Volume 7 Issue 2 2021

ISSN 2454-3055

INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

Forum for Biological and Environmental Sciences

Published by Saran Publications, India

International Journal of Zoological Investigations Vol. 7, No. 2, 1041-1067 (2021)

International Journal of Zoological Investigations
ISSN: 2454-3055
Contents available at Journals Home Page: www.ijzi.net

Causes, Symptoms, Prevention and Treatment of Mastitis (Mast) in Dairy Cows

Samuel Jawahar B.[1*] and Princess Rajendran A.[2]

[1]Department of Zoology, St. Johns College, Palayamkottai, Tirunelveli, Tamil Nadu, India
[2]Department of Zoology, Rani Anna Government College for Women, Tirunelveli, Tamil Nadu, India

**Corresponding Author*

Received: 20th November, 2021; **Accepted:** 18th December, 2021; **Published online:** 31st December, 2021

https://doi.org/10.33745/ijzi.2021.v07i02.095

Abstract: A drop in milk output and a drop in milk quality result in financial hardship. Farmers should discard milk from cows with clinical instances of mastitis (MAST) and cows receiving anti-infective therapy according to the withdrawal period to allow the antimicrobials to exit the cow's system. MAST also alters the structure and composition of milk, resulting in lower cheddar output and a shorter period between uses of the resultant dairy product. Due to the additional time necessary to treat MAST animals, medical and veterinary expenditures will increase, as will labour costs and dairy productivity. Veterinary government support is a matter for concern, notwithstanding the financial problems, because research reveals that MAST can be unpleasant and cause discomfort in cattle. As a result, cattle with proven clinical MAST or active subclinical MAST have a greater treatment risk. Certainly, udder medical issues are frequently referring to as one of the top three reasons for dairy cow separation. Another reason in dairy groups is low milk production, which might be linked to MAST. Harmful MAST, a severe form of the disease that causes significant aggravation and septicemia, can potentially cause cow death. The widespread use of antibiotics (ABX) raised worries about the growth of ABX-resistant bacteria, prompting the dairy industry to restrict ABX use. As a result, alternative treatments for the prevention and treatment of bovine MAST have been investigated, notably natural compounds derived from plants and animals. This study examines bovine MAST in terms of risk factors, management, and therapies, as well as developing therapeutic options for the treatment of bovine MAST.

Keywords: MAST, Nanoparticles, Herbal medicines, Antibiotics, Mastitis

Citation: Samuel Jawahar B. and Princess Rajendran A.: Causes, symptoms, prevention and treatment of mastitis (MAST) in dairy cows. Intern. J. Zool. Invest. 7 (2): 1041-1067, 2021.
https://doi.org/10.33745/ijzi.2021.v07i02.095

Introduction

Among bovine illnesses, MAST has a significant impact on animal welfare as well as the financial system (Harmon, 1994; Jones and Bailey, 2009; Cha *et al.,* 2011; Contreras and Rodrguez, 2011; Bardhan, 2013; Sinha *et al.,* 2014; Abebe *et al.,* 2016; Izquierdo *et al.,* 2017; Aghamohammadi *et al.,* 2018; Das *et al.,* 2018; Cheng et al., 2019). The inflammation of the mammary glands/udder in cows is known as bovine MAST. The disease is caused largely by bacterial infections and is classified into several types depending on epidemiology, including infectious and

environmental MAST (Garcia, 2004). The former is caused by infectious microorganisms (MOs) such as *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Mycoplasma* spp., which are spread from an inflammatory cow to a healthy cow during milking via bacterial reservoirs such as hands, towels, and/or the milking equipment.

Environmental MAST, on the other hand, is caused by MOs that occur often outside of the milking parlour, i.e., the causative MOs come from the cow's surroundings, which include bedding material, dirt, dung, faeces, and stagnant water (McInerne *et al.,*1992; Garcia, 2004). Furthermore, it has a negative influence on both the composition and the value of milk (Halasa *et al.,* 2007; Kalinska *et al.,* 2017; Cobirka *et al.,* 2020). Environmental MAST is greatly influenced by control methods (Garcia, 2004), necessitating the use of more advanced technological and organic equipment, as well as suitable encouragement and rewards. Farmers and field veterinarians must work in accordance with legal guidelines when using antimicrobials that are mandated (Klaas and Zadoks, 2018).

Massive advancements in managing MAST were accomplished throughout the last century; nevertheless, changing population dynamics, herd form, and more stringent processing requirements have rendered MAST a complicated illness that continues to be a major headache for the dairy industry. As a result, extensive research within the neighbourhood is also required (Ruegg, 2017). MAST is a major financial problem in farm animals and buffalo in India (Das *et al.,* 2018), Canada (Aghamohammadi *et al.,* 2018), Germany (Hamann, 2001), The United Kingdom (Bennett *et al.,* 1999), The Netherlands (Hogeveen *et al.,* 2011), and The United States of America (Hadrich *et al.,* 2018).

Bovine MAST is associated with a daily loss of 1 to 2 litters of milk in the first weeks after commencement, and a total loss of 100 to 552 kg during the lactation, depending on the parity and time of incidence. MAST also has a long-term influence on milk output, since cows will no longer be able to reclaim their peak milk yield during the last portion of the lactation (Rajala-Schultz *et al.,* 1999). Despite various improved control methods in farm animals and buffalo raising inside the dairy sector, MAST remains a terrifying disease and one of the most common financial issues faced by farmers and dairy owners. India is at the top of the milk-producing countries (farm animals and buffalo milk combined). MAST causes a monetary loss of Rs. 575 million a year in India, and it reduces milk consumption by 21% (Bardhan, 2013). Furthermore, the consumption of MAST-affected milk may be harmful to individuals since antibiotic resistant bacteria may be transferred through contaminated unpasteurized milk; hence, it is a major public health problem (Oliver and Murinda, 2012).

Furthermore, health hazards connected with increased microbial resistance and ABX residues in milk have increased consumer demand for natural products, as they believe that foods produced through conventional agricultural systems are healthier and safer to consume (Ruegg, 2009). Due of zoonotic risks, MAST milk cannot be consumed and therefore cannot be sold, resulting in significant financial losses. Infected udder lowers the price of animals on the market and places a financial strain on the owner due to treatment costs (Gonzalez and Wilson, 2003; Seegers *et al.,* 2003). Although the link between MAST and pathogenic MOs was established in 1887, the most common infections were identified most effectively during the 1940s.

The discovery of the multi-factorial aetiology of bovine MAST in the 1960s cleared the way for more MAST research (Singh and Singh, 1994; Noguda *et al.,* 2018) such as molecular epidemiology of the causative pathogens; comparative strategies for identifying the pathogens on a subspecies level; virulence gene arrays; whole genome sequencing; and investigations of *in vitro* antibiotic susceptibility pattern. As days goes, ABX (penicillin) medicine

grew more widely available until 1945; nevertheless, it lost its effectiveness against all infections that cause MAST. Control methods should aim to reduce the pre-calving time in heifers in order to reduce the risk of MAST in later phases (Naqvi *et al.,* 2018).

Subclinical MAST and IMIs in heifers at some time during calving are often caused by significant pathogens, such as coagulase-negative *Staphylococci*, which are the most common cause of heifer MAST. Many factors impact IMIs in early lactation, including the type of the disease, pathogen virulence, calving time, infection/cure duration, host immunity, pregnancy status, and managemental methods, as well as chance linked to season and herd location. A short-term prepartum ABX treatment is an effective way to manage heifer MAST, but it's almost ever recommended owing to the long-term negative effects on udder health and milk production, lowering farmers' earnings (De Vliegher *et al.,* 2012). MAST detection is the most important need of the dairy industry for simple milk production, not only for financial reasons and public health concerns, but also for animal welfare reasons. Early, rapid, and accurate diagnosis is desired for MAST prevention or early identification for control or therapeutic purposes.

Traditional techniques are clearly inexpensive, simple, surprisingly available, and subject relevant, but they are typically non-unique. Superior inspections are expensive, requiring technical expertise as well as complex infrastructure and equipment, yet they are typically accurate and unique for various MAST types (Swarup *et al.,* 1989; Malik *et al.,* 2016; Hussein *et al.,* 2018; Chakraborty *et al.,* 2019). Blanket dry cow treatment, targeted culling, and well-defined biosecurity standards are all effective ways to control and prevent the return of virulent *Streptococcus agalactiae* and *Staphylococcus aureus* strains (Kefee, 2012). Furthermore, a combination of antibiotic treatment and culling of non-responsive cows resulted in a decrease in transmission rate and IMMS (Halasa, 2012).

For the treatment of MAST, a variety of traditional and advanced therapeutic methods are available, including ABX, vaccination, nanoparticle (NPs)-based therapy, natural therapy, and bacteriocins (Gomes and Henriques, 2016). Various retailers contribute to the reduction of udder infections, including MAST in cows, as well as to the improvement of milk quality (Skowron *et al.,* 2019). ABX treatment and immunisation are the most often utilised methods for MAST treatment. Extensive and uncontrolled use of ABX for treatment, along with the formation and persistence of biofilm-related ABX resistance in MAST, has resulted in a decreased response to antibiotic treatment (Park *et al.,* 2012; Babra *et al.,* 2013). Although immunisation is ineffective against bovine MAST because so many MOs are involved in its formation, *Staphylococcus aureus, Streptococcus uberis*, and *Escherichia coli* have been identified as the most important targets for vaccine development (Wilson *et al.,* 2009; Bradley *et al.,* 2015; Collado *et al.,* 2016; Cote-Gravel and Malouin, 2019; Ashraf and Imran, 2020).

Due to the obvious ABX's and vaccines' flaws, a slew of other treatment options has arisen to fill in the gaps. Few superior healing mechanisms or methods that might be promising for the prevention of MAST include NPs production and bacteriocins [antimicrobial peptides (AMP)] (Castelani *et al.,* 2019; Godoy-Santos *et al.,* 2019). The present evaluation discusses a variety of aspects of MAST/IMIs, with a focus on the disease's genesis, rapid incidence, diagnosis, control, and improvements in treatment and the development of innovative medicines for combating this important disease that affects bovine populations and dairy herds (Fig. 1).

MAST causing MOs:

The majority of infections that cause clinical bovine MAST are found in the environment. Contagious agents, on the other hand, are mostly associated with subclinical illnesses (Martin *et al.,* 1997; Cheong *et al.,* 2008; Ryan and Adley, 2010;

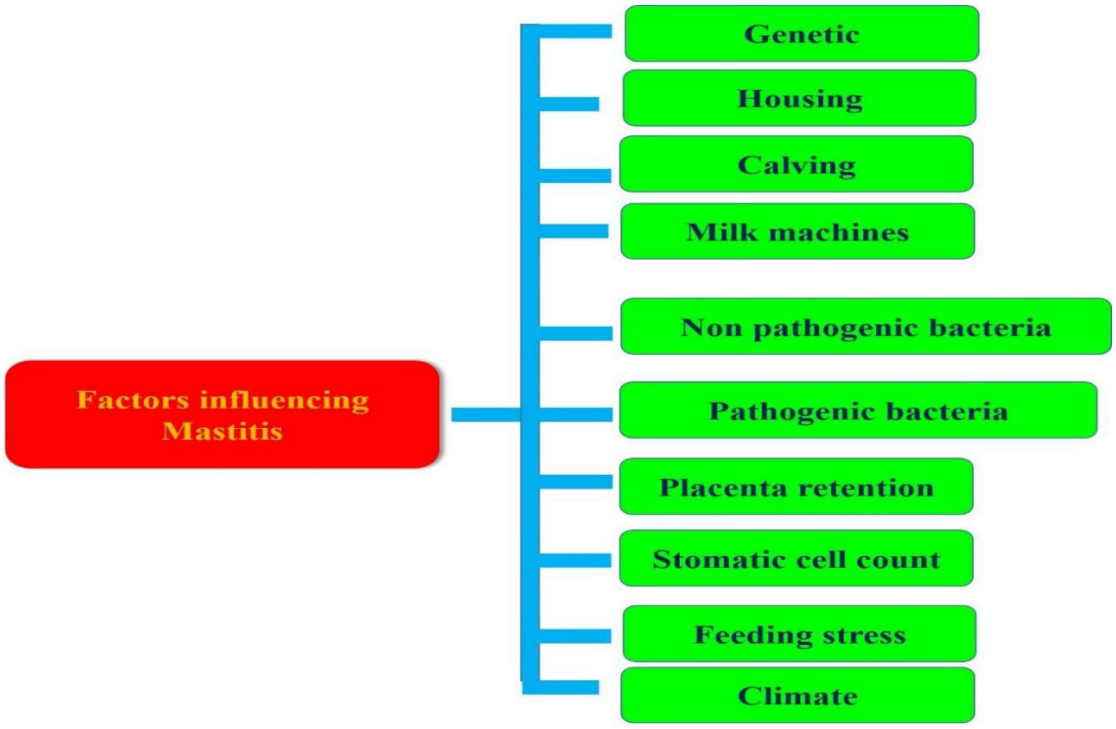

Fig. 1: MAST Influencing Factors.

Ranjan *et al.,* 2011; Abebe *et al.,* 2016; Mekonnen *et al.,* 2017; Klaas and Zadoks, 2018; Dufour *et al.,* 2019; Ngu Ngwa *et al.,* 2020). MAST is a multi-etiologic illness caused by bacteria, with clinical, subclinical, contagious, and environmental MAST being the most common. The bacteria most frequently involved are Yeast, *Nocardia*, *Yersinia ruckeri*, *Staphylococcus intermedius*, *Staphylococcus aureus*, *Vibrio fluvialis*, *Sphingomonas paucimobilis*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Kytococcus sedentarius*, *Peptococcus indolicus*, *Trueperella pyogenes*, *Mycobacterium bovis*, *Bacillus cereus*, *Escherichia coli*, *klebsiella pneumonia*, *Streptococcus canis*, *Aeromonas hydrophila caviae, Arcanobacterium pyogenes*, *Klebsiella oxytoca*, *Staphylococcus hyicus*, *Enterobacter aerogenes*, *Staphylococcus chromogenes*, *Serratia liquefaciens*, *Staphylococcus hyicus* and *Pasteurella* spp. (Williamson and Di Menna, 2007; Chen *et al.,* 2012; Verjan García *et al.,* 2015; Bi *et al.,* 2016; Levison *et al.,* 2016; Carvalho-Castro *et al.,* 2017; Vakkamäki *et al.,* 2017; Paşca *et al.,* 2017; Abdalhamed *et al.,* 2018; Shinozuka *et al.,* 2018; Zhang *et al.,* 2018; Dufour *et al.,* 2019; Tarazona-Manrique *et al.,* 2019; Ngu Ngwa *et al.,* 2020).

Staphylococcus aureus, *Streptococcus dysgalactiae* and *Streptococcus agalactiae* are among the infectious pathogens. The most common organisms are *Staphylococcus aureus*, whereas the most common environmental pathogens are members of the Enterobacteriaceae family, including *Escherichia coli* and *Streptococcus uberis* (PeterssonWolfe *et al*., 2010; Dufour *et al*., 2019). In clinical MAST, Agalactiae is the most frequent Gram-positive bacteria, followed by *Staphylococcus aureus,* with *Proteus* spp., *Brucella* spp., *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Klebsiella* spp., *Staphylococcusintermedius*, and *Escherichia coli* being the most identified Gram-negative bacteria (Kefee, 2012; Cortinhas *et al.,* 2016; Dalanezi *et al.,* 2020). Because *Streptococcus agalactiae* and *Staphylococcus aureus* are disseminated mostly by contact, herd biosecurity is an essential preventative strategy for reducing and eliminating reservoirs (Fig. 2).

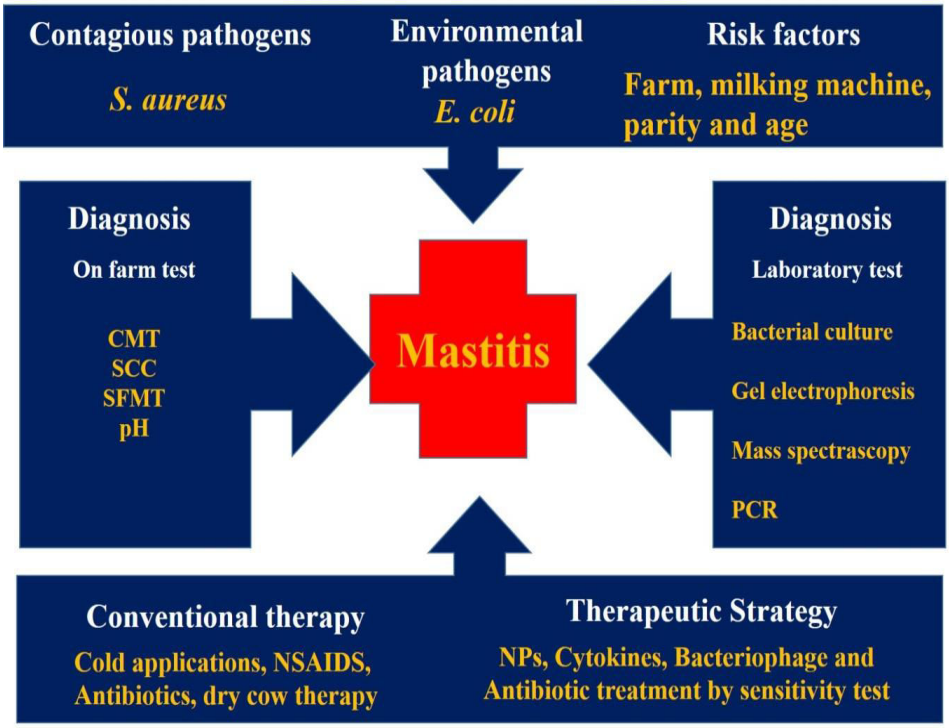

Fig. 2: MAST-causing bacteria in dairy cows.

The majority of microbial infections can induce both clinical and subclinical inflammation. *Trueperella pyogenes*, on the other hand, is responsible for only clinical inflammation (Malinowski *et al.,* 2006). *Staphylococcus aureus*, enteric bacterium species, and *Escherichia coli* are the most common causes of milk loss in mother cows. Infections by *Streptococci* spp., *Trueperella pyogenes*, *Staphylococcus aureus*, enteric bacteria spp., and *Escherichia coli* cause significant losses in older cows (Grohn *et al.,* 2004). *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Streptococcus uberis* are the most prevalent infections that cause inflammation, but *Eubacteria bovis* is less frequently involved (Wernicki *et al.,* 2014; Vakkamaki *et al.,* 2017). Coagulase-negative Staphylococci and their function in causing inflammation should also be properly considered (Krukowski *et al.,* 2001). Wilson *et al.* (1997) found that *Streptococcus agalactiae*, along with other pathogens such as *Prototheca* sp., *Streptococci* spp., and *Trueperella pyogenes*, is linked to the majority of instances of inflammation. Coliforms, CAMP-negative *Streptococci* spp., *Trueperella pyogenes*, *Streptococcus agalactiae*, fungi, and *Prototheca* spp. cause inflammation in its most severe form when infections are present (Wilson *et al.,* 1997; Bronislaw Malinowski *et al.,* 2006).

Richrd Steele and McDougall (2014) discovered *Eubacterium* spp. (40 per cent) and *Staphylococcus aureus* (32 per cent) as the most prevalent isolates in cases of sub-clinical inflammation in New Island. *Prototheca* spp. are infective algae and opportunistic infections that induce inflammation in farm herds and have the potential to cause animal illness (Alves *et al.,* 2017). *Staphylococcus aureus* is the most frequent MOs associated with inflammation (McParland *et al.,* 2019). Magro *et al.* (2018) reported penicillin-resistant *Staphylococcus aureus* (CC22-MRSA-IV) as IMMS MOs. MRSA was identified as an epidemic UK-EMRSA-15 grouping in CC22 after genotyping with DNA microarrays.

B-lactam and macrolide resistance genes were found in these isolated isolates. Milkers and farm cows provided isolates, suggesting that animal illness may be reversed. In thirteen of the total samples obtained from farm cows, routine sampling and analysis of milk revealed the presence of inflammation-causing bacteria. The most frequent pathogens discovered among the isolated pathogens were *Staphylococcus aureus*, *Streptococci* spp., *Trueperella pyogenes*, and *Corynebacterium bovis* (Cvetnic *et al.,* 2016).

Clinical significance of MAST:

MAST can be classified as infectious or environmental MAST, and they are caused by a wide range of infections. In addition, MAST can be categorised as either clinical or subclinical in nature (Garcia, 2004; Abebe *et al.,* 2016). Any increase in the amount of moisture and pollutants in the barn's environment will increase the load of pathogens in the environment. One study found a 74.7 per cent prevalence of MAST at the herd level and 62.6 per cent prevalence at the cow level. In terms of subclinical and clinical MAST, the former appears to be responsible for the majority of instances (59.2%) compared to the latter (3.4%). (Garcia, 2004; Abebe *et al.,* 2016).

Clinical MAST can be identified largely via visual signs such as redness in the afflicted half or entire breast, warmth, swelling, discomfort upon biting, milk clots, discoloration, and a change in milk quality. Udder inflammation is the most common symptom. Environmental infections that include coliforms are the most common causes of clinical MAST. Four hundredth of the 20,000 clinical MAST cases in The Netherlands were caused by *Streptococcus uberis* and *Streptococcus dysgalactiae*, 30% by *Staphylococcus aureus*, and half-hour by *Escherichia coli* (Steeneveld *et al.,* 2011).

During some conditions, the cow's mammary may exhibit shrivelled status as well as inflammatory resistance (Fig. 3). Such circumstances include long-term antibiotic medication to the mother, a greater frequency of mammalian fungal infection caused by mineral-vitamin and inhibitor insufficiency, nutritional imbalance, and bad environmental conditions such as weather fluctuations (Wawron *et al.,* 2010). Kumar *et al.* (2010) investigated the incidence and cost of clinical MAST.

In comparison to clinical MAST, there are no clinically evident symptoms in subclinical MAST, however, a change in milk composition might be an indication. As a result, it is identified and verified by a laboratory analysis of milk or an animal-side test such as the Coliform MAST Test, which is followed by a laboratory isolation of the cause. In a healthy cow, the Somatic Cell Count (SCC) in the milk should be less than 200,000 per millilitre. White blood cells (WBCs) infiltrate neutrophils and macrophages into mammalian tissue as a result of inflammation (Akers and Nickerson, 2011). *Streptococcus agalactiae* is typically found within the mammalian mammary gland, where it produces long-term infections with greater SCC (Kefee, 2012).

The immune response of the host to pathogenic microorganisms that damage the udder causes MAST (Gurjar *et al.,* 2012). The bacteria balance in a healthy udder is typically favourable. The microbiota of the IMMS is a complicated colony comprising various MOs (Rainard, 2017; Andrews *et al.,* 2019). In a healthy udder, the commensal mammary microbiota plays a crucial role in immunological homeostasis (Derakhshani *et al.,* 2018). As a result, a change in the udder microbiota's diversity may have an impact on MAST. The normal microbiome of the udder is an important factor to investigate when diagnosing MAST because healthy quarters include some bacteria. In udders, bacteria such as *Ruminococcus*, *Oscillospira*, *Roseburia*, *Dorea*, *Prevotella*, *Bacteroides*, *Paludibacter*, and *Bifidobacterium* are prevalent. MAST is caused by any udder or teat assault or congenital anomaly, such as a teat fistula, a teat spider, a leaky teat, or udder sores that expose the udder to external MOs or cause milk retention (Rambabu *et al.,* 2011).

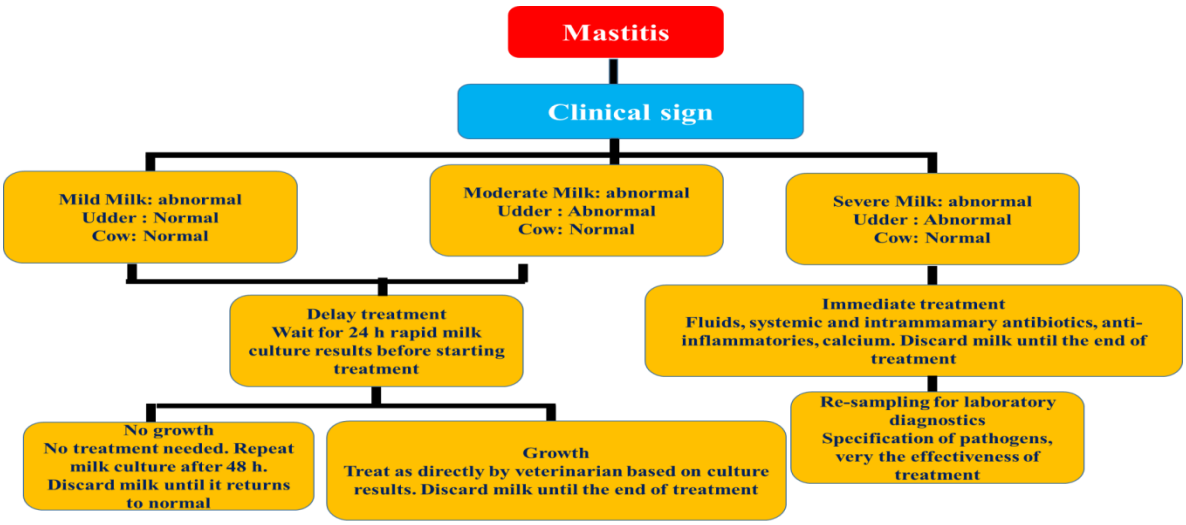

Fig. 3: MAST clinical signs and symptoms.

Severe inflammation was seen in MAST-affected tissue, as well as significant reductions in the alveolar epithelium and lumen, as well as an increase in stromal connective tissue and leucocytosis (Nickerson *et al.,* 1995). External infections are exposed to the udder, or the udder's internal defences are weakened. The presence of *Staphylococcus* spp. or *Escherichia coli*, as well as disturbance of the normal microbiome, are characteristics of the clinical form of MAST.

According to scientists, MAST develops and spreads as a result of pathogen-induced alterations in the normal microbiota or antibiotic therapy that lasts too long (Falentin *et al.,* 2016). According to a comprehensive molecular epidemiological study, the majority of dairy cattle in the United States had more than 10 coagulase-negative *Staphylococcus* spp., which were identified at different stages of lactation (Wuytack *et al.,* 2020). MAST is the consequence of numerous factors interacting at the host level, and it is a complex and damaging effect. Pathogens, their development patterns in the udder parenchyma, signalling pathways that cause clinical symptoms, and other molecular processes mediated by pathogen-associated molecular patterns are all implicated. Initiating udder inflammation induced by microbial infections, as well as a range of environmental factors, the host's pattern recognition receptors, including as Toll-like receptors, NOD-like receptors, and RIG-like receptors, make this feasible. As a result, a well-coordinated approach to diagnosis and management of this life-threatening disease is essential (Bhattarai *et al.,* 2018).

MAST Classification:

Paying care to the cows' health always pays off. When diagnosing MAST, it is essential to understand how bad the problem is. The MAST grading system (Fig. 4) is a great tool for evaluating the severity of MAST infection. Because a dairy employs a large number of people, it is important that the milkers, who are often the first to notice MAST, understand its seriousness. The chart is used to develop a standardised method and to incorporate training for all dairy employees. Using the chart, milkers may determine the exact measures to take. They know to take a sample for testing in a mild or moderate case, and they know to notify the herdsman immediately away in a severe case. If a farm can culture (on-farm or with their veterinarian) and have results within 24 h, they may be able to

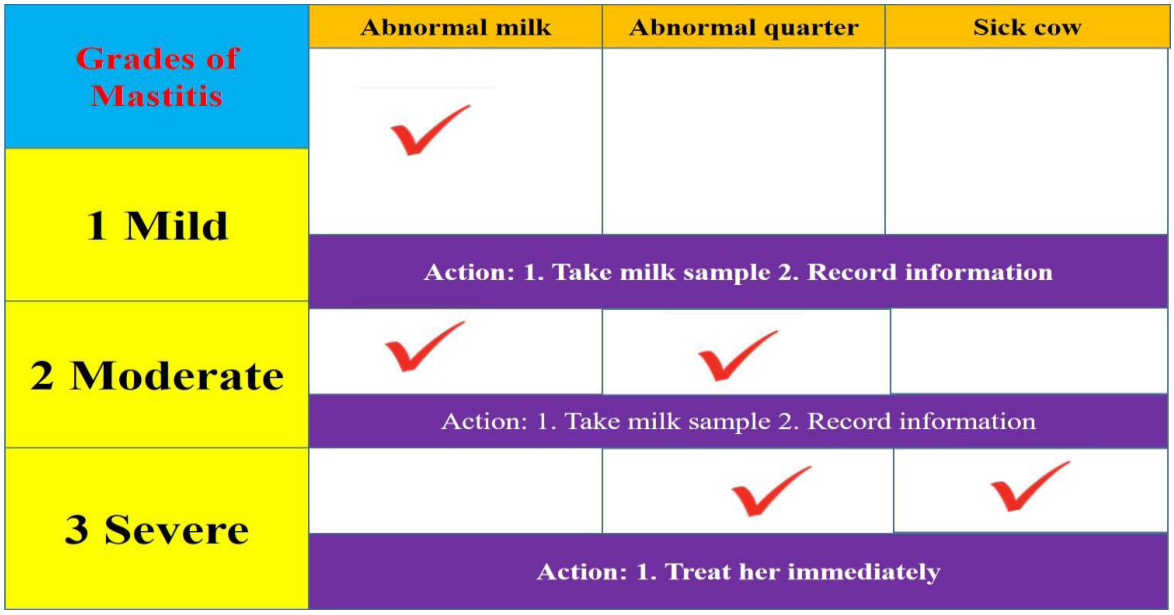

Fig. 4: MAST Classifications.

segregate mild and moderate cases to the hospital pen and postpone treatment until they have more information (Pyörälä and Pyörälä, 1998; Ruegg *et al.,* 2009; Zigo *et al.,* 2021).

Economic significance:

In addition to the cost of medication and other expenses, both clinical and subclinical MAST result in milk loss since it must be discarded (Halasa *et al.,* 2007; Kumar *et al.,* 2010). Subclinical MAST causes three times as many productivity losses as clinical MAST, accounting for 60-70 per cent of all MAST-related economic expenditures due to infections (De Vliegher *et al.,* 2012; Sinha *et al.,* 2014). Sinha *et al.* (2014) investigated the prevalence and economics of subclinical bovine MAST in India's Central Region using dairy cows. Milk value loss accounted for about 49% of MAST losses, while veterinary expenses accounted for 37%. The cost of treating an animal includes both the cost of medicine (31%) and the cost of services (5.5 per cent). Due to their high production potential, which was hindered during the MAST period, cross-bred cattle losses were much higher.

Frequently used MAST diagnostic tests:

Modern diagnoses are quantitative, highly specific, and sensitive, whereas traditional MAST diagnostic procedures are frequently qualitative, with lesser specificity and sensitivity (Godden *et al.,* 2017; Hussein *et al.,* 2018; Chakraborty *et al.,* 2019). At the species and subspecies levels, advanced molecular techniques based on phenotyping and genotyping procedures enable rapid and specific identification methods for MAST-causing infections (Gurjar et al., 2012). To choose the optimal antibiotic for medicinal purposes and to select the best processing technique for dairy products in particular, it is important to identify the type of bacteria. For this reason, identification (automated) methods such as VITEK identification cards are available, which provide consistent bacterial identification findings (Harjanti *et al*., 2018).

According to Kandeel *et al.* (2018), even if there is no overt clinical MAST, all dairy calves brought to any veterinary facility should be treated as if they have IMMS infection. Chakraborty *et al.* (2019) have reviewed many advancements in diagnostics appropriate for early and accurate MAST diagnosis, including phenotyping (general kind of testing) and genotyping (specialised type of testing). The

former comprises physico-biochemical, non-specific cultural, and proteomics testing, while the latter includes a particular culture, polymerase chain reaction (PCR) and its many variants (e.g., qRT-PCR) (Behera *et al.,* 2018), loop-mediated isothermal amplification (LAMP), and lateral flow assays (Sheet *et al.,* 2016; Barreiro *et al.,* 2017; Griffioen *et al.,* 2020).

A popular diagnostic biomarker for evaluating bovine MAST is haptoglobin (acute phase protein) (Kalmus *et al*., 2013). A label-free chemiluminescence bioassay based on magnetite nanoparticles was demonstrated in a study for the early, sensitive, and rapid detection of haptoglobin at clinically relevant levels in milk, resulting in quantitative detection of haptoglobin with a detection limit of 0.89 pg/ml (Nirala *et al.,* 2020). The oxidative state of animals with mammary gland inflammation in cows has been studied (Kleczkowski *et al.,* 2017). The synthesis of many inflammatory mediators, as well as reactive oxygen species, is involved in MAST-related inflammation (Turk *et al.,* 2017). Increased levels of inflammatory and oxidative mediators have been related to MAST. The levels of interleukins in the blood, tumour necrosis factor (TNF), acid glycoprotein (alpha-1 AG), and haptoglobin have all altered considerably (Kleczkowski *et al.,* 2017).

Differential protein expression in subclinical and clinical MAST was previously investigated using the cow serum proteome. In both preclinical and clinical situations, the comparative analysis assisted in assessing the systemic inflammatory and oxidative stress response. The findings of the study show that vitronectin, an inflammatory protein, is overexpressed in both subclinical and clinical MAST. As a result, vitronectin is an important mediator in the progression of MAST and can be utilised as a biomarker to diagnose MAST in its early stages (Turk *et al.,* 2012). In clinical and subclinical MAST, serum paraoxonase-1 activity was measured to assess systemic inflammatory and oxidative stress responses (Kovacic *et al.,* 2019).

Paraoxonase-1 activity was significantly lower in rats with clinical and subclinical MAST than in the control group, according to the findings of Kovacic *et al.* (2019). We may deduce that subclinical MAST-induced oxidative stress and inflammation significantly decreased paraoxonase-1 activity in the blood and milk of infected cows (Nedic *et al.,* 2019). As a consequence, the activity of paraoxonase-1 might be utilised as a biomarker to detect MAST in the early stages. The virulence of the causative agent determines the pathogen-invading mammary glandular response. Furthermore, the causative agent's infectivity is influenced by the microbial environment as well as the host (relative). As a result, MAST epidemiology differs depending on infections, host factors, and environment (Klaas and Zadoks, 2018). Despite the fact that the origins and epidemiology of this specific inflammatory illness of the mammary gland in food animals are well established, the difficulty of properly diagnosing the ailment remains a significant challenge (Sordillo, 2011).

Conducting research based on molecular epidemiology can thoroughly characterise the routes of transmission, sources, and prognosis of numerous diseases that cause MAST in cattle. Understanding how viruses evolve to evade host defences might aid our understanding of the host adaptation process (Zadoks *et al.,* 2011). Pathogen persistence may also be assessed more efficiently by identifying the allelic profiles of virulence or house-keeping genes, and molecular epidemiology research can help with this. In this respect, it's important to note that the development of the multilocus sequence typing (MLST) technique has aided these molecular epidemiology studies (Sordillo 2011; Shibata *et al.,* 2014). The Internet of Things (IOT) has recently been used to identify MAST and foot and mouth disease (FMD) using Neural Networks and smart sensors, which may help in a better way for a significant reduction of both diseases (Vyas *et al.,* 2019). This can benefit the Agriculture and Dairy Industries in a number of ways by reducing the poor quality of milk

supplied by cows and, as a result, lowering dairy processing expenses.

MAST treatment:

Understanding the pathophysiology of infection, devising innovative sensitive tests for early screening, implementing suitable management practises to reduce the risk of transmission, and avoiding uninfected animals are all necessary components of an effective MAST control programme. Antibiotic residue in milk and antimicrobial resistance must be addressed by a control programme that includes the strategic use of antimicrobials (Ruegg *et al.,* 2017). The underlying cause of udder infection must be identified before pharmaceutical therapy may begin.

Teat and udder affections including teat fistulas, leaking teats, teat spiders, and udder sores require immediate attention. Because these affections break the protective barrier and expose the teat canal or udder to external MOs, early treatment is necessary. According to one study, the number of cattle teat surface surgical affections, as well as the number of teat surgical affections in buffaloes, was significantly higher than the number of teat surgical affections in other areas (Misk *et al.,* 2018). Treatment was not necessary for all teat and udder issues. A total of 24 per cent of the 282 cow and buffalo cases went untreated, while 73.8 per cent were treated using medicinal and surgical treatments (Misk *et al.,* 2018).

During milking season, which is a high-risk period for new IMIs, the majority of prophylactic measures are centred (Keefe, 2012). Disinfecting the teat before and after milking, as well as full milk-out, can improve the health and hygiene of dairy cows (Keefe, 2012; Yu *et al.,* 2017). Heifers in early lactation are more likely than cows to acquire clinical and subclinical MAST due to their management and physiological state. Improved prepartum management measures in the areas of environmental and animal hygiene, such as the use of teat sealants and antiseptics, vector control, separation of heifers from older cows, and reduced MAST milk feeding to calves, are recommended to minimise heifer MAST (McDougall *et al.,* 2009). Although prepartum heifer treatment resulted in a much higher cure rate, minimal milk loss, and a lower risk of antibiotic residues, lower SCC and high milk production are not always achieved in all herds (Borm *et al.,* 2006). Furthermore, throughout the first 200 days of the first lactation, IMMS treatment showed no influence on preparturient heifer reproductive performance (Borm *et al.,* 2006).

Lactational therapies in preclinical IMIs of dairy cows led in decreased transmission rates of *Streptococcus uberis, Streptococcus dysgalactiae*, and *Escherichia coli*, as well as fewer flareups and lower IMI-related expenditures, according to the study. However, *Staphylococcus aureus* transmission was not stopped. To enhance udder health, dairy cows require lactational treatment, which must be preceded by management measures (van den Borne *et al.,* 2010). Antibiotic therapy, identifying the causal agent, parity, stage of breastfeeding, history of previous SCC, clinical MAST, and other systemic diseases all have a role in clinical MAST treatment (Steeneveld *et al.,* 2011).

Due to restrictions imposed by the organic certification process, such as no use of antimicrobials or hormones, use of organic feeds, and stress-free husbandry practises, organic farmers in the United States treat clinical MAST cases with a variety of alternative therapies, including homoeopathy, botanicals, vitamin supplements, and whey-based products (Ruegg, 2009). The recommended cow-specific treatment for clinical MAST was not demonstrated to be economically viable in a study done in the Netherlands (Steeneveld *et al.,* 2011). On the other hand, herd-specific therapies such as cow-specific medication and culling strategies against preclinical and clinical IMIs may be highly cost-effective in the management of MAST (Gussmann

et al., 2019). MAST treatment comprises both preventive and therapeutic treatments, the most frequent of which is antibiotic medication. Recent MAST treatments, on the other hand, have included the use of natural medicines such as zeolites and propolis, which might be used instead of antibiotics (Benic *et al.,* 2018).

Treatment with ABX:

ABX is widely used as a MAST preventive method during the dry season. Antimicrobial therapy of dry cows is allowed as a preventative technique among livestock animals. ABX should be chosen for the treatment of clinical MAST based on the patient's medical history, pathogenesis, antibiotic sensitivity profile, and, most importantly, proposed therapeutic principles. Antibiotic resistance has been found in pathogens isolated from MAST milk across a wide spectrum of ABX.

In a study conducted in the Zenica area of Bosnia and Herzegovina, the highest antimicrobial resistance was observed against benzyl penicillin ($C_{16}H_{18}N_2O_4S$) (56.3%) and oxytetracycline (OxyA, OxyB, OxyC, and OxyP) (46.2%). (Burovic, 2020). Antimicrobial susceptibility of *Trueperella pyogenes* infections in domestic animals was studied *in vitro*. ABX such as florfenicol ($C_{12}H_{14}C_{l2}FNO_4S$), cefoperazone ($C_{25}H_{27}N_9O_8S_2$), cephalexin ($C_{16}H_{17}N_3O_4S$), and ceftiofur ($C_{19}H_{17}N_5O_7S_3$) were shown to be effective (Ribeiro *et al.,* 2015). Antibiotic selection for MAST treatment should be based on culture and sensitivity data rather than empirical therapy, given the emergence of ABX resistance (Tiwari *et al.,* 2013). Another important drawback of ABX treatment is its proclivity for producing ABX residues in milk, which may be detrimental to the health of consumers (Oliver and Murinda, 2012; Gomes and Henriques, 2016). These ABX residues have been shown to be persistent for long periods of time and can have harmful effects on users as well as cause resistance (Kurjogi *et al.,* 2019). The use of ABX in cows, such as oxytetracycline ($C_{22}H_{24}N_2O_9$), amoxicillin ($C_{16}H_{19}N_3O_5S$), and ciprofloxacin (1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid), resulted in antibiotic residue in both raw and boiled milk at different time intervals, according to the report (Anika *et al.,* 2019).

Despite the fact that ABX are frequently used to treat MAST regardless of the severity of the disease, most cases of non-severe clinical MAST will not benefit from such uncontrolled usage. To cope with such situations, alternative approaches should be employed (Ruegg, 2017). Targeted ABX therapy aimed against particular organisms is one of the current proposed approaches for treating clinical MAST caused by Gram-positive agents. Such treatment techniques provide the remaining cases adequate time to recover on their own (Ruegg, 2017). Clinical cure rates are improved with ABX therapy that uses several administration channels, such as systemic and IMMS. This might be due to higher antimicrobial concentrations in milk and mammary tissues (Lima *et al.,* 2018).

In clinical circumstances, ABX selection based on culture and sensitivity may not guarantee 100% efficacy. This is owing to discrepancies in ABX sensitivity data in vitro and the failure of such sensitive medicines in clinical settings. *In vitro*, MAST generated by *Staphylococcus aureus* is sensitive to a variety of ABX, but owing to Staphylococci's unique biology, as well as their adaptability to the bovine host environment, the development of microabscesses, and the creation of biofilms, many ABX therapies become clinically ineffective (Rainard *et al.,* 2018). To ensure the optimal and appropriate use of ABX in suspected MAST cases in bovine species, careful and cautious interpretation of laboratory data is required to prevent antibiotic treatment of Staphylococci without considering clinical relevance (Wald *et al.,* 2019). The ABX susceptibility spectrum has a lot of variation in it. This can make the outcome of ABX treatment even more complicated. Novel compounds must be researched as soon as feasible for MAST prevention and therapy. For the prevention of new IMIs in dairy cattle, Lago *et al.* (2016) investigated post-milking barrier teat

disinfectants based on glycolic acid ($C_2H_4O_3$) and iodine (I). Glycolic acid ($C_2H_4O_3$)-based disinfectants were shown to be non-inferior to iodine (I)-based disinfectants in terms of safety and efficacy as post-milking teat disinfectants. They decreased the incidence of new IMI (NIMI) by about 17%, but had no effect on SCC or teat conditioning. Martins *et al*. (2017) studied disinfectants with high free iodine (I) and barrier quality in dairy cows to see if they might prevent new IMMS and clinical MAST from emerging spontaneously.

Teat disinfectants with barrier properties and higher free iodine content were able to reduce the risk of clinical MAST when provided after milking; however, the influence on new infections was only seen at weekly intervals. Barrier after milking teat disinfectant (BAR)-treated animals had a 46 per cent lower incidence of clinical MAST than non-barrier post-milking teat disinfectant-treated animals (NBAR). The risks of NIMI were lowered by 54 percent and 37 per cent, respectively, using NBAR disinfection.

Several studies looking at the antibiotic sensitivity of bacteria isolated from bovine MAST *in vitro* showed varying degrees of antibiotic resistance across isolates from throughout the world (Leon-Galvian *et al.,* 2015; Shah *et al.,* 2019). Penicillin, clindamycin, and cefotaxime resistance was found in bovine MAST isolates from Mexico (Leon-Galvian *et al.,* 2015). All *Escherichia coli* isolates from clinical MAST cow milk were resistant to cloxacillin in a study conducted in southern Taiwan, although some isolates were resistant to tetracycline, neomycin, gentamycin, ampicillin, ceftriaxone, cefotaxime, and ceftazidime (Shah *et al.,* 2019).

In India and Thailand, methicillin resistance genes were discovered in *Staphylococcus aureus* isolates from bovine MAST patients (Shah *et al.,* 2019). Several resistant microbial isolates have also been identified from clinical cases of cow MAST in India. Fourth-generation cephalosporins were shown to be somewhat superior than the conventional cloxacillin and ampicillin combination in the treatment of asymptomatic *Streptococcus agalactiae* MAST (Rossi *et al.,* 2019). Although oxytetracycline might be used as a first-line treatment in cattle with acute *Escherichia coli* MAST, its effectiveness is unknown (Shinozuka *et al.,* 2019).

In mild to moderate *Escherichia coli* MAST, ABX should be avoided; however, in severe cases, ABX such as fluoroquinolones and cephalosporins given parenterally are recommended to minimise the risk of bacteremia (Suojala *et al.,* 2013). The efficacy of ABX in the treatment of MAST is affected by all changes in the susceptibility spectrum, as well as the establishment of resistance. In Indian crossbred cows, ceftizoxime has been demonstrated to be effective in treating acute staphylococcal MAST (Buragohain *et al.,* 2019). Changes in the susceptibility spectrum will affect how MOs respond to antimicrobial medicines. Although extensive use of ABX for MAST prophylaxis may result in antibiotic resistance and residues in milk, the benefits of ABX much exceed the disadvantages stated above (Oliver and Murinda, 2012). Steele and McDougall (2014) looked at how protracted penethamate hydriodide (PH) therapy affected the bacteriological cure per cent and SCC in dairy cows. Following PH treatment, the proportion of bacteriological cures increased, the percentage of glands infected after therapy decreased, and SCC decreased.

As a result, the pH aids in the treatment of intramural infections in preclinical MAST; however, older cows and those infected with *Staphylococcus aureus*, particularly those resistant to penicillin, have a lower impact. Fuenzalida and Ruegg (2019) observed that IMMS ceftiofur had no effect on culling rate, milk yield or production, or SCC when used to treat non-severe culturenegative clinical MAST cases. *Klebsiella pneumoniae* MAST was worsened by intraamammalial (IMM) ceftiofur, resulting in chronic IMMS and poor clinical outcomes. IMM

ceftiofur is not considered necessary in the occurrence of *Escherichia coli* MAST (Fuenzalida and Ruegg, 2019). However, there is presently no viable alternative to ABX.

Tilmicosin intraamammary infusion during drying might be a viable option for avoiding NIMI, which is caused mostly by environmental streptococci and coagulase-negative *Staphylococci* (Dingwell *et al.,* 2002). An IMMS infusion of ceftiofur protects against *Streptococcus uberis* infection, according to an experimental study. When compared to the 2-day treatment option, the 8-day extended therapy had a greater impact (Oliver *et al.,* 2004). There were no significant variations in MAST cure rates between two ABX, tylosin base and penethamate hydriodide; 79.8% vs. 82.0% of cows treated, respectively (McDougall *et al.,* 2007). Several variables, including microbe type, udder environment, and milking technique (machine/hand), impact the efficacy rate of medications in MAST.

Non-steroidal anti-inflammatory medicines resulted in fewer SCC, reduced milk output losses, improved clinical outcomes, and lower culling rates as compared to antimicrobial therapy alone (McDougall *et al.,* 2009). Nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to be effective in the treatment of *Escherichia coli* MAST and are currently recommended for use as supportive therapy in the treatment of clinical MAST (Suojala *et al.,* 2013). Due to its unique pathophysiology, contagiousness, environmental persistence, skin or mucosal colonisation, and poor response to existing treatment drugs, *Staphylococcus aureus* is one of the few etiological organisms responsible for clinical MAST that can give the clinician/veterinarian a headache (Rainard *et al.,* 2018).

Therapeutic interventions for *Streptococcus agalactiae* can be successful rapidly, but they are usually useless against *Staphylococcus aureus* (Kefee, 2012). Increased biofilm formation among methicillin-resistant S. aureus strains has been found to enhance pathogenicity (Shah *et al.,* 2019). *Staphylococcus aureus* is the most difficult agent to eliminate from herds because of all of these features. Antibiotic therapy in *Staphylococcus aureus*-induced MAST is no longer effective, most likely due to overuse (Park *et al.,* 2012) or the development and persistence of biofilm-associated antibiotic resistance in *Staphylococcus aureus*-induced MAST (Babra *et al.,* 2013). That might reflect the continuous attempt to develop vaccines against MAST induced by *Staphylococcus aureus*, which have yet to prove successful (Cote-Gravel and Malouin 2019). According to a recent study, the NZ2114 derivative peptide H18R (H2) can be used to treat *Staphylococcus aureus*-induced MAST in a safe and promising way (Wang *et al.,* 2019).

According to one study, nasal immunisation against *Staphylococcus aureus* associated MAST in bovines results in an increase in anti-*Staphylococcus aureus* specific IgA antibodies in milk and a negative correlation between anti-*Staphylococcus aureus* specific IgA antibodies and *Staphylococcus aureus* counts in the treated udder, suggesting that nasal vaccines could be used to treat *Staphylococcus aureus* infections. To successfully incorporate antibiotic usage in MAST reduction, diagnostic effort should be enhanced so that unnecessary antibiotic use may be minimised (Kromker and Leimbach, 2017).

Prudent antibiotic use should be carried out with sufficient knowledge, a scientific foundation for minimising antibiotic use, and a legal requirement for caution, taking into account the cost of MAST therapy and the potential benefits (Doehring and Sundrum, 2019). Antimicrobial therapy of cows with newly acquired subclinical MAST (RASCM) should be conducted only in severe cases, given the current emphasis on the limited and cautious use of antimicrobials in animal husbandry treatment methods (van den Borne *et al.,* 2019). Antibiotic resistance of major bacterial infections that cause MAST in cows must be continuously monitored, as well as harmonisation of techniques and interpretations

(Chehabi *et al.,* 2019). When compared to a preparation containing tetracycline, neomycin, bacitracin, and prednisolone, an intraamammary preparation of ceftiofur hydrochloride showed no significant difference in overall clinical cure, bacteriological cure, or new infection when used to treat non-severe clinical MAST in dairy cows (Cortinhas *et al.,* 2016).

Pirlimycin was used as an extended therapy for *Staphylococcus aureus* intra-mammary infections in heifers by Skoulikas *et al.* (2018). The treated group had a considerably higher cure rate (64.8 per cent) than the control group (34.1 per cent). As a result, they predict that treating heifers with the extended treatment method right after calving will result in higher cure rates for *Staphylococcus aureus* IMMS infections. Extending the length of IMMS therapy may help prevent clinical failures, but it has no effect on cure proportion, somatic cell count, or the incidence of new infections.

McDougall *et al.* (2019) found that IMMS treatment with a combination of amoxicillin, clavulanic acid, and prednisolone administered over short (3 times at 12 h intervals) and long (5 times at 12h intervals) periods significantly reduced clinical failures while having no effect on cure proportion, SCC, or new infection rate. Because there are no effective therapies for MAST caused by *Prototheca* spp., it is exceedingly difficult to treat (Alves *et al.,* 2017). Previously, the *in vitro* algicidal efficacy of guanidine on *Prototheca zopfii* genotype 2 strains isolated from clinical and subclinical bovine MAST was studied. At low concentrations, guanidine possesses algicidal action and can be used as an alternate disinfectant, antiseptic for cleaning, chemical dry treatment of bovine teats, or even as an IMMS therapeutic agent (Alves *et al.,* 2017).

The resistance of biofilm-producing bacteria to conventional ABX makes treatment challenging. Alternative types of therapy must be utilised in such situations if the etiological culprit is to be successfully eliminated. Bacteriophages are bacteria-infecting and destroying viruses (Tiwari *et al.,* 2014). They have the capacity to target and destroy specific bacteria, as well as the ability to grow quickly, making them a viable competitor in the fight against dangerous bacteria (Carson *et al.,* 2010). The capacity of several bacteriophages to eradicate pathogenic microorganisms associated to MAST has been found and studied (Amiri Fahliyani *et al.,* 2018; VarelaOrtiz *et al.,* 2018). There have been a number of potential candidates for bacteriophage therapy of *Staphylococcus aureus* (Varela-Ortiz *et al.,* 2018), *Klebsiella oxytoca* (Amiri Fahliyani *et al.,* 2018), and *Escherichia coli* (Porter *et al.,* 2016). Because all of the evaluations were based on *in vitro* research, further *in vivo* studies are needed to show efficacy in clinical settings. Although bacteriophages are effective against bacteria, the majority of them are unstable in the environment and must be stored and managed in certain ways.

The isolated bacteriophages demonstrated thermostability and significant lytic capability, according to Amiri Fahliyani *et al.* (2018), making them good options against *Staphylococcus aureus* ntibiotic resistant strains. All of the thermostable phages maintained a high titer even after a 5-min incubation at 100 C (Amiri Fahliyani *et al.,* 2018). The use of a phage cocktail rather than a single virus is another development in bacteriophage treatment. A phage cocktail was shown to be more successful than each of the individual phages used alone in treating *Staphylococcus aureus*-induced MAST in a mouse model (Geng *et al.*, 2020).

Mice treated with phage cocktail had the highest IMMS phage titer when compared to other groups, and its efficacy was comparable to that of the antibiotic ceftiofur sodium. Phages trigger phage-specific humoral responses and memory, thereby jeopardising therapeutic efficacy (Krut and Bekeredjian-Ding, 2018). STA1, ST29, EB1.ST11, and EB1.ST27 were used to assess the lytic efficacy of a bacteriophage combination that included three phages, STA1.ST29, EB1.ST11, and EB1.ST27, against *Staphylococcus aureus* isolates.

The significant reduction in *Staphylococcus aureus* germ density showed that bacteriophage therapy could have therapeutic potential, which has to be confirmed *in vivo* (Titze *et al.,* 2020). More study is needed to show that bacteriophage therapy is effective in treating cow MAST *in vivo*.

Bacteriophage endolysins as a unique type of antibacterial agent:

Another potential therapeutic medication that is effective against Gram-positive bacteria is endolysins generated by bacteriophages. They are the proteins that allow the phage to escape from the bacterial cell by breaking the peptidoglycan layer of the bacterial cell wall during the lytic cycle (Breyne *et al.,* 2017). CHAPK, a novel bacteriophage-derived peptidase identified by Fenton *et al*. (2013), is an effective biocidal agent capable of rapidly breaking biofilm-forming *Staphylococci*. Because of CHAPK's *in vitro* efficacy, it can be used in teat-dip solutions to prevent *Staphylococcus aureus* colonisation on udder skin (Fenton *et al.,* 2013). To prevent and cure infections caused by the staphylococcal bacterial group, several new peptidoglycan hydrolases have been identified. Anti-staphylococcal peptidoglycan hydrolases include Lysostaphin, LasA, ALE-1, broth lysate, CsCl, LytM, AtlA, AtlE, LysK, SAL-1, MV-L, ClyS, and LysH5 (Gill *et al.,* 2006; Szweda *et al.,* 2012).

Herbal medicine:

Herbal therapy has no harmful side effects, making it a viable treatment choice for MAST. Ethno-veterinary medicine is a branch of veterinary medicine that focuses on treating diseases with herbal remedies (Tiwari *et al*., 2018). In the treatment of cow MAST, medicinal herbs can be used as an alternative therapy or as an auxiliary medicine. They can be used as an antibacterial, anti-inflammatory, and immunomodulatory treatment for MAST (Mushtaq *et al.,* 2018). The anti-inflammatory and anti-bacterial characteristics of Chinese herbs have been effectively employed in the treatment of cow MAST (Muluye *et al.,* 2014; Yang *et al.,* 2019). They can also be used instead of ABX and antipyretics, which are often prescribed for MAST therapy (Muluye *et al.,* 2014).

Methanolic extracts of herbal preparations including *Diploclisia glaucescens* leaf and *Curcuma longa* rhizomes in equal amounts produced analgesic and anti-inflammatory effects (Ranjith *et al.,* 2018). The analgesic effectiveness of the herbal extract was found to be comparable to that of ibuprofen and indomethacin (Ranjith *et al.,* 2018). Depending on the formulation, herbal therapy uses a number of administration techniques. Topical administration (Hase *et al.,* 2013), oral administration (Dash *et al.,* 2016), and IMMS administration are the most often used methods (Yang *et al.,* 2019). Antibiotic therapy was shown to be more successful than herbal and homoeopathic complex therapy in a research evaluating the efficacy of homoeopathic complex therapy, herbal therapy (Neem seed extract), and antibiotic therapy for the treatment of preclinical MAST in dairy buffaloes. When it came to treatment costs, herbal therapy was shown to be the most cost-effective (Younus *et al.,* 2018). As a result, it can be utilised as an adjuvant to ABX in the treatment of clinical MAST without causing major cost increases.

Some herbal extracts may have anti-inflammatory and antioxidant qualities that help with udder inflammation and oxidative stress reduction. Moringa extract has been demonstrated to decrease inflammatory mediators and increase antioxidant mechanisms in cow udder epithelial cells. TNF-a (tumour necrosis factor alpha), IL-1b (interleukin 1 beta), and IL-6 (interleukin 6) expression were all repressed, as was cyclooxygenase-2 (COX-2) expression, and nuclear factor-kappaB was downregulated, while heme-oxygenase-1, NAD(P)H, and quinone oxidoreductase-1 were upregulated (Cheng *et al.,* 2019). Numerous plant species are used in southern Brazil to prevent and cure cattle MAST due to their anti-inflammatory, immunomodulatory, and antibacterial

characteristics (Avancini *et al.,* 2008; Xu *et al.,* 2015).

Herbal medicine was made from plant stems, leaves, bark, seeds, flowers, bulbs, fruits, and aerial parts. Plant species like *Aloe vera, Achillea millefolium, Allium sativum, Muntinga calabura, Alternanthera brasiliana, Nigella sativa, Baccharis trimera, Origanum vulgare, Chenopodium ambrosioides, Cuphea carthagenensis, Ocimum sanctum, Foeniculum vulgare, Acacia nilotica, Phytolacca dioica, Sambucus nigra, Sida rhombifolia, Mentha pulegium, Solanum mauritianum, Tinospora cordifolia, Moringa oleifera, Garcinia indica, Atractylodis macrocephalae Koidz, Withania somnifera, Eugenia caryophyllus, Allium sativum, Agastache foeniculum, Solidago chilensis, Lavandula angustifolia* and *Althaea officinalis* were used orally, among *which Alternanthera brasiliana, Populus nigra, Plantago lanceolata, Baccharis trimera, Evernia prunastri, Ocimum basilicum, Crassula multicava* and *Sambucus nigra* were also used as topical agents (Paşca *et al.,* 2017; Sserunkuma *et al.,* 2017; Johri *et al.,* 2018; Mushtaq *et al.,* 2018; Maramulla *et al.,* 2019; Ren *et al.,* 2020; Kovačević *et al.,* 2021).

Ocimum basilicum and *Parapiptadenia rigida* were the two plant species that were used by IMMS route in bovine MAST (Avancini *et al.,* 2008). *Staphylococcus epidermidis* is one of the most common causes of medical device-related infections and bovine MAST, in addition to its biofilm-forming abilities. *Oxytropis glabra* is a Fabaceae plant that is commonly used as a Chinese herbal composition in Western China. According to Mihaylova *et al.* (2013) Asteraceae, Lamiaceae, and Fabaceae family plants are frequently utilised for MAST pathogen therapy in India. *In vitro* tests evaluating the effect of *Oxytropis glabra* decoction on the creation of *Staphylococcus epidermidis* biofilms discovered putative inhibitory mechanisms that may be explored further in the development of new biofilm-associated infection treatments (Ren *et al.,* 2020).

Leaf extract exhibited strong bio-enhancing and anti-oxidant properties, which can be utilised in conjunction with ABX in a research to examine the efficacy of *Ocimum sanctum* leaf juice as supportive treatment for the management of chronic staphylococcal MAST (Dash *et al.,* 2016). Rather employing herbal therapy as a stand-alone treatment for clinical MAST, integrating it in the treatment regimen as an adjuvant with other modalities of therapy can yield better results. A 500 mg/ml concentration of *Terminalia chebula* ethyl acetate extract showed the same antibacterial efficacy as conventional amoxicillin against molecularly defined isolates of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus megaterium* (Kher *et al.,* 2019). This finding raises the prospect that herbal extracts might one day replace ABX as the only therapy for clinical MAST (Zhen *et al.,* 2008; Zecconi *et al.,* 2009; McPhee *et al.,* 2011; Wang *et al.,* 2011; Leitner *et al.,* 2013; Pinedo *et al.,* 2013; Almeida *et al.,* 2015; McDougall *et al.,* 2016; Petzl *et al.,* 2018).

NPs applications:

NPs technology is another topic that is rapidly gaining traction as a delivery technique for antibacterial and other drugs (Gomes and Henriques, 2016). Several types of NPs have been tried in the past for MAST therapy, with encouraging results (Castelani *et al.,* 2019; Kalinska *et al.,* 2019; Orellano *et al.,* 2019; Pinheiro Machado *et al.,* 2019). The absorption of active chemicals by phagocytes will be increased by NPs formulations, enhancing their antibacterial effectiveness (Gruet *et al.,* 2001). They have been demonstrated to work against a wide range of multidrug-resistant bacteria that pose a serious threat to civilisation (Yu *et al.,* 2018; Castelani *et al.,* 2019).

Staphylococcus aureus-caused bovine MAST is particularly difficult to treat with conventional therapies due to its efficient pathogenesis, unique facultative intracellular parasitism, biofilm formation, and growing antimicrobial resistance.

As a result, NPs-based therapy techniques such as liposomes, nanogels, polymeric nanoparticles, inorganic NPs, and solid lipid NPs are gaining popularity as viable tools for treating *Staphylococcus aureus* MAST (Algharib *et al.,* 2020). Honey has significant antimicrobial action *in vitro* against methicillin-resistant and vancomycin-resistant coagulase-positive *Staphylococcus aureus* MAST strains when coupled with gold nanoparticles (AuNPs) (Omara, 2017). When NPs are used in high quantities, they harm numerous organs and cause pathological changes (Elbehiry *et al.,* 2019).

To identify the biological effects of NPs, more study is required (Kalinska *et al.,* 2019). Chitosan nanoparticles (CHS-NPs) (Orellano *et al.,* 2019), propolis NPs, and cationic nisin-lipid nanoparticles (Castelani *et al.,* 2019) have all been found to be beneficial in the treatment of MAST. When coupled with AgNPs, ABX which inhibit protein synthesis have a powerful synergistic effect (Ahmadi *et al.,* 2014). The antibacterial activity of antibiotics like tilmicosin and amoxicillin can be improved via nanoformulation (Yang *et al.,* 2009; Zhu *et al.,* 2018). Tilmicosin solid lipid NPs' antibacterial efficacy against *Staphylococcus aureus* and *Streptococcus agalactiae* was prolonged and enhanced (Zhu *et al.,* 2018). Amoxicillin nanoparticles improved the post-antibiotic impact and lowered the dose interval when used against pathogenic bacteria that cause bovine MAST (Yang *et al.,* 2009). *Staphylococcus aureus* strains collected from MAST patients were found to be toxic to AgNPs and AuNPs. Because *Staphylococcus aureus* strains gain resistance to AuNPs less frequently, AuNPs outperformed AgNPs (Elbehiry *et al.,* 2019). The therapeutic efficacy of an IMMS nanosuspension based on a-linolenic acid (ALA-NS) for the treatment of subclinical MAST was studied.

SREBP-1c (sterol response element-binding protein-1c), NF-jBp65 (nuclear factor kappa-light-chain-enhancer of activated B cells), and UCHL-1 (ubiquitin carboxyl-terminal hydrolase-1) expression, as well as total microbial count and somatic cell count, were all found to be significantly lower after treatment with ALA-NS (Yadav *et al.,* 2020). In the treatment of bovine MAST, CHS-NPs have been demonstrated to have a high therapeutic potential (Orellano *et al.,* 2019). Commercially available AgNPs and CuNPs decreased the *in vitro* survival of *Staphylococcus aureus* and *Escherichia coli* without causing damage to the mammary gland (*Kalinska et al.,* 2019).

In the IMMS treatment of clinical bovine MAST caused by *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumonia*, sonochemically synthesised capped zinc oxide nanoparticles (ZnONPs) demonstrated greater antibacterial activity than particles synthesised by auto-combustion method, implying its potential for MAST control (Hozyen *et al.,* 2019). *In vivo* studies are required to validate the antibacterial action of NPs. The ability of the MAST-causing opportunistic bacteria *Escherichia coli* to form biofilm causes antibiotic resistance (Yu et al., 2018). Plant-derived NPs are becoming more popular as a therapy for MAST (Chaitanya Kumar *et al.,* 2013; Yu *et al.,* 2018).

The AgNPs-decorated quercetin NPs made by combining AgNPs with plant-derived quercetin showed substantial anti-bacterial and anti-biofilm activity against MAST-infected dairy calves' multi-drug resistant *Escherichia coli* strains (Yu *et al.,* 2018).

Due to its rapid departure from the body, curcumin, a polyphenol produced from turmeric, has a low oral bioavailability, limiting its anti-inflammatory effect. In a *Staphylococcus aureus* - infected mammary tissue animal model, curcumin nanoformulation can increase oral bioavailability and reduce proinflammatory mediators (Suresh *et al.,* 2018). Similarly, silver nanoparticles produced from aloin, a key component of *Aloe vera*, exhibited significant antibacterial action against *Staphylococcus aureus* in an experimental murine MAST model (Chaitanya Kumar *et al.,* 2013). The

use of NPs in MAST therapy requires more research.

Chitosan and cloxacillin were combined to study their effects on planktonic cultures, bacterial biofilms, and intracellular growth in udder cells (Breser *et al*., 2018). It was observed that combining chitosan with cloxacillin inhibited the formation of biofilms and improved the clearance of biofilms that had already formed. It also decreased intracellular bacteria viability, which is considered to be linked to increased IL-6 production by affected mammary epithelial cells. As a result, this therapy has the potential to be a one-of-a-kind way to prevent MAST in a safe, effective, and contamination-free way, especially in the face of multidrug-resistant bacteria.

Conclusion

MAST has a negative influence on animal welfare and results in economic and production losses due to decreased milk quality, lower production performance, increased culling rate, treatment costs, and death connected to the acute phase of the illness. Both clinical and subclinical symptoms of the illness can be caused by a variety of microbiological species. Subclinical MAST is more economically important than clinical MAST because it has a higher proclivity for lowering milk quality to the point where it cannot be seen visually but has an influence on overall quality.

For the diagnosis of MAST, there are several well-established and inexpensive conventional diagnostic techniques available, however, they lack sensitivity and specificity. They can not be widely used in the current dairy sector since they can not offer quick results. Improved diagnostic methods for detecting etiological agents in MAST have recently been developed and are simple to use, fast, and sensitive, although they still lack significant specificity. Due to the need for skilled support, sophisticated technology, and infrastructure, such an approach lacks economic viability.

When MAST is discovered, the first concern for the veterinarian or producer is to treat the animals in such a way that the disease does not worsen and becomes an economic burden on the production system. Several therapeutic strategies have been evaluated for efficacy in treating MAST, including ABX, vaccines, bacteriocins, herbal therapy, immunotherapy, and nanoparticle technology, but no single technique has been found to be effective in controlling or treating the disease due to the variable response of etiological agents to therapeutic techniques.

ABX were widely used as the only therapeutic agent in the therapy of MAST until recently, but with the increase of bacterial resistance due to uncontrolled antibiotic use, alternative treatment methods are being researched. A necessity for the twenty-first century is the development of a universal therapeutic agent/technique that can be utilised instead of antibiotic therapy.

This sort of drug/method has the potential to address the growing problem of bacterial resistance. Advanced treatment approaches, such as bacteriocins and NPs technologies, should be further researched in order to discover a solution to the existing problem. Diagnostic techniques and treatment methods should be developed in tandem in order to achieve an accurate early farm level diagnosis, which may then be combined with specialised therapy against the identified microorganism to enable successful MAST management and treatment. Antimicrobial use is a problem in India. Addressing the flaws identified in our study can help minimise AMR, but the mechanism by which this happens (i.e. the change process) can be studied by involving stakeholders in the theory development process.

Interventions addressing AMR from the perspective of animal health should be promoted and organised in a way that allows for monitoring and evaluation. The National AMR Containment Program, the National Action Plan on AMR, and the National Health Policy indicate the government's commitment to addressing the country's AMR problem and should be supported.

It is time to start thinking about how to encourage more people to follow the rules. Incentives that encourage actors to change their behaviours and use AMR therapies should also be studied.

Acknowledgements

Authors are thankful to ASB Life Cell Research Technologies, Chennai, Tamil Nadu, for the technical support for this research work.

References

Abebe R, Hatiya H, Abera M, Megersa B and Asmare K. (2016) Bovine mastitis: prevalence, risk factors and isolation of Staphylococcus aureus in dairy herds at Hawassa milk shed, South Ethiopia. BMC Vet Res. 12(1): 1-11.

Aghamohammadi M, Haine D, Kelton DF, Barkema H. W, Hogeveen H, Keefe GP and Dufour S. (2018) Herd-level mastitis-associated costs on Canadian dairy farms. Frontiers Vet Sci. 5: 100.

Ahmadi M, Dastmalchi SH and Adib Hesami M. (2014) Antibacterial effect of silver nanoparticles along with protein synthesis-inhibiting antibiotics on Staphylococcus aureus isolated from cattle mastitis. Biol J Mocroorganism 2(8): 15-22.

Akers RM and Nickerson SC. (2011) Mastitis and its impact on structure and function in the ruminant mammary gland. J Mammary Gland Biol Neoplasia 16(4): 275-289.

Alva-Murillo N, Téllez-Pérez AD, Sagrero-Cisneros E, López-Meza JE and Ochoa-Zarzosa A. (2012) Expression of antimicrobial peptides by bovine endothelial cells. Cellr Immunol. 280(1): 108-112.

Alves AC, Capra E, Morandi S, Cremonesi P, Pantoja JCF, Langoni H, de Vargas APC, da Costa MM, Jagielski T, Bolaños CAD, Guerra ST and Ribeiro MG. (2017) *In vitro* algicidal effect of guanidine on *Prototheca zopfii* genotype 2 strains isolated from clinical and subclinical bovine mastitis. Lett Appl Microbiol. 64(6): 419-423.

Amiri Fahliyani S, Beheshti-Maal K and Ghandehari F. (2018) Novel lytic bacteriophages of *Klebsiella oxytoca* ABG-IAUF-1 as the potential agents for mastitis phage therapy. FEMS Microbiol Lett. 365(20): fny223.

Andrews T, Neher DA, Weicht TR and Barlow JW. (2019) Mammary microbiome of lactating organic dairy cows varies by time, tissue site, and infection status. PLoS One 14(11): e0225001.

Anika TT, Al Noman Z, Ferdous MRA, Khan SH, Mukta MA, Islam MS, Hossain MT and Rafiq K. (2019) Time dependent screening of antibiotic residues in milk of antibiotics treated cows. J Adv Vet Anim Res. 6(4): 516-520.

Ashraf A and Imran M. (2020) Causes, types, etiological agents, prevalence, diagnosis, treatment, prevention, effects on human health and future aspects of bovine mastitis. Anim Hlth Res Rev. 21(1): 36-49.

Avancini C, Wiest JM, Dall'Agnol R, Haas JS and von Poser GL. (2008) Antimicrobial activity of plants used in the prevention and control of bovine mastitis in Southern Brazil. Latin Am J Pharm. 27(6): 894-899.

Babra C, Tiwari JG, Pier G, Thein TH, Sunagar R, Sundareshan S, Isloor S, Hegde NR, de Wet S, Deighton M, Gibson J, Costantino P, Wetherall J and Mukkur T. (2013) The persistence of biofilm-associated antibiotic resistance of *Staphylococcus aureus* isolated from clinical bovine mastitis cases in Australia. Folia Microbiol. 58(6): 469-474.

Bardhan D. (2013) Estimates of economic losses due to clinical mastitis in organized dairy farms. Indian J Dairy Sci. 66(2): 168-172.

Barreiro JR, Gonçalves JL, Braga PAC, Dibbern AG, Eberlin MN and Dos Santos MV. (2017) Non-culture-based identification of mastitis-causing bacteria by MALDI-TOF mass spectrometry. J Dairy Sci. 100(4): 2928-2934.

Benić M, Maćešić N, Cvetnić L, Habrun B, Cvetnić Ž, Turk R, Đuričić D, Lojkić M, Dobranić V and Valpotić H. (2018) Bovine mastitis: a persistent and evolving problem requiring novel approaches for its control-a review. Vet Arhiv. 88(4):535–557

Bennett R, Christiansen K and Clifton-Hadley R. (1999) Preliminary estimates of the direct costs associated with endemic diseases of livestock in Great Britain. Prevent Vet Med. 39(3): 155-171.

Bhattarai D, Worku T, Dad R, Rehman ZU, Gong X and Zhang S. (2018) Mechanism of pattern recognition receptors (PRRs) and host pathogen interplay in bovine mastitis. Microb Pathogen. 120: 64-70.

Bi Y, Wang YJ, Qin Y, Guix Vallverdú R, Maldonado García J, Sun W, Li S and Cao Z. (2016) Prevalence of bovine mastitis pathogens in bulk tank milk in China. PLoS One 11(5): e0155621.

Borm AA, Fox LK, Leslie KE, Hogan JS, Andrew SM, Moyes KM, Oliver SP, Schukken YH, Hancock DD, Gaskins CT, Owens WE and Norman C. (2006) Effects of prepartum intramammary antibiotic therapy on udder health, milk production, and reproductive performance in dairy heifers. J Dairy Sci. 89(6): 2090-2098.

Bradley AJ, Breen JE, Payne B, White V and Green MJ. (2015) An investigation of the efficacy of a polyvalent mastitis vaccine using different vaccination regimens under field conditions in the United Kingdom. J Dairy Sci. 98(3): 1706-1720.

Breser ML, Felipe V, Bohl LP, Orellano MS, Isaac P, Conesa A, Rivero VE, Correa SG, Bianco ID and Porporatto C. (2018) Chitosan and cloxacillin combination improve antibiotic efficacy against different lifestyle of coagulase-negative Staphylococcus isolates from chronic bovine mastitis. Sci Rep. 8(1): 1-13.

Breyne K, Honaker RW, Hobbs Z, Richter M, Żaczek M, Spangler T, Steenbrugge J, Lu R, Kinkhabwala A, Marchon B, Meyer E and Mokres L. (2017) Efficacy and safety of a bovine-associated *Staphylococcus aureus* phage cocktail in a murine model of mastitis. Front Microbiol. 8: 2348.

Buragohain R, Sar TK, Samanta I, Biswas U andMandal TK. (2019) Disposition of ceftizoxime in staphylococcal mastitis in Indian crossbred cows. Vet J. 245: 12-14.

Carson L, Gorman SP and Gilmore BF. (2010) The use of lytic bacteriophages in the prevention and eradication of biofilms of *Proteus mirabilis* and *Escherichia coli*. FEMS Immunol Med Microbiol. 59(3): 447-455.

Carvalho-Castro GA, Silva JR, Paiva LV, Custódio DAC, Moreira RO, Mian GF, Prado IA, Chalfun-Junior A and Costa GM. (2017) Molecular epidemiology of *Streptococcus agalactiae* isolated from mastitis in Brazilian dairy herds. Braz J Microbiol. 48(3): 551-559.

Castelani L, Arcaro JRP, Braga JEP, Bosso AS, Moura Q, Esposito F, Sauter IP, Cortez M and Lincopan N. (2019) Activity of nisin, lipid bilayer fragments and cationic nisin-lipid nanoparticles against multidrug-resistant *Staphylococcus* spp. isolated from bovine mastitis. J Dairy Sci. 102(1): 678-683.

Cha E, Bar D, Hertl JA, Tauer LW, Bennett G, González RN, Schukken YH, Welcome FL and Gröhn YT. (2011) The cost and management of different types of clinical mastitis in dairy cows estimated by dynamic programming. J Dairy Sci. 94(9): 4476-4487.

Chaitanya Kumar TV, Muralidhar Y, Prasad PE, Prasad TNVKV and Alpha Raj M. (2013). Evaluation of therapeutic potential of nanosilver particles synthesised using aloin in experimental murine mastitis model. IET Nanobiotechnol. 7(3): 78-82.

Chakraborty S, Dhama K, Tiwari R, Iqbal Yatoo M, Khurana SK, Khandia R, Munjal A, Munuswamy P, Kumar MA, Singh M, Singh R, Gupta VK and Chaicumpa W. (2019) Technological interventions and advances in the diagnosis of intramammary infections in animals with emphasis on bovine population-a review. Vet Q. 39(1): 76-94.

Chehabi CN, Nonnemann B, Astrup LB, Farre M and Pedersen K. (2019) *In vitro* antimicrobial resistance of causative agents to clinical mastitis in Danish dairy cows. Foodborne Pathogens Dis., 16(8): 562-572.

Chen Y, Yang Z, Liu W, Chang Q, Wang L and Zhang N. (2012) Prevalence and major pathogen causes of dairy cows subclinical mastitis in Northeast China. J Ani Vet Adv. 11(8): 1278-1280.

Cheng J, Qu W, Barkema HW, Nobrega DB, Gao J, Liu G, De Buck J, Kastelic JP, Sun H and Han B. (2019) Antimicrobial resistance profiles of 5 common bovine mastitis pathogens in large Chinese dairy herds. J Dairy Sci. 102(3): 2416-2426.

Cheng WN, Jeong CH, Seo HG and Han SG. (2019) Moringa extract attenuates inflammatory responses and increases gene expression of casein in bovine mammary epithelial cells. Animals 9(7): 391.

Cheong HS, Wi YM, Moon SY, Kang CI, Son JS, Ko KS, Chung DR, Lee NY, Song JH and Peck KR. (2008) Clinical features and treatment outcomes of infections caused by *Sphingomonas paucimobilis*. Infect Control Hosp Epidemiol. 29(10): 990-992.

Chung PY and Khanum R. (2017) Antimicrobial peptides as potential anti-biofilm agents against multidrug-resistant bacteria. J Microbiol Immunol Infect. 50(4): 405-410.

Cobirka M, Tancin V and Slama P. (2020) Epidemiology and classification of mastitis. Animals 10(12): 2212.

Collado R, Prenafeta A, González-González L, Pérez-Pons JA and Sitjà M. (2016) Probing vaccine antigens against bovine mastitis caused by *Streptococcus uberis*. Vaccine 34(33): 3848-3854.

Contreras GA and Rodríguez JM. (2011) Mastitis: comparative etiology and epidemiology. J Mammary Gland Biol Neoplas. 16(4): 339-356.

Cortinhas CS, Tomazi T, Zoni MSF, Moro E and Dos Santos MV. (2016) Randomized clinical trial comparing ceftiofur hydrochloride with a positive control protocol for intramammary treatment of nonsevere clinical mastitis in dairy cows. J Dairy Sci. 99(7): 5619-5628.

Côté-Gravel J and Malouin F. (2019) Symposium review: Features of *Staphylococcus aureus* mastitis pathogenesis that guide vaccine development strategies. J Dairy Sci. 102(5): 4727-4740.

Cubeddu T, Cacciotto C, Pisanu S, Tedde V, Alberti A, Pittau M, Dore S, Cannas A, Uzzau S, Rocca S and

Addis MF. (2017) Cathelicidin production and release by mammary epithelial cells during infectious mastitis. Vet Immunol Immunopathol. 189: 66-70.

Cvetnić L, Samardžija M, Habrun B, Kompes G and Benić M. (2016) Microbiological monitoring of mastitis pathogens in the control of udder health in dairy cows. Slovenian Vet Res. 53(3): 131-140.

Dalanezi FM, Joaquim SF, Guimarães FF, Guerra ST, Lopes BC, Schmidt EMS, Cerri RLA and Langoni H. (2020) Influence of pathogens causing clinical mastitis on reproductive variables of dairy cows. J Dairy Sci. 103(4): 3648-3655.

Das D, Panda SK, Jena B and Sahoo AK. (2018) Economic impact of subclinical and clinical mastitis in Odisha, India. Int J Curr Microbiol App Sci. 7(03): 3651-3654.

Dash JR, Sar TK, Samanta I and Mandal TK. (2016) Effects of herbal extract of Ocimum sanctum as supportive therapy with intravenous ceftriaxone in experimentally induced staphylococcal chronic mastitis in goat. Small Ruminant Res. 137: 1-8.

De Vliegher S, Fox LK, Piepers S, McDougall S and Barkema HW. (2012) Mastitis in dairy heifers: Nature of the disease, potential impact, prevention, and control. J Dairy Sci. 95(3): 1025-1040.

Derakhshani H, Fehr KB, Sepehri S, Francoz D, De Buck J, Barkema HW, Plaizier JC and Khafipour E. (2018) Microbiota of the bovine udder: Contributing factors and potential implications for udder health and mastitis susceptibility. J Dairy Sci. 101(12): 10605-10625.

Dingwell RT, Duffield TF, Leslie KE, Keefe GP, DesCoteaux L, Kelton DF, Lissemore KD, Schukken YH, Dick P and Bagg R. (2002) The efficacy of intramammary tilmicosin at drying-off, and other risk factors for the prevention of new intramammary infections during the dry period. J Dairy Sci. 85(12): 3250-3259.

Doehring C and Sundrum A. (2019) The informative value of an overview on antibiotic consumption, treatment efficacy and cost of clinical mastitis at farm level. Prevent Vet Med. 165: 63-70.

Dufour S, Labrie J and Jacques M. (2019) The mastitis pathogens culture collection. Microbiol Resource Announcem. 8(15): e00133-19.

Elbehiry A, Al-Dubaib M, Marzouk E and Moussa I. (2019) Antibacterial effects and resistance induction of silver and gold nanoparticles against *Staphylococcus aureus*-induced mastitis and the potential toxicity in rats. Microbiol Open 8(4): e00698.

Falentin H, Rault L, Nicolas A, Bouchard DS, Lassalas J, Lamberton P, Aubrey JM, Marnet PG, Loir YL and Even S. (2016) Bovine teat microbiome analysis revealed reduced alpha diversity and significant changes in taxonomic profiles in quarters with a history of mastitis. Frontiers Microbiol. 7: 480.

Fenton M, Keary R, McAuliffe O, Ross RP, O'Mahony J and Coffey A. (2013) Bacteriophage-derived peptidase eliminates and prevents *Staphylococcal biofilms*. Int J Microbiol. 2013: 625341.

Fuenzalida MJ and Ruegg PL. (2019) Negatively controlled, randomized clinical trial to evaluate use of intramammary ceftiofur for treatment of nonsevere culture-negative clinical mastitis. J Dairy Sci. 102(4): 3321-3338.

Garcia, A. (2004) Contagious vs. environmental mastitis. https://openprairie.sdstate.edu/extension_extra/126/.

Geng H, Zou W, Zhang M, Xu L, Liu F, Li X, Wang L and Xu Y. (2020) Evaluation of phage therapy in the treatment of *Staphylococcus aureus*-induced mastitis in mice. Folia Microbiol. 65(2): 339-351.

Gill JJ, Pacan JC, Carson ME, Leslie KE, Griffiths MW and Sabour PM. (2006) Efficacy and pharmacokinetics of bacteriophage therapy in treatment of subclinical *Staphylococcus aureus* mastitis in lactating dairy cattle. Antimicrob Agents Chemother. 50(9): 2912-2918.

Godden SM, Royster E, Timmerman J, Rapnicki P and Green H. (2017) Evaluation of an automated milk leukocyte differential test and the California Mastitis Test for detecting intramammary infection in early- and late-lactation quarters and cows. J Dairy Sci. 100(8): 6527-6544.

Godoy-Santos F, Pinto MS, Barbosa AA, Brito MA and Mantovani HC. (2019) Efficacy of a ruminal bacteriocin against pure and mixed cultures of bovine mastitis pathogens. Indian J Microbiol. 59(3): 304-312.

Gomes F and Henriques M. (2016) Control of bovine mastitis: old and recent therapeutic approaches. Curr Microbiol. 72(4): 377-382.

González RN and Wilson DJ. (2003) Mycoplasmal mastitis in dairy herds. Vet Clin Food Anim Pract. 19(1): 199-221.

Griffioen K, Cornelissen J, Heuvelink A, Adusei D, Mevius D and van der Wal FJ. (2020) Development and evaluation of 4 loop-mediated isothermal amplification assays to detect mastitis-causing bacteria in bovine milk samples. J Dairy Sci. 103(9): 8407-8420.

Gröhn YT, Wilson DJ, González RN, Hertl JA, Schulte H, Bennett G and Schukken YH. (2004) Effect of

pathogen-specific clinical mastitis on milk yield in dairy cows. J Dairy Sci. 87(10): 3358-3374.

Gurao A, Kashyap SK and Singh R. (2017) β-defensins: An innate defense for bovine mastitis. Vet World 10(8): 990.

Gurjar A, Gioia G, Schukken Y, Welcome F, Zadoks R and Moroni P. (2012) Molecular diagnostics applied to mastitis problems on dairy farms. Vet Clin Food Anim Pract. 28(3): 565-576.

Gussmann M, Steeneveld W, Kirkeby C, Hogeveen H, Farre M and Halasa T. (2019) Economic and epidemiological impact of different intervention strategies for subclinical and clinical mastitis. Prevent Vet Med., 166: 78-85.

Hadrich JC, Wolf CA, Lombard J and Dolak TM. (2018) Estimating milk yield and value losses from increased somatic cell count on US dairy farms. J Dairy Sci. 101(4): 3588-3596.

Halasa T, Huijps K, Østerås O and Hogeveen H. (2007) Economic effects of bovine mastitis and mastitis management: A review. Vet Q. 29(1): 18-31.

Hamann, J. (2001). Mastitis notes from members countries. Germany Bullt IDF367: 18-21.IDF (1987) Bovine mastitis. Definition and guidelines for diagnosis. Bull IDF. 211:24.

Harjanti DW, Ciptaningtyas R, Wahyono F and Setiatin ET. (2018) Isolation and identification of bacterial pathogen from mastitis milk in Central Java Indonesia. In: IOP Conference Series: Earth and Environmental Science, IOP Publishing, 102(1): pp. 012076.

Harmon RJ. (1994) Physiology of mastitis and factors affecting somatic cell counts. Journal Dairy Sci. 77(7): 2103-2112.

Hase P, Digraskar S, Ravikanth K, Dandale M and Maini S. (2013) Management of subclinical mastitis with mastilep gel and herbal spray (AV/AMS/15). Int J Pharm Pharmacol. 2(4): 64-67.

Hogeveen H, Pyorala S, Waller KP, Hogan JS, Lam TJ, Oliver SP, Schukken YH, Barkema HW and Hillerton JE. (2011) Current status and future challenges in mastitis research. NMC 50th Annual Meeting Proc., Arlington, Virginia, United States, 36-48.

Hozyen HF, Ibrahim ES, Khairy EA and El-Dek SI. (2019) Enhanced antibacterial activity of capped zinc oxide nanoparticles: A step towards the control of clinical bovine mastitis. Vet World 12(8): 1225.

Hussein HA, Abd El KAEH, Razik AMG, Elbayoumy MK, Abdelrahman KA and Hosein HI. (2018) Milk amyloid A as a biomarker for diagnosis of subclinical mastitis in cattle. Vet World 11(1): 34.

Izquierdo AC, Guerra Liera JE, Cervantes RE, Inzunza Castro JF, Abel Villa Mancera E, Crisın RH, Juarez Mosqueda ML, Vazquez AG, Perez JO and Aparicio PS. (2017) Production of milk and bovine mastitis. J Adv Dairy Res. 5(2):2.

Johri A, Singh PK, Diwakar RP and Singh AP. (2018) *In vitro* herbal sensitivity test against mastitis milk of large animals. Int J Curr Microbiol App Sci. 7: 81-89.

Jones GM and Bailey TL. (2009) Understanding the basics of mastitis. Virginia Cooperative Extension, 404-233.

Kalińska A, Gołębiewski M and Wójcik A. (2017) Mastitis pathogens in dairy cattle - a review. World Scic News 89: 22-31.

Kalmus P, Simojoki H, Pyörälä S, Taponen S, Holopainen J and Orro T. (2013) Milk haptoglobin, milk amyloid A, and N-acetyl-β-d-glucosaminidase activity in bovines with naturally occurring clinical mastitis diagnosed with a quantitative PCR test. J Dairy Sci. 96(6): 3662-3670.

Kandeel SA, Morin DE, Calloway CD and Constable PD. (2018) Association of California mastitis test scores with intramammary infection status in lactating dairy cows admitted to a veterinary teaching hospital. J Vet Internal Med. 32(1): 497-505.

Keefe G. (2012) Update on control of *Staphylococcus aureus* and *Streptococcus agalactiae* for management of mastitis. Vet Clin North Am Food Anim Pract. 28(2): 203-216.

Klaas IC and Zadoks RN. (2018) An update on environmental mastitis: Challenging perceptions. Transboundary Emerging Dis. 65: 166-185.

Kleczkowski M, Kluciński W, Czerski M and Kudyba E. (2017) Association between acute phase response, oxidative status and mastitis in cows. Veterinarska Stanica 48(3): 177-186.

Kovačević Z, Radinović M, Čabarkapa I, Kladar N and Božin B. (2021) Natural agents against bovine mastitis pathogens. Antibiotics 10(2): 205.

Kovačić M, Samardžija M, Đuričić D, Vince S, Flegar-Meštrić Z, Perkov S, Gracner D and Turk R. (2019) Paraoxonase-1 activity and lipid profile in dairy cows with subclinical and clinical mastitis. J Appl Anim Res. 47(1): 1-4.

Krömker V and Leimbach S. (2017) Mastitis treatment - Reduction in antibiotic usage in dairy cows. Reprod Domestic Anim. 52: 21-29.

Krukowski H, Tietze M, Majewski T and Różański P. (2001) Survey of yeast mastitis in dairy herds of small-type farms in the Lublin region, Poland. Mycopathologia 150(1): 5-7.

Krut O and Bekeredjian-Ding I. (2018) Contribution of the immune response to phage therapy. J Immunol. 200(9): 3037-3044.

Kumar GSN, Appannavar MM, Suranagi MD and Kotresh AM. (2010) Study on incidence and economics of clinical mastitis. Karnataka J Agricult Sci. 23(2): 407-408.

Kurjogi M, Issa Mohammad YH, Alghamdi S, Abdelrahman M, Satapute P and Jogaiah S. (2019) Detection and determination of stability of the antibiotic residues in cow's milk. PLoS One 14(10): e0223475.

Lago A, Bruno DR, Lopez-Benavides M and Leibowitz S. (2016) Efficacy of glycolic acid-based and iodine-based postmilking barrier teat disinfectants for prevention of new intramammary infections in dairy cattle. J Dairy Sci. 99(9): 7467-7472.

Langer MN, Blodkamp S, Bayerbach M, Feßler AT, de Buhr N, Gutsmann T, Kreienbrock L, Schwarz S and von Köckritz-Blickwede M. (2017) Testing cathelicidin susceptibility of bacterial mastitis isolates: Technical challenges and data output for clinical isolates. Vet Microbiol. 210:107-115.

León-Galván MF, Barboza-Corona JE, Lechuga-Arana AA, Valencia-Posadas M, Aguayo DD, Cedillo-Pelaez C, Martínez-Ortega EA and Gutierrez-Chavez AJ. (2015) Molecular detection and sensitivity to antibiotics and bacteriocins of pathogens isolated from bovine mastitis in family dairy herds of central Mexico. Biomed Res Int. 2015:615153.

Levison LJ, Miller-Cushon EK, Tucker AL, Bergeron R, Leslie KE, Barkema HW and DeVries TJ. (2016) Incidence rate of pathogen-specific clinical mastitis on conventional and organic Canadian dairy farms. J Dairy Sci. 99(2): 1341-1350.

Lima MGB, Blagitz MG, Souza FN, Sanchez EMR, Batista CF, Bertagnon HG, Diniz SA, Silva MX and Libera AMMPD. (2018) Profile of immunoglobulins, clinical and bacteriological cure after different treatment routes of clinical bovine mastitis. Arquivo Brasileiro Medicina Veterinária Zootecnia 70(4): 1141-1149.

Malik YS, Saurabh S, Kattoor JJ, Sircar S, Deol P and Dhama K. (2016) Animal enteric viral emergencies: An overview. Int Acad Biosci. Pp.130-139.

Maramulla A, Gadige A, Kosqapati L, Bommu S and Katta P. (2019) Efficacy of herbal preparations in the therapy of sub clinical mastitis in cows of periurban areas of Hyderabad. Pharma Innov J. 8(11): 186-188.

Martins CMMR, Pinheiro ESC, Gentilini M, Benavides ML and Santos MV. (2017) Efficacy of a high free iodine barrier teat disinfectant for the prevention of naturally occurring new intramammary infections and clinical mastitis in dairy cows. J Dairy Sci. 100(5): 3930-3939.

Martin, S. W., Meek, A. H., & Willeberg, P. (1997). Epidemiología veterinaria: principios y métodos. https://dialnet.unirioja.es/servlet/libro?codigo=179914.

McDougall S, Agnew KE, Cursons R, Hou XX and Compton CRW. (2007) Parenteral treatment of clinical mastitis with tylosin base or penethamate hydriodide in dairy cattle. J Dairy Sci. 90(2): 779-789.

McDougall S, Bryan MA and Tiddy RM. (2009) Effect of treatment with the nonsteroidal antiinflammatory meloxicam on milk production, somatic cell count, probability of re-treatment, and culling of dairy cows with mild clinical mastitis. J Dairy Sci. 92(9): 4421-4431.

McInerney JP, Howe KS and Schepers JA. (1992) A framework for the economic analysis of disease in farm livestock. Prevent Vet Med. 13(2): 137-154.

McParland S, Dillon PG, Flynn J, Ryan N, Arkins S and Kennedy A. (2019) Effect of using internal teat sealant with or without antibiotic therapy at dry-off on subsequent somatic cell count and milk production. J Dairy Sci. 102(5): 4464-4475.

McPhee CS, Anderson KL, Yeatts JL, Mason SE, Barlow BM and Baynes RE. (2011) Milk and plasma disposition of thymol following intramammary administration of a phytoceutical mastitis treatment. J Dairy Sci. 94(4): 1738-1743.

Mekonnen SA, Koop G, Melkie ST, Getahun CD, Hogeveen H and Lam TJ. (2017) Prevalence of subclinical mastitis and associated risk factors at cow and herd level in dairy farms in North-West Ethiopia. Prevent Vet Med. 145: 23-31.

Mihaylova D, Georgieva L and Pavlov A. (2013) *In vitro* antioxidant activity and phenolic composition of Nepeta cataria L. extracts. Int J Agricult Sci Technol. 1(4): 74-79.

Misk N, Misk T, El-Khamary A and Semeika M. (2018) A retrospective study of surgical affections of mammary glands in cattle and buffaloes and their management in the field. J Vet Med Sci. 80(10: 1576-1583.

Moravej H, Moravej Z, Yazdanparast M, Heiat M, Mirhosseini A, Moosazadeh Moghaddam M and Mirnejad R. (2018) Antimicrobial peptides: features, action, and their resistance mechanisms in bacteria. Microb Drug Resist. 24(6): 747-767.

Muluye RA, Bian Y and Alemu PN. (2014) Anti-inflammatory and antimicrobial effects of heat-clearing Chinese herbs: a current review. J Trad

Complement Med. 4(2): 93-98.

Mushtaq S, Shah AM, Shah A, Lone SA, Hussain A, Hassan QP and Ali MN. (2018) Bovine mastitis: An appraisal of its alternative herbal cure. Microb Pathogen. 114: 357-361.

Mushtaq S, Shah AM, Shah A, Lone SA, Hussain A, Hassan QP and Ali MN. (2018) Bovine mastitis: An appraisal of its alternative herbal cure. Microb Pathogen. 114: 357-361.

Naqvi SA, De Buck J, Dufour S and Barkema HW. (2018) Udder health in Canadian dairy heifers during early lactation. J Dairy Sci. 101(4): 3233-3247.

Nedić S, Vakanjac S, Samardžija M and Borozan S. (2019) Paraoxonase 1 in bovine milk and blood as marker of subclinical mastitis caused by *Staphylococcus aureus*. Res Vet Sci. 125: 323-332.

Ngu Ngwa V, Cuteri V, Awah-Ndukum J, Tangwa BV and Manchang KT. (2020) Bacterial pathogens involved in bovine mastitis and their antibiotic resistance patterns in the Adamawa Region of Cameroon. J Dairy Res Tech. 3: 12.

Nickerson SC, Owens WE and Boddie RL. (1995) Mastitis in dairy heifers: initial studies on prevalence and control. J Dairy Sci. 78(7): 1607-1618.

Nirala NR, Harel Y, Lellouche JP and Shtenberg G. (2020) Ultrasensitive haptoglobin biomarker detection based on amplified chemiluminescence of magnetite nanoparticles. J Nanobiotechnol. 18(1): 1-10.

Noguda T. (2018) Isolation and characterization of lytic bacteriophages, a potential alternative for bovine mastitis control, Doctoral dissertation, University of the Free State.

Oliver SP and Murinda SE. (2012) Antimicrobial resistance of mastitis pathogens. Veterinary Clinics: Food Ani Pract. 28(2): 165-185.

Oliver SP, Almeida RA, Gillespie BE, Headrick SJ, Dowlen HH, Johnson DL, Lamar KC, Chester ST and Moseley WM. (2004) Extended ceftiofur therapy for treatment of experimentally-induced Streptococcus uberis mastitis in lactating dairy cattle. J Dairy Sci. 87(10):3322-3329.

Orellano MS, Isaac P, Breser ML, Bohl LP, Conesa A, Falcone RD and Porporatto C. (2019) Chitosan nanoparticles enhance the antibacterial activity of the native polymer against bovine mastitis pathogens. Carbohydrate Polymers 213: 1-9.

Oultram JW, Ganda EK, Boulding SC, Bicalho RC and Oikonomou G. (2017) A metataxonomic approach could be considered for cattle clinical mastitis diagnostics. Front Vet Sci. 4: 36.

Park YK, Fox LK, Hancock DD, McMahan W and Park YH. (2012) Prevalence and antibiotic resistance of mastitis pathogens isolated from dairy herds transitioning to organic management. J Vet Sci. 13(1): 103-105.

Pașca C, Mărghitaș L, Dezmirean D, Bobiș O, Bonta V, Chirilă F, Matei I and Fiț N. (2017) Medicinal plants based products tested on pathogens isolated from mastitis milk. Molecules 22(9):1473.

Petersson-Wolfe CS, Mullarky IK and Jones GM. (2010) *Staphylococcus aureus* mastitis: cause, detection, and control. https://www.pubs.ext.vt.edu/404/404-229/404-229.html.

Pieterse R and Todorov SD. (2010) Bacteriocins: exploring alternatives to antibiotics in mastitis treatment. Brazilian J Microbiol. 41: 542-562.

Pinedo P, Karreman H, Bothe H, Velez J and Risco C. (2013) Efficacy of a botanical preparation for the intramammary treatment of clinical mastitis on an organic dairy farm. Canadian Vet J. 54(5): 479.

Pinheiro Machado GT, Veleirinho MB, Mazzarino L, Machado Filho LCP, Maraschin M, Cerri RLA and Kuhnen S. (2019) Development of propolis nanoparticles for the treatment of bovine mastitis: in vitro studies on antimicrobial and cytotoxic activities. Canadian J Ani Sci. 99(4): 713-723.

Pyörälä S and Pyörälä EO. (1998) Efficacy of parenteral administration of three antimicrobial agents in treatment of clinical MAST in lactating cows: 487 cases (1989-1995). J Am Vet Med Assoc. 212(3): 407-412.

Rainard P. (2017) Mammary microbiota of dairy ruminants: fact or fiction?. Vet Res. 48(1): 1-10.

Rainard P, Foucras G, Fitzgerald JR, Watts JL, Koop G and Middleton JR. (2018) Knowledge gaps and research priorities in *Staphylococcus aureus* mastitis control. Transboundary Emerg Dis. 65: 149-165.

Rajala-Schultz PJ, Gröhn YT, McCulloch CE and Guard CL. (1999) Effects of clinical mastitis on milk yield in dairy cows. J Dairy Sci. 82(6): 1213-1220.

Rambabu K, Sreenu M, Sureshkumar RV and Rao TSC. (2011) Incidence of udder and teat affections in buffaloes. Tamil Nadu J Vet Ani Sci. 7(6): 309-311.

Ranjan R, Gupta MK and Singh KK. (2011) Study of bovine mastitis in different climatic conditions in Jharkhand, India. Vet World 4(5): 205-208.

Ranjith D, Nisha AR, Nair SN, Litty M, Rahman M and Juliet S. (2018) Evaluation of analgesic and anti-inflammatory activity of herbal formulation used for mastitis in animals. Int J Appl Sci Engineer. 6(1): 37-48.

Ren X, Wang L and Chen W. (2020) *Oxytropis glabra* DC. inhibits biofilm formation of *Staphylococcus epidermidis* by down-regulating ica operon expression. Curr Microbiol. 77(7): 1167-1173.

Ribeiro MG, Risseti RM, Bolaños CA, Caffaro KA, de Morais AC, Lara GH, Zamprogna TO, Paes AC, Listoni FJ and Franco MM. (2015) *Trueperella pyogenes* multispecies infections in domestic animals: a retrospective study of 144 cases (2002 to 2012). Vet Q. 35(2): 82-87.

Rossi RS, Amarante AF, Guerra ST, Latosinski GS, Rossi BF, Rall VLM and Pantoja JCDF. (2019) Efficacy of cefquinome and a combination of cloxacillin and ampicillin for treatment of dairy cows with *Streptococcus agalactiae* subclinical mastitis. PLoS One 14(4): e0216091.

Ruegg PL. (2009) Management of mastitis on organic and conventional dairy farms. J Anim Sci. 87 (13 Suppl): 43-55.

Ruegg PL. (2017) A 100-Year Review: Mastitis detection, management, and prevention. J Dairy Sci. 100(12): 10381-10397.

Ruegg PL, Godden S, Lago A, Bey R and Leslie K. (2009) On-farm culturing for better milk quality. In: Proc 2009 Western Dairy Management Conference, KS: Kansas State University Manhattan, pp. 149-159.

Ryan MP and Adley CC. (2010) *Sphingomonas paucimobilis*: a persistent Gram-negative nosocomial infectious organism. J Hospital Inf. 75(3): 153-157.

Sang Y and Blecha F. (2008) Antimicrobial peptides and bacteriocins: alternatives to traditional antibiotics. Anim Hlth Res Rev. 9(2): 227-235.

Seegers H, Fourichon C and Beaudeau F. (2003) Production effects related to mastitis and mastitis economics in dairy cattle herds. Vet Res. 34(5): 475-491.

Shah MS, Qureshi S, Kashoo Z, Farooq S, Wani SA, Hussain MI, Banday MS, Khan AA, Gull B, Habib A, Khan SM and Dar BA. (2019) Methicillin resistance genes and in vitro biofilm formation among *Staphylococcus aureus* isolates from bovine mastitis in India. Comp Immunol Microbiol Infect Dis. 64:117-124.

Sheet OH, Grabowski NT, Klein G and Abdulmawjood A. (2016) Development and validation of a loop mediated isothermal amplification (LAMP) assay for the detection of *Staphylococcus aureus* in bovine mastitis milk samples. Molec Cellular Probes 30(5): 320-325.

Shibata Y, Nomoto R and Osawa R. (2014) Development of a multilocus sequence typing scheme for *Streptococcus gallolyticus*. Microbiol. 160(1): 113-122.

Shinozuka Y, Kawai K, Takeda A, Yamada M, Kayasaki F, Kondo N, Sasaki Y, Kanai N, Mukai T, Sawaguchi M, Higuchi M, Kondo H, Sugimoto K, Kumagai S, Murayama I, Sakai Y, Baba K, Maemichi K, Ohishi T, Mizunuma T, Kawana A, Yasuda A and Watanabe A. (2019) Influence of oxytetracycline susceptibility as a first-line antibiotic on the clinical outcome in dairy cattle with acute *Escherichia coli* mastitis. J Vet Med Sci. 81(6): 863-868.

Shinozuka Y, Morita T, Watanabe A and Kawai K. (2018) Live bacteria in clots from bovine clinical mastitis milk with no growth in conventional culturing. Asian J Anim Vet Adv. 13(2): 197-200.

Singh PJ. (1994) A study on economic losses due to mastitis in India. Indian J Dairy Sci. 47: 265-272.

Sinha MK, Thombare NN and Mondal B. (2014) Subclinical mastitis in dairy animals: incidence, economics, and predisposing factors. Scient World J. 2014: 523984.

Skowron K, Sękowska A, Kaczmarek A, Grudlewska K, Budzyńska A, Białucha A and Gospodarek-Komkowska E. (2019) Comparison of the effectiveness of dipping agents on bacteria causing mastitis in cattle. Ann Agricult Environ Med. 26(1): 39-45.

Skurnik M, Pajunen M and Kiljunen S. (2007) Biotechnological challenges of phage therapy. Biotechnol Lett. 29(7): 995-1003.

Sordillo LM. (2011) New concepts in the causes and control of mastitis. J mammary Gland Biol Neoplasia 16(4): 271-273.

Sserunkuma P, McGaw LJ, Nsahlai IV and Van Staden J. (2017) Selected southern African medicinal plants with low cytotoxicity and good activity against bovine mastitis pathogens. South African J Botany 111: 242-247.

Steele N and McDougall S. (2014) Effect of prolonged duration therapy of subclinical mastitis in lactating dairy cows using penethamate hydriodide. New Zealand Vet J. 62(1): 38-46.

Steeneveld W, van Werven T, Barkema HW and Hogeveen H. (2011) Cow-specific treatment of clinical mastitis: An economic approach. J Dairy Sci. 94(1): 174-188.

Suojala L, Kaartinen L and Pyörälä S. (2013) Treatment for bovine E scherichia coli mastitis–an evidence-based approach. J Vet Pharmacol Therapeut. 36(6): 521-531.

Suresh S, Sankar P, Telang AG, Kesavan M and Sarkar SN.

(2018) Nanocurcumin ameliorates *Staphylococcus aureus*-induced mastitis in mouse by suppressing NF-κB signaling and inflammation. Int Immunopharmacol. 65: 408-412.

Swarup D, Kumar PN and Singh R. (1989) Evaluation of milk conductivity test in detecting subclinical udder infection. Indian J Anim Sci. 59(10): 1227-1229.

Szweda P, Schielmann M, Kotlowski R, Gorczyca G, Zalewska M and Milewski S. (2012) Peptidoglycan hydrolases-potential weapons against *Staphylococcus aureus*. Appl Microbiol Biotechnol. 96(5): 1157-1174.

Tarazona-Manrique LE, Villate-Hernández JR and Andrade-Becerra RJ. (2019) Bacterial and fungal infectious etiology causing mastitis in dairy cows in the highlands of Boyacá (Colombia). Revista Facultad Med Vet Zootec. 66(3): 208-218.

Titze I, Lehnherr T, Lehnherr H and Krömker V. (2020) Efficacy of bacteriophages against *Staphylococcus aureus* isolates from bovine mastitis. Pharmaceuticals 13(3): 35.

Tiwari R, Chakraborty S, Dhama K, Rajagunalan S and Singh SV. (2013) Antibiotic resistance–an emerging health problem: causes, worries, challenges and solutions–a review. Int J Curr Res. 5(07): 1880-1892.

Turk R, Koledić M, Maćešić N, Benić M, Dobranić V, Đuričić D, Cvetnić L and Samardžija M. (2017) The role of oxidative stress and inflammatory response in the pathogenesis of mastitis in dairy cows. Mljekarstvo 67(2): 91-101.

Turk R, Piras C, Kovačić M, Samardžija M, Ahmed H, De Canio M, Urbani A, Meštrić ZF, Soggiu A, Bonizzi L and Roncada P. (2012) Proteomics of inflammatory and oxidative stress response in cows with subclinical and clinical mastitis. J Proteomics. 75(14): 4412-4428.

Vakkamäki J, Taponen S, Heikkilä AM and Pyörälä S. (2017) Bacteriological etiology and treatment of mastitis in Finnish dairy herds. Acta Vet Scandinavica 59(1): 1-9.

van den Borne BH, Halasa T, van Schaik G, Hogeveen H and Nielen M. (2010) Bioeconomic modeling of lactational antimicrobial treatment of new bovine subclinical intramammary infections caused by contagious pathogens. J Dairy Sci. 93(9): 4034-4044.

Verjan García N, Almario Leiva GA, Romero Jola NJ and Fandiño LC. (2015) Múltiples abscesos en un cerdo causados por Trueperella pyogenes (Arcanobacterium pyogenes): Reporte de caso. Revista Mexicana Ciencias Pecuarias 6(1): 91-98.

Vyas S, Shukla V and Doshi N. (2019) FMD and mastitis disease detection in cows using Internet of Things (IOT). Procedia Computer Sci. 160: 728-733.

Wald R, Hess C, Urbantke V, Wittek T and Baumgartner M. (2019) Characterization of *Staphylococcus* species isolated from bovine quarter milk samples. Animals 9(5): 200.

Wang X, Teng D, Wang X, Hao Y, Chen H, Mao R and Wang J. (2019) Internalization, distribution, and activity of peptide H2 against the intracellular multidrug-resistant bovine mastitis-causing bacterium *Staphylococcus aureus*. Scient Rep, 9(1): 1-12.

Wawron W, Bochniarz M and Piech T. (2010) Yeast mastitis in dairy cows in the middle-eastern part of Poland. Bull Vet Inst Pulawy, 54(2), 201-204.

Wernicki A, Puchalski A, Urban-Chmiel R, Dec M, Stegierska, D, Dudzic A and Wojcik, A. (2014) Antimicrobial properties of gold, silver, copper and platinum nanoparticles against selected microorganisms isolated from cases of mastitis in cattle. Med Weter 70(9): 564-567.

Williamson JH and Di Menna ME. (2007) Fungi isolated from bovine udders, and their possible sources. New Zealand Vet J. 55(4): 188-190.

Wilson DJ, Mallard BA, Burton JL, Schukken YH and Grohn YT. (2009) Association of *Escherichia coli* J5-specific serum antibody responses with clinical mastitis outcome for J5 vaccinate and control dairy cattle. Clin Vaccine Immunol. 16(2): 209-217.

Wuytack A, De Visscher A, Piepers S, Haesebrouck F and De Vliegher S. (2020) Fecal non-aureus *Staphylococci* are a potential cause of bovine intramammary infection. Vet Res. 51(1): 1-13.

Xu W, Guan R, Lu Y, Su X, Xu Y, Du A and Hu S. (2015) Therapeutic effect of polysaccharide fraction of *Atractylodis macrocephalae* Koidz. in bovine subclinical mastitis. BMC Vet Res. 11(1): 1-9.

Yadav RK, Singh M, Roy S, Gautam S, Rawat JK, Singh L, Ansari MN, Saeedan AS and Kaithwas G. (2020) Evaluation of α-linolenic acid–based intramammary nanosuspension for treatment of subclinical mastitis. J Dairy Sci. 103(3): 2701-2706.

Yang WT, Ke CY, Wu WT, Lee RP and Tseng YH. (2019) Effective treatment of bovine mastitis with intramammary infusion of *Angelica dahurica* and *Rheum officinale* extracts. Evidence-Based Complement Alternat Med. 2019: 7242705.

Yang X, Ouyang W, Sun J and Li X. (2009) Post-antibiotic effect of Amoxicillin nanoparticles against main

pathogenic bacteria of Bovine mastitis *in vitro*. J Northwest A F Univ-Natural Sci. 37(6): 1-6.

Young-Speirs M, Drouin D, Cavalcante PA, Barkema HW and Cobo ER. (2018) Host defense cathelicidins in cattle: types, production, bioactive functions and potential therapeutic and diagnostic applications. Int J Antimicrob Agents 51(6): 813-821.

Younus M, Ahmad T, Sharif A, Bilal MQ, Nadeem M and Ashfaq K. (2018) Comparative therapeutic efficacy of homeopathic complex, herbal extract and antibiotic in the treatment of subclinical mastitis in dairy buffaloes. Buffalo Bull. 37(2): 221-234.

Yu J, Ren Y, Xi X, Huang W and Zhang H. (2017) A novel lactobacilli-based teat disinfectant for improving bacterial communities in the milks of cow teats with subclinical mastitis. Frontiers Microbiol. 8: 1782.

Zhu L, Cao X, Xu Q, Su J, Li X and Zhou W. (2018) Evaluation of the antibacterial activity of tilmicosin-SLN against *Streptococcus agalactiae*: *in vitro* and *in vivo* studies. Int J Nanomed. 13: 4747.

Zigo F, Vasil M, Ondrašovičová S, Výrostková J, Bujok J and Pecka-Kielb E. (2021) Maintaining optimal mammary gland health and prevention of MAST. Frontiers Vet Sci. 8: 69.