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Invited review: Risk factors for transition period disease in intensive grazing and housed dairy cattle

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ABSTRACT

Transition period (±3 wk around calving) diseases are prevalent in dairy systems. In this review we describe the physiological and behavioral changes experienced by cows during the transition period and during the dry period leading up to this. Our narrative review examines risk factors associated with these diseases in zero-grazing and grazing systems. The available research indicates that cows in these 2 systems experience similar incidences of transition diseases, and that low or high BCS and lameness are key manageable risks associated with both systems. Other cow- and herd-level risk factors identified in this review are parity, breed, and seasonal variability in disease incidence. Some risks appear to arise earlier in the dry period, outside what is normally considered the transition period; we recommend that future studies of transition period diseases should consider the entire dry period. We also encourage new work on measuring the effect of intervention strategies during late lactation on transition period diseases.
Key words: feeding behavior, disease incidence, risk factors, periparturient period

INTRODUCTION

Dairy farms range from pastoralist-extensive to intensive indoor housing systems (Robinson et al., 2011). Intensive systems are typically designed to maximize milk output per cow or per area with the majority of nutrition provided as either a TMR (a balanced mixture of forages, grains, and minerals) or with grazing as the primary forage source with variable dietary supplementation. Extensive systems are typically less dependent on the use of supplemental grain, relying more on grazing, or housed animals fed grass that is cut and carried to the animals. In this review we will focus solely on intensive systems that differ in the ways cows are housed; we refer to these as grazing and zero-grazing systems. Different production systems will have unique challenges. For example, cows housed indoors year-round may be exposed to poor lying surfaces, whereas cows kept outdoors may be exposed to rain, mud, and extreme temperatures.

Calving is a complex event and involves several physiological and behavioral changes that can affect energy balance and immune function (Bell, 1995; Grummer et al., 1995, 2004; Goff and Horst, 1997; Bradford et al., 2015). Unfortunately, cows are at high risk of disease in the weeks immediately before and after calving (Ingvartsen et al., 2003), resulting in declines in both milk and reproductive performance and increasing culling risk (Carvalho et al., 2019). This period around calving has historically been labeled as “the transition period” and is considered in the scientific literature to begin 3 wk before calving and end about 3 wk after calving (Grummer et al., 1995). However, there is evidence that at least some physiological changes related to calving and the diseases that follow may start much earlier than that (e.g., Dervishi et al., 2018). To date, the majority of research has focused on high producing Holstein cows in zero-grazing systems. However, with increasing concerns over the long-term social sustainability of zero-grazing systems (Beaver et al., 2020), we review literature regarding the transition period and the challenges to cow health for both zero-grazing and grazing systems.

This narrative review consists of 3 parts. First, we summarize the current understanding of the physiological and behavioral changes during the transition period. Second, we critically review the available literature on the epidemiology of transition period diseases highlighting the main risk factors. Finally, we compile the literature on both grazing and zero-grazing systems and identify gaps for each system. For the purposes of this review we excluded hybrid systems as it is likely that they share the risks and benefits of both systems.

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WHAT IS THE TRANSITION PERIOD?

Genetics, nutrition, and management are the main drivers for increased milk production in modern dairy cows (Baumgard et al., 2017). The genetic selection for milk yield has resulted in cows that have an improved ability to partition energy and protein from the diet and body reserves to support milk production instead of accumulating body mass (Veerkamp, 1998). The rate of milk secretion during the first 2 to 3 mo after calving increases rapidly while the rate of DMI increases at a lower rate, reaching a maximum several weeks after peak milk production (Coppock, 1985). Thus, during these first weeks of lactation, the cow needs to be able to mobilize energy (and protein) from body reserves to compensate for the gap between intake and output.

To prepare for parturition and the onset of lactation, a combination of metabolic events in the days before calving trigger the onset of lactation and milk production (Bell, 1995). Behavior also changes at this time, including reduced DMI (see reviews: Grant and Albright, 1995; Sepúlveda-Varas et al., 2013); when dietary energy intake fails to supply the energy needed to support the high levels of milk production cows will experience negative energy balance (**NEB**; see review: Grummer, 1995). These changes, in conjunction with a complex inflammatory response (see review: Bradford et al., 2015), contribute to the high incidence of metabolic and infectious diseases in this period (Ingvartsen et al., 2003) in both grazing (e.g., Olmos et al., 2009; Compton et al., 2014) and zero-grazing systems (e.g., Daros et al., 2020).

As described in the following subsections, there are multiple changes happening during this period, making it impossible to pinpoint a specific time for the start of the transition period.

Physiological Changes During the Transition Period

Due to the plentiful literature reviewing the physiological changes during the prepartum period, we only briefly describe key points and refer the reader to other literature.

Hormonal profiles are altered in the week before calving, with the majority of the acute changes taking place in the days before calving (Vazquez-Añon et al., 1994; Bell, 1995). Homeorhetic mechanisms that control pregnancy and the onset of lactation increase levels of circulating growth hormone and inhibit the production and tissue responsiveness to insulin and insulin-like growth factor-1 (Bauman and Currie, 1980; De Koster and Opsomer, 2013). These hormones trigger mobilization of body reserves from adipose tissues (Tucker, 2000; Renaville et al., 2002; De Koster and Opsomer, 2013), resulting in increased circulating nonesterified fatty acids (**NEFA**) in blood (Adewuyi et al., 2005). Nonesterified fatty acids can be used as an energy source in the peripheral tissues, sparing glucose for milk production (Herdt, 2000). Nonesterified fatty acids are cleared in the liver through several pathways: (1) complete oxidation, (2) partial oxidation, or (3) re-esterification into triglycerides (**TG**; Grummer, 1993). Triglycerides are stored in the hepatocytes and exported as very-low-density lipoproteins (**VLDL**), which can serve as an energy source in other tissues. Through partial oxidation, ketone bodies are produced (acetate, BHB, and acetone) and, as NEFA, can be used as an energy source in other tissues. Partial oxidation is promoted when there is not enough energy available to sustain maintenance and production, a phenomenon that is often the case in periparturient cows (Herdt, 2000). During complete oxidation, NEFA enter the tricarboxylic cycle producing energy for the liver (Drackley, 1999).

The liver has limited capacity to export VLDL and to complete oxidize NEFA. Thus, NEFA are mostly metabolized through partial oxidation, resulting in increased serum BHB levels (Drackley, 1999; Herdt, 2000). Cows that fail to regulate adipose tissue mobilization or fail to export VLDL from the liver are likely to develop fatty liver and ketosis, characterized by high levels of ketone bodies in blood (Herdt, 2000). High hepatic NEFA oxidation also decreases appetite (Allen et al., 2009), potentially contributing to NEB.

More recently, the link between energy balance and immune function during the transition period has been further explored. The list of hormones and metabolites and the pathways involved in inflammation are numerous and have been reviewed elsewhere (Bradford et al., 2015; Aleri et al., 2016; Trevisi and Minuti, 2018). Increased immune response, which often results in inflammation, facilitates calving and is responsible for placental detachment (Kimura et al., 2002; Mordak and Stewart, 2015), so some inflammation is beneficial, but prolonged systemic inflammation is likely detrimental to cow health (Bradford et al., 2015).

During the transition period acute lipolysis stimulates a proinflammatory response in the adipose tissue (Contreras et al., 2015). In the liver, increased oxidation of NEFA increases the production of reactive oxygen species, which in turn stimulates the transcription of proinflammatory cytokines (Sordillo et al., 2009; Gessner et al., 2013). After calving uterine tissues are disrupted, but the risk of pathological bacteria reaching the endometrium remains high because the cervix is still open. This is ideally counteracted by an inflammatory response that can fight infections and stimulate tissue recovery (Chapwanya et al., 2012).

The events taking place in the adipose tissue, liver, and uterus likely result in the cows experiencing systemic inflammation during the transition period (Bradford et al., 2015), that combined with the energy required to mount an effective immune response (Kvidera et al., 2017), contributes to the energy deficit.

Recent studies link the dry-off phase with systemic inflammation (Mezzetti et al., 2020), nutrient metabolism, and oxidative stress (Putman et al., 2018), which have been proposed to influence the subsequent cascade of physiological events during the prepartum period (Mezzetti et al., 2021).

Behavioral Changes During the Transition Period

Most of the work assessing transition period behavior has been conducted in animals under zero-grazing systems. Grummer et al. (2004) looked at data from several studies to explore the pattern of DMI during the prepartum period with the objective of describing DMI curves (Hayirli et al., 2003). They concluded that DMI starts decreasing 3 wk precalving with the greatest drop in DMI in the days close to calving, though the authors also noted that heifers and cows that were considered thin (BCS <3.5) had more consistent DMI during the precalving period, reducing intake only a couple of days before calving (Hayirli et al., 2002; Hayirli and Grummer, 2004). Similarly, other studies have found that cows that did not succumb to disease maintained consistent DMI throughout most of the prepartum period, showing marked DMI reduction only in the days before calving (Hammon et al., 2006; Huzzey et al., 2007; Goldhawk et al., 2009). Rumination shows a similar pattern as that of DMI, with a marked drop on the day of calving and a gradual increase thereafter (Kaufman et al., 2016a). There is also evidence that restlessness (i.e., transitioning from standing and lying) increases in the days around calving; on the day of calving cows increase the time they spend standing by an average of approximately 2 h (Huzzey et al., 2005).

There are several techniques to estimate individual DMI in herbivores (Dove and Mayes, 2006), including lactating grazing cows (Lahart et al., 2019; Méndez et al., 2020). To our knowledge, no data have been published on changes in DMI of grazing animals during the transition period. Once these data are collected it could be used to consolidate our existing DMI models. Lying behavior and daily steps (measure of activity) have been assessed from 3 wk before to 5 wk after calving in a few grazing herds in New Zealand. Cows are consistent in their daily lying times up to 3 d before calving followed by a marked drop until nadir at the time of calving; although lying times are lower than precalving, there is a short increase in lying time a day after calving but then time spent lying levels out and remains constant. Lying bouts followed an inverse pattern to that observed for lying time. Also, fewer daily steps are taken during the precalving period compared with the postcalving period with the increase taking place beginning 2 d before calving to 1 d after, after which it levels out again (Hendriks et al., 2019).

Management Changes for Transition Cows

There are differences in how veterinarians and farmers define the transition period (Mills et al., 2020). These differences may be a result of how the dairy herd is being managed (e.g., pen changes, diet changes). The rationale that has led to these management recommendations is presented below.

Research done in zero-grazing systems has focused on nutritional strategies to avoid over-conditioning (obesity) during the dry period (prepartum) and to prevent clinical hypocalcemia (Goff, 2006). Briefly, obese cows are likely to develop “fat cow syndrome,” an affliction with a high incidence of metabolic and infectious diseases and mortality, particularly during the first 2 wk postpartum (Morrow, 1976). To prevent obesity, some recommendations suggest using low-energy diets during the dry period (NRC, 2001). However, when low-energy diets are fed prepartum cows have lower DMI (Hayirli et al., 2002), so some have argued that higher energy diets should be used prepartum to compensate and prevent the detrimental effects of a long period of NEB (Hayirli and Grummer, 2004). However, feeding high-energy diets (as a means to increase DMI) during the prepartum phase is known to be associated with a greater depression in DMI before calving and lower DMI after calving compared with cows fed diets to meet their nutrient requirements (Janovick and Drackley, 2010).

Increased understanding of the role of parathyroid hormone, vitamin D, and blood pH on calcium metabolism has led to the development of high anion diets, so called “DCAD diets,” and also diets low in calcium (Goff, 2006). In zero-grazing herds the DCAD diets are usually fed during the late dry period (3 to 4 wk before calving). Recent meta-analyses concluded that DCAD is effective at reducing the risk of hypocalcemia and increasing milk production (Lean et al., 2019; Santos et al., 2019). In grazing herds supplementation and effectiveness of DCAD diets is often hindered given difficulties in managing groups of cows at different stages of lactations; for instance, far-off and close-up cows are often commingled (Sepúlveda-Varas et al., 2013), allowed to graze on high K pastures, and have higher rumen pH (Goff, 2014), making it difficult to reach targeted cationic balance. Nonetheless, some studies in grazing herds have been successful in elevating postpartum serum Ca levels through the use of prepartum DCAD diets (Roche et al., 2003; Melendez et al., 2018).

To facilitate feeding different diets during the dry period in zero-grazing systems, cows are often regrouped according to predicted calving date, with the first regrouping taking place 3 to 4 wk prepartum. In the days before parturition cows are moved to the maternity pen where they will calve and then moved to the hospital or "fresh" pen for several days until again regrouped into the main lactating herd. In contrast, most grazing systems keep dry cows as a single group that may or may not receive dietary supplements as calving approaches.

In addition to feeding strategies, other management factors have been studied exclusively in zero-grazing systems, such as the effect of regrouping and stocking density in relation to changes in behavior, immunity, and transition period diseases. We further discuss this literature below (but see also Sepúlveda-Varas et al., 2013; Proudfoot and Habing, 2015; and Chebel et al., 2016). Little research has focused on the management of cows during the transition in grazing systems (see review by Kay et al., 2015).

EPIDEMIOLOGY OF TRANSITION PERIOD DISEASES

In this review we focus on retained placenta (**RP**), metritis, and subclinical ketosis (**SCK**) but we also include mastitis and hypocalcemia where appropriate. We included these diseases as they are the most prevalent, or exclusively prevalent (e.g., RP), within the transition period. Other transition problems include displaced abomasum (**DA**), but given the lack of specific epidemiological research on this malady and also because DA seems to be a secondary issue associated with other transition diseases (e.g., SCK; McArt et al., 2012), we have not included it in this review.

One of the main challenges in reviewing the epidemiology of cattle diseases is the range of disease diagnosis definitions. In this review we decided to retain the definitions used by the authors because reinterpreting the data based on a fixed definition for each selected disease would be impossible; moreover, most of the publications did not provide access to the raw data. That said, we saw a range of definitions for metritis, RP, and SCK. In brief, the definition for metritis included foul watery vaginal discharge with or without fever and with or without signs of systemic illness between 0 to 21 DIM. Retained placenta was defined as failure to pass fetal membranes within 12 or 24 h after calving and SCK was defined as blood BHB >0.96 mmol/L [ranging from 0.96 mmol/L (Ribeiro et al., 2013) to 1.4 mmol/L (Duffield et al., 2009)] or milk BHB >0.15 mmol/L from 0 to 21 DIM. For both metritis and SCK, blood sampling times ranged from multiple times per week to once during the 3 wk after calving. This variation in sampling is conveyed in how we report the data in Table 1, as multiple measures allow for estimative of incidence, whereas from cross-sectional data only prevalence can be estimated (except for RP).

High milk production is possible in both zero-grazing and pasture-based systems but between-system differences likely result in different risk factors for transition diseases. A summary of the occurrence of the most common transition period diseases in zero-grazing and

Table 1. Mean and range in incidence and prevalence estimates across studies documenting 3 common transition period diseases, separately for zero-grazing and grazing-based systems

	Production system[2]					
	Zero grazing			Grazing		
Disease[1]	Mean	Range (min–max)	No. of studies	Mean	Range (min–max)	No. of studies
Metritis[3]						
Incidence	21.5	16.7–29.7	6	20.7	17.3–25	2
Prevalence	18.7	NA	1	7.7	5.3–11.2	2
RP[4]						
Incidence	13.1	8.9–18.7	4	4.3	1.7–13.9	5
SCK[5]						
Incidence	37.4	19.7–43.2	5	49	16.6–66.5	2
Prevalence	24	10–58.8	12	24.8	10.8–35.4	5

[1]The mean of disease incidence and prevalence was weighted by the number of cows assessed in each study. The list of studies used to generate this table can be found in Supplemental File S1 (https://doi.org/10.5683/SP3/Q3WGOI, Daros et al., 2022).

[2]Zero grazing includes studies on tiestall, freestall, and other loose housing systems. Grazing includes seasonal and year-round intensive grazing systems. Min = minimum; max = maximum.

[3]A range of metritis definitions was found in the assessed studies and included foul watery vaginal discharge with or without fever and with or without signs of systemic illness.

[4]Retained placenta (RP) defined as failure to pass fetal membranes within 12 or 24 h after calving.

[5]Subclinical ketosis (SCK) defined as blood BHB >0.96 mmol/L or milk BHB >0.15 mmol/L from 0 to 21 DIM.

grazing systems is provided in Table 1; these results suggest that disease risk is similar in the 2 systems, although specific risk factors may vary as we review below. Risk factors are separated into cow and herd level. Where available, controlled studies that have focused on the causal relationship between risk factor and disease will be highlighted.

Cow-Level Risk Factors

Body Condition. Body condition is correlated with the amount of adipose tissue (Gregory et al., 1998), making it useful for assessing cow condition and longer term nutritional status. In both grazing (Roche et al., 2007a) and zero-grazing (Hoedemaker et al., 2009; Zachut and Moallem, 2017) systems, the BCS of cows changes dramatically from calving to peak lactation (usually from 50 to 100 DIM), with cows losing condition due to NEB in the first weeks following parturition. The controlling mechanisms of body fat mobilization include both homeorhetic mechanisms (described above), which are mainly dependent on genetic traits (e.g., Zachut and Moallem, 2017) and homeostatic mechanisms, that are highly influenced by environmental factors, such as diet (e.g., Roche et al., 2006) and feed availability. The BCS at calving, nadir BCS in early lactation, time from calving to nadir BCS, and amount of BCS lost from calving to nadir have all been associated with lower productive and reproductive performance, and disease occurrence (grazing: Roche et al., 2007b, 2015; zero grazing: Hoedemaker et al., 2009). The BCS at calving is associated with nadir BCS and BCS loss in early lactation (grazing: Roche et al., 2007b; zero grazing: Chebel et al., 2018), making this parameter useful to predict cows at risk of developing transition period disease in grazing and zero-grazing cows.

In cows managed under zero-grazing systems, moderate to high BCS (BCS $\geq$3.25) at calving is associated with metabolic disease, especially SCK (e.g., McArt et al., 2013; Daros et al., 2020), whereas low BCS ($\leq$3.0) at calving is associated with uterine diseases, mainly RP and metritis (e.g., Duffield et al., 2009). A similar relationship has been found in grazing herds (e.g., Roche et al., 2013; Daros et al., 2017). In controlled studies conducted in zero-grazing herds, higher BCS (>3.5) cows had reduced DMI after calving (Hayirli et al., 2002). In grazing herds a similar pattern was observed; cows with high BCS in the prepartum period lost more weight and body condition in the weeks after calving (Roche et al., 2013). Under experimental conditions, again in zero-grazing and grazing herds, fatter cows had lower activation of immune function–related genes and altered proteomic profile indicating an acute inflammatory response (Crookenden et al., 2017; Ghaffari et al., 2020), linking high fat mobilization and decreased immune function. Unfortunately, the causal link between low BCS (<3.0) at calving and uterine diseases remains unknown. Low BCS may reflect a current subclinical disease, but more work is needed to address this hypothesis. Alternatively, low BCS at calving may reflect BCS loss from dry-off to calving. Several studies have uncovered the association between BCS at dry-off and precalving BCS loss. In general, cows that are fatter (BCS $\geq$3.5) at the end of lactation eat less during the dry period (Daros et al., 2021) and are more likely to lose BCS and subsequently develop uterine diseases (Chebel et al., 2018; Daros et al., 2020). This idea is supported by experimental work done on grazing (Roche et al., 2013) and zero-grazing herds (Schuh et al., 2019) assessing the effect of dietary management to achieve targeted BCS during the dry period; dry cows that were induced to have medium BCS at the end of lactation had lower NEFA and BHB levels compared with cows managed to have higher BCS (Roche et al., 2013, 2015; Schuh et al., 2019).

Breed. Few studies have found breed to be a risk factor for transition period diseases. In Canada, in zero-grazing systems, Jersey cows were found to have a higher prevalence of SCK compared with Holsteins cows (Tatone et al., 2017). In grazing systems, Jerseys have been found to have increased odds of SCK in at least one study (Daros et al., 2017). Conversely, in 2 seasonal-calving pasture-based dairies in Florida, Jersey cows had a lower prevalence of SCK but a higher prevalence of subclinical hypocalcemia compared with Holstein cows (Ribeiro et al., 2013). A large multi-country European study found no evidence of breed differences in SCK prevalence (Berge and Vertenten, 2014); it should be noted that in this study most herds were zero grazing and these systems tended to have only a single breed. With single breed herds some unknown farm variables may act as confounding factors, making it difficult to draw conclusions about breed difference. Ideally, differences between breeds should be studied within herd.

Why disease incidence should vary across breeds is not clear. It has been suggested that Jersey cows have lower levels of $1,25(OH)_2D$ receptors in their intestines compared with Holsteins cows, making Jerseys more susceptible to hypocalcemia (Goff, 2014). However, some field studies failed to detect this relationship (Quiroz-Rocha et al., 2009; Chapinal et al., 2011; Daros et al., 2017).

Parity. Primiparous cows have a higher incidence of uterine disease and a lower incidence of metabolic disease during the transition period when compared with multiparous cows (e.g., Giuliodori et al., 2013). In most dairy production systems, heifers calve around 24 mo of age, increasing the chances of calving difficulty (i.e., dystocia) due to their narrower birth canal compared with fully grown cows (Mee, 2008). Dystocia is reported across different production systems and breeds and results in increases in RP and metritis. Although some studies have identified a higher risk for metritis in primiparous animals (zero grazing: Chapinal et al., 2011; Ghavi Hossein-Zadeh and Ardalan, 2011), others have found no association between parity and metritis risk (grazing and zero grazing: Dubuc et al., 2010; Daros et al., 2017; Vallejo-Timaran et al., 2021). Some insights are provided in an observational study on seasonally housed cows in Europe where a quadratic relationship between parity and metritis was noted. The authors speculate that this may be explained both primiparous and older cows (>3 lactations) being at higher risk of metritis, but only when indoors and when afflicted with a comorbidity (Bruun et al., 2002). Neutrophil function of older cows is impaired compared with younger cows (Gilbert et al., 1993), potentially explaining why cows of third parity or higher are more susceptible to infectious diseases. Multiparous cows have reduced numbers of parathyroid hormone and $1,25(OH)_2D$ receptors in the kidney and intestines, respectively, hence the higher incidence of hypocalcemia in older cows (Goff, 2014). From the 21 studies (see Supplemental File S1, https://doi.org/10.5683/SP3/Q3WGOI, Daros et al., 2022) on SCK occurrence compiled for this review, 3 did not include parity in their analysis, one failed to detect an association between parity and SCK, and one found that primiparous cows were at increased risk of SCK. The remaining 16 studies reported that higher parity animals were at increased risk of SCK. Despite numerous studies identifying increased parity as a risk factor, no study has assessed why multiparous cows have a higher prevalence of SCK compared with primiparous cows. The last third of gestation is the period of greatest accumulation of energy in the fetus and gravid uterus (Bell et al., 1995). Thus, the mere fact that dairy cows are both lactating and gestating at the same time may place multiparous cows at greater risk for experiencing NEB. Cows of higher parity may mobilize more lipids to compensate for NEB in early lactation (Coffey et al., 2004), potentially explaining the positive relationship between parity and SCK. In zero-grazing systems the dynamics of BHB are different between parity groups, with primiparous cows having higher BHB at the beginning of the lactation followed by a gradual decline, and multiparous cows showing a more continuous increase from the day of calving until this peaks at 9 to 11 DIM, followed by a gradual decrease (Santschi et al., 2016; Tatone et al., 2017). To our knowledge no study has attempted to provide further insights as to why this difference in the epidemiology of SCK of primiparous and multiparous cows exists.

Age at First Calving, Gestation, and Dry Period Length. Heifers that calve at 25 mo of age or older, and cows having longer dry periods (>70 d), have higher prevalence of SCK (Tatone et al., 2017). These factors are associated with higher BCS at calving (Roche et al., 2009). Some experimental research has manipulated dry period length from 0 to 60 d in zero-grazing herds, but findings are inconclusive with the exception that prolonging lactation until calving (i.e., no dry period) seems to improve metabolic health (van Knegsel et al., 2014; van Hoeij et al., 2017) without detrimental effects on uterine health postpartum (Chen et al., 2017). The majority of these studies have been performed in zero-grazing systems with high producing Holstein cows and thus may not extend to lower producing cows on pasture. There have been no published studies on the effect of dry period length on metabolic diseases and metritis in pasture-based systems, but a longer dry period (≥112 d) was associated with a higher incidence of clinical mastitis after calving in grazing herds in New Zealand (Bates and Dohoo, 2016). This could have been driven because the intramammary dry-cow antibiotic has a finite period of efficacy; when antibiotics are combined with teat sealants, cows with long dry period have lower postcalving mastitis incidence (Berry and Hillerton, 2007).

Shorter gestation length has been associated with higher incidences of RP (Muller and Owens, 1974); it is likely that in shortened gestations the placentomes are not fully matured (Laven and Peters, 1996) and the hormonal balance required for placental detachment is not fully in place (Beagley et al., 2010). Heat stress is associated with short gestations (Tao and Dahl, 2013); however, RP incidence is higher during cooler months across production systems (e.g., Quiroz-Rocha et al., 2009). More details on seasonal effects are provided below.

Milk Yield and Components. There is no evidence of an association between milk production and the likelihood of cows developing metritis or RP (Ingvartsen et al., 2003). Tatone et al., (2017) found that herd-level milk production and milk fat percentage before dry-off were negatively associated with SCK. It is likely that herds that produce more milk also have better general management and thus may have implemented more effective ketosis prevention protocols. However, at the cow-level, previous lactation milk yield was not associated with metritis, RP, or SCK in a study of 6 zero-grazing herds (Daros et al., 2020).

Mastitis is the only disease that is consistently positively associated with milk production, both in grazing (Bates and Dohoo, 2016) and zero-grazing herds (Ingvartsen et al., 2003). The exact mechanism for this association has not been fully elucidated. Although Ingvartsen et al. (2003) suggests that this may be related to teat sphincter issues and that high volume of milk may wash out more of the protective keratin layer.

Physiological Parameters. All studies reported in this section were performed in zero-grazing herds. Circulating NEFA levels can serve as a proxy for changes in energy balance during the transition period (e.g., Dubuc et al., 2010; Ospina et al., 2010), with SCK showing the strongest correlation with NEFA (Ospina et al., 2013). Unfortunately, there is no cow-side test for NEFA assessment (Overton et al., 2017). Serum or milk BHB have both been used to identify cows for clinical ketosis, and at risk for displacement abomasum and uterine disease, but the predictive value of BHB for transition period diseases is higher during the postpartum period (Overton et al., 2017) when it is often too late to implement prevention strategies. However, the availability and reliability of cow-side tests for BHB make this a powerful tool to improve transition period management (Ospina et al., 2013).

A few other markers show promise as predictors of transition period disease. Inflammation markers, such as haptoglobin, have been associated with transition period disease; however, the predictive value of these markers is greater postpartum (Dubuc et al., 2010; Huzzey et al., 2015). Studies investigating metabolomics and proteomics have identified a range of parameters (e.g., serum lactate and IL-6 for metritis, and boron, aluminum, and potassium for SCK) associated with metabolic and infectious diseases (Dervishi et al., 2016b; Zhang et al., 2017). Parameters associated with immune function and inflammation were different in healthy and affected cows in the postpartum period as much as 8 wk before calving (Dervishi et al., 2016a; Trevisi and Minuti, 2018). Although metabolomic studies are promising, the work to date suffers from poor replication with the majority of studies making use of very few animals (Zhang et al., 2017; Dervishi et al., 2018). Overall, these metabolic changes indicate that the "transition period" should be considered as starting much before what is typically considered.

Italian researchers have proposed the use of indexes, such as the liver activity index, liver functionality index, and postpartum inflammatory response index, to categorize cows at risk for transition period disease (see review: Trevisi and Minuti, 2018). These indexes combine several blood inflammation markers and high values for these indexes are associated with lower reproductive performance. However, most of this research has been limited to a few zero-grazing experimental herds in Italy (Trevisi et al., 2012), so the use of these indexes across herds should be viewed with caution, especially as immune function markers may be herd dependent (Zecconi et al., 2018). Although these indexes were designed for postpartum measurements, recent findings of a variety of markers during the dry period indicate the possibility of new indexes (Trevisi and Minuti, 2018).

Behaviors and DMI. Dry matter intake is a function of feeding behavior, specifically feeding rate (meal size/meal time) and total time spent feeding (number of meals × meal time; Nielsen, 1999; DeVries et al., 2003b). Because it is hard to measure these variables in grazing systems, most of the studies on the association between feeding behavior and transition disease were conducted in zero-grazing systems.

Feeding behaviors have been used to identify cows at risk for metritis (Urton et al., 2005; Huzzey et al., 2007) and at risk for clinical ketosis and SCK (González et al., 2008; Goldhawk et al., 2009). In these studies cows that were sick had lower daily feeding times and DMI during the prepartum period. Conversely, DMI was higher in the weeks prepartum for cows that developed subclinical hypocalcemia compared with cows that had normal levels of calcium on the day of calving; daily feeding time was not reported (Jawor et al., 2012). To our knowledge there are no studies assessing prepartum DMI and transition disease risk in grazing herds, but the use of rumination monitors in grazing cattle has shown promise as a surrogate measure to assess feeding behavior in this system. In one very recent study, grazing cows with metritis had lower daily rumination times in the prepartum period compared with cows that did not developed metritis, but this association was only present during the autumn period and when temperature-humidity index was above 68 (Held-Montaldo et al., 2021).

In a zero-grazing herd, Schirmann et al. (2016) also found decreased DMI and feeding time per day during the prepartum period, but only for cows that were diagnosed with metritis and SCK at the same time and not for cows diagnosed with metritis only. Dry matter intake may be intrinsically correlated with levels of circulating NEFA (Allen et al., 2009), which has been described as a major risk factor for ketosis and metritis (Ospina et al., 2010). The relation between NEFA, DMI, BHB, and metritis has been previously described by Hammon et al. (2006) who reported that high NEFA levels in the week prepartum were associated with decreased DMI, which in turn was associated with lower immune function and the development of metritis and SCK. These results suggest that studies using prepartum feeding time to predict disease should also measure energy balance markers or at least control for changes in BCS during the dry period (Daros et al., 2021).

In zero-grazing systems standing and lying behavior prepartum are associated with dystocia (Proudfoot et al., 2009a), subclinical hypocalcemia (Jawor et al., 2012), metritis (Neave et al., 2018), and ketosis (Itle et al., 2015), but not SCK (Kaufman et al., 2016b). The direction of these relationships may be disease specific. For example, cows diagnosed with dystocia exhibit more standing or lying bouts during the day of calving (Proudfoot et al., 2009a). For other diseases, such as ketosis and metritis, changes in standing or lying behavior before calving may reflect an indirect association. It has been speculated that cows that develop ketosis are disproportionally of low social rank (i.e., subordinate animals) and thus avoiding agonistic interactions at the feed bunk by waiting longer to feed (Itle et al., 2015). Lameness has been associated with higher odds of transition diseases in zero-grazing systems (Daros et al., 2020) and affects lying behavior (Ito et al., 2010); hence, this could explain the association between standing behavior and the disease. In grazing systems, lameness does not have a major effect on standing behavior (Thompson et al., 2019) and only weak associations between standing behavior and transition diseases after controlling for lameness have been found in grazing herds (Sepúlveda-Varas et al., 2014).

Social behaviors have also been assessed in relation to transition period diseases in cows under zero-grazing systems (see reviews: Proudfoot et al., 2012; Sepúlveda-Varas et al., 2013). Decreased agonistic behavior at the feed bunk is usually associated with increased risk of metritis and SCK (Huzzey et al., 2007; Goldhawk et al., 2009; Neave et al., 2018; but see also: Sahar et al., 2020), though the causal mechanisms for these findings have not been explored. Social behavior is dependent on environmental factors and the animal's social rank. Subordinate cows may have higher levels of glucocorticoids (Huzzey et al., 2012), which impair immune function. Few studies have considered social rank as risk factor for transition disease.

Agonistic behavior and feeding synchrony have been identified as a way of studying feeding strategies prepartum and assessing if different strategies are associated with metritis risk in a zero-grazing experimental herd; although the relationship between such strategies and metritis is not straightforward, it seems that metritic cows may change their feeding strategy more often than healthy cows (Foris et al., 2020).

Prepartum social behavior has been rarely studied in grazing cows. Because competition for feed is expected to be lower in grazing systems, we suggest that the association between social status and disease may be less evident for grazing cows. However, competition for water access can be high in grazing systems (Coimbra et al., 2012). In an observational study on small-scale grazing herds, restricted water access was associated with a higher risk of SCK (Daros et al., 2017). Monitoring drinking behavior in grazing cows may be a way of identifying individuals at risk.

Herd-Level Risk Factors

Management Factors. Cows show synchronized behaviors and have a complex social hierarchy (DeVries et al., 2003a; Val-Laillet et al., 2008). Regrouping and overcrowding increase agonistic interactions, disrupting feeding and lying behavior in zero-grazing herds (Schirmann et al., 2011). There is a sharp increase in agonistic interactions in the first day following regrouping that quickly resume to baseline levels after few days (von Keyserlingk et al., 2008). Conversely, overcrowding is a more chronic stressor and cows take longer to adapt (Proudfoot et al., 2009b). Overcrowding has been associated with increased glucocorticoids (Huzzey et al., 2012; Fustini et al., 2017), suggesting that overcrowding during the prepartum period may be particularly detrimental to cow health. The effect of overcrowding is greater in subordinate than in dominant cows (Huzzey et al., 2012). The effect of regrouping and stocking density on physiological parameters, disease incidence, reproductive, and milk performance of cows in zero-grazing systems has been reviewed at length elsewhere (Chebel et al., 2016). In brief, weekly regroupings during the dry period did not affect energy and immune status, reproductive and production performance, or disease incidence compared with cows that stayed in a stable group throughout the dry period (Silva et al., 2013a,b). The effect of stocking density (80 vs. 100%) during the dry period on feeding and standing behavior were reported (Lobeck-Luchterhand et al., 2015); however, these changes did not translate into higher incidence of postpartum disease (Luchterhand et al., 2016). The researchers calculated the stocking density at feed bunk based on a 61-cm head space, that is, feed bunk fitted with 61-cm-wide head locks, which may be considered as providing more than the standard feed bunk space for Jersey cows, given their smaller stature compared with Holsteins, which were used in much of the work done on feeding behavior (e.g., DeVries et al., 2003b).

Few other management practices have been associated with transition period disease. Early mastitis (clinical cases within 30 d of calving) is affected by different management strategies during the dry period, such as dry-cow therapy strategies and cleaning routine (Berry and Hillerton, 2007; Green et al., 2007). Cows housed on pasture during the dry period benefit from rotational grazing, possibly by having cleaner lying surfaces, whereas cows kept indoors benefit from routine stall and calving pen cleaning (Green et al., 2007). These results highlight the importance of clean lying surfaces to control mastitis. Cleaner farms also experienced fewer cases of metritis in a study of small-scale grazing herds (Daros et al., 2017).

One study reported that cows in herds with no access to pasture had higher odds of developing metritis (Bruun et al., 2002). Conversely, another study reported that cows allowed to graze in the summer had a higher prevalence of SCK (Berge and Vertenten, 2014). An experimental study by Olmos et al. (2009), comparing health of housed and grazing cows, found that grazing cows had higher BHB and lower rumen fill compared with housed cows. Combined, these results suggest that grazing cows may experience longer periods of NEB, explaining the relatively high prevalence of SCK 3 to 5 wk after calving in some grazing herds (Compton et al., 2015).

Experimental studies varying on management practices are difficult to perform and require interventions that last for long periods with large numbers of cows. Epidemiological studies require a large number of farms to capture the variability in management practices with sufficient replication (i.e., enough farms using the same management practice). Large epidemiological studies have been carried out in Europe and North America (e.g., Chapinal et al., 2011; Berge and Vertenten, 2014) where most cows are kept indoors; such studies are still required to identify management practices associated with transition disease risk in grazing herds.

Ambient Factors. In zero-grazing herds there are seasonal effects on transition period disease incidence. In Europe, during the spring months SCK incidence tends to be higher than in winter months (Suthar et al., 2013; Berge and Vertenten, 2014; Vanholder et al., 2015). In Canada there is a high incidence of SCK during May, but not for the other spring months (Tatone et al., 2017). Season is also a risk factor for metritis and RP, with higher incidences during the winter months (Muller and Owens, 1974; Bruun et al., 2002; Quiroz-Rocha et al., 2009; Chapinal et al., 2011).

Most of the studies in grazing herds did not report an effect of season on transition period disease. However, rainfall at calving is associated with higher odds of clinical mastitis in the first 90 d postpartum in grazing systems in New Zealand (Bates and Dohoo, 2016).

Association Between Different Diseases During the Transition Period

As discussed previously, early fat mobilization and uncontrolled inflammation can lead to disease. For cows managed either in grazing or zero-grazing systems increased levels of NEFA overwhelm liver capacity to metabolize fat, impairing liver function causing fatty liver, SCK, which may lead to the development of clinical ketosis and DA. High levels of circulating BHB and liver inflammation negatively affect the immune system, increasing susceptibility to infectious diseases such as metritis and mastitis. At the same time, low calcium level impairs immune system functionality leading to RP (Kimura et al., 2002, 2006). There is also a high energetic cost to mounting an inflammatory response (Kvidera et al., 2017), further exacerbating NEB. Moreover, in zero-grazing herds the sudden change from high-fiber, low-energy to low-fiber, high-energy diets common around calving likely contributes to SARA, which in turn increase rumen wall permeability ("leaky gut"), allowing endotoxins to enter the bloodstream resulting in an inflammatory response (Zebeli et al., 2015). Together this research highlights the complexity of events and how one disease may contribute to another.

Lameness has been considered one of the main health problems affecting cows in zero-grazing systems (Solano et al., 2015; Randall et al., 2019) but has also been identified as a highly prevalent issue in grazing herds (Ranjbar et al., 2016; Bran et al., 2018). We argue that lameness has been underappreciated as a risk factor for transition diseases. The associations between lameness and lower feed intake (Bach et al., 2007), increased levels of haptoglobin (Tadich et al., 2013), and the high incidence of lameness during the dry period (Daros et al., 2019) are all evidence of this potential association.

Only a few studies have addressed the link between lameness and transition period disease (Calderon and Cook, 2011; Daros et al., 2020). Calderon and Cook (2011) followed lame cows between 1 to 3 wk before calving and found that they had higher blood levels of BHB compared with nonlame cows. These authors also reported that lame multiparous cows in the close-up period lay down longer and suggested that these cows might have given up feeding time to spend more time lying time. Multiple studies on indoor-housed cows report that lame cows lie down for longer, spend less time feeding, and have lower DMI compared with nonlame counterparts (Bach et al., 2007; Ito et al., 2010; Miguel-Pacheco et al., 2014). Lameness prevalence in the 2 wk before calving was associated with increased risk of being treated for transition period diseases within 30 d of calving (Vergara et al., 2014). In a longitudinal study in zero-grazing herds, the relationship between lameness, time spent feeding, and development of transition disease was explored; cows that developed lameness or were chronically lame during the dry period had decreased feeding time and were more likely to develop transition diseases, after controlling for changes in BCS, parity, previous milk yield, and other factors

(Daros et al., 2020). We are not aware of similar studies in grazing systems but argue that the mechanisms linking lameness to transition period disease are likely to be similar.

FINAL REMARKS AND FUTURE DIRECTIONS

For the transition period diseases that we reviewed it is evident that the occurrence is high in both grazing and zero-grazing intensive systems. We identified risk factors for these transition diseases in both grazing and zero-grazing systems that seem to develop earlier than what is normally considered the transition period and suggest that the transition period should be considered more fluidly, focusing on preventive health protocols starting at different time points depending upon the risk factors at play.

Future intervention studies should test practices that improve conditions in the early dry period. As for zero-grazing herds, studies should include nutritional strategies for mid- to late-lactation cows that are overconditioned and following up lameness cases more frequently as a way of reducing lameness incidence and chronic cases during the dry period. Research on grazing systems should focus on dry period management and mitigating environmental risks, including heat stress and wet conditions. Lameness in grazing herds is often overlooked and prevention strategies for grazing herds should also be investigated. We also highlight other risk factors that are not manageable such as breed, parity, or season. Understanding these factors may aid in the data analysis of future studies to avoid confounding and misinterpretation of results.

Although cross-sectional studies help estimate the prevalence of health issues, they contribute little to the understanding of causal relationships between risk factors and disease. We urge more longitudinal studies to measure the effect of managing risk factors in reducing disease incidence in both grazing and zero-grazing systems.

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