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Future Sentinels of Uterus Defense System in Cows and Buffaloes-A Review

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ABSTRACT

In dairy animals treatment of uterine infections are always in confrontation with increasing global threat of dissemination of antimicrobial resistance. Immunomodulators, a novel treatment strategy works as a precise modulation mechanism and evade complications while immunosuppressive or immunopotentiation efforts are made to improve animal health. This review provides an insight into natural and synthetic immunomodulator substances, and it is speculated that the most natural regime for enhancement of disease resistance will be useful for research scientists, veterinary professionals, pharmaceutical industry, dairy animal owners and dairy industry to create a healthier future for both human and dairy animals.

Keywords: Immunomodulator; Endometritis; Probiotic; Infertility; Buffalo

Abbreviations: LPS: Lipopolysaccharide; PMNs: Polymorphonuclear Neutrophils; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; rbG-CSF: Recombinant Bovine Granulocyte Macrophage Colony Stimulating Factor; OG: Oyster Glycogen; NEFAs: Nonesterified Fatty Acids; CFU: Colony Forming Unit

Introduction

Dairy animals play a major role in accomplishment of sustainable food production system worldwide. The economic progress of dairy farming depends on optimal reproductive health of each animal in the herd. Any deviation from normal reproductive pattern results in extended dry period, reduced milk and calf production, increased management cost and early culling that leads to huge economic losses to the dairy industry. In recent times, major challenges faced by dairy breeders are infertility with poor reproductive performance and prolonged inter calving intervals in dairy animals. Infertility in dairy animals is highly correlated with repeat breeding that leads to drastic reduction in dairy farm return. A repeat breeder is any cow or buffalo in true estrus but not conceived by three or four services and therefore creates an expensive hitch in successful dairy production. Incidence of repeat breeding is higher in cows as compared to buffaloes [1]. Since buffaloes have inherited delayed puberty, high age at first calving, and one month longer gestation period than cows therefore repeat breeding contributes to significant economic losses [2] to the dairy farmer. Repeat breeding is a multifactorial syndrome and caused be reproductive abnormalities, uterine infections, inappropriate diet, poor breeding, and health management. Among multiple factors uterine infections are considered major cause of repeat breeding in dairy animals. Therefore, treatment and prevention of uterine diseases are crucial aspects of fertility management in dairy animals [3-21].

Prevalence of Uterine Infections

The prevalence rate of uterine infections in buffaloes found to be higher than cows. Contributing factors might be poor hygienic conditions, vaginal stimulation for milk letdown and possibly wallowing. The reported prevalence of uterine infections in postpartum cows and buffaloes varied between 3 and 68% (Table 1).

Table 1: Prevalence of uterine infections in dairy animals worldwide.

Country	Dairy Animals	Prevalence Percent	Uterine Infections
Austria [4]	Cow	15	Subclinical
Australia [5]	Cow	10.9	Clinical
Brazil [6]	Cow	3	Clinical
China [7]	Cow	17	Clinical
Denmark [8]	Cow	6.25	Clinical
Egypt [9]	Buffalo	38	Clinical
India [10,11]	Buffalo	25	Postpartum
		25	
Iraq [12]	Buffalo	48	Clinical
Iran [13,14]	Buffalo	33	Clinical
		29	
Korea [15]	Cow	47.6	Clinical
Pakistan [3]	Buffalo	24	Clinical
Poland [16]	Cow	15	Subclinical
Rwanda [17]	Cow	68	Clinical
Spain [18]	Cow	4.5	Clinical
United States of America [19,20,21]	Cow	10.3,53	Clinical
		26	Subclinical

Immunomodulators and Uterine Health

Theory of species evolution is also true for microorganisms trying to escape microbicidal consequences of antibiotics. Among a wide range of antibiotics few are reckoned as potential antimicrobials exceeding the rapid antibiotic resistance in microbes [22,23]. Therefore it is decisive to find alternative treatment strategies to protect animal health and production. Immunomodulators are used to enhance the immune potential of the body emerge as solitary substitute to control infections in humans and animals. An immunomodulator is defined as any natural or artificial substance that has ability to enhance or repress either innate or adaptive or both armaments of the immune system [24]. According to their mode of action these substances are divided into specific and non or specific immunomodulators. Specific immunomodulators are restricted to a single type of antigen as in case of vaccine. While nonspecific immunomodulators exhibit broad change in innate and adaptive immune response and therefore lead to altered host reactivity to a wide range of antigens. In dairy animals basic purpose of immunomodulation is to prolong immune response and enhance production with particular focus on local protection at certain vulnerable sites including udder and reproductive tract [25]. Furthermore, in dairy animals these substances are speculated as best substitute of antibiotics with short term withdrawal period ,little tissue residues, and safe with no toxic effect even at high dose rate. Since strong uterine defense mechanism prevents colonization of microorganisms in the uterus treatment strategies targeting modulation of naïve immune system in periparturient dairy animals have the potential for treatment and prevention of uterine infections.

Escherichia Coli Lipopolysaccharides

First use of intrauterine *E.coli* lipopolysaccharide (LPS) has been reported in mares [26]. Bacterial lipopolysaccharides exhibit chemotactic activity and enhance influx of polymorphonuclear neutrophils (PMNs) serum proteins, and immunoglobulins in uterus. In cows *E.coli* lipopolysaccharide enhance nonspecific cellular immunity during uterine infections. In dairy animals with endometritis and repeat breeding intrauterine infusion of 100µg *E.coli* eliminated endometritis along with improved pregnancy rate after recovery [27]. After treatment with *E.coli* lipopolysaccharide total leukocyte count increases 100-fold with specifically enhanced phagocytic activity of polymorphonuclear neutrophils (PMNs). In repeat breeders single intrauterine infusion of 100µg *E.coli* lipopolysaccharide at estrus is reported to be effective in elimination of bacterial infections within one estrus cycle [28]. In cows *E.coli* lipopolysaccharide increases polymorphonuclear neutrophils (PMNs) infiltration rate in postpartum endometritis cases and conception rate after recovery [29].

Serum and Platelet Rich Plasma

Blood plasma has potential to enhance chemotaxis and accelerate phagocytic activity of polymorphonuclear neutrophils (PMNs) at

a significant level. In mares use of blood plasma in subclinical and clinical endometritis increased pregnancy rate by 90% and 52% respectively [30]. In cows same line of treatment was adopted in endometritis with intrauterine infusion of platelet rich plasma increased conception rate by 52.85% [31]. Likewise, use of platelet rich plasma as intrauterine infusion at dose rate of 1:10 of total bacterial load resulted in 75% recovery rate with 70% conception rate in dairy animal [32].

Neutrophil Extracts

Polymorphonuclear neutrophils (PMNs) extract from cows have significant bactericidal activity against wide range infectious microbes [33]. This antibacterial activity is associated with small antibiotic peptides known as defensins [34] and has been observed in numerous studies. The cells derived from rabbits have shown 100% antibacterial activity against bacterial isolates derived from mare uterus. Therefore, it could be rationalized that polymorphonuclear neutrophils (PMNs) are potential candidates as alternative non antibiotic treatment of uterine infections in dairy animals.

Mycobacterium Cell Wall Extracts

Mycobacterium cell wall contains mycolic acid and a chemotactic component that accelerates chemotaxis and influx of polymorphonuclear neutrophils (PMNs) responsible for elimination of uterine infections. These cells further stimulate interleukins, interferons IL-6 and IL-2, TNFα and myeloperoxidase production and repression of 1L-10 production [35]. In mares experimental induction of endometritis with *Streptococcus zooepidermicus* was treated with intrauterine infusion of mycobacterial cell wall extracts resulted in elimination of infection in 35% mares by the time of ovulation and 70% by 7 days postpartum. Mycobacterial cell wall extracts either used locally or systematically are equally effective in treatment of endometritis in dairy animals [36].

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

Granulocyte macrophage colony stimulating factor (GM-CSF) enhances generation and demarcation of polymorphonuclear leukocytes by progenitor cells in the bone marrow [37]. In cows administration of granulocyte macrophage colony stimulating factor around parturition is associated with leukocytosis and increased neutrophil surface adherence proteins expression, increase in phagocytic and cytotoxic activity of the immune cells. Genetically engineered granulocyte macrophage colony stimulating factor enhanced the transmigration of polymorphonuclear neutrophils (PMNs) by 12-fold. Therefore, it is a potential candidate to be explored as alternative treatment in uterine infections in cows (Hughes and Couto,1988). Recombinant bovine granulocyte macrophage colony stimulating factor (rbG-CSF) was combined with polyethylene glycol (PEG-rbG-CSF) pegbovigrastim in a covalent bond and used as prophylactic measure to combat periparturient immune suppression in commercial dairying system. Cows treated with pegbovigrastim showed significant increase in expression of genes associated with cell adhesions (AM1), pattern recognition (TLR2), inflammation cytokines response (PTGS2) and cell lysis (CASP2) in polymorphonuclear neutrophils (PMNs). Pegbovigrastim treatment did not induce any difference in expression of genes associated with antimicrobial activities. There are controversial consequences after treatment with pegbovigrastim on circulating polymorphonuclear neutrophils (PMNs), incidence of uterine infections, health and reproductive performance in dairy animals [38].

Leucotriene B4 (LTB4)

Leucotriene B4 is an arachidonic acid metabolite physiologically produced by macrophages, mast cells and other stimulated granulocytes. It accelerates polymorphonuclear neutrophils (PMNs) accumulation during inflammation [39]. In cows use of LTB4 enhanced phagocytic activity of polymorphonuclear neutrophils (PMNs) [40]. It also accelerates production and activity of cytokines released by lymphocytes, natural killer cells and monocytes [41]. In cows with endometritis LTB4 given at a concentration of 30μ mol/L eliminated uterine infections with 83 % recovery rate. Successful treatment was declared on the basis of white side test, mucus pH and presence of polymorphonuclear neutrophils (PMNs) in uterine secretions [42].

Oyster Glycogen (OG)

In healthy cows intrauterine administration of oyster glycogen (OG) accelerated influx of polymorphonuclear neutrophils (PMNs) in uterine lumen and 90% of cell population of uterine secretions comprised of these cells [43]. In two experiments cows with endometritis were given intrauterine infusion with 500mg oyster glycogen that enhanced polymorphonuclear neutrophils (PMNs) influx, eliminated bacterial infections and increased conception rate by 66.67% and 41.6% respectively [44,45]. Likewise in one study in cross bred cows OG treatment improved conception rate by 75% after recovery from endometritis.

Phytotherapy

In cows treatment of uterine infections with alcoholic extracts of numerous plants including chamomile, marigold, confrey, salvia and yarrow improved conception rate by 84% after recovery from uterine infections [46]. Neem oil reduced 96% bacterial load and improved conception rate by 71% in cows after recovery from endometritis [47]. Likewise, aqueous extract of *Tinospora cordifolia* used for the treatment of endometritis in cows resulted in improved recovery and conception rate by 66% and 27% respectively [48]. Use of garlic as nonspecific immunomodulator reduced bacterial load at following estrus in dairy animals [49]. Antifungal plants along with free radical scavenger properties including *Rosemarinus officinalis* and *Thymus vulgaris* are also reported as effective treatment of Candida albicans

induced endometritis in cows. Likewise, herbs including dutchman's pipe, Indian madder, hermal, myrrhand, and lepadenia also have uterotonic, anti-inflammatory and antimicrobial actions and can be used as an alternative treatment of endometritis in buffaloes [50].

Proteolytic Enzymes

Hydrolytic enzymes including trypsin, chymotrypsin and papain have the capacity to break proteins and fat bonds. The immunomodulatory effect of these proteolytic enzymes occurs either directly or indirectly. Papain works directly as a cysteine protease, in a similar manner as bacterial cysteine proteases of gram-negative anaerobic microbes, on the CD14 molecule of inflammatory cells particularly macrophages and monocytes and raises their level of efficacy to insurge acute phase reaction. Administration of proteolytic enzymes in buffaloes with subclinical mastitis resulted in better pregnancy rates as compared to other immunomodulators [51,52].

Vitamin E

During periparturient period, dairy animals are more prone to uterine infections due to naïve immune system. Vitamin E acts as an immunomodulator and enhance function of polymorphonuclear neutrophils (PMNs). Numerable studies also concluded that vitamin E associated chemotaxis takes place by an increase in receptor-bound urokinase-plasminogen activator in polymorphonuclear neutrophils (PMNs) [53]. Vitamin E supplementation at dose rate of 3000 IU per day prevented uterine immunosuppression in prepartum and postpartum period in dairy animals [54].

Minerals

Zinc is an important trace mineral for maintenance of normal physiological functions. Numerous studies focused on vital role of zinc in immune system. It maintains structure of epithelium a natural barrier in nonspecific defense system [55]. Acute deficiency of zinc is associated with decreased innate immunity, complement cascade impairment, decreased phagocytic and cytotoxic activity of polymorphonuclear neutrophils (PMNs), natural killer cells and monocytes [56]. Zinc modulates inflammation via toll like receptors (TLRs) signaling mechanism via multiple pathways. It is responsible for inhibition of NF-kB activity which leads to decrease in production and function of proinflammatory cytokines TNF-α, Interleukins (IL-1B, and IL-6) [57]. In animal model copper supplementation repress mRNA levels of TLR4 and downstream MyD88 signals in E. coli lipopolysaccharide induced infections in intestine [58]. Copper is an essential trace mineral with multiple immune functions. It acts as a co-factor for superoxide dismutase enzyme that regulates innate toll like receptors response and enhance antimicrobial activity of macrophages [59].

Ozone

Ozone inactivates microorganisms including bacteria, viruses, and fungi inducing infections in dairy animals. It suppresses inflammatory reaction by inhibiting proinflammatory cytokines and enzymes phospholipase A2 and by stimulating immunity repressive cytokines including IL-10 and TNFβ1. Incidence of subclinical endometritis is reduced when cows are treated with ozonized intrauterine distilled sterile solution at dose rate of 50µg /ml prepartum. Treatment with ozone also increased first service conception rates when compared with untreated control group by 50% vs 16.2% [60].

Probiotics

The word 'Probiotic' is acquired from the Greek word meaning 'For Life'. In the early 20th century, a Russian Nobel laureate Elie Metchnikoff also known as 'Father of Probiotics' suggested that ingestion of certain microorganisms could impart significant health benefits in humans. According to World Health Organization (WHO) probiotic is denoted as 'Live microorganisms when supplemented in adequate amounts grant good health to the host'. Lactic acid producing bacilli including *Lactobacillus acidophillus*, *Lactobacillus casei* and *Lactobacillus rhamnosus* are designated as probiotics. Likewise, Bifidobacterium (*Bifidobacterium longum, Bifidobacterium bifidum*) and yeasts *Saccharomyces bolurdii* and *Saccharomyces cerevisiae* are used as probiotics [61]. Numerous studies evaluated the benefits of immunomodulation by blend of lactic acid bacteria in clinical endometritis and other uterine infections in dairy animals [61]. In one study blend of lactic acid bacteria composed of *Lactobacillus sakei* FUA 3089, *Pediococcus acidilactia* FUA 3138, *Pediococcus acidilactia* FUA 3140 was evaluated for its effect on incidence of clinical endometritis, acute phase plasma protein levels and milk yield in cows [62]. Treatment was given one week before parturition and 4 weeks postpartum. Incidence of clinical endometritis decreased, and concentration of acute phase proteins reduced 3 weeks postpartum. Milk yield also improved in treated group as compared with control group. In another study prophylactic administration of same blend of microorganisms in cows around parturition reduced incidence of uterine infections by 6% as compared to untreated control group with 38% infections.

Lactobacilli blend lowered incidence of postpartum uterine infections in cows in association with increased production of immunoglobulin A in vaginal mucus. Intravaginal treatment with Lactobacilli lowered systemic inflammatory reaction as characterized by low concentrations of serum amyloid A and lipopolysaccharide binding proteins in dairy animals. In another study blend of lactic acid bacteria was used and evaluated for occurrence of metritis, nonesterified fatty acids (NEFAs) levels, expression of proinflammatory cytokines genes in blood polymorphonuclear neutrophils (PMNs) and endometritis. The blend was prepared with final cell count of 4.5 ×1010 colony forming unit (CFU) in one dose and comprised of *Lactobacillus rhamnosus* CECT 278, *Lactobacilli reuteri* DSM 20016 and *Pedicoccus acidilactia* CECT 5915. The blend was given as intrauterine infusion weekly 3 weeks prepartum, one dose after calving and control group left without any treatment.

The incidence of uterine infections was reduced by 31% in control group to 13% in treated group associated with reduced expression of proinflammatory cytokines genes in blood polymorphonuclear neutrophils (PMNs) [62].

Recombinant IL-8

Interleukin-8 is produced by epithelium, endothelial cells, innate immune system cells fringed with toll like receptors and smooth muscles and plays vital role in chemotaxis and maintains uterine health in cows. It is a major chemoattractant for polymorphonuclear neutrophils (PMNs). IL-8 binds with CXCR1 and CXCR2 receptors present on surface of polymorphonuclear neutrophils (PMNs) and induce activation of these cells, stimulate chemotaxis, enhance phagocytosis and lytic activity [63]. Cows with lower plasma IL-8 concentrations around parturition developed placenta retention, a major hurdle in normal involution of uterus. In contrast cows with high plasma IL-8 concentrations showed normal involution of uterus after parturition [64]. Therefore, it might be assumed that IL-8 contributes its immunostimulant role by enhancing chemotaxis and migration of polymorphonuclear neutrophils (PMNs) into the uterus and maintains reproductive health of dairy animals. Recombinant bovine interleukin-8 (rbIL-8) used as intrauterine infusion within 12 hrs postpartum at low doses (11.25µg) and high doses (125µg) to evaluate its effects on occurrence of puerperal metritis. Treatment either with low dose or high dose rbIL8 reduced occurrence of puerperal metritis with significant increase in milk yield when compare with placebo-treated control group [65].

Conclusion

In the present era of one health one medicine a novel strategy is to manipulate host immune mechanism to combat ever increasing threat of infections. An antimicrobial system with multiple defense armaments repress the development of microbial response as pathogen and counters numerous modes of attack against a system that remained effective in keeping them at bay under any circumstances. In recent times methods of regulating the immune response via immunomodulators are discovered and evolved as candidate therapies in animal reproductive disorders. High prevalence of uterine infections are attributed in part to impaired innate immune response around parturition. Therefore, postpartum immunomodulation of uterus in cows and buffaloes is applicable solution in management of fertility and reproductive diseases and will be meaningful in future dairying regime.

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