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Current Advances in Genetic Resistance to Mastitis in Cattle and the development of sensors.

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Abstract

Bovine Mastitis is as an inflammatory condition of the mammary gland. During lactation Mastitis is one of the most common diseases affecting dairy cattle and the prevalence of mastitis in the lactating mothers is 3% to 33%.As Bovine mastitis is an infectious and multifactorial disease. The major pathological agents are the bacteria. Bovine mastitis reduces milk yield, increases culling rate, incur treatment cost, and may cause death of the animal in severe infection. Mastitis not only to a greater extent reduces the productivity but also affects the quantity and the quality of milk yield. Generally, as mastitis is the most infectious disease, the major factors that increases the chances of mastitis are microbial exposure, defense mechanism of cow, and environment and managemental factors. The resistance of Mastitis is a great matter of concern due to its impact, not only on the economy of milk production but also on the health status of the animal. To the consumers and society mastitis has become a concern because of problems about antimicrobial residues, antimicrobial resistance and milk quality. In recent years, the growing concern about functional traits in dairy

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production has fostered many studies on the background of genetically modulated variability in resistance to mastitis. Additionally, new tools became available for including respective outcome into dairy cattle breeding. Resistance to mastitis could be improved by breeding. The mastitis resistance involves several selection methods. Current breeding programs, use somatic cell count and clinical mastitis cases as resistance traits could prove useful in succeeding generations of cows to improve the natural genetic resistance, As mastitis is associated with inflammation and many such factors get released during the course of time. These factors can act as biomarkers for the diagnosis of this disease. Therefore by using the potential utility of these sensors many of the inflammatory factors can be measured. The quality and the quantity of the milk are affected by these inflammatory components. For the detection of CM many sensors can be used that will determine electrical conductivity, pH, Somatic cell count, Color and Homogeneity.

Therefore it has become a matter of greater concern to discuss the future direction of mastitis research, given the recent developments in the areas of dairy farming, dairy processing and societal concerns.

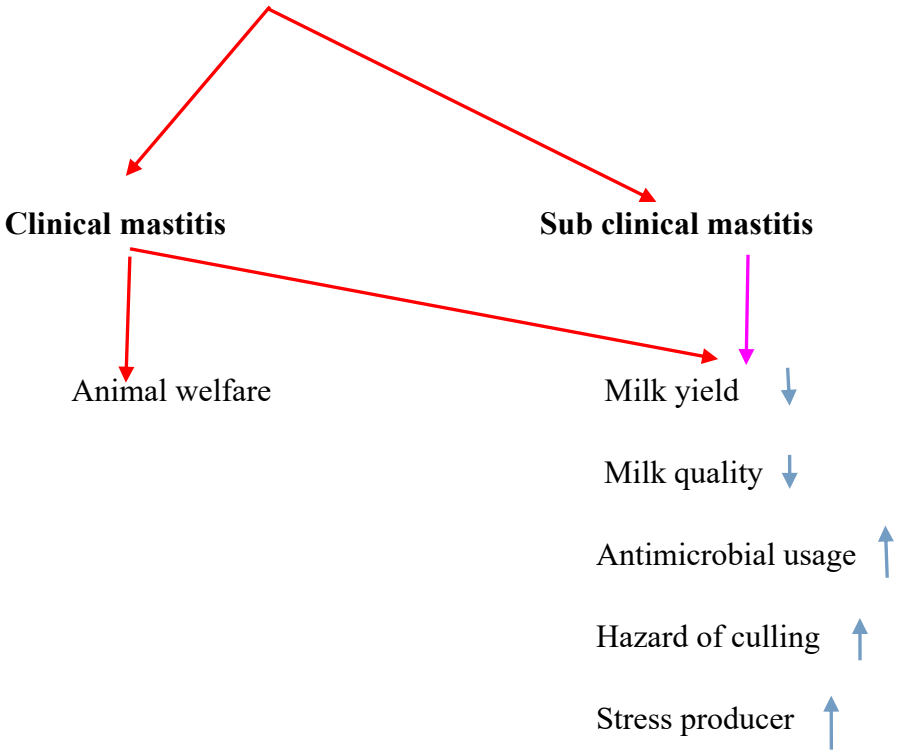
Keywords: **Clinical mastitis, Subclinical mastitis, Sensors, SCC, Electrical conductivity, Modulators, Resistance.**

Introduction:-

Mastitis is one of the significant diseases with multi-factorial origin, worldwide distribution resulting in large economic losses to the industry (DeGrave and Fetrow,1993).As Mastitis is an infectious disease and is usually caused staphylococci, streptococci, and/or corynebacteria. Usually Staphylococcus aureus has been considered as the main etiological agent of acute mastitis, While as in both human and veterinary medicine Staphylococcus aureus is emerging as the leading cause of chronic mastitis .Mastitis can be associated with symptoms or without any visual signs. Mastitis can be either clinical or subclinical. In Clinical mastitis there are visible symptoms. If there are flakes or clots in the milk then it is a case of Mild CM, whereas symptoms like heat, swelling and discoloration of the udder, as well as abnormal secretion are associated to severe cases. Severe CM can also exhibit systemic reactions, such as fever and loss of appetite. If there is absence of any visible signs of infection in that case it is then referred to as subclinical mastitis (SCM). The most prevalent form of mastitis is the SCM (Akers, 2002).. The presence of pathogens in bacteriological cultures

of milk can be considered as a diagnostic measure of SCM, but bacteriological sampling is not practically feasible as a routine test. For the detection of SCM the current gold standard method is to measure SCC. Besides SCC there are many other inflammatory parameters, that have the potential of being used in detection and Such parameters which have the tendency of being used as indicators of SCM are electrical conductivity, lactose, lactate dehydrogenase, acute phase proteins, etc (Pyörälä, et al 2003). Based on the duration of infection mastitis can be further classified as acute or chronic mastitis. If there is a sudden onset of a disease then it is an acute case, whereas an inflammatory process that causes progressive development of fibrous tissue and lasts for months defines chronic mastitis(Jain, 1979). In both forms of mastitis whether clinical or subclinical the quantity and the quality of the milk are affected (Ma et al.,2000;). Additionally, mastitis causes a rise in antimicrobial usage (Grave et al., 1999), hazard of culling (Beaudeau et al., 1995) and stress for dairy producers (Lam et al., 2013).The incidence of mastitis are also affected by seasons and it has been reported that the cases of CM are highest during the winter months (Steeneveld et al., 2008; . Furthermore, by inflicting pain clinical mastitis affects animal welfare(Medrano-Galarza et al., 2012) (Figure 1.2).

Intramammary infection



HISTORICAL PERSPECTIVE OF MASTITIS

From the historical perspective of view the agents which cause mastitis can be either as 'contagious' or'environmental' (Blowey & Edmondson, 1995). Within the mammary gland of the host the organisms that have adapted to survive and particularly spread from cow to cow at or around the time of milking are called as contagious pathogens (Radostits et al., 1994,).The organisms that are opportunistic and particularly invade the mammary gland are best described as environmental pathogens. Like contagious pathogens these organisms are not specially designed to survive within the host. When the environmental pathogens enter the body of the host, they undergo multiplication, and the defense system of the organism produces an immune response. Due to this illicit immune response produced by the host the invading organisms are eliminated. The major pathogens which are considered as contagious include Staph. aureus ,Strep. dysgalactiae and Strep. agalactiae and the major pathogens which are regarded as environmental are the Enterobacteriacae and Strep. Uberis. The infections with both Strep. uberis (Todhunter et al 1995) and E. coli (Bradley & Green, 2001b) are persistent has been reported. It has been found that about 9.1% (Lam et al., 1996) and 4.8% (Dopfer et al.,1999) of clinical E. coli mastitis recurred in a quarter according to the studies which were carried out in Netherlands. According to the recent studies which were carried out in U.K by using DNA Fingerprinting technique it was found that E.coli alone was responsible for causing clinical mastitis in 20.5% cases(Bradley & Green, 2001b). For prolonged periods if the environmental pathogens like Strep. Uberis continue to remain in the mammary gland of the animals, a contagious spread of mastitic infection is mostly liking going to occur (Zadoks, 2003). From the milk samples which were taken from the mastitic bovine mammary gland, about 100 different pathogens were isolated. Bovine mastitis is associated with intramammary infections and the main etiological agents are the bacteria, besides these some of the intramammary infections have been reported to be caused by algae, fungi and yeast(Watts, 1988).

The pathogens of mastitis can be grouped on the following basis

1 Potential damage

2.Epidemiology

3.Staining

On the basis of potential damage they cause to the host organism, they can be classified as major and minor pathogens. On the basis of epidemiology they can be classified as environmental and contagious pathogens. On the basis of staining particularly Gram staining the pathogens of mastitis can be classified as :- Gram-positive and Gram-negative pathogens.

The pathogens particularly major pathogens are responsible for causing clinical mastitis. These major pathogens are more virulent and cause significant loss in milk yield and also raise the SCC to a higher level as compared to the minor pathogens (Timms and Schultz, 1987).

During milking the pathogens that spread host to host(i.e cow to cow) are regarded as Contagious pathogens whereas the pathogens found in bovine environment that have adapted to survive and particularly spread from environment to cow are termed as environmental pathogens(Schukken and Zadoks 2006). It has been reported that pathogens like Streptococcus dysgalactiae show a mixed contagious-environmental epidemiology(Zadoks et al., 2011).The pathogens which are the main causes of Gram-positive IMI are Staphylococci and streptococci (Watts, 1988). In countries like Canada and Ireland in most of the infections of clinical mastitis the major contagious pathogen that has been frequently isolated, found and reported is Staphylococcus aureus (Keane et al., 2013) and at the same pathogen has been found to be the main causative agent of subclinical mastitis in Flanders (Piepers et al., 2007). S. aureus has the ability to evade both the immune system and antimicrobial agents, thereby resulting in chronic IMI and poor treatment results and this property of evading is provided by the virulence factors such as biofilm formation and intracellular survival(Bardiau et al., 2014). From the milk samples of bovine animals the pathogens that are most frequently isolated and are considered as minor pathogens are the coagulase-negative staphylococci (Piepers et al., 2007;).In Flanders and other regions these minor pathogens are responsible for causing heifer mastitis(De Vliegher et al., 2012).However they show very less effect on the SCC and milk yield and cause transient infections (Timms and Schultz, 1987). It has been found that the Coagulase-negative staphylococci infected Heifers even outproduce non-infected herdmates (Piepers et al.,2013).It

has also been reported that few species of coagulase-negative Staphylococcus appear to be more host-adapted whereas from environmental habitats other species were isolated(De Visscher et al.,2014). The streptococci that are the major pathogens are associated with bovine mastitis and particularly include the following three pathogens i.e Streptococcus uberis, Streptococcus dysgalactiae and Streptococcus agalactiae(Watts, 1988). Among these the environmental pathogen Streptococcus uberis is a typical pathogen, although its cow-to-cow transmission has also been reported (Zadoks et al., 2003).The organisms like Streptococcus uberis, Enterococcus spp. and Lactococcus spp belong to the group of esculin-positive cocci. In laboratories where routine detection of the pathogens is done, these Streptococcus uberis pathogens and not always differentiated from other esculin-positive cocci(Piepers et al., 2007). It has been reported in the cases of CM that the pathogen which was frequently isolated was the Streptococcus uberis and also a report of British study founded that the pathogen which was often isolated from cultures was Streptococcus uberis (Bradley et al., 2007). According to the Milk Control Centre it was found that in the cases of clinical mastitis that Streptococcus uberis was isolated from 17% of the samples which were submitted there.(Milk Control Centre Flanders, 2012).Streptococcus uberis has the property to remain in udder of the bovine for several months and also capable of penetrating the cells.(Schukken et al., 2011). Streptococcus dysgalactiae which is often cultured from the samples of clinical and subclinical mastitis shows both host to host transmission and environment to host transmission(Olde Riekerink et al., 2008). The milk samples which were collected from the Flemish high SCC cows about 4% of Streptococcus dysgalactiae was isolated from cultures(Piepers et al., 2007). In Flanders and other developed regions the major causative agent of clinical and subclinical mastitis was a contagious pathogen i.e Streptococcus agalactiae(Keefe, 1997) , however the samples of milk which are used today it is rarely being isolated.(Barkema et al., 2009);Escherichia coli and Klebsiella spp. which are the coliforms and mostly cause Gram-negative IMI. The infections which are caused by these coliforms pathogens have limited time but in certain cases result in severe clinical mastitis. Although chronic coliform IMI has been reported (Dopfer et al., 1999). The milk samples which were taken from the Flemish high SCC cows and were cultured, it was found that about 2% of coliforms were isolated(Piepers

et al., 2007). A study which was carried out in large herds in Wisconsin (US) the main causative as agent of Clinical mastitis to be found was Escherichia coli, and also the milk samples which were submitted to the Milk Control Centre, showed that in the cases of Clinical mastitis the percentage of Escherichia coli, was 17%.(Oliveira et al., 2013). In mastitis a damage is caused to the host animal along with an acute inflammatory response. The substance which causes this damage and response are present in the cell wall of the pathogen and the substances which are particularly found are Lipopolysaccharide and endotoxin (Hogan and Larry, 2003).

Physiological background of mastitis resistance

Mastitis resistance is the ability to either avoid contact to pathogens (e.g., due to favourable conformation or behaviour) or to successfully fight a pathogen after invasion (Figure 1). The latter can be impaired by a genuinely deficient immunological response or by factors decreasing immunological capacity (e.g., metabolic disequilibrium). (Melendez et al. (2009) described mastitis being prominently at risk in cows with severely elevated plasma nonesterified fatty acids (NEFAs) level compared to mates with average to slightly increased NEFA levels. (Nyman et al. (2008) agreed in NEFAs as an informative predictor of elevated SCS in primiparous heifers. This fits the observation of Morris et al. (2009) describing impaired splenic expression of genes relevant in immune response in individuals with severe negative energy balance. Furthermore, there is increasing evidence for a physiological link between fat metabolism and immune response in mammals providing a tie between the increased mastitis incidence and the lipomobilisation at the start of lactation (e.g., Moyes et al., 2009. Commonly, mastitis is recorded in a global definition without considering, e.g., the major host-driven differences affecting the course and the outcome of the disease. Some common protective mechanisms are in place that seem to act upon a variety of pathogens. Strandberg- Lutzow et al. (2008) identified upregulated mRNA and protein levels for S100 calciumbinding protein A12 (S100A12) and Pentraxin-3 (PTX3) in the mammary gland, when challenged with S. aureus, and demonstrated a growth inhibiting effect of S100A12 on E. coli in vitro. Correspondingly, there was a correlation between S100A12 and SCS in milk. However, there is growing evidence that frequently specific mechanisms are in action for fighting

invading pathogens depending on the pathogen itself (Petzl et al., 2008), because signaling pathways and speed of response to invasion can differ markedly. Jiang et al. (2008) provided evidence of the relevance of liver acute phase response to intra-mammary LPS challenge, which points to the divergent protecting mechanisms against E. coli (LPS) and e.g., Streptococcus/Staphylococcus (Lipoteichonic acid).

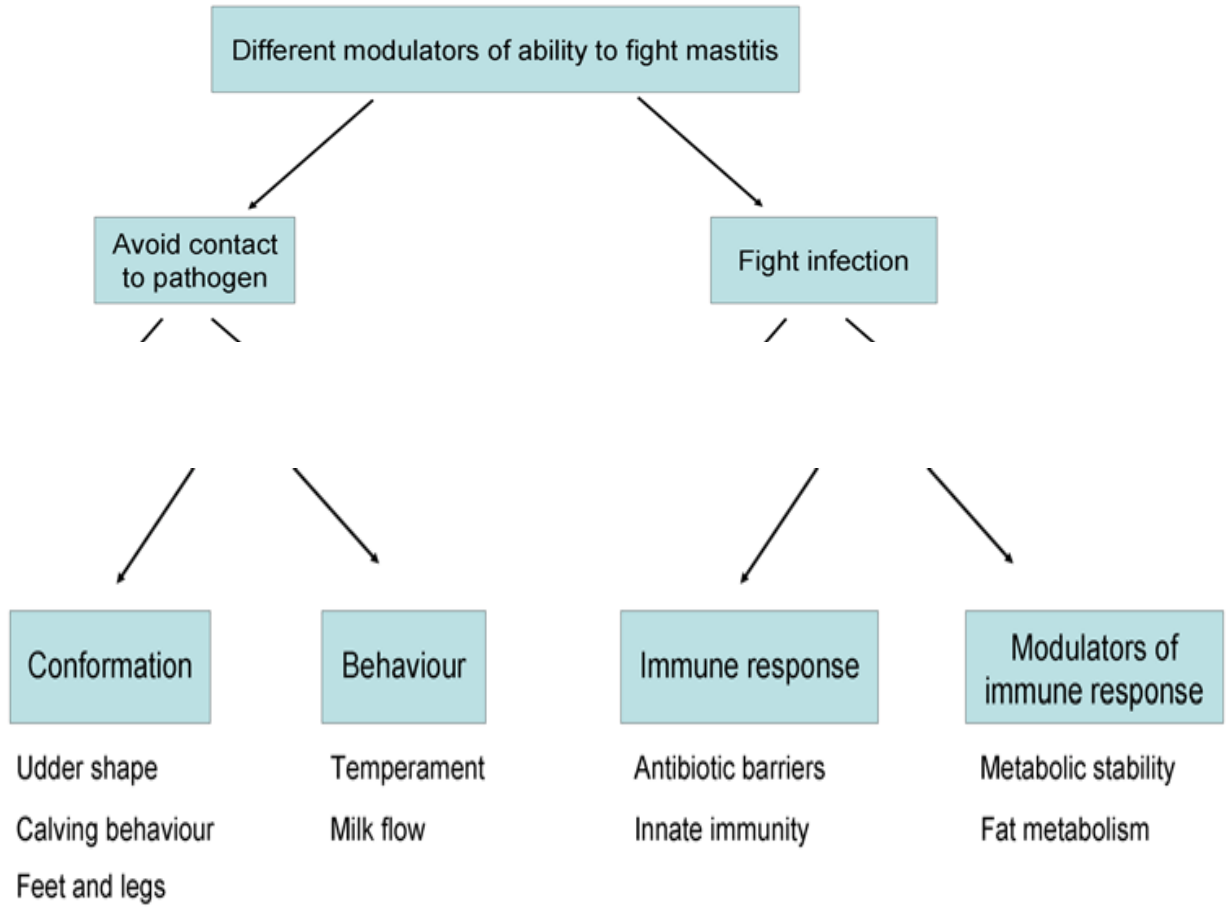


Figure 1: Potential strategies of the cow to fight mastitis

Sensors

Due to the physiological changes that occur in udder which cause intramammary infections which in turn lead to the major alterations in the composition of the

milk. To measure these inflammatory parameters many sensors have been proposed and developed to deal with these one or more inflammatory parameters. For the detection of clinical mastitis some of the important sensors which can be utilized are as.

Electrical conductivity :-

The resistance of a particular material to an electric current gives the measure of E.C. The measurement of E.C is based on the ionic changes that occur during the inflammatory mastitic conditions. Since the main components present in milk are the ions and these ions inforth are responsible for electric conductivity. The main ions present are sodium and potassium and the concentration of these ions increase during mastitis.[Kitchen.BJ et al 1995].The secretory cells of the mammary gland that involve active and passive transport systems in the milk maintain the level of sodium-potassium in the ratio of 1:3,whereas in the blood or extracellular fluid the ratio is 30:1.In the milk the concentration of chloride is much lower than in blood. The ducts of the mammary gland are impermeable for the passage of ions. Due to the destruction that occurs in the tight junctions and the active ion pumping system there occurs a change in permeability of the blood capillaries, which in turn changes the ionic concentration. The scientific research reveals that milk is isosmotic with blood, the secretory cells of the mammary gland stabilize the osmotic pressure which in turn causes a change in the E.C [Linzell et al 1971]. Due to this change E.C can be used as a indicator for CM. Besides mastitis E.C is also affected by many other factors like such as temperature, the fat content of milk and milk fraction[Nielen et al 1992]. The sensors that measure E.C are commercially available as the principle of measuring is relatively easy and simple. Basically there are two types of systems available:(1) The systems that measure the conductivity of the whole milk, (2) systems measuring the conductivity per udder quarter, Since mastitis is an event which occurs on udder quarter, EC measurements on quarter level give the possibility to compare udder quarters, thus increasing the test characteristics [Mollenhorst et al 2010].

L-Lactate dehydrogenase

There are a number of enzymes that are a part of the glycolytic pathway and Lactate dehydrogenase is one of the enzymes of this pathway. In the body LDH is found in the cytoplasm of all cells and tissues. During the course of infection the host body produces an illict immune response and in that period LDH serves as a positive responsive indicator of mastitis. Due to the cellular changes in the membrane LDH is released which could act as a potential

marker of mastitis. As a result of this fact LDH has got a great potential in detection of mastitis particularly CM [Friggens, et al 2007]. Recently by using dry-stick technology a bio-sensor has been developed. In one research farm where milk samples were analyzed by using this biosensor good results were obtained. [Chagunda et al 2007]

Color

To distinguish between the normal and the abnormal milk, one of the best ways is the direct measure of the physical characteristics of milk. The color is one of the best visible aspects of milk. For the detection of this visible aspect of milk a sensor has been developed which is online based measure the intensity of the color. In this sensor light is generated by a LED. This sensor is based on the principle of reflection of light. The whiter the milk, the more light is reflected. Red, Green and Blue wavelengths of light are measured by this sensor. Besides this principle of reflection of light which was used by these sensors ,now a days a new version of color sensor have been developed. These newly developed sensors are based on the transmission of light and not on reflection of light. These newly developed color sensors show better possible results than the older versions.[Song, X. Et al 2010].

Somatic cell count

Somatic cell count or shortly SCC determines the number of somatic cells in the milk. During the period of Mastitis when the infection spreads to the mammary gland becomes infected, there is a large and rapid influx of polymorphonuclear leukocytes which ultimately leads to an increase of the SCC [Wergin,et al 1979]. The measurement of SCC which is carried out routinely in laboratories is a rapid and reliable method and because of its great reliability and sensitivity it can be used to monitor udder health. Thus for the control of mastitis SCC is an important tool. In the raw milk it has been shown that SCC can be measured by the Near infrared (NIR) (e.g., [Tsenkova et al 1999]). on-line Sensors that measure SCC are based on the principles of the Californian mastitis test [Whyte,D et al 2005]. The basic principle of these sensors is the gel-formation process, same as that of Californian mastitis test. In combination with EC the potential value of this sensor has been studied at the cow level. The detection model had an sensitivity of 80% when the threshold levels were set, The measurement of SCC online gave similar results as that of EC. When the detection models measuring SCC and EC were combined the performance of these models improved significantly[Kamphuis, C et al 2008].

Homogeneity

During clinical mastitis when the udder of the cow is infected there occurs visual changes in the milk. Before milking these visual changes in milk can be detected by checking first few squirts of milk. By analyzing these changes it is possible to detect whether the cow is mastitic or not. If the color of the milk is not white or the milk is not homogeneous, the cow is said to have clinical mastitis. Therefore for the detection of mastitis homogeneity of milk can be an interesting parameter.

Conclusion

It is very clear that mastitis is a significant disease occurring in the dairy cattle which in turn causes heavy economic losses to the farmers. It is necessary that proper managemental steps should be followed. The factors like poor hygienic and milking procedure, poor animal health service and lack of proper attention to health of the mammary gland are the important risk factors that increase the prevalence of mastitis. In order to elevate the problem of mastitis proper santitation along with regular screening by different cow side tests and treatment of mastitic cases should be followed. Further studies in this regard need to be carried out to elute this burden so as to minimize the damage caused by this disease.

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