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International Journal of Recent Scientific Research
Vol. 4, Issue, 5, pp. 543- 548, May, 2013

International Journal of Recent Scientific Research

ISSN: 0976-3031

REVIEW ARTICLE

BOVINE MASTITIS: A REVIEW

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ARTICLE INFO

Article History:

Received 13th, March, 2013
Received in revised form 17th, April, 2013
Accepted 26th, May, 2013
Published online 28th May, 2013

Key words:

Bovine mastitis, dairy animals, bacteriocins, pathogenesis, prevention and treatment

ABSTRACT

Bovine mastitis is a disease complex which occurs in acute, gangrenous, chronic, and subclinical forms of inflammation of the bovine udder, and is due to a variety of infectious agents. Animal care, hygiene, and management are important factors in this dairy cow disease of great economic importance. Mastitis continues to be the most costliest disease of dairy animals affecting the entire Dairy industries throughout the world. With overuse of antibiotics in bovine mastitis and continuing appearance of antibiotic-resistant bacteria, search for alternative substances for antibiotics is imminent. Over time, some bacteria have developed ways to dodge the effects of antibiotics. Widespread use of antibiotics is thought to have made evolutionary changes in bacteria that allow them to survive these powerful drugs. With many of the antibiotics already being used in bovine mastitis are also used in human medicine, and with the way antibiotic resistant bacteria can easily transfer their resistance traits to unrelated bacteria once inside the human body, this can be a major problem we have to face in the near future. Therefore, the bacteriocins produced by micro organisms may represent new antimicrobial peptides with potential applications in the prevention and treatment of bovine mastitis. Recent focus on managing subclinical mastitis and minimizing antibiotic use in food animals has led to a renewed interest in evaluating bacteriocins as a tool in managing mastitis. In this review we have focus on the overview of mastitis, direct and indirect measures corresponding to the diagnosis of infection, bacteriological analysis of milk and exhaustive information on infected quarters, pathogen involved, pathogenesis of the mastitis in dairy cows, existing antibiotic treatments and function of bacteriocin. An extensive review is also made on mastitis applications that exploit their attributes, potential drawbacks in their use, and current status of bacteriocin-based mastitis products, possible alternative for application of bacteriocins from bacteria in the prophylaxis, treatment and prevention of this disease.

INTRODUCTION

The general health and well being of individuals depends largely on meeting basic nutritional needs. Milk and fermented milk products such as cheese, cultured milks and yoghurt have formed an important part of daily nutrition, and the variety of products produced from milk has increased dramatically over the years, as modern food processing technologies have improved. An increase in global population coupled with the increasing demands for milk as an economic food and as an industrial raw food product has necessitated an increase in production by dairy farmers. Consumption of dairy products has also increased at similar levels with a sharper increase in recent years, primarily due to a larger personal income base for individuals (Mantovani *et al.,* 2002). In a commercial milking environment, dairy cattle need to be in perfect physical condition to maintain a high level of milk production. The risk of lesions and infections that develop in modern dairy farming has consequently increased. Low milk production has been attributed to a large extent to the control of diseases in dairy cattle, of which mastitis accounts for the largest economic losses on dairy farms in many countries in the world, including the USA, United Kingdom, Europe, Australia and South Africa (Petroviski *et al.,* 2006). Improving udder health and decreasing the incidence of udder infection and inflammation in dairy herds, will result in increased milk production as huge losses are directly or indirectly incurred through loss of milk during treatment periods, culling of cows and death of clinically infected cattle. Mastitis control programmes addressing various aspects of dairy farming such as feeding practices, animal husbandry, hygiene and general health care can contribute towards reducing the incidence of udder infections. Treating infection with antimicrobials can, in conjunction with good farming practices, assist in this endeavor to eliminate, or at least decrease, the incidence of mastitis infection within a dairy herd. “Mastitis” describes an inflammatory reaction in the mammary gland. The term comes from the Greek derived word elements *masto-* referring to the mammary gland and *–it is* meaning – “inflammation” (Blood and Studdert, 1999). Although “mastitis” could technically be used to describe any udder injury that may result in inflammation, it is generally accepted that the causative agents for the inflammatory reaction are microorganisms that have gained entry into the teat canal and mammary tissue. The extent of the infection that occurs as microorganisms multiply and proliferate within the mammary tissue determines the type

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of mastitis affecting the cow udder. Bovine mastitis is a disease complex which occurs in acute, gangrenous, chronic, and subclinical forms of inflammation of the bovine udder, and is due to a variety of infectious agents; animal care, hygiene, and management are important factors in this dairy cow disease of great economic importance. Mastitis continues to be the most costly disease of dairy animals. Clinical mastitis is characterized by sudden onset, swelling, and redness of the udder, pain and reduced and altered milk secretion from the affected quarters. The milk may have clots, flakes or of watery in consistency and accompanied by fever, depression and anorexia. The sub clinical mastitis is characterized by having no visible signs either in the udder or in the milk, but the milk production decreases and the Somatic cell count (SCC) increases, having greater impact in older lactating animals than in first lactation heifers. A negative relationship generally exists between SCC and the milk yield (Khan and Khan, 2006). Milk from normal uninfected quarters generally contain below 200,000 somatic cells /ml. A value of SCC above 300,000 is abnormal and an indication of inflammation in the udder. There is a plethora of evidence that the dairy cow milk has a natural level of 100,000-150,000 somatic cells/ml and higher SCC indicates secretory disturbance (Hillerton, 1999). In addition, mastitis impairs the quality of milk and milk products (Philpot, 2003). Field surveys of major livestock diseases have ranked mastitis as number one disease of dairy animals (Khan and Khan, 2006). Mastitis is considered to be the most costly disease of dairy animals affecting the dairy industry. Management strategies involve the extensive use of antibiotics to treat and prevent this disease. Prophylactic dosages of antibiotics used in mastitis control programmes could select for strains with resistance to antibiotics. In addition, a strong drive towards reducing antibiotic residues in animal food products has lead to research in finding alternative antimicrobial agents. In this review we have focused on the pathogenesis of the mastitis in dairy cows, existing antibiotic treatments, control measures and possible alternative for application of bacteriocins from bacteria in the treatment and prevention of this disease.

Pathogenesis

Mastitis in dairy animals occurs when the udder becomes inflammed and bacteria invade the teat canal and mammary glands. These bacteria multiply and produce toxins that cause injury to the milk secreting tissue, besides, physical trauma and chemical irritants. These cause increase in the number of leukocytes, or somatic cells in the milk, reducing its quantity and adversely affecting the quality of milk and milk byproducts. The teat end serves as the first line of defense against infection. From outside, a sphincter of smooth muscles surrounds the teat canal which functions to keep the teat canal closed (Murphy *et al.,* 1988). It also prevents milk from escaping, and bacteria from entering into the teat. From inside, the teat canal is lined with keratin derived from stratified squamous epithelium. Damage to keratin has been reported to cause increased susceptibility of teat canal to bacterial invasion and colonization (Bramley and Dodd, 1984). The keratin is a waxy material composed of fatty acids and fibrous proteins in the teat. The fatty acids are both esterified and non-esterified, representing myristic acid, palmitoleic acid and linolinic acid which are bacteriostatic (Treece *et al.,* 1966). The fibrous proteins of keratin in the teat canal bind electrostatically to mastitis pathogens, which alter the bacterial cell wall, rendering it more susceptible to osmotic pressure. Inability to maintain osmotic pressure causes lysis and death of invading pathogens (Murphy and Stuart, 1953; Treece *et al.,* 1966). The keratin structure thus enables trapping of invading bacteria and prevents their migration into the gland cistern (Habbit *et al.,* 1969). During milking, bacteria present near the opening of the teat find opportunity to enter the teat canal, causing trauma and damage to the keratin or mucous membranes lining the teat sinus (Capuco *et al.,* 1992). The canal of a teat may remain partially open for 1-2 hr after milking and during this period the pathogens may freely enter into the teat canal (Jones, 2006).

Mastitis-Causal Organisms

The causative organisms of mastitis in buffaloes have been reported to be Staphylococci, Streptococci, *Escherichia coli,* Pseudomonas spp., Corynebacterium, Mycoplasma, *Streptococcus dysgalactia*, and *Mycobacterium tuberculosis*. Among all the pathogens of bovine mastitis, *Staphylococcus aureus* is the predominant organism (Kapur *et al.,* 1992; Allore, 1993). The etiological agents of mastitis in buffaloes have been reported to be *Staphylococcus aureus*, *Staphylococcus hyicus*, *Staphylococcus epidermidis*, *Staphylococcus capotus, Streptococcus dysaglactiae, Streptococcus agalactiae, Streptococcus pyogenes and Corynebacterium bovis* (Ahmed, 1966; Ghumman, 1967; Qamar, 1992; Allore, 1993; Ahmad, 2001; Akram, 2002; Khan, 2002). The main etiological agents responsible for mastitis infections can be divided into different groups of organisms depending on the source of the organism involved. These include contagious pathogens, environmental bacteria, opportunistic bacteria and other organisms that cause mastitis less frequently (Philpot, 1999).

Contagious microorganisms are usually found on the udder or teat surface of infected cows and are the primary source of infection between uninfected and infected udder quarters, usually during milking. *Staphylococcus aureus* is the species most frequently isolated from bovine mastitis, a disease responsible for significant economic losses all over the world (Oliveira, *et al.,* 1998). The organisms that fit into this category include: *Staphylococcus aureus* (coagulase positive staphylococci), *Streptococcus agalactiae* and the less common sources of infection caused by *Corynebacterium bovis* and *Mycoplasma bovis* (Quinn, *et al.,* 1999).

Environmental pathogens are found in the immediate surroundings of the cow, such as the sawdust and bedding of housed cows, the manure of cattle and the soil. Bacteria include streptococcal strains other than *S. agalactiae,* such as *Streptococcus dysgalactiae*, *Streptococcus uberis* and *Streptoccous bavis*, *Enterococcus faecium* and *Enterococcus faecalis* and coliforms such as *Escherichia coli*, *Klebsiella pneumonia* and *Enterobacter aerogenes* (Schroeder, 2009). Mastitis caused by environmental organisms is essentially opportunistic in nature and becomes established if the immune system of the host is compromised or if sanitation and hygiene is not adequately practiced (Schukken *et al.,* 2009).

Opportunistic pathogens result in mild forms of mastitis and include coagulase-negative staphylococci. The coagulase test correlates well with pathogenicity and strains that are coagulase-negative are generally regarded as non-pathogenic

(Quinn, *et al.,* 1999). These staphylococci occur commensally and may be isolated from milk but usually illicit a minor immune response in cattle and infections caused are slight. They include *S. epidermidis*, *S. saprophyticus, S. simulans* (Nascimento, *et al.,* 2005) and *S. chromogenes* (Vliegher *et al.,* 2003) .

Many other bacteria and even yeasts may be responsible for causing mastitis, but are less common and occur if conditions in the environment change to increase exposure to these organisms. A condition known as “summer mastitis” occurs mostly in European countries in the summer months when wet, rainy conditions prevail. The source of infection is usually traced to an increase in exposure of the cows to flies in pastures that transmit infecting *Arcanobacterium pyogenes* and *Peptostreptococcus indolicus* strains and is more common in non-lactating cows (Sol, 1984). Mastitis caused by *Pseudomonas aeruginosa* is often traced to contaminated water sources and will result in a condition similar to coliform mastitis infections where endotoxemia occurs. *Nocardia asteroides* causes severe cases of mastitis resulting in fibrosis and permanent damage to mammary tissues (Quinn, *et al.,* 1999). Treatment is usually ineffective and has a high mortality rate occurs. The source of the infection caused by *Nocardia asteroides* is usually from the soil and could be prevented by ensuring that effective sanitation measures are enforced before treatment with intramammary infusions (Philpot and Nickerson, 1999). Less common causes of bovine mastitis include *Bacillus cereus,* resulting in peracute and acute mastitis and also the human pathogens *Streptococcus pyogenes* and *S. pneumonia* that causes acute mastitis and is accompanied by fever symptoms in the host (Quinn, *et al.,* 1999).

Role of Antibiotics in Mastitis

One of the important reasons for the failure of treatment of mastitis is the indiscriminate use of antibiotics without *in vitro* sensitivity of causal organisms. This practice of treating mastitis at one hand increases economic losses and on the other hand results in the development of resistances to commonly used antimicrobials (Owens *et al.,* 1997). For suitable antibiotic therapy, bacterial isolation and antibiotic sensitivity studies are always essential. Mastitis is considered as one of the major cause for antibiotics in dairy animals (Kaliwal *et al.,* 2011). The emergence of antimicrobial resistance among pathogens that affects animal health is of growing concern in veterinary medicine. Antimicrobial resistant pathogens in animals have also been considered as a potential health risk to humans from the possible pathogens. Mastitis is the single largest cause of antimicrobial use in dairy farms (Moon *et al.,* 2006). Consequently, this has severe economic implications for the milk producer, as such milk cannot be markets and simultaneously other cattle’s are easily infected. Cost of treatment and decrease in milk quantity also causes considerable loss (Anakalo *et al.,* 2004).

Antimicrobial activity

Bacterial strains with antimicrobial activity play an important role in the food industry, agriculture and pharmaceutical industry. Many bacterial species inhabit the ecological niches with a limited amount of nutrients. Because of this, many bacterial species produce a variety of antimicrobial substances, such as lactic acid, acetic acid, diacetyl, hydrogen peroxide and the other substances including enzymes, defective phages and lytic agents with potential importance for food fermentation and biopreservation (Tolinacki, *et al.,* 2010). Bacteriocin production seems to be aimed to compete against other bacteria which are present in the same ecological niche (Barefoot *et al.,* 1993; Dykes, 1995; Riley, 1998). Some of these inhibitory substances are active against food borne pathogens and they become the focus of research interest concerning their potential role as food preservatives. The ability of various bacteria to inhibit the growth of other bacteria is well documented (Hardy,1975; Tagg *et al.,* 1976). In many cases it was demonstrated that the antagonistic activity was attributable to molecules of a proteinaceous nature, termed bacteriocins. The first bacteriocins to be discovered were the colicins produced by *Escherichia coli*, and extensive knowledge is available concerning their genetics (Graaf, 1986; Belkum *et al.,* 1991). Use of either bacteriocin-producing LAB strains, which are generally regarded as safe (GRAS), or their bacteriocins in food production could have a positive effect on food preservation and safety. Bacteriocins produced by LAB have been classified on the basis of their size, chemical properties, mode of action and mechanism of export. Much of the interest in bacteriocin research also rests on its potential application in bacterial interference as a strategy for prevention of certain infectious diseases (Jack *et al.,* 1995). There are two main classes of Bacteriocins: the lanthionine-containing bacteriocins (class I) and the unmodified, heat stable bacteriocins (class II) (Cotter *et al.,* 2005). Class II bacteriocins are heterogeneous and may be further divided into four subgroups: (i) pediocin-like bacteriocins, (ii) twopeptide bacteriocins, (iii) cyclic peptides, and (iv) non-pediocin one-peptide linear bacteriocins (Cotter *et al.,* 2005). Most of the genetically characterized class II bacteriocin gene clusters are composed of three gene modules: a module that includes the structural and immunity genes, a transport gene module, and a regulatory gene module. The structural gene for the bacteriocin is cotranscribed with the corresponding immunity gene located downstream, although there are exceptions to this genetic organization (Franz et al. 1999; Franz *et al.,* 2000). Class III bacteriocins include large, heat labile proteins with a molecular mass of 30 kDa and higher. Many bacteriocins are capable of resisting inactivation at the high temperatures used in food processing and can remain functional within a broad pH range. Bacteriocins are usually inactivated by proteolytic enzymes in the human digestive tract and would be digested just like any other protein in the diet. Nisin, by far the best characterized bacteriocin of Gram-positive bacteria, is the only bacteriocin approved for use in foods. Worldwide, nisin is used in a variety of products including pasteurized, flavored and long-life milk, aged and processed cheeses, and canned vegetables and soups (Muriana and Luchansky 1993).

Prevention of Mastitis

While mastitis cannot be totally eliminated from a herd, the incidence can be held to a minimum. The key elements in the control of mastitis include: sound husbandry practices and sanitation, post-milking teat dipping, treatment of mastitis during non-lactating period, and culling of chronically infected animals. The efficacy of therapy during the non-lactating period has proved to be superior to that which can be achieved during lactation. Monitoring of somatic cell counts, prompt identification and treatment of mastitis in dairy animals help in the reduction of mastitis. Dry animal therapy can eliminate 70% of environmental streptococcal infections. The fundamental principle of mastitis control is that the disease is controlled by either decreasing the exposure of the teat to potential pathogens or by increasing resistance of dairy animals to infection. Jones (2006) has suggested approaching the treatment in the same way a surgeon approaches surgery. Wash hands with soap and water, wash teats and udder in sanitizing solution, thoroughly dry teats and udder with individual towels, dip teats in an effective germicidal teat dip. Allow 30 seconds of contact time before wiping off teat dip with an individual towel; thoroughly scrub the teat end with a cotton swab soaked in alcohol. If all four quarters are being treated, start by cleaning the teat farthest from you and work toward the closest teat, use commercial antibiotic products in single dose containers formulated for intramammary infusion. Dip teats in an effective germicidal teat dip after treatment.

Control measures of mastitis

Staphylococcus aureus infections remain the largest mastitis problem of dairy animals. Cure rate with antibiotic therapy during lactation is very low. Many infected animals become chronic eases and have to be culled. *Streptococcus agalactiae* respond well to antibiotic therapy and can be eradicated from dairy herds with good mastitis control practices, including teat dipping and dry animal treatment. *Streptococcus dysgalactiae* may live almost anywhere: in the udder, rumen, and feces, and in the barn. They can be controlled with proper sanitation and are moderately susceptible to antibiotics (Khan and Khan, 2006). The early findings have indicated that mastitis can be controlled by hygienic conditions in herds like keeping animals away from stagnant water, use of germicidal solution for washing udder before milking and culling of infected animals (Kurjogi and Kaliwal, 2011). Reduction in the incidence of mastits can be achieved by reducing the number of bacteria to which the teat end is exposed. The animal's environment should be as clean and dry as possible. The animal should have no access to manure, mud, or pools of stagnant water and calving area must be clean. Post milking teat dipping with a germicidal dip is recommended. Attempts to control environmental mastitis during dry period, using either germicidal or barrier dips, have been unsuccessful. Proper antibiotic therapy is recommended for all quarters of all animals at drying off; it helps to control environmental streptococci during the early dry period.

Treatment Strategies

The economic implication of mastitis as a recurrent disease in dairy farming warrants further research into developing new technologies in antimicrobial therapy. Phenotypic measures of mastitis resistance are usually classified into two groups: Direct measures, corresponding to the diagnosis of infection (bacteriology, observation of clinical cases), and indirect measures, which consist in a prediction of the bacteriological status of the udder based on inflammatory parameters (somatic cell counts, conductibility). The bacteriological analysis of milk is the most accurate direct criterion, because it provides precise and exhaustive information on infected quarters, pathogen involved. As a further approach to classical genetic analyses, epidemiological modeling, Quantitative Trail Loci detection and candidate gene approach, and developing functional genomics may be useful tools in understanding the genetic determinism of mastitis resistance (Rupp and Boichard, 2003).

Bacteriocins can be considered as an alternative and does offer some advantages over conventional antibiotic therapy. Increasing concerns for human health, primarily due to the emergence of antibiotic resistance in pathogenic bacteria, also necessitates the development of alternative anti-infective agents. Bacteriocins are usually active against specific bacterial strains based on target receptors on the surface of sensitive strains. When diagnosing mastitis, the causative bacteria needs to be clearly identified and a targeted approach for specific pathogens should be considered. Bacteriocins can kill susceptible organisms quickly by cell lysis. This rapid action could ensure that resistance is less likely to develop in pathogens. Antibiotics used are usually broad-spectrum, killing all Gram-positive or Gram-negative bacteria to which it is exposed to, not only those causing infection. Bacteriocins offer the advantage of a target-specific action. If a broader spectrum of activity is required, a combination of two or three bacteriocins could be considered to ensure that more than one pathogen be targeted during treatment. The lowest minimum inhibitory concentration (MIC) of the bacteriocin should be established, as this would reduce the amount of bacteriocin used in the treatment product. The bacteriocin should also remain active and should persist in the target environment for a given period of time in order to come in contact with potential pathogens.

The method of drug delivery in a treatment strategy for mastitis is important and a teal seal offers many advantages. Firstly it acts as a physical barrier and is prophylactic. By combining an antibacterial agent in a teat seal, the inhibitor is localized in the teat canal, targeting pathogens that may be present near the teat opening and thus prevent bacteria from colonizing the mammary tissue. Topical preparations can also be used and due to the lack of invasiveness are more easily accepted as a form of drug delivery. The persistence and stability of the bacteriocin on the surface of the teat skin is essential but should not cause irritation or an allergic reaction to further inflame the teat area. Bacteriocin-based products have been successfully tested in the past. Nisin has been used throughout the lactation period, while lacticin 3147 has been evaluated for use as a dry cow therapy in a teat seal formulation (Ryan *et al.,* 1998) and Nisin is also used as a teat disinfectant in the commercial product (Cotter *et al.,* 2005). Thus the route of administration, considering the teat-canal environment of the cow, as well as the production cycle of the cow are important considerations when determining the type of treatment product produced. Bacteriocins produced by LAB are considered to be GRAS (generally regarded as safe) and would therefore be more acceptable when compared to the antibiotics. Antibiotic therapy during lactation requires a withdrawal period, which results in economic losses due to wastage and loss of production time. Bacteriocin residues in milk are more acceptable as digestive enzymes easily destroy the peptides. Thus, the withholding periods would be significantly reduced if bacteriocin therapy were used instead of antibiotic therapy.

CONCLUSION

Considering the extensive costs of a disease such as mastitis to the dairy industry, research directed towards viable and safe alternatives should be considered. The emergence of antimicrobial resistance among the pathogens that affects animal health is of growing concern in veterinary medicine. However, any such incursion can be rapidly identified through appropriate surveillance utilizing sensitive and specific molecular diagnostic assays. Establishing an antibiogram of pathogens is very important from the clinical and economic view point. Bacteriocins can thus be viewed as a real treatment solution to augment other management strategies and reduce the amount of antibiotics used in the treatment of mastitis.

Acknowledgements

The authors are grateful to the Post Graduate Department of Studies in Microbiology and Biotechnology, Karnatak University Dharwad for providing the necessary facilities.

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