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Colibacillosis and Colisepeticemia in Newborn Calves: Towards Pragmatic Treatment and Prevention

Akbar Nikkhah[1*] and Masoud Alimirzaei[2]

[1]*Chief Highly Distinguished Professor and Nutritional Scientist, National Elites Foundation, Iran*
[2]*Behroozi Dairy Complex, Tehran, Iran*

*Corresponding author's Email: anikkha@yahoo.com

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ABSTRACT

Diarrhea is the most perturbing disease in dairy and beef industries worldwide, leading to significant rates of morbidity and mortality as well as economic losses. The objective of this review article was to delineate the pathophysiology and practical biology of colisepticemia in neonatal calves. Preventive and therapeutic protocols were also presented and discussed from a new integrative perspective. Notably, the situation can be the most deleterious in case diarrhea turns into septicemia. Under such circumstances, the mortality rate may be remarkably high and hard to control. *Escherichia coli* (*E. coli*) is an invasive and opportunistic bacteria causing severe diarrhea (colibacillosis) and colisepticemia in newborn calves. Colisepticemia is commonly prevalent in 2-5 days old calves, and colostral immunity is considered the first defensive line against *E. coli* infection. In addition to colostrum feeding quality and management, other management factors, such as dry cow nutrition and welfare, newborn calf welfare and nutrition, housing system, sanitation protocols, as well as early identification and treatment of sick calves, are important in preventing colisepticemia. In conclusion, understanding the mechanism of action and transmission routes of pathogenic *E. coli* will provide scientific and practical insight to plan preventive and therapeutic protocols decisively and successfully.

Keywords: Diarrhea, Mortality, Newborn calf, Pragmatic Prevention, Septicemia

INTRODUCTION

Diarrhea and septicemia have long been recognized as major causes of economic damage to neonatal management due to significant rates of morbidity and mortality. Nowadays, despite many advances in veterinary sciences, calf loss in the early stages of life is still a major concern. Unfortunately, often farmers and calf-raising staff are not aware of the interactions in disease agent behavior, host response, and environment. Thus, they are not able to prevent disease outbreaks or treat patients appropriately. In the case of calf diarrhea and colisepticemia, describing the disease's pathophysiology to farm personnel is critical because workers should be educated on how to manage sepsis cases (Nikkhah and Alimirzaei, 2022a).

Generally, diarrhea can be classified into two forms of infectious and non-infectious or nutritional diarrhea (Barteis et al., 2010). Infectious diarrhea, a major cause of neonatal calf mortality, is caused by a wide range of microorganisms (bacteria, viruses, and protozoa) with different severities. Severe cases can lead to septicemia, coma, and death. Sudden death can be a direct consequence of septicemia regardless of whether diarrhea occurs or not (Bashahum and Amina, 2017). Septicemia, caused by pathogenic *E. coli*, is the main fatal condition in newborn calves (Bashahum and Amina, 2017). The pathogenic *E. coli* is a gram-negative bacteria invading calves. It damages small intestine cells at very young ages (2-5 d of age) when the immune system is weak. Thus, *E. coli* have a chance to overgrow and produce toxins (Constable, 2004). It has been reported that the *E. coli* number could be increased 5-10000 fold in the duodenum, jejunum, and ileum of calves with diarrhea (Constable, 2004). When bacterial toxins reach the bloodstream, they cause severe systemic inflammation and trigger subsequent cascade reactions that lead to organ failure and finally death.

Host immunity and environmental contamination are two critical factors determining the calf's susceptibility to infectious diseases in the first week of life (Nikkhah and Alimirzaei, 2022b). Unhygienic calf ambiance accompanied by a weakened immune system due to poor colostrum feeding management could result in severe diarrhea or even septicemia during the first week of life (Nikkhah and Alimirzaei, 2022b). Since moderate cases of diarrhea can be treated successfully, decreasing the number of sepsis calves is considered the first step in controlling diarrhea-related calf mortalities. In addition, providing a comfortable place for both the dam in the late-pregnancy period and neonatal calf would be an appropriate management practice to reduce calf susceptibility to infectious diseases. As the diarrhea-inducing mechanisms and the importance of prevention protocols have been less understood in dairy farms, addressing

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the mechanisms of action for colisepticemia incidence will provide a practical framework to control and treat neonatal calf diarrhea pragmatically.

E. coli PATHOGENICITY

Although *E. coli* is thought to be a fully harmful bacteria, not all of its serotypes are pathogenic (Kaper et al., 2004). *E. coli* is a natural inhabitant of the calf's gastrointestinal tract and can be an invasive agent if the host and environmental conditions favor its replication (Croxen and Finlay, 2010). Unfortunately, many farmers or even farm experts are not aware of the mechanisms that are involved in newborns' diarrhea or septicemia development, hence making it difficult to treat or prevent the problem. Colibacillosis is a common consequence of pathogenic *E. coli*, frequently seen in newborn calves (Croxen and Finlay, 2010). Pathogenic *E. coli* is responsible for extra-intestine infections such as coliseptisemia as well as urinary tract and nervous system issues (Croxen and Finlay, 2010). In this case, pathogenic *E. coli* can be divided into two main pathotypes including diarrhoeagenic *E. coli* and extra-intestinal *E. coli* (Kaper et al., 2004). According to virulence attributes, Enteropathogenic *E. coli* (EPEC), Enterotoxigenic *E. coli* (ETEC), Enterohemorrhagic *E. coli* (EHEC), Enteroinvasive *E.coli* (EIEC), Enteroaggregative *E.coli* (EAEC), and Diffusely Adherent *E. coli* (DAEC) are six well-described serotypes for diarrhoeagenic *E. coli* (Kaper et al., 2004; Croxen and Finlay, 2010).

Extra-intestinal *E. coli* includes two common serotypes, uropathogenic *E. coli* and (UPEC) and neonatal meningitis *E. coli* (NMEC, Kaper et al., 2004). The major *E. coli* serotypes that infect newborn calves and cause severe diarrhea and colisepticemia are EPEC, ETEC, and EHEC (Janke et al., 1980; Kaper et al., 2004; Bashahum and Amina, 2017). As noted, the pathogenicity of such strains is mediated through plasmid-encoded virulence factors, enabling them to attach to intestinal cells (Janke et al., 1980; Croxen and Finlay, 2010). For instance, ETEC expresses fimbriae or pili to adhere intestinal surface without disrupting mucosal epithelium. It has been demonstrated that ETEC expresses several types of pili, such as K88, K99, 987P, and F41, to attach to intestinal cells (Janke et al., 1980; Bashahum and Amina, 2017). The *E. coli* K99 is believed to be the most common strain inducing colibacillosis in newborn calves.

Following attachment, enterotoxins produced by the bacteria trigger epithelial cells to secrete fluids into the lumen and result in diarrhea (Acres, 1985; Zhang et al., 2022). Heat-labile (LT), heat-stable (STa and STb) toxins are produced by ETEC following adherence and subsequent colonization. Altering ion exchange across the intestinal cells is likely to be the mechanism of ETEC to induce diarrhea. It has been reported that the LT toxin stimulates the cAMP pathway leading to secrete Cl^- into the lumen of small intestine while inhibiting Na^+ absorption (Fleckenstein et al., 2019). On the other hand, ST toxin triggers cGMP accumulation inside epithelial cells. Similarly, cGMP limits Ns/H ion exchanger channel (Fleckenstein et al., 2019). Accordingly, accumulation of salt can lead water into the intestine lumen resulting in diarrhea. The mechanism of ETEC action is schematically summarized in Figure 1.

Enteropathogenic *E. coli* is another cause of diarrhea in newborn calves that results in death. The development of 'attaching and effacing' lesions (A/E) (a histopathologic lesion) on the intestinal cell surface is the most important characteristic of EPEC (Knutton et al., 1993). The attaching bacteria efface microvilli and disturb its action, causing distinct pedestals beneath the site of adherence (Croxen and Finlay, 2010). In addition, EPEC uses pili named bundle-forming pili to attach epithelial cells. Concurrently, bundle-forming pili are used to interact with other EPEC to create localized adherence (Hyland et al., 2008). Enteropathogenic *E. coli* expresses adhesive proteins (tir and intimin) to attach host cells intimately. Pedestal structure and its related factors are schematically described in Figure 2. Moreover, EPEC possesses some multifunctional effectors that translocate into the host cells and subvert normal cell processes, such as mitochondria structure and function, failure of phagocytosis, and tight junctions dysfunction (Ma et al., 2006; Quitlard et al., 2006; Guttman et al., 2006). Attaching and effacing are the main mechanisms inducing diarrhea in newborn calves. Notably, maldigestion and malabsorption of nutrients resulting from effacing of intestine microvilli may exacerbate the health status of diarrheic calves.

Shiga toxin-producing *E. coli* (STPE) is another important bacteria in the etiology of calf diarrhea. In comparison with ETEC and EPEC, STPE pathogenesis has not been comprehensively investigated in calves. Nonetheless, it has been demonstrated that *E. col* 026 and 0111 are responsible for diarrhea in calves (Lee et al., 2008). It belongs to a family of shiga toxin-producing bacteria (Bashahum and Amina, 2017), and similar to other types of *E. coli*, EHEC can infect calves of less than 2 weeks of age. In humans, diarrhea, hemorrhagic colitis (HC), and hemolytic uremic syndrome (HUS) are frequently seen, whereas diarrhea and dysentery are common in calves (Sandhu and Gyles, 2002). Virulence attributes of STEE are related to toxin production and intestinal colonization (Sandhu and Gyles, 2002). Investigating STEC adherence properties has revealed A/E lesions in the intestinal epithelial cells of calves (Sandhu et al., 1999; Bashahum and Amina, 2017). It is important to note that other diarrhea causes may induce similar results, so it should not be confused with *E. coli*-induced diarrhea. A differential diagnosis is needed to determine the exact origin of the infection. Nonetheless, diarrhea and septicemia during the first week of life are mostly associated with *E. coli* in dairy and beef breeds (Bashahum and Amina, 2017).

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Practically, loss of water and electrolyte imbalance induce some hematological and metabolic alterations, resulting in metabolic acidosis, coma, and death (Dratwa-Chalupnik et al., 2012). Hyponatremia, hypochloremia, and hyperkalemia are common consequences of intestinal damage in neonatal calves (Dratwa-Chalupnik et al., 2012). Furthermore, malabsorption of nutrients such as glucose implicates energy deficits and exacerbates calf general health (Bashahum and Amina, 2017). Correcting such conditions by replacing nutrients and electrolytes lost during diarrhea is vital for establishing normal body homeostasis.

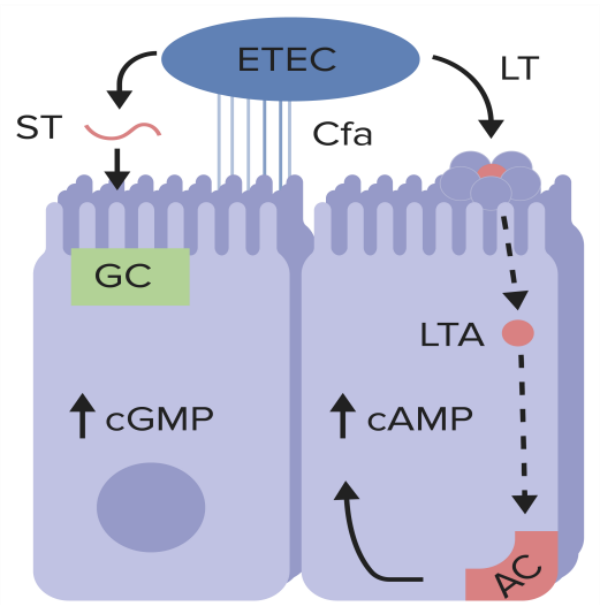

Figure 1. Attachment of Enterotoxigenic *E. coli* (ETEC) and water loss. CFa: Colonization factor antigen; cAMP: Cyclic adenosine monophosphate; GC: Guanylyl cyclase; AC: Adenylyl cyclase

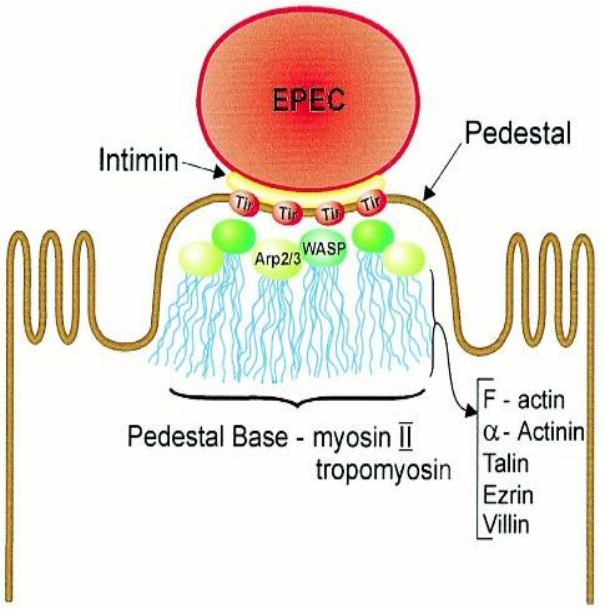

Figure 2. Pedestral structure in Enteropathogenic *E. coli* (EPEC) infection (Vallace and Finlay, 2000). Tir: bacteria's own receptor; Arp2/3: and WASP: Protein complexes recruited towards pedestal tip.

COLISEPTICEMIA AND RELATED CONSEQUENCES

Septicemia is an acute invasion of systemic circulation by bacteria and occurs when bacteria enter the bloodstream and circulate throughout the body after replication (Calfcare.ca). In new definitions, sepsis is considered a life-threatening dysfunction of body organs resulting from dysregulated response to infectious agents (Wasyluk and Zwolak, 2021). In such definitions, nutrient metabolism is emphasized in addition to the inflammatory response addressed in the traditional definition. Bacteria are considered the main cause of septicemia in neonatal calves. The *E. coli-induced* septicemia and colisepticemia, are responsible for high rates of calf mortality in dairy farms worldwide (Vallance and Finlay, 2000; Bashahum and Amina, 2017). All *E. coli* strains described above, ETEC, EPEC, and STEC, have the potential to cause colisepticemia. Signs can vary from severe diarrhea to sudden death without any clinical symptoms (Bshahum and Amina, 2017). With respect to the aggressive nature of colisepticemia, observing some clinical symptoms such as recumbency, suckling inability, and sudden and severe diarrhea in 2-5 d old calves can lead farmers to suspect colisepticemia (Figure 3). Immediate treatment might be effective in saving sepsis calves. If the sepsis time period is extended and invading of bacteria is not controlled, joint arthritis and meningitis are expected due to infectious agent localization (Fecteau et al., 2009).

Figure 3. A two day old recumbent calf (captured by the authors)

A sepsis calf undergoes many physiological abnormalities, resulting in compromised body homeostasis, uncontrolled inflammatory response, organ failure, shock, and death (Vallance and Finlay, 2000). Inflammation is a direct consequence of bacterial invasion to the host tissues. If the local inflammation spreads and the infectious agent has an opportunity to enter into circulation, systemic inflammation may occur (Jaffer et al., 2010). Systemic inflammatory response syndrome (SIRS) and organ dysfunction occur following systemic inflammation, leading to shock and death

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(Jaffer et al., 2010). In other words, SIRS reflects uncontrolled inflammatory responses observed in sepsis cases. The inflammatory response is controlled by pro- and anti-inflammatory cytokines which work together to determine the course of the disease (Bone, 1996). It has been reported that the number of these cytokines is associated with the occurrence of SIRS (Jaffer et al., 2010). Lipopolysaccharide (LPS) of gram-negative bacteria is one of the most powerful stimuli to produce pro-inflammatory cytokines and develop systemic inflammation. Interleukin 1 and TNF-α are the main pro-inflammatory cytokines produced in response to stimulants and stimulate releasing of other cytokines that act in concert (Jaffer et al., 2010). It is believed that these two cytokines levels are related to poor outcomes from sepsis (Pinsky et al., 1993). Accordingly, endothelial damage, loss of vascular tone, myocardial dysfunction as well as coagulation cascade can lead to reduced blood flow to vital organs such as the kidneys, central nervous system, heart, and eventually death (Caraballo and Jaimes, 2019).

In addition to unregulated systemic inflammation, altered cell metabolism has been suggested as the major disturbance during sepsis (Wasyluk and Zwolak, 2021). It is an important area of interest in terms of sepsis treatment because most studies have focused on inflammatory response control. Sepsis-induced dysfunction and mitochondrial damage are likely the major causatives for disturbing cell metabolism. Mitochondrial damage changes the normal metabolism of cell macronutrients (Wasyluk and Zwolak, 2021). It is important to note that all such biochemical reactions are mediated by producing pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) (Pinsky et al., 1993). The pro-inflammatory cytokines activate catalytic processes that can lead to increased circulating levels of glucose and fatty acids (Wasyluk and Zwolak, 2021). Accordingly, the failure of pyruvate entering into the tricarboxylic cycle leads to increased lactate formation (Wasyluk and Zwolak, 2021). As a result, lactate would accumulate, and metabolic acidosis is expected. Moreover, oxygen usage by sepsis patients is poor, that further contributes to lactate production. Notably, hypoglycemia occurs as sepsis continues (Wasyluk and Zwolak, 2021). Metabolic acidosis may be the primary cause of death in calves with diarrhea or septicemia, induced by gram-negative bacteria (Kasari, 2016). Correcting acidosis should be a primary goal in the treatment of septic calves.

PREVENTIVE STRATEGIES

Prevention of diarrhea or septicemia is the primary goal in controlling calf mortality in dairy farms. Prevention is important from this point of view and severe cases of septicemia can be reduced. Since sick calves are major contaminants of surroundings, decreased number of sick calves would help reduce the shedding of bacteria in the environment (Nikkhah and Alimirzaei 2022b). Prevention of colisepticemia could be addressed from two distinct visages: nutritional or environmental. The importance of colostrum feeding is emphasized in all studies (Tedia, 2012; Bashahum and Amina, 2017). It is necessary to note that high-quality (Brix index > 22 when refractometer is used to determine colostrum quality) and uncontaminated (bacteria count < 100000 cfu/ml) colostrum must be fed in the first 6 hours of life to ensure maximal passive transfer (Phipps et al., 2016; Nikkhah and Alimirzaei, 2022b). On the other hand, colostrum temperature should be checked, especially in cold seasons, and heated in warm water if needed. Low-temperature colostrum (< 37˚C) itself can lead to diarrhea (Vallance and Finlay, 2000). In addition to animal studies, it has been reported in a recent human study that bovine colostrum can be useful in preventing and treating gastrointestinal diseases such as infectious diarrhea (Fasse et al., 2021). As noted above, attachment is an essential process in the pathogenicity of *E. coli*; thus, blocking bacterial attachment is a key factor in preventing bacterial overgrowth. In addition to the role of IgG in local (small intestine) and systemic immunity of calves, colostral IgG has a critical role in preventing bacterial attachment by occupying attachment sites located on the surface of intestinal epithelial cells (Lopez and Heinrichs, 2021).

Millions of microbes are inhabitants in the gastrointestinal tract of mammalians, performing many beneficial biological functions. Immune modulation, nutritional digestion, and protection against pathogenic microbes such as *E. coli* are the most important duties of the gut microbiota (Malmuthuge and Guan, 2016; Zhang et al., 2022). It has been reported that gut microbiota composition and establishment of beneficial bacteria such as *lactobacillus acidophilus or Lactobacillus Plantarum*, *Bifidobacterium bifidum*, and *faecalibacterium prausnitzii* are associated with enteric pathogenic bacteria colonization (Malmuthuge and Guan, 2016). In this regard, using probiotics may be useful in controlling pathogenic bacterial attachment and its subsequent adverse effects. The positive effects of probiotic bacteria in alleviating diarrhea severity has been reviewed (Cangiano et al., 2020). The blockage of bacterial attachment to the intestinal epithelium may provide an opportunity for preventing bacterial overgrowth inside the host. Despite the advantages of diverse gut microbiota, it should be considered that the gut microbiota has a dynamic nature in the early stages of calf life, and many environmental factors affect its composition (Malmuthuge and Guan, 2016). Therefore, modulating the gut microbiota to control enteric infections such as colibacillosis and colisepticemia provides a perspective for research in this critical area. From a pragmatic viewpoint, feeding probiotics in newborn calves' diets is an attempt to optimize the gut environment through the prevention of pathogenic bacterial attachment. The positive effects of including probiotics in calf diets during the early two weeks of life have been reviewed (Cangiano et al., 2020).

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In addition to the nutritional protocols for preventing bacterial overgrowth, other management practices, such as dry cow nutrition and welfare as well as sanitary protocols, can impact calf immune system efficacy and bacterial environmental overload (Cangiano et al., 2020). It has been illustrated that nutritional deficiencies and stress in the dam during late gestation may disturb intestinal function and impair colostral immunoglobulin absorption (Alimirzaei and Nikkhah, 2021). As a result, producers must pay attention to dry cow's comfort to ensure the successful transfer of passive immunity. The pregnant cow must give birth in a comfortable and clean area. It seems that calving in a dirty pen increases the risk of infectious agent shedding by the newborn calf (Nikkhah and Alimirzaei, 2022b). Removing contaminated bedding materials and renewing them after each calving are recommended to reduce pathogenic organisms' transfer from the maternity pen to the calf-rearing area. Furthermore, disinfecting calving pens should be a regular practice on dairy farms. In addition to sanitary protocols, the natural calving process is important in terms of calf health and its performance (Cho et al., 2014). It has been reported that dystocia is closely associated with calf performance as well as susceptibility to diarrhea (Cho et al., 2014). Calves born with dystocia may have a poor ability to absorb colostral IgG, which further predisposes them to colisepticemia. As a result, for a good start, the birth must take place in a clean calving pen under natural parturition. Calf pens, hutches, or barns are considered major centers of pathogenic organisms unless the farm has routine and regular sanitary programs. All facilities and equipment, including bottles, milk containers, colostrum feeding containers, personnel boots, and cloths, must be disinfected after each use.

TREATMENT GUIDELINES

Early identification and treatment of infected calves is the most important practice in blocking *E. coli* prevalance in calf-rearing farms. Sick calves shed the pathogenic agent during the disease period and after recovery (Nikkhah and Alimirzaei, 2022b). Therefore, affected calves must be diagnosed early and treated immediately to reduce the risk of further bacterial shedding. Severe diarrhea, sunken eyes, loss of appetite, recumbency, failure of suckling reflex, and low body temperature, especially in cold seasons, are the most important signs of colibacillosis or colisepticemia in newborn calves (Bashahum and Amina 2017). Treatment of diarrheic or sepsis calves is difficult, especially when the severity of infection is high. Understanding calf physiology during sepsis or diarrhea will help better react to severe cases. Importantly, and as emphasized earlier in this article, farmers must concentrate on decreasing the number of severe cases, because it needs antibacterial or fluid therapy to save affected calves. Treatment of infected calves totally depends on their general health status. According to calf standing ability, four treatment charts have been developed: 1) calf recumbent/unable to stand, 2) calf standing securely, 3) calf stands confidently, enophthalmos, and 4) calf stands confidently with no enophthalmos (Constable et al., 2020). Importantly, in some severe cases of sepsis, it seems that calves need a more therapeutic period with the administration of antibiotics and fluid therapy. As a result, to increase the calf survival chance, treatment protocols in the first diagnosis of sepsis cases are recommended. It is important to note that there is no single antibiotic or fluid therapy protocol on all farms, as it depends on the calf's general health status. For instance, some calves could recover with only using 1 or 2 liters of intravenous therapy; however, in some cases, 8-10 liters of intravenous fluid therapy may be needed. Furthermore, nursery is a critical practice that many dairy farms disregard. Accordingly, calf recovery is a direct function of proper treatment and gentle nursery (Nikkhah and Alimirzaei, 2022a,b; Zhang et al., 2022).

As described, cardiovascular dysfunction, hypotension, and metabolic acidosis are common consequences of sepsis. Administration of anti-inflammatory drugs plus intravenous antibiotics to alleviate inflammatory reactions and eliminate pathogenic *E. coli* are essential in treating sepsis calves. Dexamethasone is an anti-inflammatory drug which can be used successfully in controlling inflammation in sepsis calves. Antibiotics against the infectious agent must be administered intravenously, which could be different from one farm to another (farm observations and experience). Thus, antibiotics should be selected according to the farm's veterinarian protocols. As noted, fluid therapy, both orally or intravenously, is the first line of defense against colisepticemia or colibacillosis. Recumbent and sick calves with suckling inability must be treated intravenously by isotonic dextrose-saline solution to recover electrolytes and glucose loss during sepsis and diarrhea (Nikkhah and Alimirzaei, 2022b). Using hypertonic saline solution (7.2 % NaCl, 2400 mOsm/L) may increase blood pressure, improve oxygenation, and cardiac output, allowing calves to reinstate vital organ functions (Constable et al., 202). As such, providing hypertonic sodium bicarbonate solution (8.2% $NaHCO_3$) may help correct acidosis and return the HCO_3 lost during diarrhea (Wasyluk and Zwolak, 2021). Nursing sepsis calves are vital for monitoring their health status because extra antibacterial or fluid therapy may be needed.

CONCLUSION

Colisepticemia is a threatening neonatal calf disease worldwide with significant mortality rates. Poor dry cow management and welfare, poor colostrum feeding management, unclean calving area, and contaminated calf barns all could predispose newborn calves to diarrhea and septicemia. Early diagnosis through clinical examination of calf general

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health such as standing ability, suckling reflex, abnormally high or low body temperature, and the calf appetite can lead us to suspect colisepticemia. Treatment must be initiated immediately. Effective and innovative treatment of sick calves can be a perfect preventive practice in minimizing bacteria recycling between the calf and its ambiance. Fluid and antibacterial therapy must be the first therapeutic action. Additionally, sick calves need extensive nursing programs because some calves may need extra therapeutic practices such as antibiotics and vitamin injections, and heavy intravenous or oral fluid therapy. As a result, understanding septicemia biology and calf behavior provide pragmatic opportunities for producers to manage infected calves effectively.

DECLARATIONS

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Authors' contribution

The authors contributed equally to this work, including conceptualization, review, strategic contemplation, writing development, editing, and revising. Akbar Nikkhah Led the project. All authors checked and confirmed the final draft of the manuscript.

Competing interests

None.

Ethical considerations

Ethical considerations (e.g., plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been made by the authors.

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