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Association between passive immunity and health status of dairy calves under 30 days of age

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ABSTRACT

Calves are highly susceptible to disease and mortality occurrence within the first month of life. Even if failed transfer of passive immunity (**FTPI**) is commonly recognized as a main factor affecting calf health and survival, conflicting results are reported in literature about the association between passive immunity (**PI**) and calf health, especially regarding enteric diseases. Therefore, a prospective cohort study was conducted on 78 calves of three Italian dairy farms during winters of years 2014–2016, with the specific aim of evaluating the association between PI and health status of calves within 30 days of age under field conditions. Blood samples were collected between 1 and 5 days of age from each calf included in the study, and disease and mortality occurrence was monitored throughout the first month of life. Additionally, fecal samples were collected from calves with scours before treatment. Blood serum samples were tested by an electrophoretic method for the assessment of immunoglobulin (**Ig**) concentration, whereas fecal samples were submitted to ELISA test for positivity to *Escherichia coli* K99, rotavirus, coronavirus, and *Cryptosporidium* spp. Only enteric diseases occurred in calves of this study. Calves that suffered from diarrhea or died within the first month of life had lower serum Ig concentrations than those that remained healthy or survived ($P < .05$). Even if not significantly ($P = .127$), lower serum Ig concentrations were observed in sick calves that had been treated with antibiotics compared to those that had not been treated. The odds of disease and mortality occurrence were 24 (95% CI = 3–231) and 11 (95% CI = 1–111) times higher, respectively, for calves with FTPI (serum Ig concentration < 10.0 g/L) than for those with an adequate PI transfer ($P < .05$). Calves with adequate PI transfer had also a 6-day delay in the age at first disease onset compared to those with FTPI ($P < .01$). Even if estimated on a small number of calves, those with FTPI had higher risks of enteric infections by rotavirus (odds ratio = 12; 95% CI = 1–137) and Cryptosporidium spp. (odds ratio = 9; 95% CI = 1–72) ($P < .05$). In this study, the PI level influenced the occurrence of enteric diseases and mortality in calves under one month of age, confirming the importance of a proper colostrum provision to calf health and, consequently, to the reduction of antimicrobial use in dairy farming. However, further investigations are needed, particularly focusing on the relationship between PI and specific enteropathogen infections in calves.

1. Introduction

The most critical period of dairy heifer rearing is the first month of life, due to the high risk of disease and mortality occurrence (Sivula et al., 1996; Svensson et al., 2006). In this period, calves suffer mainly from enteric diseases caused by infectious pathogens like *Escherichia coli*, rotavirus, coronavirus, and *Cryptosporidium parvum* (Maunsell and Donovan, 2008; McGuirk, 2008). Calves that survive to diarrhea usually show lower growth rates and are more susceptible to other diseases (especially bovine respiratory disease complex) with the possibility of long-term negative consequences on performances in the first lactation (Curtis et al., 1988; Donovan et al., 1998a; van der Fels-Klerx et al., 2002). Because calves are born nearly devoid of antibodies, colostrum management is one of the most crucial factors that affect calf health and survival: inadequate colostrum intake could result in failed transfer of passive immunity (**FTPI**, i.e. calf serum immunoglobulin (**Ig**) G

Abbreviations: BVD, bovine viral diarrhea; CI, confidence interval; FTPI, failed transfer of passive immunity; Ig, immunoglobulin; LSM, least squares mean; OR, odds ratio; PI, passive immunity; SEM, standard error of the mean; SD, standard deviation

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concentration lower than 10.0 g/L at 48 h of age), which lead to a higher risk of disease and mortality occurrence (Godden, 2008; Maunsell and Donovan, 2008). The economic consequences of FTPI should also be considered: a recent study by Raboisson et al. (2016) estimated that the total costs per dairy calf with FTPI could range from 52 € (best scenario) to 285 € (worst scenario), with an increase of about 50% in the case of beef calves. The same work, which revised the literature about FTPI and its consequences to calf health and performances, pointed out that few studies were actually published regarding the association between FTPI and calf health, and particularly concerning FTPI and diarrhea occurrence. Moreover, unlike respiratory diseases, the association between passive immunity (**PI**) level and scours occurrence in calves is still unclear (Donovan et al., 1998b; Furman-Fratczak et al., 2011; Meganck et al., 2015). Responding the need for further investigations on this topic, the present study examined the association between PI and health status of calves within the first month of life under field conditions, particularly focusing on enteric diseases.

2. Material and methods

The study was conducted on three commercial dairy farms of the Veneto Region (northeastern Italy) during winter months (November to February) from the year 2014 to the year 2016. The number of farms to involve was conveniently established in order to meet the minimum number of calves needed for the study. The latter was estimated based on the formula by Daniel (1999): for a confidence level set at 95%, an expected calf disease prevalence set at 20% (Lundborg et al., 2005; Windeyer et al., 2014), and a relative precision set at 10%, the estimated calf sample size was 61. However, the minimum sample size for this study was set at 67 calves considering a dropout rate of 10%. The farms included in the study were similar in terms of cow breed reared (Italian Holstein), herd size (50–150 lactating cows), housing (loose with cubicles), feeding (total mixed ration) and milking (milking parlor) systems, management of calving (use of calving pen; parturition monitored by the farmer; calf separated from dam immediately after birth) and calves (navel disinfection; colostrum of the own dam provided by nipple-bottle; single housing until at least 5 wk of age), and adoption of a voluntary plan for bovine viral diarrhea (**BVD**) control that required blood sampling on newborn calves to identify persistently infected animals. On the three farms, cows were moved to a straw-bedded calving pen 3 days before the expected calving date, according to the routine management. Only calves both born from eutocic calving and separated from dams within 10 min of birth were included in the study, irrespective of their sex and genotype (Holstein purebred or Holstein-beef crossbred). Navel disinfection was performed as first by dipping into a 7% tincture of iodine, then calves were moved to clean straw-bedded single pens, where they were provided their dams' colostrum by nipple-bottle according to the own farm practices. Fresh water, grass hay, and calf starter feed were available from the third day of life. The person in charge of carrying out the study visited the farms two times per week together with the veterinarian responsible for the BVD control plan. At each farm visit, the veterinarian collected blood samples from the jugular vein of calves between 1 and 5 days of age using a 10 mL Vacutainer® tube without anticoagulant (Becton Dickinson, Franklin Lakes, NJ, USA). The same blood sample collected for the BVD control plan was used to assess also calf PI level. The health of the enrolled calves was monitored at each farm visit from birth to 30 days of age, and data on disease and mortality occurrence (i.e., type of disease, cause of mortality, age at disease onset or mortality occurrence, and antibiotic treatments on sick calves) were recorded. Additionally, the veterinarian collected fecal samples into a 100 mL tube from the rectum of those calves that both showed signs of clinical diarrhea (i.e., profuse liquid feces) and had not been treated yet at the time of the farm visit. Fecal samples were intended to be tested for enteric pathogens. Sick calves were treated according to the own farm therapeutic protocol. Blood and fecal samples were transported to the laboratory at refrigeration temperature (4 °C) and delivered within 1 h of collection.

At the laboratory, blood samples were centrifuged at 3076 × *g* for 10 min at 20 °C and serum was spiked into two tubes, one for BVD virus testing and the other for Ig detection. Serum and fecal samples were stored at −20 °C until the day of the analysis. Serum Ig concentration was determined by the same method used in Lora et al. (2017), based on agarose gel electrophoresis. This method was conveniently chosen rather than the RID (radial immunodiffusion) gold standard method for IgG assessment based on both the diagnostic services provided by the laboratory and its recognized good accuracy for Ig assessment compared with RID (from 89% to 97%) (Pfeiffer et al., 1977; Rumbaugh et al., 1978; Massimini et al., 2006).

Fecal samples were thawed at room temperature and were tested by two commercial ELISA kits ("Rota-Corona-K99" kit and "Cryptosporidium Ag test" kit, Idexx, Montpellier, France) to detect antigens of *E. coli* K99, rotavirus, coronavirus, and *Cryptosporidium* spp. The ELISA tests were performed according to the manufacturer instructions, and the plates were read by spectrophotometer (Tecan Sunrise, Tecan trading AG, Männedorf, Switzerland) at a wavelength of 450 nm. The sensitivity and specificity of the tests reported in literature were 68% and 95% for rotavirus ELISA and 33% and 80% for coronavirus ELISA when compared with lateral flow immunochromatography (Izzo et al., 2012), 100% and 91% for *E. coli* K99 ELISA when tested against PCR (Izzo et al., 2011), and 94% and 96% for *Cryptosporidium* spp. ELISA when evaluated against other three diagnostic techniques (another EISA test, an immunofluorescence assay, and an immunochromatographic assay) (Geurden et al., 2008).

Differences in serum Ig concentration between sick and healthy calves, dead and survived calves, and sick calves treated or not with antibiotics were assessed as first by PROC GLM (SAS Institute Inc., Cary, NC), including the farm in the model as fixed effect. The assumptions of the linear model were visually inspected by plotting the graphs of the residuals of the model. Because the effects of calf sex, calf breed, and year of sampling were nested within farm, the latter was considered as proxy variable of the other three in this and the subsequent statistical analyses. Calves were then divided into two categories based on serum Ig concentration: having FTPI (serum Ig concentration < 10.0 g/L) or not having it (serum Ig concentration ≥ 10 g/L). As in previous works (Furman-Fratczak et al., 2011; Lora et al., 2017), the threshold for FTPI definition was chosen based on the level commonly indicated for IgG concentration, as the latter accounts for approximatively 90% of serum Ig concentration (Godden, 2008). The effect of FTPI, considered as predictive factor, on disease and mortality occurrence, antibiotic treatments for sick calves, and specific enteropathogen infections was investigated by PROC LOGISTIC (SAS Institute Inc., Cary, NC), including the farm in the model. Particularly, an exact logistic regression was performed for mortality, due to the low number of occurrence. Moreover, the effect of FTPI on specific enteropathogen infections was evaluated by considering only healthy calves and calves whose fecal samples were positive for the enteropathogen included in the model. Odds ratio and 95% CI were calculated for the dependent variables that were significantly affected by FTPI. Finally, a Kaplan-Meier survival plot was used to evaluate the age (days) at first disease outbreak of the 78 calves stratified by presence or absence of FTPI. The equality over strata was tested by Log-rank and Wilcoxon statistics. A Cox proportional hazard model was then used to assess the risk of disease outbreak over the time, and hazard rate ratios and 95% CI were determined. Test for proportionality was carried out by visual inspection of the Schoenfeld residuals. The level of significance was set at $P < .05$ for all the statistical analyses performed in this study.

3. Results and discussion

Seventy-eight calves were ultimately included in the study: 57

females and 21 males, 54 Holstein purebreds and 24 Holstein-beef crossbreds. The overall mean (± SD) of calf serum Ig concentration was 12.6 ± 6.2 g/L, with a minimum of 1.6 g/L and a maximum of 30.9 g/L. The overall percentage of calves with FTPI was 34.6%, and it was in line with the most recent prevalence of FTPI reported for Italian dairy calves (41.0%), which was found in a previous study by the same authors (Lora et al., 2017). Considering the 21% incidence risk for calf neonatal diarrhea in dairy herds reported by Lundborg et al. (2005) and Windeyer et al. (2014), the percentage of calves with scours found throughout this study was high (50.0%), but it was almost comparable with the findings by Furman-Fratczak et al. (2011) in a similar study, where 37% of the 175 heifer calves considered suffered from diarrhea. The absence of respiratory disease cases observed during this study was not surprising, because calves under 30 days of age usually suffer from diarrhea, whereas respiratory diseases are more typical of older animals (McGuirk, 2008). On the other hand, probably due to the high percentage of scours recorded, the mortality rate found in this study (6.4%) was greater than those reported by other authors (ranging from 3.1 to 5.7%), even if they were calculated on larger numbers of calves (Svensson et al., 2006; Raboisson et al., 2013; Windeyer et al., 2014). Calves that suffered from diarrhea within 30 days of age had lower serum Ig concentrations (least squares mean (LSM) ± SEM: 11.1 ± 1.0 g/L) than asymptomatic calves (LSM ± SEM: 14.4 ± 1.1 g/L; $P < .05$). Moreover, calves that died in the first month of life had serum Ig concentrations nearly two times lower than calves that had survived (LSM ± SEM: 7.4 ± 2.7 vs 13.0 ± 0.7 g/L; $P < .05$). Therefore, being also in accordance with the previous studies by McGuire et al. (1976) and Blom (1982) that reported an association between low serum Ig concentrations and disease and mortality occurrence in dairy calves, our results confirmed the importance of a proper PI transfer to calf health. The FTPI, in particular, was a relevant risk factor for both disease and mortality occurrence among the calves considered in this study ($P < .01$ and $P < .05$, respectively; Table 1). Even if only few papers in literature focused on the relationship between FTPI and enteric diseases in calves (Raboisson et al., 2016), other authors found a greater risk of disease and mortality occurrence for calves with FTPI compared to those with an adequate level of serum Ig concentration (Donovan et al., 1998b; Berge et al., 2005). However, the level of immune protection in calves could affect not only disease occurrence, but also disease severity. In this regard, Furman-Fratczak et al. (2011) found that calves with higher PI levels suffered from milder forms of both enteric and respiratory diseases, whereas calves with serum Ig concentration higher than 15.0 g/L at 30–60 h of life avoided respiratory tract infections at all. Even if no specific indicators of calf diarrhea severity were measured in this study (e.g. dehydration, body temperature, fecal scoring), the tendency of having a lower Ig concentration observed in sick calves that needed antibiotic treatments (25.6% of the overall sick calves) compared to those that were not treated (LSM ± SEM: 8.6 ± 1.8 vs 12.2 ± 1.2 g/L; $P = .127$) reasonably suggested a greater severity of the disease in calves with lower PI levels. On the other hand, even if not being statistically significant, the latter result highlighted how an adequate PI level could affect the antimicrobial use in dairy farming, in accordance with Berge et al. (2005), who actually found a relationship between FTPI and a higher risk of antibiotic treatments in calves.

Table 1
Percentage, odds ratio (OR) and 95% CI of diarrhea and mortality occurrence in 78 calves under 30 days of age with or without failed transfer of passive immunity (FTPI – serum immunoglobulin concentration < 10.0 g/L) ($P < .05$).

FTPI	Diarrhea occurrence			Mortality occurrence		
	%	OR	95% CI	%	OR	95% CI
Absent	43.1 (22/51)	1.00	–	2.0 (1/51)	1.00	–
Present	63.0 (17/27)	24.12	2.52–231.09	14.8 (4/27)	10.59	1.01–110.78

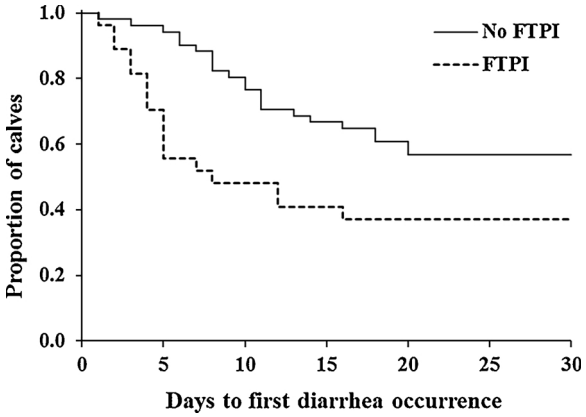

Fig. 1. Kaplan-Meier plot showing days to first diarrhea occurrence in 78 calves under 30 days of age stratified by having or not failed transfer of passive immunity (FTPI – serum immunoglobulin concentration < 10.0 g/L) (Wilcoxon test of equality over strata: $\chi^2 = 8.27$; $P < .05$).

In this study, FTPI affected also the age at the first disease outbreak (Fig. 1; Wilcoxon test of equality over strata: $\chi^2 = 8.27$; $P < .01$), with a higher hazard of becoming sick over the time for calves with FTPI than for those with an adequate PI transfer (hazard ratio = 2.1; 95% CI = 1.12–3.98). Moreover, the onset of diarrhea was delayed by about 6 days in calves with an adequate PI transfer compared to those with FTPI (mean ± standard error: 16 ± 1 vs 10 ± 1 days; $P < .01$). The latter result, which reflected the report by Davidson et al. (1981) about calf respiratory infections (disease onset was delayed by 5–7 days for calves with higher serum Ig concentrations), could be of a crucial importance to dairy practice, because it might not be excluded that a delay in the age at disease outbreak could significantly enhance the possibility of calf recovery.

With regards to specific enteropathogen infections, *Cryptosporidium* spp. and rotavirus were the major agents of calf diarrhea in this study, as it was expected from findings by other authors (de la Fuente et al., 1999; Bartels et al., 2010; Meganck et al., 2015), whereas positivity to *E. coli* K99 and coronavirus were rarely detected and exclusively in mixed infections. Particularly, out of the 28 fecal samples that were collected from the 39 calves with scours, 13 (46.4%) were positive only to *Cryptosporidium* spp., five (17.9%) were positive only to rotavirus, four (14.3%) were positive to more than one infectious pathogen (two to rotavirus and *Cryptosporidium* spp., one to rotavirus and coronavirus, and one to *E. coli*, rotavirus and *Cryptosporidium* spp.), and six (21.4%) were negative to all the tested enteropathogens. Even if data on specific enteropathogen infections collected in this study resulted to be few, FTPI was a predisposing factor for infections caused by rotavirus and *Cryptosporidium* spp. ($P < .05$; Table 2). Although a larger dataset

Table 2
Percentage, odds ratio (OR) and 95% CI of rotavirus and *Cryptosporidium* spp. infections in calves under 30 days of age with or without failed transfer of passive immunity (FTPI − serum immunoglobulin concentration < 10.0 g/L) ($P < .05$).

FTPI	Rotavirus infection[a]			*Cryptosporidium* spp. infection[a]		
	%	OR	95% CI	%	OR	95% CI
Absent	14.7 (5/34)	1.00	–	25.6 (10/39)	1.00	–
Present	28.6 (4/14)	11.85	1.02–137.48	37.5 (6/16)	8.64	1.04–72.07

[a] Only healthy calves (n = 39) and calves whose feces were positive for the specific pathogen included in the model (n = 9 for rotavirus and n = 16 for *Cryptosporidum* spp.) were considered for the statistical analysis.

would be needed for confirming the latter results, they provided an interesting indication, because if on one hand there is evidence that specific PI in calves is protective against diarrhea caused by rotavirus (Kohara and Tsunemitsu, 2000), on the other hand it is still unclear whether maternal immunity can protect against *Cryptosporidium* spp. Trotz-Williams et al. (2007), for example, did not find any association between FTPI and *Cryptosporidium parvum* shedding in dairy calves with diarrhea. Therefore, given that PI actually affects enteric diseases occurrence in young calves, further studies are needed to better understand the relationship between PI and specific enteropathogen infections, such as those caused by *Cryptosporidium* spp.

4. Conclusions

This study showed that FTPI in calves of less than one month of age was associated with an increased risk of diarrhea and mortality occurrence. Moreover, low PI levels were associated with a younger age at disease onset and, potentially, with the need of antibiotic treatments for recovery. Therefore, ensuring an adequate transfer of maternal immunity to calves (through proper colostrum management practices) is of fundamental importance to calf health, allowing to avoid severe enteric infections, to improve calf probabilities of recovery, and to reduce antimicrobial use in dairy farming. In this study, an adequate PI transfer was protective also against infections by specific enteropathogens like rotavirus and *Cryptosporidium* spp. However, due to the small dataset referred to the specific enteropathogen infections available in this study, further in-depth investigations are needed to confirm the latter results.

Conflicts of interest

None.

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