American-Eurasian Journal of Scientific Research 14 (2): 31-38, 2019
ISSN 1818-6785

DOI: 10.5829/idosi.aejsr.2019.31.38

Review on Bovine Mastitis in Dairy Cow

Desiye Tesfaye Tegegne

Animal Biotechnology Research Program, National Agricultural Biotechnology Research Center, Ethiopian Institute of Agricultural Research, P.O. Box: 249, Holeta, Ethiopia

Abstract: Bovine mastitis is a disease which occurs in acute, chronic and subclinical forms of inflammation of the bovine udder and is due to a variety of causative agents. Animal care, hygiene and herd management are important factors in this dairy cow disease of great economic importance. It 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 microorganisms 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 I have focused on the overview of mastitis, direct and indirect measures corresponding to the diagnosis of infection, pathogen involved, pathogenesis of the mastitis in dairy cows, existing antibiotic treatments and function of bacteriocin.

Key words: Bovine mastitis · Dairy cows · Bacteriocins · Pathogenesis · Prevention and Treatment

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 [1]. 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 [2].

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

Corresponding Author: Desiye Tesfaye Tegegne, Animal Biotechnology Research Program, National Agricultural Biotechnology Research Center, Ethiopian Institute of Agricultural Research, P.O. Box: 249, Holeta, Ethiopia.

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" [3]. 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 of mastitis affecting the cow udder [4].

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 which 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 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 [5]. 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 [6]. In addition, mastitis impairs the quality of milk and milk products. Field surveys of major livestock diseases have dairy animals (ranked mastitis as number one disease) [7].

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 [8].

Pathogenesis: *Staphylococcus aureus,* to cause mastitis initially must gain access to the mammary gland through the teat canal and then has to avoid removal by the flushing of the fluids during the milking processes. Therefore, the ability to adhere to the epithelial cells and extracellular matrix proteins is instrumental to colonize the gland and develop the pathologic process. The adhesion mechanism of *S. aureus* is complex and includes multiple proteins able to specifically recognize components of the microbial surface that recognize adhesive matrix molecules [9], allowing bacterial anchorage in normal and inflamed tissues [10].

Adhesive molecules are pivotal in the diffusion of *S. aureus* within and among herds, but they are only one of the several virulence factors involved in the pathogenesis of *S. aureus* infections. *S. aureus* infections can occur in at all stages of lactation, but clinical mastitis is more common during drying off. Once the bacteria adhere to the milk fat inside the udder it can float upwards deeper into parenchyma tissue of the udder [11]. *Staphylococcus aureus* has the ability to avoid phagocytosis by producing a polysaccharide containing mucus around itself causing the phagocytes not to recognize it. It is further shielded from the body's defenses by living intracellularty [12].

The extracellular defense mechanisms of the host cannot attack intra-cellular organisms and the lower intra-cellular pH reduces the efficacy of many antimicrobial drugs used for treatment of mastitis. Unlike most bacteria, *S. aureus* can resist the phagocytosis and can even multiply inside a phagocyte. It also uses the phagocyte as a vehicle to carry it deeper into udder tissue. When the phagocyte dies, the *Staphylococcus aureus* is released and it colonizes deep in the udder parenchyma [4]. Certain strains of *Staphylococcus aureus* may produce enzymes like coagulase, deoxyribonuclease, hyaluronidase, fibrinolysin, lipase and protease. Enzymes produced by *Staphylococcus aureus* destroy oxygen radicals and protect the bacteria against oxidizing agents such as lactoperoxidase, one of the humoral defense mechanisms of the udder [12]. The presence of coagulase and deoxyribonuclease correlates positively with the virulence of the bacteria and is used for identification purpose [8].

Various toxins are produced by *S. aureus* such as alpha, beta, gamma and delta hemolysin, leukocidin and enterotoxin gangrenous, of these the most destructive being alpha-hemolysin which can lead to gangrenous mastitis, which can be fatal to the cow [8].

Mastitis Causing 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 [13]. The etiological agents of mastitis in buffaloes have been reported to be *Staphylococcus aureus*, *Staphylococcus hyicus*, *Staphylococcus epidermidis*, *Staphylococcus capotus, Streptococcus dysglactiae, Streptococcus agalactiae, Streptococcus pyogenes* and *Corynebacterium bovis* [14]. 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 [15].

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 [16]. The organisms that fit into this category include: *Staphylococcus aureus* (coagulase positive staphylococci), *Streptococcus agalactiae* and the less common sources of infection are caused by *Corynebacterium bovis* and *Mycoplasma bovis* [8].

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 bovis*, *Enterococcus faecium* and *Enterococcus faecalis* and coliforms such as *Escherichia coli*, *Klebsiella pneumonia* and *Enterobacter aerogenes* [17]. 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 [18]. 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 [19]. 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* [20] and *S. chromogenes* [21].

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 [22]. 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 [8]. Treatment is usually ineffective and has a high mortality rate. 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 [15]. Less common causes of bovine mastitis include *Bacillus cereus,* resulting in peracute and acute mastitis and also the human pathogens *Streptococcus pyogenes* and *S. pneumoniae* that cause acute mastitis and is accompanied by fever symptoms in the host [23].

Role of Antibiotics in Bovine 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 [24]. For suitable antibiotic therapy, bacterial isolation and antibiotic sensitivity studies are always essential. Mastitis is considered as one of the major causes for antibiotics in dairy animals [25]. 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 [26]. 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 cause considerable loss [27].

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 [28]. Bacteriocin production seems to be aimed to compete against other bacteria which are present in the same ecological niche [29]. 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 [30]. 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 [31]. 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 [32]. There are two main classes of Bacteriocins: the lanthionine-containing bacteriocins (class I) and the unmodified, heat stable bacteriocins (class II) [33]. Class II bacteriocins are heterogeneous and may be further divided into four subgroups: (i) pediocin-like bacteriocins, (ii) two peptide bacteriocins, (iii) cyclic peptides and (iv) non-pediocin one-peptide linear bacteriocins [33]. 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 co-transcribed with the corresponding immunity gene located downstream, although there are exceptions to this genetic organization [34]. 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 [35].

Diagnosis of Bovine Mastitis: Early diagnosis is very imperative as a result of increased economic costs of mastitis. Some of the assays that are frequently employed to examine the milk quality through detection of the swelling of mammary gland and diagnosis of the infection and its causative pathogens include California mastitis test, flow cytometry, culture test and Polymerase Chain Reaction [36]. Mastitis-causing pathogens usually are identified by culturing techniques, but their disadvantages lies with prolonged periods of laboratory work and cost effective materials [23].

California Mastitis Test: The California Mastitis Test (CMT) is a cow-side test that is performed on dairy farms using a detergent to identify subclinical mastitis by an indirect estimation of the somatic cell count in milk. The detergent (bromocresol purple) breaks down the cell membrane of somatic cells and followed by the liberation and combination of nucleic acid which then generates a gel-like medium with thickness that is relatively equal to the number of leukocytes [37]. For reliable results, tests should be conducted just before milking after stimulating milk let down and discarding the foremilk. Managers of herds with high somatic cell count may have to cull heavier for mastitis, increase treatments for intramammary infections, increase efforts to avoid antibiotic residues in milk and cull animals, increase cost on facilities or milking equipment and improve management to reduce the spread of new infections. Thus, emphasis should be on proper milking techniques, improved sanitation, effective use of teat dipping and dry period therapy and maintenance of milking equipment. Lower somatic cell count should result in higher milk yields and better milk quality [38].

Culture Tests: The surest way of diagnosing mastitis is by directly isolating and identifying any pathogenic microorganisms which may be present in the milk. This can be achieved by cultural methods and a number of additional determinative tests. To obtain correct results and avoid contamination and hence bias, it is important to work as securely and as accurately as possible under the circumstances. Similarly, the procedure of routine mastitis testing should be standardized and work protocols instituted [37].

Molecular Biological Methods Used for Mastitis Diagnosis: Molecular biological methods used for mastitis diagnosis include various DNA-based identification assays which can be used for the characterization of pathogens at different phylogenetic levels according to the aim of the test and primer design. These methods can detect either DNA or RNA. While the extraction or detection of DNA is more common and often technically easier than that of RNA due to the higher stability of DNA than RNA. For this reason, the DNA-based detection assays can detect non-viable and/or inactivated pathogens in opposite to those assays targeting the mRNA which is less stable and therefore can detect only viable pathogen. On the other hand, the detection of the genes encoding antibiotic resistance does not necessary mean that the bacteria are resistant against antibiotics, but the detection of mRNA resulting from gene expression will deliver more accurate results [39].

Molecular Markers of Infectious Mastitis Inducers: A Deoxyribonucleic acid signature means the identification of unique DNA sequences in the genome of a particular organism, which is absent in all other, even the closely related microbes. These Phylogenetic markers help in bacterial characterization such as the *16S rRNA or 23S rRNA* genes [39]. Such highly conserved genetic sequences are usually the first choice for primer design. In opposite to those highly conserved markers, it is not common to depend on virulence genes alone for bacterial identification as they are highly dynamic among related bacterial species/subspecies due to their location on mobile genetic elements which can even be transmitted from one species to another. However, if the planned reaction aims to differentiate among different genotypes of the invading microbe, certain genomic hotspots, polymorphic sequences, intergenic spacers and accessory/ virulent genes can be selected for this purpose [40].

Polymerase Chain Reaction (PCR): Polymerase chain reaction is an *in vitro* amplification of unique organism specific target DNA sequences using sequence specific oligonucleotide primers and heat stable polymerase. The selected primers must have an exclusive sequence that bind specifically and selectively to previously defined DNA target sequence. The primers may either be designed to differentiate among members of the same species or to identify the organisms at subspecies level. By so doing, the primers allow the amplification and quantification of certain sequences. For the diagnosis of present pathogens, the primer target sequence must be highly conserved within all strains of the suspected species to avoid false negative results but variable among other species to avoid cross reaction resulting in nonspecific annealing leading to false positive results [41].

Different PCR systems were developed to offer a rapid, accurate and economic diagnosis of causative agents of mastitis. PCR can be applied on quarter, pooled - and bulk milk samples. The sensitivity of detection limit decreases with the more dilution (pooling/ mixing) of infected milk with healthy milk. The quarter milk samples deliver the most accurate data about the predominant pathogen in the farm with a clear higher level of sensitivity and specificity in comparison to pooled or bulk milk samples. On the other hand, the application of modern molecular tools in investigating pooled or bulk milk samples can deliver accurate data comparable with that data delivered when using quarter samples [41].

Treatment of Bovine Mastitis: The success of bovine mastitis therapy depends on the etiology, clinical presentation and antimicrobial susceptibility of the etiological agent among other factors [42]. Therapy failure in the management of mastitis could result from pathological changes that occur in the udder, etiology related factors, pharmacokinetic properties of the antimicrobial drugs, poor animal husbandry and inadequate veterinary services. However, the control of mastitis has been successfully achieved through the establishment of effective herd health control programs [43]. Antimicrobial agents are the main therapeutic tools for the treatment and control of mastitis. Among the main reasons of low efficacy of antibiotic treatment of mastitis cases is the resistance of the bacteria to antimicrobials.

Recently, several studies have been conducted to determine the antibacterial susceptibility patterns of mastitis pathogens isolated from clinical studies or submitted to diagnostic laboratories [44, 45].

Antimicrobial agents are widely used for the treatment of bovine mastitis, respiratory tract infections and diarrhea in cattle. During acute infections and outbreaks of infectious disease in groups or herds it is important to use an effective antimicrobial treatment as early as possible. This empirical treatment is generally based on knowledge of the resistance pattern of the different bacterial pathogens to antimicrobial agents used in the particular animal species. Antimicrobial resistance is an increasingly important problem among several bacterial species causing infection in animals and humans in recent year. The problem for some bacterial species is so critical that there is few treatment options left [46, 47]. The initial treatment of animals is commonly based on the experience regarding the expected resistance of the infectious agent. The fact that occurrence of antimicrobial resistance varies between countries and regions has the potential to complicate that matter. Furthermore, knowledge of expected resistance is limited by the small proportion of different bacterial pathogens from infected animals that actually are investigated for their antimicrobial resistance pattern [48].

Control and Prevention: A successful *S. aureus* control program will eliminate existing infections, prevalent new intra-mammary infections and have a system for on-going monitoring of the infection status of the herd [24, 49]. Eliminate existing infections, by using selective removal of chronic cases from the herd, dry cow treatment and therapy during lactation are the predominant methods used to eliminate existing *S. aureus* infections from dairy herds [43]. Culling of cows with chronic mastitis is one of the cornerstone recommendations of the original point of mastitis control programs and it achieves, both a reduction in herd prevalence and a reduction in the risk subsequent spread of infection [49].

The use of long-acting intramammary treatment at the time drying-off is another cornerstone of recommended mastitis control programs [50]. Dry cow treatment has a higher cure rate of existing infection than therapy during lactation. With the use of dry cow therapy before freshening, clinical mastitis at calving is reduced. Even with the use of long acting antibiotics, the risk of contamination of saleable milk is minimal. With all of these benefits, treatments of all quarters of all cows at drying off have become a standard recommendation [51].

Programs involving the selective treatment of dry cows have been attempted for several reasons such as the reduction of treatment costs, the preservation of protective minor infections and to prevent the development of resistant bacteria. Until more sensitive and specific diagnostic indicators are developed, as well as better methods to prevent new dry period infections, blanket dry cow therapy is recommended [51].

CONCLUSIONS

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 affect 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.

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