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Management Updates on Prepartal Stress Effects on Transition Cow and Calf Health

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ABSTRACT

The transition phase is thought to be the most critical period in high-producing dairy cows' productive cycle. Maternal stresses during the peripartum period affect both dam and newborn calf health. The objective of this review article was to describe the role of prepartal metabolic and environmental stressors on postpartum-related disorders in both cows and newborn calves. The transition phase (21 d before to 21 d after calving) is considered the most critical period in dairy cattle life. Decreased dry matter intake coincides with increased nutrient demands due to the onset of lactation. It can lead to negative energy balance and tremendous metabolic challenges for high-producing dairy cows. During this time, insulin concentrations and peripheral tissue sensitivity decrease, leading to fat mobilization from adipose tissue. Such incidences would increase levels of non-esterified fatty acids and beta-hydroxybutyric acid in plasma. The success in the transition from the dry to lactating phase depends on how the cow could deal with such challenges. Failure to handle such metabolic alterations may predispose cattle to costly metabolic disorders such as ketosis, fatty liver, retained placenta, displacement abomasum, and infectious diseases, including metritis and mastitis in the postpartum period. The energy content of dairy cow diets in the dry-off (40 days before calving) or close-up (21 days before calving) periods may influence cow physiology and health in the peripartum period. The role of a transition period diet on cow health and productivity in the early or overall lactation period has been frequently investigated. However, the role of stressors such as nutritional deficiencies, heat stress, stocking density, and grouping in the late gestation period on the health and performance of cows and calves are much less addressed. Therefore, the present review delineates and reviews updates on the role of maternal stresses during the peripartum period on dam as well as newborn calf physiology and behavior.

Keywords: Immunity, Management, Metabolic disease, Prepartal stress, Transition cow

INTRODUCTION

The transition phase (21 days before to 21 days after calving) is the most critical period in the high-producing dairy cows' productive cycle (Huzzey et al., 2005). A successful transition from a dry to lactating period is associated with delivering a healthy calf with the minimum occurrence of metabolic (displacement abomasum, ketosis, fatty liver, and milk fever) and infectious diseases (such as mastitis and metritis) for the dam in the postpartum period. Reduced feed intake and impaired immune function, alongside increased nutrient demands due to the onset of lactation, are the major challenges dairy cows face during the transition period (Lopreiato et al., 2020). Numerous studies on the transition period have mostly focused on dry matter intake (DMI) and negative energy balance (NEB) as the main factors determining cow health and subsequent milk production (Hayirli et al., 2002; Grummer et al., 2004; Pérez-Báez et al., 2021). However, the role of the immune function and welfare of prepartum cow on both dam and neonatal calf has been much less addressed in the literature or practice on farms.

Understanding the biology of high-producing dairy cows in the periparturient period may provide practical insights into the optimal management of this critical phase. As calving approaches, dairy cows undergo tremendous metabolic alterations to support fetus growth and subsequent milk production (Allen and Piantoni, 2013). Insulin concentrations and sensitivity of adipose tissues and muscles to this anabolic hormone decrease in the prepartum period, resulting in lipolysis that can be extended to the postpartum period (Allen and Piantoni, 2013). On the other hand, it seems that increased growth hormone (Balogh et al., 2008) and pro-inflammatory cytokines levels play a significant role in inducing insulin resistance in both humans (de Luca and Olefsky, 2008) and bovine adipocytes (Du et al., 2022). Lipolytic status in cows during the periparturient period leads to elevated levels of non-esterified fatty acids (NEFA) in plasma. Non-esterified fatty acids released from adipose tissue are taken up by the liver, which can be partially oxidized to ketone bodies, such as beta-hydroxybutyrate (BHBA) or stored as triacylglycerol (Grummer, 2008). The elevated levels of

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NEFA and BHBA in the periparturient period are likely associated with postpartum disorders such as ketosis and fatty liver (Overton et al., 2017). Some scientists recently indicated that immune dysfunction and inflammation are key factors causing depressed feed intake and related metabolic and infectious diseases postpartum (Horst et al., 2021). In addition, it is believed that stressors, such as heat stress, can worsen the situation with negative impacts on immune function (Mezzetti et al., 2021). According to the new findings, a comfortable environment with minimal stress could be a preventive strategy against postpartum metabolic and infectious diseases on-farm (Mezzetti et al., 2021).

The importance of stress during the prepartum period has been emphasized recently (Chebel et al., 2016; Mezzetti et al., 2021). Metabolic stresses in the peripartum period reduce feed intake and NEB in the postpartum period. The NEB is expected to be exacerbated when cows are exposed to stressful conditions. Maximizing feed intake of high-producing dairy cows in the prepartum period was an outstanding theory regarding transition cow management for many years (Drackley, 1999; Grummer et al., 2004). However, academic research and practical observations indicated that postpartum complications are more serious than expected (Drackley, 1999; Grummer et al., 2004). As such, the role of other management factors on the welfare of the prepartum cow was obtained. With respect to the growing number of studies investigating peripartum cow immunity and related postpartum issues, the present review aimed to offer updates on some serious practical management factors (such as nutritional management, stocking density, and regrouping) influencing transition cow health and early lactation disorders.

Traditional and current perspectives on transition cow biology

The transition period has a vital influence on the lactation period in dairy cows after parturition. This period is characterized by tremendous physiological alterations in hormonal activity and nutrient partitioning to help nourish the growing fetus and support the onset of new lactation (Allen and Piantoni, 2013). Growth hormone and somatotropin levels are increased, whereas circulating insulin levels and sensitivity of tissues to this hormone are decreased, leading to the mobilization of fatty acids from adipose tissue (Drackley, 1999). Non-esterified fatty acids are then used as an energy source by the liver and other peripheral tissues sparing glucose for fetus growth and lactose synthesis in the mammary glands (Allen and Piantoni, 2013). Because feed intake is suppressed naturally in prepartum cows, mainly over the two weeks pre-calving, glucose produced by the liver is limited due to inadequate gluconeogenic precursors derived from daily feed intake (Horst et al., 2021). Despite the benefits of NEFA as a fuel for the peripheral tissues, higher levels of NEFA and BHBA can lead to fatty acid deposition in the liver (fatty liver syndrome) or ketosis postpartum (Horst et al., 2021). Traditionally, the elevated levels of NEFA and BHBA accompanied by hypocalcemia are believed to be the main factors associated with the incidence of metabolic and infectious diseases postpartum (McArt et al., 2013). However, recent studies have argued that the association between NEFA and BHBA concentrations and the incidence of postpartum metabolic disorders are inconsistent, implying that other factors could be responsible (Pascottini et al., 2020; Mezzetti et al., 2021; Horst et al., 2021). In this regard, the role of immune dysfunction and pro-inflammatory cytokines (tumor-necrosis factor α, interleukin 1 and 6) in the etiology of early lactation disorders has been widely emphasized.

Moreover, the traditional transition period (3 weeks before to 3 weeks after parturition) may be modified from the current new perspective, given that metabolic adaptations may originate from the dry-off period (Pascottini et al., 2020). In this case, NEFA, cortisol, and positive acute phase proteins (such as haptoglobin) levels seem to be high following two days of drying off (Putman et al., 2018). The systemic inflammation occurring in the dry-off period might be the most important contributor to developing immune dysfunction and inflammatory status in the transition period (Mezzetti et al., 2021). However, the immune system inadequacy is remarkably initiated in 2 or 3 weeks relative to calving as the maximum immune dysfunction occurs at the time of calving until two days post-calving (Vlasova and Saif, 2021). It is believed that reduced polymorphonuclear cells and lymphocytes function accompanied by systemic inflammation would predispose dairy cows to metabolic and infectious diseases in early lactation (Biswas and Lopez-conzalo, 2009; Mezzetti et al., 2021). In a recent study to evaluate the relationship between prepartum immune function and sub-clinical ketosis (SCK) in early lactation, the authors found inflammatory status, altered immune function, and impaired kidney and liver function in the affected animals (Mezzetti et al., 2019). Furthermore, interferon-γ (INF-γ) levels were greater in the SCK cows. The greater INF-γ levels were related to increased insulin resistance and elevated levels of blood glucose, NEFA, and BHBA prepartum. As such, the increased circulating glucose coincided with increased energy needs for immune activation may exacerbate NEB (Horst et al., 2021). The severity of reduced immune competence and inflammatory status around calving may determine the magnitude of metabolic and infectious diseases in early lactation (Mezzetti et al., 2021). In light of the increasing scientific evidence regarding the role of immune adequacy during the prepartum period on the etiology of postpartum disorders, mitigating stressors in the dry period (60 d before expected calving) may prevent further immune challenges in transition cows.

Physiology of stress and animal response

Despite the beneficial effect of stress in helping animals escape from threats, it can be a harmful physiological situation affecting animal welfare and productivity (Edris and Feki, 2021). Earlier, stress was defined as a condition in which the sympathy-adrenomedullary (SAM) system is activated to regulate body homeostasis in response to

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various stimuli (Cannon, 1925). This system responds quickly to the stimuli leading to epinephrine and norepinephrine secretions from the adrenal medulla (Godoy et al., 2018). Epinephrine and norepinephrine would result in elevated levels of glucose and free fatty acids in the blood because of the catalytic nature of such hormones (Godoy et al., 2018). Moreover, epinephrine and norepinephrine stimulate gluconeogenesis. In addition, the hypothalamic-pituitary-adrenal axis (HPA) is actively involved when animals are exposed to internal or external stressors (Godoy et al., 2018). Social contacts, stocking density, cold and hot environments, nutritional deficiencies, transportation, weaning, as well as calf dehorning are the common stressors for dairy cows provoking the HPA axis and subsequent physiological events potentially (Godoy et al., 2018). The SAM and HPA systems are interrelated and considered the main parts of the adaptive response in stressed animals. Activation of the HPA axis would increase blood glucocorticoids, mainly cortisol (Wadsworth et al., 2019). Cortisol is also known as the main stress hormone. Corticotrophin-releasing factor (CRF) is secreted from the paraventricular nucleus (PVN) of the hypothalamus and stimulates the anterior part of the pituitary gland. Consequently, adrenocorticotropic hormone (ACTH) is released into the blood stream. Then, the ACTH hormone targets the adrenal cortex to release glucocorticoids (Godoy et al., 2018). It has been reported that corticosteroids released during stressful conditions potentially regulate many metabolic actions, such as immune and behavioral responses (Burdick et al., 2011).

It is important to note that stress can be classified into two main acute or chronic forms (Salak-Johnson and McGlone, 2007). The adaptation is quick and complete in the acute form, allowing physiological reactions to be balanced (Grelet et al., 2022). However, in the chronic form, the stress is long-lasting and continuous, leading to disrupted physiological adaptations, environmental resistance, and exhaustion (Grelet et al., 2022). It is believed that prolonged exposure to chronic stress may lead to impaired metabolic, endocrine, and immune status, compared to acute stress (Salak-Johnson and McGlone, 2007; Trevisi and Bertoni, 2009). In dairy cows, a recent cohort study indicated that prolonged exposure to stress could influence welfare, health, and production (Grelet et al., 2022). In a 4-week stressful period (overstocking and regrouping of cows), greater milk loss and lower rumination were observed in the stressed cows. Moreover, elevated hair cortisol and blood fructosamine levels were proposed as biomarkers of chronic stress in dairy cows (Grelet et al., 2022). It has been reported that glucocorticoids and catecholamines secreted during stressful situations may suppress the immune function, predisposing the host to various diseases (Salak-Johnson and McGlone, 2007; Trevisi and Bertoni, 2009; Burdick et al., 2011). In human studies, chronic exposure to higher levels of cortisol is associated with immune system resistance and additional production of inflammatory cytokines compromising the immune response (Morey et al., 2015). In farm animals, the risk of bovine respiratory disease increases following weaning or transportation (Kumar et al., 2012). In addition, reproductive performance and growth can be negatively affected by stressors existing in animals' environments (Kumar et al., 2012).

Unfortunately, the negative effects of stress are not limited to the animal herself. In pregnant animals, especially those in late gestation, the growing fetus could be negatively affected by environmental stressors, which can be extended to the postnatal period (Merlot et al., 2013). Dairy cows suffer from metabolic stresses, lipid mobilization, immune activation, inflammation, and oxidative status during the periparturient period, causing postpartum metabolic and infectious diseases (Ling et al., 2018). Such alterations may have carryover effects on the health and welfare of neonatal calves (Ling et al., 2018). The immune function of a dam exposed to environmental stressors is impaired, influencing the neonate's health (Merlot et al., 2013). It is believed that the origin of the disorders that the offspring face later in life may be explored in the prenatal period (Fowden et al., 2006; Reynolds and Caton, 2012). Such a process is called fetal or intrauterine programming that occurs at gene, cell, organ, and system levels resulting in fundamental changes in the physiology of neonates, and may lead to metabolic and infectious diseases in the future (Fowden et al., 2006). For instance, diarrhea, the most important disease-causing mortality in newborn calves, is the most prevalent disease in calves born to underfed or stressed mothers (Nikkhah and Alimirzaei, 2022). It has recently been reviewed that stressors such as malnutrition and heat stress during late pregnancy may have prominent effects on both dam and neonate immune and organ development (Osorio, 2020). In this case, the intestinal development and the ability of the epithelial cells to absorb colostrum IgG may be disrupted (Osorio, 2020). In addition, calves born to cows that were cooled in the late gestation had greater birth and weaning weights and tended to have greater average daily gain (ADG) than the group during heat stress (Lay et al., 1997). Calves exposed to stress (repeated transportation) in the prenatal period exhibited greater heart rate and cortisol levels (Lay et al., 1997). Such calves were less able to respond to stress than the other groups, resulting in reduced welfare. Generally, it appears that the immunity and health status of both dam and offspring could be affected by maternal stress in the late-gestation period. Therefore, minimizing stress in the dry cow environment would be a perfect management decision to transition from dry to milking phase optimally.

Nutritional deficiencies, stocking density, high and low ambient temperatures, transportation, and regrouping are among the most important stressors affecting dry cow and calf health and welfare negatively. The effects of these factors on cow and calf physiology and health are discussed below.

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Late-gestation stress sources

Nutritional management

A successful transition from the dry period to lactating period in a dairy cow needs metabolic adaptations to support fetal development and milk synthesis with the onset of the new lactation cycle (Pascottini et al., 2020). Failure to adapt to such metabolic and hormonal changes, especially during the last 3 weeks of gestation, may lead to postpartum health disorders (Pascottini et al., 2020). In addition to the metabolic stresses that high-producing dairy cows face during the transition period, oxidative stress may be another challenge for transition cows with the potential to compromise their immune function (Sordillo and Aitken, 2009). Nutritional and management strategies of the periparturient cow are the most important factors influencing dairy cows' health and reproductive performance (Janovick et al., 2022). Energy intake during the prepartum period is critical for the liver function and susceptibility of dairy cows to metabolic diseases postpartum (Janovick et al., 2022). Recently, it was demonstrated that overnutrition in the dry period would compromise liver function and genes related to peroxisome proliferator-activated receptors (PPAR) in the early lactation phase (Janovick et al., 2022). A recent study recommends restricting energy intake to 1.3-1.39 Mcal of NEl/kg of DM (Cardoso et al., 2020). The advantages of energy-restricted feeding strategies seem related to lower blood NEFA, BHBA, and liver triglyceride levels in the postpartum period (Mann et al., 2015).

Accumulation of lipids in the liver may be associated with inflammation in the periparturient cow. It has been illustrated that mRNA for serum amyloid A, an acute phase protein, was upregulated (increased) during the periparturient period, which may be related to postpartum disorders (Loor et al., 2005; Horst et al., 2021). Moreover, lipid accumulation in the liver of late lactation cows was reported following TNF-α administration (Drackley and Cardoso, 2014). Overall, a review of articles investigating the transition of cow health would propose that nutritional and management strategies must be adjusted toward attenuating excessive lipid mobilization and inflammation. Besides controlling the energy intake of dry cows, the body condition score (BCS) should also be monitored to avoid cow's fattening. Over-conditioned animals may reduce feed intake and mobilize fatty acids more than those with lower BCS (Drackley and Cardoso, 2014). As such, these cows are believed to have impaired immune function and elevated inflammation biomarkers (Drackley and Cardoso, 2014). As a practical guideline, the optimal BCS is about 3 out of 5 (Drackley and Cardoso, 2014).

In addition, micronutrient deficiencies due to increased animal requirements and fetus growth in the late gestation period seem to be a risk factor. It is well known that transition cows may suffer from oxidative stress that can affect their immune function negatively and increase micronutrient requirements (Sordillo and Atiken, 2009). It is believed that the imbalance between the production of oxidants and the presence of anti-oxidants may lead to oxidative stress (Yenilmez et al., 2022). Investigating the plasma levels of Vitamin E indicates that the blood Vitamin E drops to minimum levels around calving (Mary et al., 2021) while the immune system is impaired. Vitamin E is a fat-soluble anti-oxidant that appears to be effective against oxidative stress. The results of the cows treated with 20 ml of Vitamin E indicated that it could protect them against oxidative stress (Yenilmez et al., 2022). It has been demonstrated that Vitamin E administration could reduce malondialdehyde (MDA, a biomarker of oxidative stress) concentrations 4 hours post-calving (Mokhber-Dezfouli et al., 2008). Furthermore, the risk of postpartum disorders such as retained fetal membrane and mastitis may be increased when cows suffer from Vitamin E deficiency (Qian et al., 2021). In a recent review article regarding the effects of hypovitaminosis E on transition cows, the authors strongly proposed that Vitamin E deficiency is a risk factor for the incidence of postpartum diseases (Haga et al., 2021). It is important to note that, in addition to the impact of Vitamins deficiency on both dam and offspring, as discussed above, deficiency of trace minerals such as zinc, copper, selenium, and manganese may have profound effects on maternal and offspring health and later performance (Van Emon et al., 2020).

As noted, dairy cows suffer from metabolic and immune stresses during the dry period, especially in late gestation. All nutritional and environmental factors that affect the dam might have carryover effects on the neonatal calf. In addition to metabolic and immune dysfunction, nutritional imbalance may negatively influence the fetus's development and organ function, which can have long-lasting effects on calf physiology and susceptibility to a wide range of diseases (Abuelo, 2020). Given that maternal and intrauterine conditions would affect the health and performance of the newborn calves, it could be concluded that some of the complexities that the young calves experience in the pre-weaning period can be explained by the nutrition and management of the dam in the dry period. The role of maternal nutrition and stress on neonatal calf diarrhea has been discussed recently (Alimirzaei and Nikkhah, 2022). The developing fetus may negatively respond to environmental disruptions which would be reflected in the organ defect of adults (Abuelo, 2020). For instance, placenta changes such as alterations in the placenta function would affect nutrient transport between mother and fetus resulting in altered fetal growth and organ development (Abuelo, 2020). Besides maternal nutritional conditions, undernutrition is thought to be an important factor influencing fetal growth and health (Abuelo, 2020). It is important to note that undernutrition and developmental programming are integrated because restricted nutrient intake is the main part of fetal programming. In beef cows vaccinated with the bovine diarrhea vaccine, restricting energy intake by 70% of the daily energy

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requirements in the last 40 d of gestation resulted in a lower titer of bovine diarrhea antibody in calves at 306 d of life (Moriel et al., 2016). On the other hand, adequate nutrition is needed for milking pregnant cows to avoid nutrient competition between the dam and the growing fetus (Abuelo, 2020). Inadequate nutrient intake of milk-producing pregnant animals would result in calves with poor health and low efficiency (Abuelo, 2020).

Stocking density

Providing a comfortable environment with minimum stress is a golden key in modern dairy cows' management. The transition period, as mentioned above, is considered the most critical period of the dairy cows' life cycle, needing considerable nutritional and non-nutritional considerations. The role of the environmental stressors in the prepartum cows can be considered at the maternal and neonate levels. It has been demonstrated that non-nutritional stressors (such as stocking density and grouping) could reduce the DMI of prepartum cows and increase the risk of postpartum disorders (Drackley and Cardoso, 2014). Additionally, offspring health and performance could also be affected by maternal stresses. It is believed that offspring brain development may be impaired when the mother is exposed to stressful conditions (Charil et al., 2010). From a practical outlook, some of the sources of stress for dry cows may be ignored by owners or farm managers. It is quite natural in large dairy herds that many animals give birth during the same time (a season or a month). In such herds, the prenatal animals may be overcrowded in their pens. As a result, overcrowding or higher stocking density can be a stressor and may alter their behavior and physiological status, predisposing them to various health problems. In a study conducted to investigate the laying and ruminating behavior of prepartum cows under different density rates (80, 100, and 120%), the results indicated more laying and ruminating time for the density of 80% between d -21 to d -7 relative to parturition (Jiang et al., 2021). Blood metabolites analysis also showed a higher calcium level for cows in the 80% group. Milk yield in the first month of lactation was also greater for the 80% group. In another study investigating the effects of high stocking density in late gestation on calf health, behavior, and welfare, the authors described that maternal high stocking density could affect offspring behavior in the pre-weaning period (Fujiwara et al., 2020). In this study, calves born to dams under overcrowding stress (H calves) showed increased reactivity to weaning. In addition, the H calves had decreased laying time around (just before and after) weaning. As such, the results provide evidence that calves' welfare during the pre-weaning period can be a function of maternal conditions such as stocking density. The role of maternal exercise on circulating cortisol and subsequently increased weaning stress in offspring has been recently reported (Black et al., 2017). Investigating the role of stocking density during the dry period indicated elevated levels of dehydroepiandrosterone (DHEA) and cortisol in the overstocked group relative to the control group (Fustini et al., 2017). Higher stocking density may result in limited access to feed bunk and altered animal behavior, leading to feed sorting, rumen acidosis, and reduced feed intake (Proudfoot et al., 2009). These events might induce further metabolic stresses in prepartum cows that could increase the risk of postpartum disorders. The stocking density in the prepartum period should be at least one cubicle of resting space per cow (Cook et al., 2005).

Regrouping

At the farm level, dairy cows are moved between pens according to their milk yield, days in milk (DIM), and BCS. In addition, dairy cows are transferred to dry groups following the drying off and maybe regrouped into the close-up pen until calving. Moving to new pens or places is stressful for cows because they try to reestablish their social relationships and modify physical and non-physical interactions with their new pen-mates (Huzzey et al., 2006). The common competition occurs at feed bunk where the prominent cows try to reach the feed first, which can affect feed intake (Huzzey et al., 2006). Such competition is frequently seen in higher stocking density pens; thus, overcrowding must be avoided (Huzzey et al., 2006). It seems that regrouping may induce some behavioral and physiological alterations in transferred cows (Zelena et al., 1999; Von Keyserlingk et al., 2008). It has been reported that cows spent 15 minutes less time eating following introduction to a new group (Von Keyserlingk et al., 2008). In that experiment, cows were displaced more than 25 times during the day after regrouping, whereas this value was 10 before regrouping. As such, in dry cows, regrouping has been reported to impact the feed intake of moved cows. Similar to lactating cows, a study on the effects of regrouping on dry cows' behavior showed that cows reduced their DMI by approximately 9% after moving to a new pen (Schirmann et al., 2011). The authors concluded that regrouping could affect dry cows' feeding and social behavior. It seems that cows and heifers have different responses to new environments. Heifers are more sensitive to regrouping than cows (Soonberg et al., 2021) because cows are more experienced and settle in a new environment more quickly than heifers (Soonberg et al., 2021).

CONCLUSION

Dairy cows undergo tremendous metabolic adaptations during the transition period. It is widely accepted that nutritional and management strategies for dry cows must be in line with decreased metabolic and environmental stresses to optimize fresh cow and calf health and performance. Under- or over-nutrition of dry cows as well as trace minerals and vitamins

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deficiency, may have a profound effect on both dam and offspring health and their susceptibility to metabolic and infectious diseases. As a result, providing a balanced diet is critical for the optimal health of transition cows. In addition, minimizing the environmental stressors such as stocking density and regrouping of dry cows can contribute to overcoming metabolic adaptations and immune stresses during the periparturient period.

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Data availability and materials

Data from the study are available according to a reasonable request.

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Authors' contributions

The authors contributed to writing the initial manuscript almost equally. Akbar Nikkhah led the project, conceptualized the review idea, strategized the topic development, and did the ultimate writing and editing. The final manuscript was checked by all authors.

Competing interests

None.

Ethical consideration

The authors have made necessary ethical considerations (e.g., plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy).

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