically, are transferred from the cow's circulation into the mammary gland ([Barrington et al. 2001](#)). Bovine colostrum composition is not constant among cows and varies greatly in IgG concentration ([Kehoe et al. 2007](#); [Morrill et al. 2012](#)), nutritional components ([Kehoe et al. 2007](#)), and bacteria content ([Elizondo-Salazar and Heinrichs 2009](#)). Colostrum has a unique composition and one of its major differences compared with mature milk has been attributed to its greater IgG concentration ([Table 1](#); [Barrington et al. 2001](#)). Colostrum has an average IgG concentration of 50–70 g·L⁻¹, accounting for 70%–80% of total protein ([Barrington et al. 2001](#)), whereas mature milk has an IgG concentration range of 1.2–3.3 g·L⁻¹ ([Whitney et al. 1976](#)). In contrast, colostrum has low IgM and IgA concentrations (3.0 and 0.4 g·L⁻¹,

respectively; [Butler 1994](#)). Various results from [Kehoe et al. \(2007\)](#), [Swan et al. \(2007\)](#), [Baumrucker et al. \(2010\)](#), and [Morrill et al. \(2012\)](#) have reported a substantial variation in mean colostrum IgG concentrations in dairy cows (34.96, 76.7, 37.5, and 68.6 g·L⁻¹; respectively).

Timing of colostrogenesis

It is known that bovine colostrum is produced and accumulated during late pregnancy ([Baumrucker and Bruckmaier 2014](#)). Colostrum formation occurs during Lactogenesis I, which is the event in which cells in the mammary gland differentiates and changes from a non-secretory to a secretory status ([Tucker 1981](#)). Lactogenesis I is part of the various differentiation processes that occur during lactation, including Lactogenesis I (differentiation), Lactogenesis II (lactation), and involution ([Baumrucker and Bruckmaier 2014](#)). However, the exact time of colostrogenesis onset is unknown as various reports state that it may begin from 3 to 7 wk prior to calving ([Brandon et al. 1971](#); [Sasaki et al. 1976](#); [Barrington et al. 2001](#)).

Immunoglobulin G₁ and G₂ transferred to colostrum are derived from maternal circulation ([Fig. 1A](#); [Butler 1983](#)), and it has been reported that IgG transport begins weeks prior to parturition and peaks 1–3 d before calving ([Brandon et al. 1971](#); [Sasaki et al. 1976](#)). Recently, [Baumrucker and Bruckmaier \(2014\)](#) attempted to quantify colostrogenesis as beginning when IgG concentrations in mammary secretions are greater than IgG concentrations in maternal circulation. The decreased IgG concentration in the dam's serum in comparison with its mammary secretion occurs at different times prior to parturition among animals ([Baumrucker and Bruckmaier 2014](#)), which could partially account for the distinct ability of specific animals to produce higher

Fig. 1. A schematic of the synthesis and (or) transfer of specific bioactive compounds in the bovine mammary gland and their absorption and effects in the neonatal calf enterocyte as created using Adobe Illustrator (CC 2018). (A) Synthesis of sialylated oligosaccharides (Huizing 2005; Smilowitz et al. 2014), fatty acids (reviewed in Bauman and Grinari 2003), and transport of immunoglobulin G (Butler 1983; Ollivier-Bousquet 1998), insulin (Malven et al. 1987), and IGF-I (Malven et al. 1987; Prosser et al. 1991; Weber 2012) in the bovine mammary gland and their transport into bovine colostrum. (B) Absorption and effects of colostral oligosaccharides (Gill et al. 1999; Martin et al. 2002; Marbocal et al. 2010, 2011; Yu et al. 2013), IgG (Cervenak and Kacsokovics 2009; Tzaban et al. 2009), insulin (Pierce et al. 1964; Shulman 1990; Huo et al. 2006; Kirovski et al. 2008), IGF-I (Roffler et al. 2003; Pyo et al. 2020), and fatty acids [Gooden et al. 1971; De Santis et al. 2015 (review paper)] in the neonatal calf intestine. Dashed arrows represent proposed mechanisms/pathways, and solid arrows represent mechanisms/pathways that are well established. CMP, cytidine monophosphate; OS, oligosaccharide; SA, sialic acid; ST, sialyltransferase; IgG, immunoglobulin G; FcR, Fc receptor; INS, insulin; INSR, insulin receptor; IGF-I, insulin-like growth factor-I; IGF-IR, insulin-like growth factor-I receptor; FA, fatty acid; NEFA, non-esterified fatty acid; TG, triglyceride; LPL, lipoprotein lipase; MFG, milk fat globule.

amounts of colostral IgG (Kehoe et al. 2007; Baumrucker et al. 2010). It is thought that IgG₁ transfer into the mammary secretory lumen occurs by the receptor complex known as the neonatal crystallizable fragment receptor (FcRn; Baumrucker and Bruckmaier 2014), and that transcytosis is responsible for the mass appearance of IgG₁ in colostrum (Fig. 1A; Ollivier-Bousquet 1998). Specifically, FcRn are located within endosomes in which attachment and transport of IgG₁ molecules occurs (Baumrucker and Bruckmaier 2014). Thereafter, colostral IgG₁ is transferred to the neonate by intestinal cells binding to IgG₁ molecules and forming an endosome, which is transcytosed to the apical side of the cell (Fig. 1B; Tzaban et al. 2009; Baumrucker and Bruckmaier 2014).

Factors influencing colostrogenesis and colostrum composition

Various factors affect colostrum composition, yet, most research focuses specifically on IgG concentration or IgG mass. Few studies, such as Dunn et al. (2017), have characterized the factors that affect colostrum components apart from IgG concentration, including fat, protein, and lactose concentration. Colostrum composition in dairy cattle is affected by parity, dry period length, colostrum volume, breed (Weaver et al. 2000), vaccination protocols (Dunn et al. 2017), disease exposure, diet (Mann et al. 2016), individual variation (Parrish et al. 1950), colostrogenesis onset (Baumrucker and Bruckmaier 2014), individual farm variation (Gulliksen et al. 2008), systematic and endocrine regulation (Guy et al. 1994a, 1994b). Whereas factors previously associated with colostrum composition in beef cattle are breed, parity, and body condition score (reviewed by McGee and Earley 2019).

A multitude of management practices have been associated with differences in colostral IgG concentration. Controlled studies have largely found no differences in dry period length (i.e., a short, <6 wk dry period compared with a conventional, ~8 wk dry period) on colostrum quality (Klusmeyer et al. 2009; Shoshani et al. 2014) and serum IgG concentrations of calves (Mayasari et al. 2015; O'Hara et al. 2019). However, Morrill et al. (2012) determined that dam parity can have a large influence on colostral IgG concentrations, with reported mean colostrum IgG concentrations for first, second, and third parity dams of 42.4, 68.6, and 95.9 g·L⁻¹, respectively. Yet, Morrill et al. (2012) did not find differences in IgG concentration among breeds and reported similar mean colostral IgG values for Holstein and Jersey cows of 74.2 and 65.8 g·L⁻¹, respectively. Producing large volumes of colostrum likely dilutes the colostrum IgG concentration (Guy et al. 1994a), an affect that may also attribute to the variation in colostral IgG when colostrum is collected at differing times following parturition (Baumrucker et al. 2010). Yet, Quigley et al. (1994) found that volume and IgG concentration were not correlated in colostrum from Jersey cattle. However, the possible

negative relationship between colostrum volume and colostral IgG concentration could be the result of the onset of Lactogenesis II during parturition (Quigley and Drewry 1998). If Lactogenesis II occurs around parturition, milk may begin accumulating in the udder and consequently dilute colostrum and its IgG concentration (Guy et al. 1994b; Winger et al. 1995). Although the factors controlling colostrum yield are not well understood, it is pertinent to determine dry cow management strategies that maximize colostrum yield while maintaining adequate IgG concentrations to ensure TPI in neonatal calves.

Existing management, environmental, and nutritional factors associated with colostrum composition have been reported throughout previous years, but strategic interventions that enhance colostrum composition have not yet been employed. There is clear evidence that colostrum varies among cows, farms, and geographical regions; as a result, there must be specific factors or metabolic components controlling this degree of variation. Specific experiments researching individual factors and their potential role in altering composition are needed. In addition, it is known that changes in the nutrition and management practices during the dry period affect overall colostrum composition, but the specific mechanisms controlling the appearance of distinct colostral immune and bioactive components is not clear.

Ensuring transfer of passive immunity

The transfer of immunoglobulins is mainly composed of two molecular processes: (1) maternal: secretion and concentration of IgG in colostrum, and (2) offspring: transport of absorbed intestinal IgG into the systemic circulation and tissues of the neonatal calf (Figs. 1A, 1B; Besser and Gay 1994). Specifically, immunoglobulins are absorbed in the small intestine (Bush and Staley 1980); however, whether this process is a specific, receptor-mediated process, or unspecific remains controversial. For decades, it was assumed that intestinal IgG absorption occurred via non-specific pinocytosis, in which intestinal cells at the basal side of the intestinal cell enclose and form an endosome containing IgG molecules (Cervenak and Kacskovics 2009; Tzaban et al. 2009) and are thereafter transported to the calf's blood stream through the thoracic duct (Besser and Gay 1994). In rats and humans, intestinal IgG absorption occurs via a specific receptor-mediated process via FcRn (Simister and Rees 1985; Shah et al. 2003). In neonatal calves, research has provided evidence of a specific, receptor-mediated intestinal transport of IgG carried out by specialized vesicles (Jochims et al. 1994); yet, whether this process occurs via FcRn remains to be elucidated. However, the rate of IgG transfer into peripheral circulation can be affected by time at first feeding (Fischer et al. 2018b), mass of IgG consumed (Quigley and Drewry 1998), and level of colostrum bacterial contamination (Gelsinger et al. 2015; Saldana et al. 2019).

Quantity, quality, and quickness of colostrum feeding

It is recommended to feed newborn dairy calves 4 L of colostrum containing an IgG concentration $>50 \text{ g}\cdot\text{L}^{-1}$ or at 10%–12% of birth BW (as reviewed by [Godden et al. 2019](#)). Currently, colostrum feeding practices among studies are not constant, as some studies feed calves according to a specific volume: 4 L ([Lago et al. 2018](#); [Saldana et al. 2019](#)) or 3 L ([Mokhber-Dezfooli et al. 2012](#); [Desjardins-Morrisette et al. 2018](#)); or as a proportion of calf BW ([Fischer et al. 2018b](#); [Hare et al. 2020](#)). Feeding a specific amount to all calves has been controversial, as it has been stated that feeding large amounts of colostrum can slow the emptying rate of colostrum from the abomasum, which could reduce IgG absorption due to increased time to reach the site of absorption in the small intestine ([Mokhber-Dezfooli et al. 2012](#)). It is also hypothesized that feeding larger amounts of colostrum or a high total IgG mass could comprise the apparent efficiency of absorption (AEA) of colostral IgG ([Lopez et al. 2020](#)). [Conneely et al. \(2014\)](#) fed calves different volumes of colostrum at 7%, 8.5%, or 10% of birth BW. The authors reported that calves fed colostrum at 8.5% of birth BW achieved the greatest serum IgG concentration at 24 h, as well as the greatest AEA compared with calves fed at 7% or 10% of BW. However, colostrum IgG concentrations in this study were not standardized among treatment groups and on average ranged from 100.3 ± 43.5 (mean $\pm$ standard deviation) to $120.4 \pm 47.2 \text{ g}\cdot\text{L}^{-1}$ ([Conneely et al. 2014](#)). In addition, two thirds of calves were provided with more IgG by feeding transition milk (IgG content not reported) anywhere from 3 to 20 h postnatal (56% of calves $>12 \text{ h}$). The findings from [Lopez et al. \(2020\)](#) and [Conneely et al. \(2014\)](#) suggest a possible physiological limit to the amount of IgG that can be absorbed by enterocytes, likely due to the saturation of IgG receptors ([Leece 1973](#); [Jaster 2005](#)); however, further research utilizing a pooled source of maternal colostrum with a standardized IgG concentration fed at different volumes is required to determine if this physiological phenomenon of “gut saturation” occurs. Yet, it is important to note that more than 80% of US producers do not measure the quality of colostrum ([Urie et al. 2018b](#)) on farm. To ensure that calves do not experience FPTI and its associated effects, especially when average or low-quality colostrum may unknowingly be used, it is recommended that calves are consistently fed 3–4 L ($\sim 10\%$ BW) of colostrum (see review by [Godden et al. 2019](#)). Small calves (i.e., Jersey calves or Holstein calves $<30 \text{ kg BW}$) should be fed two meals of colostrum based on BW (~ 2 to 3 L per meal) within the first 12 h of life, with producers ensuring that colostrum IgG concentration is $>50 \text{ g}\cdot\text{L}^{-1}$ ([Jaster 2005](#)).

In addition to considering the volume fed to a calf, colostrum IgG concentration must be considered equally because the total IgG mass consumed is the determining factor in circulating serum IgG concentration at 24 h. Maternal colostrum quality is based on its IgG

concentration (reviewed by [Godden 2008](#)). Recently, [Lombard et al. \(2020\)](#) concluded that the threshold to determine colostrum quality should remain at $\geq 50 \text{ g}\cdot\text{L}^{-1}$, as previously defined in a review by [McGuirk and Collins \(2004\)](#). In addition to adequate IgG concentration, high-quality colostrum can also be defined as colostrum containing total bacteria and coliform counts $<100\,000$ and $<10\,000 \text{ cfu}\cdot\text{mL}^{-1}$, respectively (reviewed by [McGuirk and Collins 2004](#)). The impact of bacterial counts on TPI has been researched ([Gelsinger et al. 2014](#); [Gelsinger et al. 2015](#); [Saldana et al. 2019](#)), and it is hypothesized that high bacterial counts may interfere with immunoglobulin absorption ([Corley et al. 1977](#); [James et al. 1981](#); [Gelsinger et al. 2014](#)). Research has concluded that heat treatment of colostrum at 60°C for 30–60 min to reduce its bacterial count does not affect colostral IgG concentrations but positively affects IgG absorption ([Godden et al. 2012](#); [Gelsinger et al. 2014](#); [Armengol and Fraile 2016](#)), as well as reduces the incidence of morbidity and mortality ([Godden et al. 2012](#); [Armengol and Fraile 2016](#)). However, a 2018 study reported that only 5% of Canadian dairy operations feed heat-treated colostrum, despite its well-known benefits of reducing harmful bacterial counts and improving TPI ([Winder et al. 2018](#)).

Along with colostrum quality and quantity, the quickness of first colostrum feeding is a primary factor influencing the degree of TPI as enterocytes lose the ability to absorb intact macromolecules as time after birth increases ([Staley and Bush 1985](#)). In 2014, [Osaka et al.](#) found that calves fed colostrum within the first hour of life, from 1 to 6 h or 6 to 12 h of life did not differ in serum IgG concentrations. The authors concluded that AEA in the initial hours of life is influenced to a greater extent by mass of IgG rather than age at first colostrum feeding. However, colostrum intake widely varied among calves (1.5–5.2 L) and colostral IgG concentrations were not standardized ([Osaka et al. 2014](#)). Recently, [Fischer et al. \(2018b\)](#) fed calves pooled colostrum (62 g of $\text{IgG}\cdot\text{L}^{-1}$) at 7.5% of birth BW ($\sim 200 \text{ g}$ of IgG total) either within the first hour of life, at 6 h or at 12 h of life and demonstrated that calves fed within the first hour of life had the greatest serum IgG concentrations and AEA compared with calves fed at 6 and 12 h. Contrary to expectations, serum IgG and AEA were not different between calves fed at 6 and 12 h. Despite the discrepancies between studies, industry recommendations typically state to feed colostrum within 1–2 h after birth ([Godden et al. 2019](#)). However, further research is needed to determine the calf and environmental factors that influence gut closure over the first 12 h of life to implement optimal colostrum management strategies that increase the chances of achieving successful TPI.

Additional considerations: feeding method and extended colostrum feeding

The quantity, quality, and quickness of colostrum feeding are among the most common factors considered

in proper colostrum management practices. However, United States Department of Agriculture-National Animal Health Monitoring System (USDA-NAHMS) research has clearly demonstrated that additional factors can impact TPI (Shivley et al. 2018). Godden et al. (2009) was the first controlled study to investigate the effect of feeding method on TPI, demonstrating that feeding 1.5 L (100 g of IgG) of colostrum replacer (CR) via esophageal tube or nipple bottle resulted in FPTI rates of 58.3% and 0%, respectively. However, feeding 3 L (200 g of IgG) of CR via esophageal tube or nipple bottle resulted in no differences in TPI (Godden et al. 2009) as corroborated by Desjardins-Morrisette et al. (2018). Similarly, Bonk et al. (2016) found no differences between feeding methods when 3.5 L of pooled, maternal colostrum was fed to calves. Researchers have suggested that feeding small volumes of colostrum or CR via an esophageal tube causes a delay in a large proportion of the meal, and consequently IgG, reaching the small intestine (Godden et al. 2009; Sharifi et al. 2009). Indeed, feeding 3 L of CR by either nipple bottle or tube feeding did not alter the rate of abomasal emptying, confirming that a delay in abomasal emptying does not occur when moderate (~3 L) volumes are fed (Desjardins-Morrisette et al. 2018). At the population level, feeding colostrum via esophageal tube and nipple bottle is associated with FPTI rates of 9% and 14%, respectively (Shivley et al. 2018), indicating that the risk of FPTI may be reduced when esophageal tube feeding colostrum is consistently practiced. Esophageal tube feeding is an efficient, appealing strategy as it only takes ~1 to 5 min to feed 3 L of colostrum compared with bottle feeding, which requires an average of 18 min per meal (K. Hare et al. unpublished data; Desjardins-Morrisette et al. 2018). It may be possible that esophageal tube feeding allows for a more timely and consistent delivery of colostrum compared with feeding via nipple bottle, thus conferring benefits on FPTI rates at the population level. Yet, as controlled studies have shown no differences in serum IgG concentrations via esophageal tube or bottle feeding, either feeding method can be used to ensure adequate passive transfer when >3 L of colostrum is fed within the first hours of life.

Multiple studies have also demonstrated that providing a second colostrum feeding can increase serum IgG concentrations (Stott et al. 1979; Morin et al. 1997; Halleran et al. 2017; Hare et al. 2020). Halleran et al. (2017) fed calves one 4 L meal of colostrum within 4 h of birth or 3.7 L within 4 h, followed by 1.9 L prior to 12 h of birth. The authors demonstrated that calves fed two colostrum meals had markedly higher serum IgG concentrations (39.5 ± 1.7 g·L⁻¹) compared with their one meal counterparts (23.5 ± 1.3 g·L⁻¹). Recently, Hare et al. (2020) standardized the amount of pooled, maternal colostrum fed (7.5% BW) to all calves at 2 h postnatal, after which calves were fed subsequent meals of either pooled, maternal colostrum or WM at 5% BW at 12 h

intervals for 3 d of life. Calves fed subsequent meals of colostrum had greater maximum serum IgG concentrations (30.4 ± 0.8 g·L⁻¹) compared with calves fed WM (23.9 ± 0.8 g·L⁻¹). Despite all calves achieving successful TPI as defined by the traditional serum IgG cut-point of 10 g·L⁻¹, providing colostrum after 24 h of life conferred little additional benefit to increasing serum IgG concentrations. Thus, although providing colostrum after 24 h is an inefficient strategy to improve TPI, the authors suggest a minimum of one additional meal of colostrum should be provided within 12 h of the initial colostrum meal to increase serum IgG (Hare et al. 2020). Yet, it is important to note that serum IgG concentrations do not differ among calves fed 191.4 g of IgG in a single meal at 45 min of life compared with calves fed the same total IgG mass split over two meals (~120 g of IgG at 45 min and ~65 g of IgG at 6 h; Cabral et al. 2012, 2014). This implies that studies in which positive effects on TPI were observed (Stott et al. 1979; Morin et al. 1997; Halleran et al. 2017; Hare et al. 2020) may be largely due to differences in total IgG mass consumed.

In summary, it is important to consider the method for colostrum feeding used depending on the colostrum volume fed. In dairy calves, 3 L of colostrum containing >50 g of IgG·L⁻¹ is the minimum volume to be consumed in the first hours of life via either esophageal tube or nipple bottle. As well, it is fundamental to ensure that colostrum is being fed during the first hours of life when the gut is hyperpermeable to IgG; however, providing a second high-quality colostrum meal within 12 h of the initial meal may confer additional benefits to TPI. To improve colostrum quality through reduced bacterial contamination, heat-treatment of colostrum is a practice that should be further considered by dairy producers.

Colostrum bioactive components

In this review, colostrum bioactive components are defined as compounds or molecules (apart from nutrients) that are present in colostrum in micro quantities that stimulate physiological responses systemically or locally within the gastrointestinal tract of the neonate. Although there is an abundance of bioactive compounds in bovine colostrum (see reviews by Blum and Hammon 2000; McGrath et al. 2016), this review will focus specifically on the potential bioactivity of OS, fatty acids, hormones belonging to the insulin-relaxin superfamily, unique classes of proteins within the colostrum proteome, microRNAs, and nucleotides, on calf development.

Oligosaccharides and sialic acid

Bovine OS are small polymers of simple sugars that largely consist of a lactose backbone elongated by one or more sialic acid residues and are present at high concentrations in colostrum (~1.0 g·L⁻¹) compared with WM (<0.2 g·L⁻¹; Nakamura et al. 2003; Fischer-Tlustos et al. 2020a). Sialic acids are a family of more than 50 structurally different nine-carbon sugars, with the most

abundant being 5-N-acetylneuraminic acid (Neu5Ac) and 5-N-glycolneuraminic acid (Peri et al. 2018). When subjected to neuraminidase treatment, bovine colostrum contains 27–34 nmol·mL⁻¹ of Neu5Ac and 1.2–2.7 nmol·mL⁻¹ of 5-N-glycolneuraminic acid, demonstrating that Neu5Ac is the prominent sialic acid in bovine colostrum (Vicaretti et al. 2018). There are four primary Neu5Ac-containing OS present at significant concentrations in colostrum, including 3'sialyllactose (3'SL), 6'sialyllactose, 6'sialyllactosamine, and disialyllactose (Martin-Sosa et al. 2003; Tao et al. 2009; Fischer-Tlustos et al. 2020a). Among these four primary OS in colostrum, 3'SL accounts for over 55%, whereas 6'sialyllactose, disialyllactose, and 6'sialyllactosamine only account for 10%, 22%, and 13%, respectively (Fischer-Tlustos et al. 2020a). However, recent research has identified up to 62 different colostrum and milk OS resolvable by capillary electrophoresis, including sulfate-, N-acetylglucosamine-, and fucose-containing OS, albeit present at low concentrations in colostrum (Vicaretti et al. 2018; Fischer-Tlustos et al. 2020b). Yet, the concentrations of specific OS required to evoke physiological responses, as discussed below, in the neonatal calf is currently unknown.

Recently, a wide array of research has been conducted in regard to the beneficial effects that human milk OS have on infant health and physiology (as reviewed by Zivkovic et al. 2011; Plaza-Diaz et al. 2018). Specifically, promoting the growth and development of the intestinal microbiota is one of the most well-established roles of human milk OS in newborn infants (Zivkovic et al. 2011). In contrast, the potential role of bovine colostrum in promoting the initial establishment and subsequent development of the calf intestinal microbiome has only recently been characterized (Malmuthuge et al. 2015; Fischer et al. 2018b; Ma et al. 2019; Song et al. 2019). Importantly, moderate correlations have been observed between colostrum OS and the beneficial bacteria, *Bifidobacterium*, in the small intestine of calves within the first 12 h of life, suggesting that bovine colostrum OS may be important in establishment of the calf intestinal microbiome (Fischer et al. 2018a). In addition to *Bifidobacteria* (Yu et al. 2013), species belonging to the genus *Lactobacillus* can utilize OS monosaccharide units, including glucose and galactose, and possibly trisaccharide OS to promote their growth (Schwab and Ganzle 2011; Boudry et al. 2017), whereas *Bacteroides* uniquely cleave and catabolize sialic acid residues (Marcobal et al. 2010; Marcobal et al. 2011), possibly conferring a selective advantage for this beneficial bacterial genus within the neonatal calf gastrointestinal tract (GIT) (Fig. 1B).

Promoting the establishment of a balanced neonatal microbiome is only one of multiple proposed functions of colostrum OS. In vitro research has demonstrated that OS can act as “pathogenic decoys”, as they contain structural moieties similar to cell surface glycoconjugates utilized in cell recognition by bacterial fimbriae, thus inhibiting the adhesion of pathogens to host target cells

(Karlsson 1995; Fernandez and Berenguer 2000). Interestingly, bovine colostrum and milk OS are inefficient at inhibiting human colonization factor antigen-fimbriated enterotoxigenic *Escherichia coli* (Martin-Sosa et al. 2002), but they are highly efficient at inhibiting K99-fimbriated enterotoxigenic *E. coli* isolated from more than 80% of diarrheic samples from calves (Fig. 1B; Martin et al. 2002). This suggests that an evolutionary mechanism may be responsible for the secretion of OS specific to pathogens commonly encountered during early life to prevent infection in the young calf. Recent work has also demonstrated that bovine IgG is highly glycosylated with sialic acid, specifically Neu5Ac, with Neu5Ac glycosylation being highest in colostrum and undetectable in milk at 10 d postpartum (Table 1; Feeney et al. 2019). Furthermore, desialylation of neonatal rat microvillus membranes by neuraminidase treatment reduced the binding of IgG by 42% (Fig. 1B; Gill et al. 1999). Similar to calves, rat pups acquire passive immunity postnatally through the ingestion of colostrum and milk IgG (Pentsuk and van der Laan 2009). Collectively, this research further suggests an evolutionary reasoning for high levels of sialic acid-containing OS in the colostrum of species that require postnatal TPI via colostrum to establish an innate immune system. In addition to the aforementioned beneficial effects, the supplementation of bovine OS in mice fed an unhealthy Western diet (40% fat, 16% protein, and 44% carbohydrates) partially restored the diversity of the gut microbiota, fully reversed impairments of colonic barrier function and normalized levels of the inflammatory marker TNF- α compared with those fed only a Western diet (Boudry et al. 2017). These findings have significant implications in young calves, specifically in restoring gut barrier function and immunity when diarrhea incidence is high during the initial weeks of life (Urie et al. 2018a); however, research at the calf level to determine the potential direct effects bovine OS may have on maintaining a homeostatic gut environment during health or production challenges, as well as during normal physiological conditions, is required.

Despite recent research revealing reasons for high concentrations of bovine OS in colostrum, there is a lack of research characterizing the synthesis of OS in the bovine mammary gland. In the human mammary gland, the process of OS synthesis begins with the formation of lactose, which is then elongated to lacto-N-biose or N-acetylglucosamine (as reviewed by Smilowitz et al. 2014). Sialic acid is synthesized in the cytosol and imported to the nucleus and converted to CMP-Neu5Ac, followed by translocation to the Golgi apparatus for modification and conjugation to glycoconjugates by sialyltransferases (Fig. 1A; Huizing 2005). A total of 92 glycosylation-related genes, with 29 genes identified as important for the synthesis and metabolism of sialylated OS, have been characterized in milk somatic cells of Holstein and Jersey cows at 15 and 250 days in milk

(Wickramasinghe et al. 2011); yet, the expression patterns of these genes during early lactation, as well as the specific enzymes and cofactors that catalyze the formation of the major OS in bovine colostrum, have not been elucidated.

The concentrations and number of OS secreted by individual cows is highly variable. The concentrations of the major OS in colostrum, 3'SL, can range from 147.0 to 1149.8 $\mu\text{g}\cdot\text{mL}^{-1}$ (Fischer-Tlustos et al. 2020a), and the total number of OS secreted in colostrum can vary from 14 to 32 even when breed, parity, nutrition, and season of calving are controlled for (Barile et al. 2010). In humans, one of the most well-known sources of variation in OS composition is genetic variability (Ninonuevo et al. 2006), specifically Lewis blood group and secretor status (Smilowitz et al. 2014). To our knowledge, no studies have been conducted regarding the effect of genetic variability on bovine OS composition. Conversely, studies often focus on management, environmental or dam factors that may influence OS concentrations. Research has shown parity can influence colostrum OS yield, with multiparous cows having greater yields than primiparous cows (Fischer-Tlustos et al. 2020a). To the authors' knowledge, only one study has examined the effect of breed on colostrum OS concentrations, demonstrating that Jersey colostrum contains higher levels of disialyllactose and 3'SL and lower levels of 6'sialyllactose than Friesian colostrum (McJarow and van Amelsfort-Schoonbeek 2004). Unfortunately, this study only analyzed the four primary acidic OS in colostrum, whereas it has been clearly demonstrated that breed (Robinson et al. 2019) and production type (i.e., beef vs. dairy; Sischo et al. 2016) can have significant effects on the abundance of up to 13 different OS structures during both early and mid-lactation. The differences in diet composition between production type may partially explain the observed differences in OS abundance (Sischo et al. 2016); however, recent research found no differences in colostrum OS composition in cows ($n = 3$ per treatment) fed prepartum diets consisting of either exclusively grass or corn and alfalfa silage, earlage, and grain (Vicaretti et al. 2018). Further studies investigating the effects of prepartum diet composition on OS concentrations using large sample sizes, while controlling for breed and parity, are required.

It is possible that prepartum health status of the dam may also affect colostrum OS concentrations. In an effort to elucidate prepartum serum biomarkers that precede the development of clinical mastitis during lactation, Zandkarimi et al. (2018) found that cows that developed clinical mastitis post-calving displayed a 1440%-fold increase in serum 3'SL at 21 d prior to calving compared with healthy cows. At calving, a 125%-fold change was still observed; however, authors did not measure 3'SL concentrations in colostrum to determine if high serum 3'SL was correlated with high levels of colostrum 3'SL (Zandkarimi et al. 2018). Research has shown that 3'SL

and 6'sialyllactosamine in colostrum are moderately correlated with colostrum somatic cell counts (Fischer-Tlustos et al. 2020a); however, research pertaining directly to potential roles of OS in the mammary immune response, and consequently their concentrations in colostrum, is required.

Fatty acids

The colostrum and transition milk (TM) FA profiles are distinct from that of WM (Contarini et al. 2014; O'Callaghan et al. 2020). Concentrations of long-chain saturated FA (LCSFA) are increased in colostrum and TM, whereas short-chain saturated FA (SCSFA) concentrations are decreased compared with WM, and medium-chain saturated FA (SFA) concentrations do not dramatically change (Contarini et al. 2014; O'Callaghan et al. 2020). The major FA biosynthesis pathways within the mammary gland (preformed and de novo pathways; Fig. 1A) are presumably conserved in Lactogenesis I and II; however, the activities of the preformed and de novo pathways likely differ between those stages due to relative differences in endocrine stimulation and substrate supply during pregnancy and lactation, consequently altering the FA composition of colostrum relative to WM. Peripartum negative energy balance might elevate colostrum LCSFA by causing the release of long-chain FA from adipose tissue for incorporation into colostrum fat (Belyea and Adams 1990; McGrath et al. 2016). By extent, McGrath et al. (2016) suggested in their review that increased long-chain FA might reduce colostrum SCSFA concentrations through inhibition of de novo SCSFA synthesis within the mammary gland (Bauman and Davis 1974). Contarini et al. (2014) observed lower SCSFA concentrations concurrent with greater LCSFA concentrations in colostrum. However, over-supplying metabolizable energy (ME) to dairy cattle relative to cows consuming ME at requirements did not confirm that preformed and de novo FA are present in opposing concentrations in colostrum (Mann et al. 2016). To our knowledge, it is unknown whether a severe prepartum ME restriction would increase preformed FA to an extent that could inhibit de novo FA synthesis in colostrum.

There are numerous FA species that have been identified in colostrum and a detailed description of the concentrations and patterns of change of all FA within colostrum is beyond the scope of this review. Thus, we focus on FA that have well-established importance during development. Colostrum and TM long-chain polyunsaturated FA (such as the elevated ω -3 and -6 FA, Table 1; Contarini et al. 2014; O'Callaghan et al. 2020) are particularly important for neonatal calves because placental transport of long-chain FA is limited in ruminant species (Bell and Ehrhardt 2002). ω -Fatty acids are essential to neonatal development (reviewed by Moallem 2018); yet, evidence suggests that neonates may be marginally deficient in α -linolenic (ALA, C18:3 ω -3) and linoleic (LA, C18:2 ω -6) acid (Payne 1978; Noble et al. 1985; Garcia et al.

2014). The LA concentration is increased in colostrum compared with WM (Leiber et al. 2011). By contrast, ALA concentrations remained relatively stable after calving and were only reduced (by 31%–35%) at the second milking when compared with colostrum and WM (Hare et al. 2019a). Within the ω -3 and -6 biosynthetic pathways, ALA is the precursor to the essential ω -FA, eicosapentaenoic (C20:5 ω -3) and docosahexaenoic (C22:6 ω -3), whereas LA precedes arachidonic acid (C20:4 ω -6). Neonates have some capacity to synthesize arachidonic acid from LA (Noble et al. 1978), but their ability to convert ALA to eicosapentaenoic and docosahexaenoic acid is less clear. Coincidentally, arachidonic, eicosapentaenoic, and docosahexaenoic acid concentrations in colostrum (0.52%, 0.11%, and 0.014% FA, respectively) are all elevated (Contarini et al. 2014; Hare et al. 2019a) and drastically decrease in WM by 67%–72% of their initial concentration in colostrum (Hare et al. 2019a).

Colostrum fat is readily absorbed by the small intestine in neonatal calves (Fig. 1B) in a manner similar to that of mature ruminants (Gooden et al. 1971). The post-absorptive effect of specific colostrum FA on neonatal calf development is generally understudied and mainly focused on ω -FA (Garcia et al. 2014, 2016; Coleman et al. 2018; Opgenorth et al. 2020a, 2020b, 2020c; Ricks et al. 2020). Several studies have evaluated indirectly supplementing ω -FA to neonatal calves by feeding more ω -FA prepartum to increase colostrum concentrations (Garcia et al. 2014; Jolazadeh et al. 2019b; Ricks et al. 2020). Although these studies highlighted that indirect ω -FA supplementation can affect IgG absorption by neonatal calves and possibly elicit developmental programming responses (Garcia et al. 2016; Marques et al. 2017), it is difficult to discern whether these effects are due to the colostrum FA content, placental transport (i.e., in utero programming; Salehi and Ambrose 2017), or both. Directly supplementing ω -FA in colostrum may be a more efficacious strategy to ensure that neonatal ω -FA intake is adequate; however, we are only aware of one group that has evaluated supplementing ω -3 FA directly in colostrum to neonatal calves (Opgenorth et al. 2020a, 2020b, 2020c). Adding fish and flaxseed oil and α -tocopherol to colostrum did not alter indicators of health or growth performance; but, supplementation increased plasma ω -3 FA concentrations, decreased plasma α -tocopherol and oxidant status index during week 1 postnatal, and tended to decrease reactive oxygen and nitrogen species (Opgenorth et al. 2020b). When ω -FA are supplemented in WM or milk replacer, calves are often healthier and grow at faster rates (Karcher et al. 2014; Garcia et al. 2015, 2016; Worden et al. 2018; McDonnell et al. 2019; Śpitalniak-Bajerska et al. 2020). Similar responses are observed when ω -FA are supplemented in starter postweaning (Kadkhoday et al. 2017). However, Opgenorth et al. (2020a, 2020b, 2020c) did not observe differences in growth rate due to fish and flaxseed

oil and (or) α -tocopherol supplementation in colostrum; although, improvements and tendencies for improvements in health scores were found in some studies (Opgenorth et al. 2020b, 2020c).

Butyrate (C4:0) has also received attention in preweaned calves as it enhances gastrointestinal, enzymatic, and pancreatic development when supplemented in liquid feed, consequently improving growth performance and health parameters (reviewed by Górka et al. 2018). Though little is known about the effect of colostrum butyrate on neonatal development, preliminary evidence suggests that it may adversely affect dairy calf immunity (Hiltz and Laarman 2019). By supplementing butyrate (2.5% w/v) in CR, serum IgG concentrations were reduced from 21.1 to 14.0 g·L⁻¹ at 24 h and remained low for the remainder of the study (Hiltz and Laarman 2019). Baumwart et al. (1977) observed that feeding potassium-isobutyrate in colostrum at 1 h postpartum decreased neonatal absorption and serum concentrations of γ -globulin, IgG, and IgM. It has been speculated that butyrate might accelerate intestinal development in neonates by causing premature loss of giant-sized vacuoles in fetal-type enterocytes that uptake and translocate macromolecules into the periphery (reviewed in Skrzypek et al. 2018); thereby, diminishing absorption of colostrum IgG. Although this mechanism is yet to be confirmed, it is interesting to consider respective to the fact that the abundance of colostrum butyrate is low and only increases in TM on day 3 post-calving (O'Callaghan et al. 2020). Theoretically, the low butyrate concentrations in colostrum and the initial TM might help to prolong the period in which the neonatal gut is permeable to macromolecules. Based on these results, maternal factors that increase colostrum butyrate should be avoided, and butyrate should not be supplemented to newborn calves during the first 1–2 d postnatal.

Season, dry period length, parity, and concentrate or fibre consumption all alter colostrum fat and FA content (Coroian et al. 2013; Dunn et al. 2017; O'Callaghan et al. 2020). Prepartum ME and metabolizable protein intake also influence colostrum fat concentrations (Mann et al. 2016; Hare et al. 2019b), possibly by maternal plasma insulin modulating the release of non-esterified FA from adipose tissue (Mann et al. 2016; Zinicola and Bicalho 2019). Prepartum ME intake can also alter the colostrum FA profile (Mann et al. 2016). Similarly, multiple studies have concluded that prepartum fat intake and source can be used to influence the FA present in colostrum (Leiber et al. 2011; Garcia et al. 2014; Salehi et al. 2016; Marques et al. 2017; Coleman et al. 2018; Jolazadeh et al. 2019a; Ricks et al. 2020). As FA participate in a wide variety of physiological functions (De Carvalho and Caramujo 2018; Moallem 2018), further consideration should be given to how maternal prepartum factors influence colostrum fat and FA content to understand the downstream influence on neonatal calf development.

Insulin–relaxin superfamily

Colostrum contains high concentrations of numerous bioactive hormones [reviewed previously by [Blum and Hammon \(2000\)](#) and [McGrath et al. \(2016\)](#)] that can be broadly grouped as either steroid or peptidic hormones ([Jouan et al. 2006](#)). Colostral hormones that are commonly discussed are growth hormone, epidermal growth factor, transforming growth factor- β ([Gauthier et al. 2006](#); [Jouan et al. 2006](#); [Ontsouka et al. 2016](#)), and several peptide hormones (insulin-like growth factors) clustered within the insulin–relaxin superfamily. This family of peptides have been previously reviewed ([Blum and Hammon 2000](#); [Blum and Baumrucker 2002](#); [Blum and Baumrucker 2008](#)), and herein, we expand the discussion to include the remaining members of the ancestral insulin–relaxin superfamily. These peptides are grouped into subfamilies: (1) insulin (INS), (2) insulin-like growth factors (IGF), (3) the insulin-like peptides and polypeptides (INSL), and (4) the relaxins (RLN). Although the superfamily is structurally conserved, they may differ in expression and physiological roles between species ([Hoffman and Opazo 2011](#)).

Insulin, IGF-I, and IGF-II are all bioactive, and their concentrations are elevated in bovine colostrum relative to WM (reviewed in [Blum and Hammon 2000](#)). Though RLN has also been identified in porcine colostrum and is documented to impact neonatal reproductive development ([Frankshun et al. 2011](#); [Bagnell and Bartol 2019](#)), it is not anticipated to be present in bovine colostrum as ruminant species lack the ability to produce RLN due to evolutionary gene erosion ([Roche et al. 1993](#); [Hoffman and Opazo 2011](#); [Malone et al. 2017](#)). Bovine colostrum also contains elevated concentrations of IGF-binding proteins-2, -3, -4, and -5 ([Sejrsen et al. 2001](#); [Sparks et al. 2003](#)) that may modulate the activity of colostral IGF-I or possibly have their own direct action on mammary or intestinal development (reviewed by [Blum and Baumrucker 2002](#)). To our knowledge, INSL have not been identified in bovine colostrum; though, it is plausible that they could be present as INSL3, INSL5, and INSL6 (but not INSL4) are putatively functional in the bovine genome ([Hoffman and Opazo 2011](#); [Malone et al. 2017](#)), and INSL3 is expressed in ovarian follicles ([Anand-Ivell et al. 2011](#); [Satchell et al. 2013](#); [Dai et al. 2017a, 2017b](#)). Interestingly, female ruminants produce exceptionally high concentrations of ovarian INSL3 relative to other species ([Bathgate et al. 1996, 1999](#)) and, as INSL3 acts on the same G-protein coupled receptors as RLN (RXFP1 and RXFP2; [Bathgate et al. 2013](#); [Dai et al. 2017b](#)), it has been proposed that INSL3 is a compensatory homologue for the lack of endogenous RLN production ([Bathgate et al. 1996](#); [Anand-Ivell et al. 2011](#)). Should INSL3 be confirmed in bovine colostrum, it may speculatively influence neonatal reproductive development similar to RLN in porcine colostrum, possibly more so in male than female calves ([Anand-Ivell et al. 2011](#)).

Insulin-like growth factors-I and -II target the GIT of calves, and the greatest binding capacity for IGF is in the ileum and colon (IGF-IR) or the duodenum (IGF-IIR; [Georgiev et al. 2003](#); [Georgieva et al. 2003](#)). Colostral IGF-I concentrations are twice that of IGF-II ([Blum and Hammon 2000](#)) and are approximately 2 and 3.4 $\times$ greater than neonatal ([Hadorn et al. 1997](#); [Schäff et al. 2016](#)) and antepartum maternal ([Piechotta et al. 2015](#)) serum IGF-I, respectively. Lactal IGF-I and -II must be sourced from maternal circulation ([Malven et al. 1987](#); [Prosser et al. 1991](#)) given that there is limited evidence that either hormone is synthesized by the mammary gland ([Campbell et al. 1991](#)), indicating that movement of IGF-I and -II into mammary secretions must occur transcellularly by active transport to establish concentrations in colostrum greater than in blood ([Fig. 1A](#)); although, it is also possible that some movement of IGF-I and -II into colostrum could occur paracellularly via molecular sieving ([Fig. 1A](#)) by “leaky” tight junctions (reviewed by [Weber 2012](#)) during Lactogenesis I.

The greater IGF-I concentration in colostrum coupled with its role in regulating postnatal growth (whereas IGF-II action predominates during fetal growth; reviewed by [Breier et al. 2000](#)) could suggest that colostral IGF-I likely has a greater role in neonatal calf development than colostral IGF-II. However, the extent to which IGF-I can solely influence postnatal intestinal development is unclear, as results are contradictory (discussed by [Blum and Baumrucker 2002](#)), but it is accepted that colostral bioactive growth factors, including IGF-I, synergistically promote intestinal maturation ([Fig. 1B](#); [Roffler et al. 2003](#); [Pyo et al. 2020](#)). Insulin-like growth factor-I and -II are additionally not believed to permeate the intestine ([Blum and Baumrucker 2002](#); [Hammon et al. 2020](#)), as recombinant human IGF-I was absorbed in negligible quantities from isolated jejunal loops in 1-d-old feed-deprived calves ([Vacher et al. 1995](#)); however, there is some evidence to the contrary ([Skaar et al. 1994](#); [Sparks et al. 2003](#)). Colostral IGF-I absorption by neonatal piglets is also controversial ([Xu and Wang 1996](#); [Burrin 1997](#); [Donovan et al. 1997](#)); yet, orally supplemented IGF-I in colostrum or milk replacer supported cervical and uterine development in neonatal gilts ([Camp et al. 2018](#); [George et al. 2018](#)). These recent data demonstrate that colostral IGF-I can be absorbed by neonates whilst the intestine is hyperpermeable and suggests that its absorption by calves may need to be re-evaluated within the first hours of life, as opposed to 1 d of life ([Vacher et al. 1995](#)). Similar to its movement within the mammary gland, absorption of IGF-I could occur via active transport once IGF-I binds to its receptor in the intestinal tract or, to some extent, IGF-I could permeate the intestinal epithelial barrier passively prior to intestinal maturation ([Fig. 1B](#)). Furthermore, hepatic GH binding is low in the neonatal liver ([Gluckman et al. 1983](#); [Badinga et al. 1987](#); [Breier et al. 1988](#)), leading to

inadequate stimulation of hepatic IGF-I and is partially responsible for the typically low serum IGF-I concentrations of neonatal calves (reviewed by Breier and Gluckman 1991). Therefore, absorption of colostral IGF-I could be a compensatory mechanism to bypass the GH arm of the somatotrophic growth axis and promote growth and development of the calf during the immediate postnatal period.

Similar to IGF-I, it is probable that colostral INS also plays a major role in neonatal development. Substantial quantities of INS are sequestered by the mammary gland prior to calving (Malven et al. 1987), such that colostral INS concentrations are between 41 and 76× greater than antepartum maternal (Malven et al. 1987; Hare et al. 2019b; K. Hare et al. unpublished data) and neonatal plasma INS concentrations (Rauprich et al. 2000; Hammon et al. 2000). As with IGF-I, it is probable that transfer of INS into mammary secretions predominantly occurs by active transport against its concentration gradient (Malven et al. 1987; Whitmore et al. 2012) after binding to its receptor (Fig. 1A); though, it is again possible that some translocation could occur by molecular sieving through “leaky” tight junctions (Fig. 1A) during Lactogenesis I. In the neonatal intestine, insulin receptor mRNA is most highly expressed in the jejunum and colon of full-term calves prior to colostrum feeding but binding capacity is equivalent through the small intestine and colon (Georgiev et al. 2003). Colostral INS likely enhances intestinal growth and maturation through mitogenic signaling and other undefined mechanisms after binding its intestinal INS receptor (Fig. 1B). Oral INS delivery promotes gastrointestinal cell proliferation and enzymatic activity in rodents (Menard et al. 1981; Simon et al. 1982; Arsenault and Menard 1984; Buts et al. 1990; Albert et al. 1994) and increases small intestinal mass and disaccharidase activity in suckling piglets (Shulman 1990). Additionally, INS and GH receptor mRNA expression was greater in the ileum of neonatal piglets supplemented with INS (Huo et al. 2006). In addition, insulin treatment caused jejunal leucine aminopeptidase activity and 3 d BW to increase (Huo et al. 2006). In 30-h-old neonatal calves, rumen mass and abomasal wet digesta weight were reduced after they were fed colostrum containing INS concentrations 5 and 10× greater than that of the control (control: 16.8 µg INS·L⁻¹; K. Hare et al. unpublished data). Colostral INS supplementation also increased duodenal tissue density (g tissue·cm⁻¹ length) and tended to increase wet digesta weight in the colon (K. Hare et al. unpublished data). Speculatively, this preliminary data indicates that supplementary colostral INS may have increased gut motility and accelerated digesta passage through the neonatal calf intestine, possibly by insulin-induced hypoglycemia (Fellows et al. 1987; Schvarcz et al. 1993; Schvarcz et al. 1995; Russo et al. 2005).

Gastrointestinal INS absorption has been demonstrated in many species, including neonatal and mature

rats (Mosinger et al. 1959; Kidron et al. 1982; Morishita et al. 1993; Asada et al. 1995), neonatal pigs (Asplund et al. 1962; Shen and Xu 2000), and dogs (Chernikov et al. 1972). Speculatively, absorption may occur via binding to INS receptors within the intestinal tract, or possibly by passive diffusion across the “open” neonatal gut (Fig. 1B). In neonatal calves, consuming supraphysiological concentrations of INS shortly after birth causes plasma glucose to decrease as early as 1 h after treatment (Kirovski et al. 2008), sometimes inducing a hypoglycemic coma (Pierce et al. 1964). The absorption of colostral INS in neonatal calves is contended (Hammon et al. 2013; Hammon et al. 2020), as a study that delayed feeding and did not control macronutrient intake between treatments did not observe an appreciable rise in immunoreactive insulin when insulin was supplemented in colostrum (Grütter and Blum 1991). It is possible that first-pass hepatic INS clearance might mask intestinal absorption unless large concentrations of colostral INS are consumed. Intestinal absorption of whole and biologically active INS likely compensates for the underdeveloped pancreatic response (Grütter and Blum 1991), promoting the flux of nutrients into peripheral tissues, storage of hepatic glycogen, and supporting the rapid neonatal metabolism and growth (Vermorel et al. 1983; Sadri et al. 2017).

Additional bioactive components for consideration

The bioactive factors in colostrum are not limited to the aforementioned molecules and compounds; a plethora of additional colostral factors have the potential to improve calf immune and developmental function. For instance, microRNAs (miRNA), specifically those related to immune regulation, are present at higher concentrations in colostrum compared with milk (Izumi et al. 2012; Zhou et al. 2012; Sun et al. 2013; Table 1). These miRNA are highly resistant to RNase and acidic conditions (Izumi et al. 2012) and neonatal rats fed colostrum have a higher number of immune-related miRNA in serum compared with those fed mature milk (Izumi et al. 2014). This suggests a mechanism for miRNA absorption by the neonatal intestine, and their potential role in immune regulation both systemically and locally in the mucosal immune system of the GIT (Liang et al. 2015). Similarly, nucleotide concentrations are 17× greater in bovine colostrum compared with WM (Gill et al. 2011; Table 1), with uridine 5′ monophosphate (5′UMP) being the predominant nucleotide (Gil and Sanchez-Medina 1981). Mashiko et al. (2009) demonstrated that calves 4–10 d of age supplemented with 5′UMP in milk replacer had improved immune function, specifically increased interferon-γ concentrations by peripheral blood mononuclear cells and greater IgA concentrations in the ileal mucosa, compared with control calves. Due to the high concentrations of 5′UMP in bovine colostrum, it can be hypothesized that its effect on immune function during the first day of life, as opposed to days 4–10, may be more

pronounced; however, the effects of dietary 5'UMP and other nucleotides in colostrum on the immune response of neonatal calves has not been investigated.

Recent advancements in high-throughput laboratory techniques have allowed the dairy research community to thoroughly evaluate the bovine colostrum and milk proteome. Researchers have identified many unique classes of proteins that are upregulated or exclusively detected in dairy colostrum compared with WM, including osteopontin, antibody and complement components, antimicrobial proteins, anti-proteolytic proteins, and multiple growth and differentiation factors (Le et al. 2011; Nissen et al. 2017; Fahey et al. 2020). Additionally, the colostrum proteome in beef calves has been of research interest. The whole colostrum proteomes and 2 d calf serum samples from beef cows fed at 100% or 133% of MP requirements for approximately 8 wk prior to calving (Hare et al. 2019b) revealed that a total of 213 distinct detectable proteins were found in whole colostrum, 11 of which increased and 16 of which decreased >2 log₂ fold between maternal diets. The serum proteome of 2-d-old calves identified 179 proteins pre-and post-colostrum consumption. Of these, 28 were increased, and 19 were decreased >2 log₂ fold between calves. A number of these differentially detected proteins in calf serum tended towards pathways shifts in decreasing innate and increasing adaptive immune response factors from colostrum of high MP fed dams (Radford et al. 2018). There has also been increasing interest in the proteome specific to the milk fat globule membrane (MFGM). Although the MFGM constitutes only 1%–4% of milk protein in dairy cows (Yang et al. 2015), it contains a diverse profile of hundreds of proteins (Reinhardt and Lippolis 2008; Ji et al. 2017) that have been implicated in positively influencing the host gut microbiome and the immune system (Rasmussen 2009; Bhinder et al. 2017). Honan et al. (2020) found that 78% of proteins affected by days in milk had a higher abundance in colostrum compared with day 7 milk, including proteins involved in pathogen detection and supporting host immunity.

From the abundance of research reviewed previously (Pakkanen and Aalto 1997; Blum and Hammon 2000; McGrath et al. 2016) and described herein, it is clear that colostrum has an integral role in not only ensuring TPI but also in stimulating the metabolism, development of the GIT, and mucosal and systemic immune system of the neonatal calf. The recent characterization of the multitude of colostrum bioactive factors that positively influence neonatal calf health and development highlights the potential need for redefining the term “colostrum quality” to encompass more than IgG. However, future research at the calf level is required to evaluate the specific mechanisms by which certain bioactive compounds influence the neonatal calf. Elucidating these mechanisms will allow the dairy research community to rank colostrum components by level of importance to determine the specific compounds that fit within the scope

of the modern definition of “colostrum quality”. It may be possible to utilize colostrum IgG concentrations as a “indicator” of colostrum containing adequate or high concentrations of the aforementioned bioactive compounds, given its strong positive correlations with the major OS in bovine colostrum, 3'sialyllactose (Fischer-Tlustos et al. 2020a). It may be possible that IgG can reliably indicate high concentrations of the plethora of additional bioactive compounds in bovine colostrum; yet further work characterizing the correlations between IgG and specific bioactive compounds, as well as the concentrations at which these bioactive compounds are of physiological relevance to the neonatal calf, is required. As colostrum IgG concentrations can be accurately and easily measured on farm using a Brix refractometer (Deelen et al. 2014), determining these associations would provide the dairy industry with an efficient cow-side test to ensure that colostrum not only meets the gold-standard for providing passive immunity but also the bioactive compounds required for proper development and health.

Summary and Conclusions

In summary, maximizing colostrum quality and enhancing colostrum feeding practices will undoubtedly translate into improved health and well being of calves and improved profits for dairy and beef producers. Although the research community is conducting more colostrum research now than ever before, surveys around the world and in Canada still report alarming incidences of poor colostrum feeding strategies and high morbidity and mortality levels. These statistics highlight a great opportunity to improve the basic concepts of colostrum feeding (quality, quantity, and quickness) and newer concepts like extended colostrum feeding. Colostrogenesis is a key research area that has been neglected in bovine research and requires more attention. Future studies investigating nutritional and management strategies for dry cows will enable us to maximize the synthesis of colostrum bioactive components that are beneficial for calf developmental programming and lifetime performance. Furthering our understanding and definition of colostrogenesis and colostrum quality — as both are currently focused solely on IgG — will also be essential to move bovine colostrum research forward. Characterizing not only IgG, but also the hundreds of bioactive compounds in colostrum, as well as elucidating the mechanisms that control their synthesis, would be invaluable to our industry. It is also critical to understand the degree of absorption and functionality of each bioactive component within colostrum and how it relates to health and long-term productivity. Once we understand how differing concentrations of these bioactive components impact calf performance, our definition of colostrum, and colostrogenesis, will inevitably evolve.

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