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# Assessment of the innate immune response in the periparturient cow

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ABSTRACT

The transition period is the most critical phase in the life of high yielding dairy cows. Within a few weeks, cows are submitted to many challenges (physiological, nutritional, psychological, management) that require prompt and effective adaptive responses. The immune system is involved in this process, and many changes of the cow's immune system components have been observed around calving. Cows are considered to be immunosuppressed in late lactation, and available data suggest that the immune system is dysregulated around parturition. Significant attention has been focused on modification of cellular functions (e.g. the reduction of phagocytosis and diapedesis), but growing interest concerns the components of the innate immune system, which often exhibits increased responses such as susceptibility to inflammatory events and the related acute phase response (APR). Systemic inflammation plays a significant role in early lactation, affects many liver functions and has been associated with the impairment of cow performance (i.e. reduced feed intake, milk yield, fertility, welfare). The assessment of variations in immune-metabolic indices offers opportunities to predict the onset of the health troubles and to anticipate the proper therapies needed to guarantee health, good welfare and fertility in the following lactation. The frequency of diseases (metabolic and infectious) before calving is rare, but several clues suggest that various metabolic and immune variations can begin during the dry period. Interesting preliminary results encourage this perspective and possible candidates are suggested.

## 1. Critical points in the transition period of dairy cows

The transition period of dairy cow has previously been defined by Grummer (Grummer, 1995) and Drackley (Drackley, 1999) as the interval from 3 wk. before to 3 wk. after calving. Many authors have described this critical stage (Drackley, 1999; Goff & Horst, 1997; Grummer, 1995; Trevisi et al., 2011; Van Knegsel et al., 2014), which is characterised by dramatic and sudden physiological changes, but often the emphasis has focused on a single relevant aspect, disregarding or minimizing other factors. In accordance with the knowledge acquired in the last decades, it is possible to summarize at least five critical points of the transition period:

reduction of immune competence (Goff & Horst, 1997; Kehrli et al., 1989a; Kehrli et al., 1989b; Lacetera et al., 2005; Mallard et al., 1998)

negative energy balance (NEB), resulting in mobilization of adipose and muscle tissue (Drackley, 1999; Grummer, 1993; Grummer, 1995)

hypocalcemia, as a consequence of the delayed availability of calcium in the blood for the sudden and huge demand of the mammary gland for milk synthesis (De Garis & Lean, 2009; Goff & Horst, 1997; Martinez et al., 2012)

an overt systemic inflammatory response around the time of calving, which commonly occurs immediately after calving even in the absence of signs of microbial infections or other pathologies (Bertoni & Trevisi, 2013; Bionaz et al., 2007; Cappa et al., 1989; Sordillo et al., 2009; Trevisi et al., 2012)

a situation of oxidative stress, due to the unbalanced availability of antioxidants in presence of phenomena that increase the production of potent pro-oxidant molecules (Bernabucci et al., 2005; Bionaz et al., 2007; Celi, 2011; Sordillo & Aitken, 2009)

To some extent, all these situations could be considered physiological adaptations of changing from a non-lactating to lactating state and from a pregnant to non-pregnant condition. Nevertheless, when they are dramatic and prolonged (Trevisi et al., 2016) some proper adaptations of certain peculiar metabolic pathways are difficult, particularly at the beginning of lactation. Cows struggle to recover homeostasis and some adaptive mechanisms can be dysregulated, explaining the appearance of metabolic (Drackley, 1999) and infectious diseases (e.g. mastitis; (Goff & Horst, 1997)).

The key mechanism(s) that disturb the balance of the physiological (immune and metabolic) variations in the transition period have not yet

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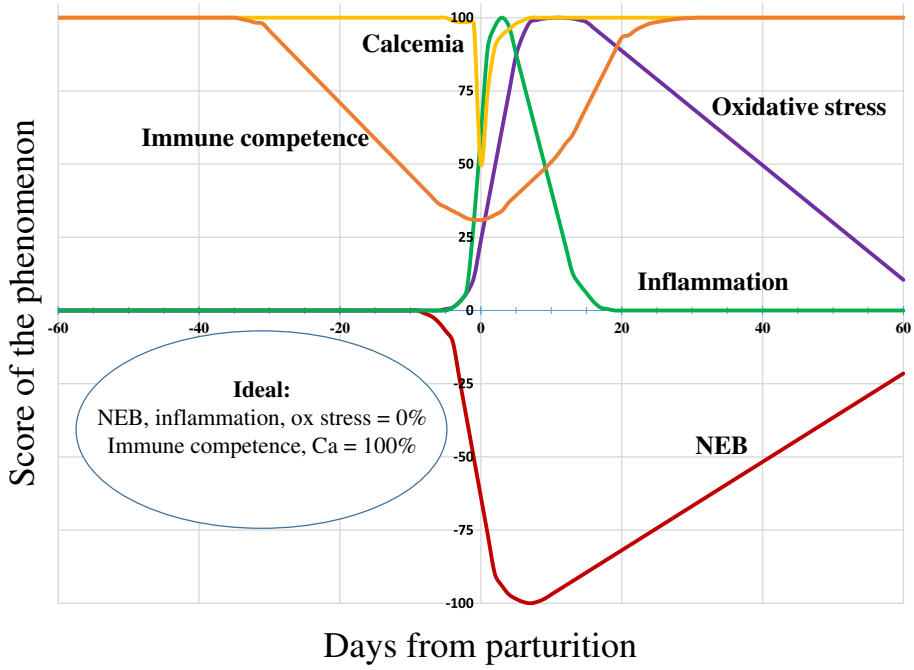


**Fig. 1.** Theoretical pattern of changes in the main physiological aspects of healthy subjects during the transition period. Ideally, the Negative energy balance (NEB), inflammation, and oxidative stress would be close to zero (i.e. absence of the phenomena), whereas the immunocompetence and the calcemia would be close to 100% of their optimal level.

been identified. Fig. 1 reports the evolution of the above five critical phenomena that characterize the transition period of healthy animals, as described by the available literature. Most of the changes are concentrated at the time immediately after calving, with only a few modifications of the immune system occurring days before at parturition (Goff & Horst, 1997; Kehrli et al., 1989a; Kehrli et al., 1989b; Lacetera et al., 2005; Mallard et al., 1998). Thus, a comprehension of the origin of these modifications and the time of their appearance with respect to calving seems pivotal for the discovery of the breaking-point in the homeostasis of the transition period.

## 2. Changes of the immune system during the transition period

The immune system is an interactive network of lymphoid organs, cells, and humoral factors, such as cytokines, that is organized to recognize, resist and eliminate contaminants (biotic or abiotic) that penetrate the body membranes (Bertoni et al., 2015). Conventionally, the system is divided into two components (innate and adaptive) on the basis of the speed and specificity of the reactions, but in reality the two parts are highly integrated and in continuous interplay (Daha, 2011). Recent evidence suggests that the innate component also has a memory-like behavior (Bordon, 2014) and this concept may deeply modify the current understanding of many immune functions. Innate immunity encompasses the physical, chemical and cellular elements of the immune system which provide immediate non-specific defense to the host against both biotic and abiotic inducers. Daha (Daha, 2011) suggests that approximately 95% of infectious challenges are resolved by the response of the innate system, through a coordinated action of cells (neutrophils, monocytes, macrophages), humoral factors (i.e. complement, lysozyme), and the network of cytokines. Cells recognize specific molecules (e.g. pathogen associated molecular patterns and damage-associated molecular patterns) through receptors (PRRs, pattern-recognition receptors) which induce two types of responses: inflammation and phagocytosis (by neutrophils and macrophages) (Trevisi et al., 2016). The responses occur even if the host has never previously been exposed to these agents and are driven by the synthesis of several biochemical mediators. Among them, vasogenic compounds (such as histamine) and pro-inflammatory cytokines (PIC, for instance TNFα, IL1β, IL6) attract immune cells into the damaged area and induce local inflammation, by the activation of the nuclear factor -kB signaling pathway. At a systemic level PIC also promote the acute-phase response in the liver (Heinrich et al., 1990; Medzhitov, 2008).

It is important to recognize that there is bidirectional communication between the immune and neuroendocrine systems (Taub, 2008). The two systems share a common set of hormones and receptors. Thus, the immune system is under the control of sex hormones, which play a role as modulators of autoimmune disease onset/perpetuation (Cutolo et al., 2004). Examples are the hypothalamic-pituitary-adrenal axis, which has a suppressive role in the presence of long term or chronic stressors (Sapolsky et al., 2000), and metabolic hormones (growth hormone, thyroid stimulating hormone, insulin), which are essential for the development of the immune system and its functions (Taub, 2008).

Variations occur in pro-inflammatory cytokine secretion around parturition. In the last part of pregnancy, the functionality of the immune system should remain active to counteract infectious agents and any possible injury. Nevertheless, several pieces of data suggest a reduction in the immunocompetence of mammals at this stage (Kehrli et al., 1989b; Lacetera et al., 2005; Orsi et al., 2006; Raghupathy et al., 2000). The ratio among Th1 and Th2 (T helper cells which produce cytokines with opposite pro- and anti-inflammatory effects, respectively), is low during pregnancy (Kruse et al., 2000; Raghupathy et al., 2000; Reinhard et al., 1998). These authors suggested that this low ratio is useful for a successful parturition, because it optimizes the feto-maternal immune interaction and vascularization. Under these conditions, the concentration of PIC in plasma before parturition should be low, because they are mainly released by Th1 cells. At parturition, the ratio of Th1/Th2 should increase rapidly in the uterus, switching from a condition that provides tolerance for the foetus (high Th2) to a condition that offers protection against infectious agents (high Th1). Moreover, Saito et al. (Saito et al., 2010) suggest that the T-cell paradigm in pregnancy should also include Th17 and the regulatory T (T reg) cells. These latter cells play central roles in immunoregulation, but their activity can be suppressed by immunoregulatory cytokines, including transforming growth factor (TGF)-β and IL10, or by cell-to-cell interaction. An imbalance between T reg and Th17 cells could be the pathogenic mechanism involved in preterm labour and preeclampsia, both associated with exaggerated systemic inflammatory changes (Saito et al., 2010). On the other hand, Orsi et al. (Orsi et al., 2006) indicated that the Th1-Th2 dichotomy only poorly describes complex immunological process, such as pregnancy in mice. Indeed, very high