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BOVINE MASTITIS AS AN EVOLVING DISEASE AND ITS IMPACT ON THE DAIRY INDUSTRY

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ABSTRACT

Worldwide, mastitis is emerging as a major challenge in dairy development, on account of being the cause for severe wastage and undesirable milk quality, besides breed development, nutritional management, control of infections and internal parasitic diseases. The major factors found to be important and affecting the prevalence of subclinical mastitis included flock size, regional agro climatic conditions, distinctive socio-cultural practices, marketing of milk and its byproducts, literacy level of the animal owner, feeding system and administration. The continuing presence of the disease may be attributed to poor practices which includes unhygienic conditions, improper milking practices, faulty milking equipment, lack of veterinary medicines, poor housing besides breeding strategies for ever-increasing milk yield. It is important to be aware of the fact that being an infectious disease, all methods of commercial milk production may provide suitable breeding conditions for mastitis organisms and thus spread mastitis from cow to cow. On account of insights provided by a considerable body of evidence it is suggested that to increase exposure of cows to mastitis organisms and thereby get infected, several management and environmental factors interact together which compromise the cows natural resistance to disease help organisms in gaining entrance through the teat canal to milk secreting tissues of the udder where they cause infection. The incidence of disease is thus result of interplay between the infectious agents and management practices emphasizing the importance of udder defense.

Key Words: Mastitis, Subclinical mastitis, Clinical mastitis, Dairy farms, Milk

INTRODUCTION

Bovine mastitis defined as 'parenchymal inflammation of the mammary gland' is characterized by a range of physical and chemical changes of the milk and pathological changes in the udder glandular tissues (Radostits et al., 2000). Mastitis, one of the most widespread and common diseases is characterized as an endemic disease affecting dairy herds worldwide (Halasa et al., 2007). It is the most cost intensive production disease in dairy industry, causing a considerable financial burden in terms of medical treatment, reduced fertility, extra labor and reduced milk yield (Schroeder et. al., 2010).

Worldwide, mastitis is one of the most widespread and expensive diseases affecting the dairy business (Petrovski et al., 2006). Mastitis, a multi-etiological complex disease associated with dairy production is the most costly production disease inflicting major economic losses to dairy industry worldwide, especially in developed countries (Seegers et al., 2003). Economic losses associated with mastitis derive mainly from a reduced milk production, discarded milk, early cow replacement costs, reduced cow sale value and to a lesser extent, from the culling of continually infected cows, veterinary services, cost of veterinary treatment, drugs, labor and penalties on milk quality (Seegers et al., 2003).

The continuing incidence of the disease in spite of exhaustive research and the implementation of various mastitis control strategies over the decades may be attributed to deficient management, improper milking procedures, faulty milking equipment, inadequate housing and breeding for ever-increasing milk yield (Pyorala et al., 2002). It is important to be aware of the fact that being an infectious disease, all methods of commercial milk production provide suitable breeding conditions for mastitis organisms and thus spread mastitis from cow to cow. The incidence of disease is the result of interplay between the infectious agents and management practices stressing proper udder defense strategies. According to Kennedy and Miller (1993) mastitis is expressed by tissue injury caused by tissue invasive or toxigenic organisms, which become dominant due to upset of balance

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in microbial population or suppression of the innate immune response. Mastitis as per the present scenario has symbolized itself as a most challenging disease in high yielding dairy animals in India next only to FMD (Foot and Mouth Disease) (Varshney & Mukherjee, 2002). But as per reports of its occurrence in dairy animals, it places itself at first position with its prevalence reported in more than 90% of high yielding cows (Sharma et al., 2003).

Mastitis according to the clinical symptoms may be classified as Clinical mastitis or Sub- Clinical mastitis. In general Clinical mastitis portrays itself by rapid onset, inflammation, reddishness of the udder, tenderness, and reduced and altered milk discharge from the affected quarters. Clinical mastitis is also accompanied by fever, despair and anorexia, in addition the milk may have clots, flakes, gargot (Fibrin clots), off color, bloody or of watery in consistency. The Sub clinical mastitis on the other hand have no visible signs either in the udder or in the milk, but temporary decrease of milk quality may be observed. Subclinical mastitis can be detected by monitoring the number of somatic cells in the milk (Somatic Cell Count-SCC) (Schukken et al., 2003). Subclinical mastitis according to Shearer & Harris (2003) is important due to the fact that it is 15 to 40 times more prevalent than the clinical form. Subclinical mastitis usually leads the clinical form as it is of longer period, difficult to diagnose, adversely affects milk production and quality and comprises a reservoir of pathogens that lead to disease of other animals within the herd.

CAUSES

Mastitis is a complex disease, mainly caused by a variety of pathogens, with substantial differences in infection patterns (clinical versus subclinical, acute vs. chronic) with no simple model encompassing all possible facets of the disease (Fetrow et. al., 2000). Mastitis is usually caused by bacterial pathogens which can be classified into two groups; the contagious pathogens including *Streptococcus agalactiae, Staphylococcus aureus and Mycoplasma bovis* which reside predominantly in the udder and spread during milking and environmental pathogens including *Streptococcus species (Streptococcus uberis and Streptococcus dysgalactiae)* and environmental coliforms (Gram negative bacteria *Escherichia coli, Klebsiella spp., Citrobacter spp., Enterobacter spp., Enterobacter faecalis* and *Enterobacter faecium*; and other gram negative bacteria such as *Serratia, Pseudomonas and Proteus*) (Radostits et al. 2000).

The bovine mammary gland is protected by innate and specific immune responses (Sordillo & Streicher, 2002) however; abnormal environmental and physiological factors could compromise the defense mechanism of the mammary gland (Waller et al., 2000). Milking by means of machines has been found to contribute to teat damage thereby increasing the vulnerability of mastitis causing pathogen colonization. Besides poor management practices including poor housing environment, increased cow densities per unit, low ventilation, unhygienic conditions, improper milking practices and lack of veterinary medicines can also increase the susceptibility to bovine mastitis (National Mastitis Council, 1996). Nevertheless, the lactation stage of a cow especially is the most important factor in contributing to increased susceptibility of bovines to mastitis (Oliver & Sordillo, 1988). The genetic selection of cows for milk production has increased milk productivity but decreased resistance to mastitis, contributing to higher incidence (Waller et al., 2000).

PATHOGENESIS

Mastitis in dairy cattle's takes place when the udder becomes inflammed as a result of pathogenic (most often bacterial) invasion of the teat canal. These bacteria once inside the teat canal migrate up the teat canal and colonize and multiply in the alveoli. These colonized organisms then produce toxic substances, which causes injury to the milk secreting tissue besides physical trauma and chemical irritants.

According to Sordillo (1987), the predominant cells found in the mammary tissue and mammary secretions during early stage of mastitis infection constituting >90% of the total leukocytes are neutrophils. The neutrophils exercise their bactericidal effect through a respiratory burst and produce oxygen and hydroxyl radicals that kill the bacteria. During phagocytosis, bacteria are also exposed to several oxygen independent reactants such as peroxidases, lysozymes, hydrolytic enzymes and lactoferrin. In addition to their phagocytic activities, neutrophils are a source of antibacterial peptides called defensins, killing a variety of pathogens that cause mastitis (Selsted et al., 1993). As a result of mammary invasion by pathogenic species, masses of neutrophils pass between the milk secreting cells into the lumen of the alveoli, increasing the somatic cell counts besides injuring the secretory cells. The increase in the number of leukocytes in milk results in the increased number of somatic cells as well. This aggregation of leukocytes and blood clotting factors results in the formation of clots which may perhaps block the lacteal ducts and prevent complete removal of milk, resulting in scar formation along with proliferation of connective tissue elements (Jones et al., 2006). Macrophages, the chief cells found in milk and tissue of healthy involuted and lactating mammary glands (Sordillo & Nickerson, 1988), ingest bacteria, cellular debris and accumulated milk components. The phagocytic activity of mammary gland macrophages can be increased in the presence of indiscriminate ingestion of fat, casein and milk components, usually less effective at phagocytosis than blood leukocytes (Sordillo & Babiuk, 1991). Macrophages also play a role in antigen processing and presentation (Politis et al., 1992).

In general invading pathogens are known to induce an immune response by exciting the native immune system in the mammary gland. The major pathogenic element of *Staphylococcus aureus* is Lipoteichoic Acid (LTA) and one of the chief pathogenic components of *E. coli* is Lipopolysacharide (LPS) (Beutler & Rietschel, 2003). However, LTA is considered the gram-positive counterpart of LPS (van Amersfoort et al., 2003). Other cell wall components such as peptidoglycans also have immunological effects in gram-positive bacteria (Fournier & Philpot, 2005).

The significant systemic response of the organism to local or systemic disturbances in its homeostasis caused by infection, tissue injury, trauma or surgery, neoplastic growth or immunological disorders is Acute Phase Response (APR) (Gruys et al., 1999). For the development of an effective immune response the importance of inflammatory cytokines against mastitis has been documented in several researches, which collectively have evaluated changes in their concentrations in milk during tests on animals with experimentally infected udders (Bannerman et al., 2009).

Acute Phase Index when applied to healthy animals separated from animals with some disease, much better results are achieved than with single analytes and statistically acceptable results for culling individual dairy animals may well be reached (Gruys et al., 2005). Since serum concentration of APPs (Acute Phase Proteins) during impaired physiological conditions changes by as much as 25%, APPs have been thought-out to be exploitable as potential biomarkers in the future for the diagnosis and prognosis of both companion and farm animal disease, examining health status, and assessing responses to primary and adjunctive therapy in veterinary practice.

The pattern of protein synthesis by the liver is considerably changed within a few hours after infection resulting in an increase of some blood proteins, the APPs (Ingenbleek & Young, 1994). Hepatic mRNA upregulation of the positive APPs is associated with a decreased synthesis of some normal blood proteins, like Retinol Binding Protein (RBP), Transthyretin (TTR), and Cortisol Binding Globulin, Albumin and Transferrin, representing the negative APPs. The positive APPs, like C - reactive protein (CRP), Serum Amyloid A (SAA) and Haptoglobin (Hp) are mainly the proteins released by the hepatocytes after cytokine stimulation (Heinrich et al., 1998). Besides the decreased level of zinc, iron and albumin in serum, a decrease of Transferrin, Cortisol-Binding Globulin, Transthyretin (TTR) and Retinol-Binding Protein (Retinol; Vitamin A) have also been described indicating a momentarily increased availability of free hormones bound to these proteins. On the farm, APP analysis may be used to help scrutinize the health and welfare of production animals for their optimal growth (Eckersall et al., 2000).

In cattle, (Haptoglobin) is an effective marker in the diagnosis and prognosis of mastitis, peritonitis, pneumonia, enteritis, endometritis, and endocarditis (Murata et al., 2004; Petersen et al., 2004). Similarly Bovine Serum Amyloid A (SAA) is found to be elevated more by acute rather than chronic inflammatory conditions (Jacobsen et al., 2005). Investigational representations of mastitis have confirmed that both Hp and M-SAA3 (Mammary Associated Amyloid A3) are synthesized in the infected mammary gland (Eckersall et al., 2006) stressing their possible role as biomarkers to assess naturally-occurring (Gerardi et al., 2009) or experimentally-induced (Moyes et al., 2009; Simojoki et al., 2009; Zecconi et al., 2009) mastitis.

Toll like Receptors (TLRs), belong to a family of conserved innate immune recognition receptors that trigger adaptive immune responses (Zhang et al., 2011). So far about 10 TLRs have been identified in cattle, (Menzies & Ingham, 2006). In the mammary gland, cells from the immune system together with epithelial cells are responsible for recognizing the invading microorganism via Toll-like receptors, or TLRs (Griesbeck et al., 2008). The expression of inflammatory cytokines and other intermediaries related to immune response, cell differentiation and apoptosis are triggered via activation of TLRs (Cates et al., 2009). Development of an effective immune response against mastitis as documented in several researches have recognized the importance of inflammatory cytokines by evaluating changes in their concentrations in milk during tests on animals with experimentally infected udders (Bannerman et al., 2009). The genes involved in the immune response have been indicated as strong candidates in determining host resistance response because of the complex nature of mastitis (Fonseca et al., 2009). The intracellular TIR domain since its involvement in engaging signaling pathways within cells is highly conserved with functional resemblance among species and TLR genes, (Beutler and Rehli, 2002). The extracellular TLR domains however, exhibit significantly-higher variance reflecting their involvement in MAMP (Microbe Associated Molecular Patterns) recognition from multiple microbial sources (Zhou et al., 2007). The molecular patterns recognized by TLR4 are mainly presented by lipopolysacharide (LPS) that is a component of the ectoblast of Gram-negative bacterium, and stimulate the over expression of inflammatory factors like , IL-1, IL-6, and IL-8, which participate in innate immune response and then confer resistance (Shizuo et al., 2001). TLR4 is the only important pattern recognition receptor of the TLRs family that recognizes endotoxins associated with gram-negative bacterial infections (McGuire et al., 2005). Because of its role in pathogen recognition and consequent initiation of the immune and inflammatory response makes it an appropriate candidate gene for enhancing disease resistance in dairy cattle (Sharma et al., 2006). Bovine TLR4 gene was discovered in 2003 and mapped to chromosome 8 (McGuire et al., 2005). The result indicated that mastitis strongly increased mRNA expression, thereby suggesting that TLR4 gene might be related with mastitis. TLR9 recognizes CpG DNA motif present in bacterial and viral genomes as well as non-nucleic acids such as hemozoin from the malaria parasite (Akira et al., 2006; Uematsu S et al., 2006).

ECONOMIC DRAWBACKS

The economic consequences of bovine mastitis are not restricted only to the farm but expand beyond the dairy farm (related to production losses, treatment, culling and changes in milk quality) thereby have a significant impact on the farm business. In India, the first comprehensive report on economic losses caused by mastitis was published in 1962 indicating annual losses of Rs. 52.9 Crores (Dandha & Sethi, 1962). However in later years with the launching of operation flood, tremendous thrust was given on cross breeding program which resulted in tremendous increase in high yielding bovine population, leading to many fold increase in economic loss. The fact is evidenced from a recent report where in annual economic losses sustained by dairy industry in India on account of udder infections have been projected about Rs. 6053.21 crores. Out of this, loss of Rs. 4365.32 crores (70%-80% loss) was credited to sub clinical version of udder infections (Dua et al., 2001). The annual economic losses due to bovine mastitis are estimated to be Rs. 7165.51 crores in India, out of which 57.93% (Rs. 4151.16 crores losses) has been attributed to subclinical mastitis. Control of bovine mastitis is constrained because of multiple etiological agents. A rapid, sensitive and specific diagnostic method capable of simultaneously detecting multiple causative agents is essential for surveillance and monitoring of udder health.

Mastitis, a multi-etiological complex disease associated is the most expensive production disease inflicting major economic losses to dairy industry worldwide especially in developed countries (Seegers et al., 2003). In U.S., the annual loss per cow from mastitis in 1976 were estimated to be $117.35 and losses of milk yields caused by mastitis were 386 kg/cow per year and losses of discarded milk 62 kg/cow per year (Blosser et al., 1979), which increased to $185 to $200 per cow per year (Costello et al., 2004). Similarly in 1976 losses from mastitis were $1.294 billion in U.S. which increased up to $2 billion in the year of 2009 (Viguier et al., 2009).

Mastitis has been and continues to be recognized as one of the major disease problems concerning the dairy industry. Mastitis is a global problem as it adversely affects animal health, quality of milk and economics of milk production and every country including developed ones suffer huge financial losses (Sharma et al., 2007). Economic losses associated with are due to reduced milk yield (up to 70%), milk discard after treatment (9%), cost of veterinary services (7%) and premature culling (14%) (Bhikane & Kawitkar, 2000). In both clinical and subclinical mastitis there is a substantial loss in milk production. A recent study by Wilson (2004) at Cornell University showed that clinical mastitis tends to strike high able producing animals in second-plus lactation. In other words mastitis often hits the cows with the highest production potential, which expands the loss due to mastitis. According to the study, the estimated loss following clinical mastitis was almost 700 kg for cows in first lactation and 1,200 kg for cows in second or higher lactation (Wilson et al., 2004). Rajala et al., (1999) reported in that cows with clinical mastitis did not return to the same production level within the remainder of the lactation, according to Miller et al., 2004.

PREVENTIVE AND CONTROL STRATEGIES

Monitoring udder health performance is possible only by the use of reliable but affordable diagnostic methods. Therefore, there is a constant need to improve diagnostic methods, in terms of their accuracy, cost, or convenience. The most commonly used diagnostic methods are SCC and bacteriological culturing of milk. The diagnostic approach to mastitis starts with visual examination of the udder and of the milk through the fore stripping, which is also an important part of udder preparation (Reneau et al., 2001). In case of any noticeable change in quarter or any noticeable abnormality in the milk, the quarter is defined as having clinical mastitis.

There is a considerable body of evidence suggesting that the normal dairy cow milk has a regular level of 100,000-150,000 somatic cells/ml and higher SCC point to secretory disturbance rather than any disease (Hillerton et al., 1999). The somatic cell count for the composite milk for an udder with four healthy quarters should not exceed 100,000 cells /ml (Ma et al., 2000). A value of SCC exceeding above 200,000 cells/ml in a composite sample of a cow is abnormal with 60% probability of inflammation in one or more quarters of the udder (Mellerberger et al., 1999). Other enzymatic tests include the esterase detection secreted by somatic cells using an enzymatic assay on a dipstick. Lately, bioluminescence-determination assays, based on estimation of the ATP concentrations in somatic cells or the recognition of somatic cell DNA by fluorescent staining, have also been used for the reliable determination of elevated SCC levels and hence the possible presence of mastitis (Frundzhyan et al.,2008). The identification of pathogens causing mastitis is important for disease control and epidemiological studies. Bacteriological culturing each specifying its own goal can be carried out at herd, as well as cow and quarter level. Conventionally identification of the microbial species is carried out according to biochemical, serological and cultural properties. Commercially biochemical kits for species identification are available but they have been proved unreliable for the identification of veterinary pathogens. For this reason, the use of molecular techniques like PCR (Polymerase Chain Reaction) has been employed in pathogen detection for a number of mastitis pathogens (Zadoks et al., 2006).

Recently techniques like multiplex PCR tests in which several pathogens can be tested at the same time have been developed (Phuektes et al., 2003). Additionally, real-time PCR assays are being developed for detection and quantifying mastitis pathogens in milk. Recent advances in relevant proteomics techniques, such as two-dimensional gel electrophoresis and mass spectroscopy, have led to the identification of various new proteins implicated in mastitis. The proteomics have revealed new information on the diverse protein expression pattern obtained from mastitis- infected milk and on the proteins expressed by invading pathogens. The information can further be applied not only in the discovery of new therapeutic targets but also in the search for identification of new diagnostic biomarkers. Recent advances in microfluidics and so-called 'biochips' have the capacity to revolutionize diagnostics (Viguier et al., 2009).

The clinical management of mastitis has become a concern to the veterinarians, as the conventional antibacterial therapy through intramammary route is largely associated with failures. Isolation of the causative organism also does not help much in the clinical management of the disease as the organisms frequently change their sensitivity and develop resistance against antibacterial. The selection of antibiotics for treatment of mastitis should be made on the basis of sensitivity testing and pharmacokinetics characteristics of the drug (Srivastava et al., 2000). Moreover the efficacy of antibiotic following intramammary administration is governed by factors like lipid solubility, tissue protein binding, pH and presence of inflammatory exudates. On the basis of observations done, it has been concluded that parenteral antibacterial therapy following cultural sensitivity testing may be recommended as the immediate therapeutic measure to save udder damage (Malik et al., 2004).

In view of better prevention and control, National Mastitis Council in 2003 proposed the "Five Point Plan" summarizing numerous approaches for controlling herd mastitis. The plan was based upon implementation of preventive and control tactics including better diagnosis, isolation of the animals and the use of better hygiene and remedial protocols (Bramley et al., 2003). The key objectives of the plan were to reduce the scale and the strength of the infection to prevent inclusion of further cases. In India, it is important to educate the farmers regarding the risk factors of mastitis and also about teat dipping as a preventive measure to be practiced regularly by dairy farmers (Kavitha et al., 2009).

FUTURE PROSPECTS

The `Holy Grail' for effective mastitis control remains vaccination and the use of reliable but affordable diagnostic methods. Despite decades of research no `truly effective' vaccine is yet commercially available. The most exciting progress possibly in the field of mastitis vaccination has been the development of a subunit vaccine, the plasminogen activator pau A against Str. uberis (Leigh et al., 1999; Fontaine et al., 2002; Pereira et al., 2011)

In the premise, for the effective management of the mastitis we need to focus our efforts on improving environmental management and also to approach the management of mastitis in a more holistic manner by ensuring optimal nutrition, minimizing stress and encouraging farmers to pay attention to various awareness programs in detail (Green & Bradley, 2001).

DISCUSSION

Worldwide Bovine Mastitis remains the most costly production disease, considered as a complex disease with its management an increasing challenge to the dairy industry. The mastitis control program by the implementation of the Five-Point Plan and other such programs worldwide have led to a remarkable decrease in the occurrence and prevalence of disease, however this progress could be rapidly lost in the absence of continued implementation of these control strategies. The cost estimation associated with mastitis is notoriously difficult, with even more difficult to quantify the losses associated with subclinical mastitis being unnoticeable to the farmer. The economics of mastitis needs to be addressed at the herd level depending included flock size, regional agro climatic conditions, distinctive socio-cultural practices, marketing of milk and its byproducts, literacy level of the animal owner, feeding system and administration.

CONCLUSION

In general to establish and thereby implement an efficient mastitis management program in the herd, each dairy producer should create a mastitis advisory team to assess his herd's situation in terms of management, facilities, current level and types of mastitis, etc. The control programs in particular should contain realistic goals that can be attained, which once attained; should help in establishing more challenging goals. A program evaluation and goal reorganization process should be done as frequently as required for the herd, but certainly after a fixed period of time after every six months or as such.

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