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Recent Advancement in Therapeutic and Managemental Approaches of Mastitis in Dairy Animals

Saksham Mandawat*, Rashmi Singh, Anita Sewag, Y.P. Singh, D.S. Meena and N.K. Jeph

Post Graduate Institute of Veterinary Education and Research, Jamdoli, RAJUVAS Jaipur 302 031, India

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***Correspondence**
Saksham Mandawat
mandawatsaksham@gmail.com

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Abstract: Mastitis, an inflammation of the udder in dairy animals, continues to pose a significant challenge, affecting both animal welfare and the economic sustainability of the dairy industry. It leads to decreased production efficiency and increased culling rates, resulting in considerable financial losses. Bovine mastitis, primarily caused by bacterial pathogens, necessitates early detection for effective management. Although various diagnostic techniques are available, conventional therapies like antibiotics face limitations, particularly with the growing issue of antibiotic resistance. This highlights the urgent need for early and efficient pathogen identification in farm settings to enable targeted interventions. Efforts to address these challenges have led to the development of alternative methods such as stem cell therapy, natural secretory compounds, and nutritional strategies. However, the efficacy of these approaches in managing mastitis remains inadequately studied. Future research must prioritize the evaluation of these novel therapeutic options and focus on developing sustainable solutions to replace conventional antibiotic treatments, ensuring effective mastitis management while combating antibiotic resistance.

Key words: Mastitis, antibiotic resistance, bacteriophages, nano particle technology, welfare.

Mastitis an inflammatory disorder of mammary gland in dairy animal, can result in partial or complete damage to the udder, leading to impaired function, decreased body weight and slower growth rate. Mastitis, an inflammation within the mammary gland triggered by infectious agents, remains a significant challenge in dairy animals. It affects animal welfare and causes significant economic losses in the dairy industry by reducing milk production and increasing culling rates. Mastitis is primarily caused by bacterial infection and is classified into two types based on epidemiology: contagious and environmental mastitis. The former is caused by contagious bacteria such as *Staphylococcus aureus, Staphylococcus agalactiae and Mycoplasma* spp. These pathogens are typically transmitted from infected cows to healthy ones during milking, often via hands, towels or milking machines, which serves as bacterial

Table 1. Pathogen causing mastitis and their symptoms

Bacterial	Clinical signs
Staphylococcus aureus	Persistent udder swelling, clots or flakes in milk, sometimes fever
Streptococcus agalactiae	Thickened or stringy milk, fever, swollen udder.
E. coli	Acute mastitis, sudden decrease in milk production, watery milk, fever, swollen udder.
Klebsiella spp.	Environment mastitis, sudden onset of fever, swollen udder, thickened or clotted milk.
Streptococcus uberis	Clinical mastitis with variable signs including fever, udder swelling and abnormal milk consistency.
Mycoplasma spp.	Chronic mastitis, persistent inflammation, variable milk production, sometimes apparent clinical signs.
Fungal	
Candida spp.	Fungal mastitis thickened or discoloured milk, presence of fungal hyphae in milk, sometimes fever and udder swelling.
Prototheca spp.	Protothecal mastitis, chronic inflammation, abnormal milk consistency, sometimes skin lesions on udder or teats
Neospora caninum	Protozoal mastitis, neurological symptoms, reproductive issues, sometimes no apparent clinical signs.
Viral	
Bovine herpesvirus	Viral mastitis, fever, decreased milk production, udder swelling, sometimes respiratory signs.

Table 2. Physcial Causes of mastitis

Causes	Description
Trauma /Teat damage	Physical injury to the udder, often caused by rough handling during milking or by environmental hazards in the barn. Damage to the teat canal or teat end, which can occur due to improper milking machine setting or aggressive machine stripping.
Poor hygiene	Inadequate udder and teat sanitation practices.
Environmental stress	Stressors such as extreme temperature, overcrowding, or poor ventilation in the barn, which weaken the cow's immune system
Improper milking technique	Inefficient or improper milking technique, including overmilking, incomplete milking, or failure to maintain proper milking machine function.

Table 3. Chemical causes of Mastitis

Chemical	Effect
Iodine	Chemical burn, irritation
Chlorhexidine	Irritation, chemical burn
Quaternary Ammonium compounds	Skin and mucus membrane irritation
Hydrogen peroxide	Irritation, burn
Phenolic disinfectant	Chemical burn, irritation
Formaldehyde	Severe irritation, chemical burn
Sodium Hypochlorite	Severe irritation, chemical burn
Glutaraldehyde	Systemic toxicity
Heavy metals (lead, cadmium, Arsenic)	Increased infection risk
Pesticide and herbicide (Organophosphates, Glyphosate)	Systemic toxicity, inflammation

reservoirs. Environmental mastitis occurs when various pathogens, including bacteria (*E. coli*, *Klebsiella spp.*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Enterobacter spp.*, *Trueperella pyogenes*, *Pseudomonas* spp.), fungi (*Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Trichosporon* spp.), viruses (Bovine leukemia virus, Bovine herpesvirus 1, FMD virus, Bovine viral diarrhoea virus), or parasites (*Stephanofilaria* spp., *Fasciola hepatica*, *Toxoplasma gondii*, *Neospora caninum*), invade the udder and cause infection (Garcia, 2004). Symptons of these pathogens are detailed in Table 1.

Mastitis caused by *E. coli* is typically clinical and transient. Symptoms can vary widely, ranging from mild cases with localized signs, such as redness and swelling of the udder, to severe cases with systemic symptoms, including fever. In severe instances, *E. coli*-induced clinical mastitis can result in irreversible damage to mammary gland tissue, total loss of milk production, and, in some cases, the death of the affected dairy cow (Nee *et al.*, 2020). Mastitis adversely affects both the composition and economic value of milk (Halasa *et al.*, 2007; Kalinska *et al.*, 2017). Environmental mastitis, in particular, is strongly influenced by management practices on dairy farms. Physical and chemical factors leading to mastitis are detailed in Table 2 and 3. Over the past century, significant progress has been made in controlling mastitis.

In some cases, mastitis presents visible symptoms, such as udder inflammation and changes in milk, primarily caused by environmental pathogens like coliforms. However, subclinical mastitis, which lacks obvious signs, affects milk composition and can only be detected through laboratory testing. These include prolonged administration of antibiotics through the udder, increased occurrence of udder mycosis due to deficiencies in minerals, vitamins, and antioxidants, dietary imbalances, poor environment conditions and changes in weather. These factors can compromise the cow's immune system and make the udder more vulnerable to infections and inflammatory responses. Mastitis in cow can be classified into three main types based on the causative agent: contagious, environmental and summer mastitis (Fig.1) (Kibebew *et al.*, 2017).

*Contagious mastitis***:** This form of mastitis is triggered by bacteria residing on the teat's skin and within the udder. Contagious mastitis spreads between cows during the milking process and can be further categorise as follows

Clinical Mastitis: This type of mastitis is marked by clear signs of inflammation, including swelling, heat, redness and pain. It is often evidenced by visible clots or discoloration in milk and commonly accompanied by swollen, tender under, fever and decrease in appetite. Clinical mastitis can be divided into (i) per-acute mastitis (severe inflammation, marked reduction in milk yield, changes in milk composition and systemic symptoms like fever, shivering, depression, loss of appetite and weight loss) (ii) acute mastitis (similar to per-acute mastitis but less intense systemic signs including fever and mild depression) (iii) sub-acute mastitis (minimal inflammation in the mammary gland signs and no signs are visible (Sears *et al.*, 1993).

Subclinical Mastitis: This form lakes obvious inflammation or changes in milk appearance but involves alterations in milk composition, such as increased somatic sale count (SCC), higher leucocyte and epithelial cell presence and shifts in milk Ph and ion level. In healthy lactating animals milk SCC is generally <100,000 cells per ml, while subclinical mastitis can elevate SCC beyond1,0000,000 cells/ml. Inflammatory infection (IMM) are the main contributors to SCC increases at both herd and individual levels.

Chronic Mastitis: A prolonged inflammatory condition that may span months and continue from one lactation period to another. It often remains subclinical but can have periodic sub-acute or acute episodes.

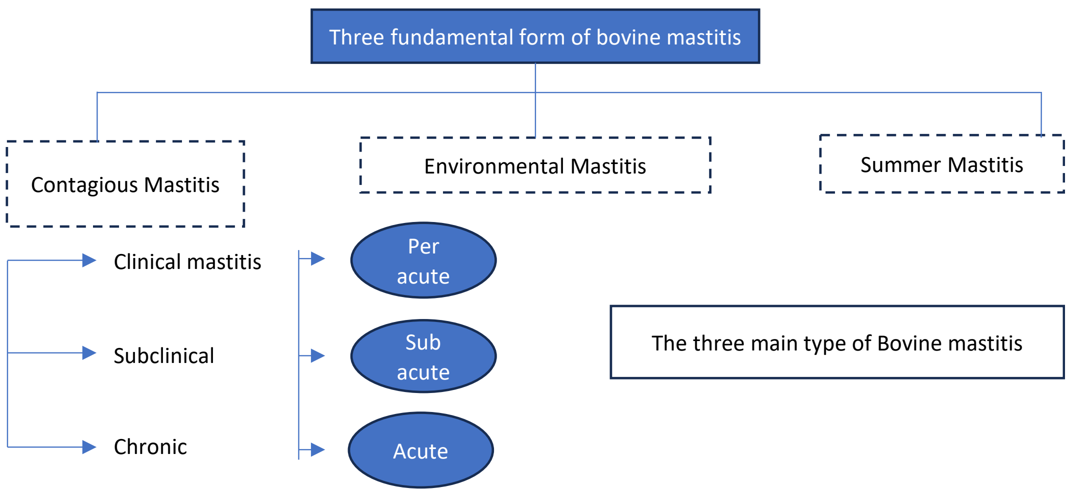

Fig. 1. Classification of mastitis.

Environmental Mastitis: Caused by pathogens such as *Escherichia coli* that do not typically inhabit the teat or udder, but invade through contact with contaminated surroundings, like faeces, bedding and feed.

Summer Mastitis: Specific form affecting dry cows and heifers, characterised by acute inflammation leading to significant udder damage. The infected quarter often suffers irreversible harms, frequently resulting in early culling. It is more common in environments where teat damage and fly exposure are prevalent. Symptoms include a swollen, hot and hard quarter, emitting thick, foul smell secretions.

Economic significance

Mastitis significantly impacts the productivity and economic viability of dairy farming. It not only reduces milk value yield but also leads to the culling of animals at an unacceptably young age. Surveys in major milk-producing countries indicate that each year, mastitis affects 15 to 20% of cows, with estimates showing a 30% reduction in productivity per affected quarter and a 15% reduction in production per cow per lactation (Ibrahim, 2017). Both clinical and subclinical mastitis have significant economic implications. Milk affected by mastitis must be discarded, resulting in direct loss of revenue. Additionally, there are costs associated with treatment, veterinary expenses and potential decreases in future milk production. Subclinical mastitis although less visibly apparent. Cross- bred cattle, with their higher production potential, often experience more pronounced losses during mastitis episodes.

The economic losses in India due to mastitis are substantial. Mastitis is considered the most costly disease in the Indian dairy industry. Studies and reports have shown that it causes significant economic losses, impacting milk yield, cow health, and leading to increased culling rates. The direct economic impact of mastitis includes reduced milk yield, increased veterinary costs, and higher labour costs for managing affected cows (Harmon, 2012; Heeschen *et al.*, 2012). For instance, infections caused by *Streptococcus dysgalactiae* resulted in 20% reduction in yield, while E. coli infections led to 50% decline (Stanek *et al.*,2024).

Advancement in diagnosis of mastitis

Advancement in mastitis diagnosis have significantly improved detection accuracy and efficiency. In contrast, advanced diagnostic test provides quantitative data and are characterised by higher specificity and sensitivity. This shift toward advanced testing methods has been noted by researchers in recent years. (Godden *et al.*, 2017; Hussain *et al.*, 2018; Chakraborty *et al.*, 2019). Determining the bacterial species is crucial for selecting the appropriate antibiotics for treatment and the right processing methods for dairy products. Mastitis related inflammation triggers the release of inflammatory mediators and reactive oxygen species (Turk *et al.*, 2017). leading to elevated levels of inflammatory and oxidative markers. The response of the mammary gland to invading pathogens is influenced by the virulence of the causative agents, along with factors related to the microbial environment and host. Consequently, the epidemiology of mastitis varies depending on the interplay between pathogens. By utilizing neural networks and smart sensors, IoT application significantly reduce disease occurrence. Various diagnostic techniques exist, but current therapies like antibiotics have limitations, including emerging antibiotic resistance (Fig. 2).

Advancement in treatment of mastitis

Antibiotic therapy: Antibiotics are commonly given as a prophylactic for mastitis during the dry period, with dry cow therapy using antimicrobials permitted as a prophylactic

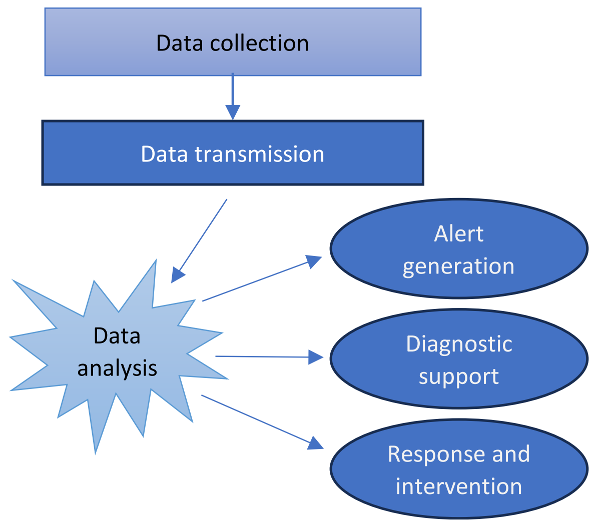

Fig. 2. Working principle of Internet of Things (IoT).

Table 4. Combinations of drugs used in antibiotic therapy

Antibiotic combination	Purpose	Example
Penicillin + Aminoglycosides	Broad spectrum coverage	Ampicillin + Gentamycin
Cephalosporin + Macrolides	Extended coverage	Cefalexin + Erythromycin
Beta lactam + fluoroquinolone	Dual action against gram -ve and gram + ve bacteria	Amoxicillin +Enrofloxacin
Third generation cephalosporin + Lincosamide	Effective against resistance strain	Ceftiofur + Clindamycin
Penicillin + Tetracycline	Broad coverage with minimum resistance	Penicillin + Doxycycline

measure across livestock species. When selecting antibiotics for treating clinical mastitis, its crucial to consider the history, aetiology, antibiotic sensitivity profile and adhere to recommended therapeutic principle. One notable advancement involves the development of targeted antibiotic treatment based on pathogen identification through advanced molecular technique. Examples of antibiotic combinations commonly used in mastitis treatment, categorised by their purpose and example of specific antibiotics within each combination are given in Table 4.

Interpreting results carefully is vital to avoid using antibiotics indiscriminately for staphylococcus mastitis in cows. It's essential to consider clinical relevance alongside sensitivity data for optimal antibiotic use, reducing the risk of ineffective treatment and promoting responsible antibiotic management (Wald *et al.,* 2019).

Bacteriophage therapy: Their ability to target specific bacteria and replicate exponentially makes them potential tools against pathogenic bacteria (Carson *et al.*, 2010). However, many bacteriophages lack environmental stability and require specific storage and handling conditions, limiting their practical usage. Dias *et al.* (2013) reported findings that the isolated bacteriophages possessed features such as thermostability and high lytic potential, rendering them suitable candidate against antibiotic- resistant strains of *S. aureus.* Practical applications of phage therapy in symptomatic mastitis cases reported a cure rate of 66.6% when phage cocktails targeting *Bacillus* and *Escherichia* species were applied. However, further research is needed to address variability in treatment outcomes due to environmental and host factors (Imklin *et al.,* 2024).

Herbal therapy: The use of herbal therapy is gaining popularity as a viable therapy for mastitis due to its minimal risk of side effects. Ethnoveterinary practices, a subset of veterinary medicine, emphasize employing herbal formulations to address diseases such as mastitis (Kachhawa *et al.,* 2022). In regions like southern Brazil, plants such as *Achillea millefolium* and *Allium sativum* are traditionally utilized for mastitis prevention and management, attributed to their anti-inflammatory, antimicrobial, and immune-boosting properties. According to Ranjith *et al.* (2018), methanolic extracts derived from a 1:1 combination of *Diploclisia glaucescens* leaves and *Curcuma longa* rhizomes exhibited noteworthy analgesic and anti-inflammatory effects. Moreover, research by Cheng *et al.* (2019) highlights that *Moringa* extract plays a significant role in regulating inflammatory markers and strengthening antioxidant systems in bovine udder epithelial cells. It also inhibited NF-κB activity while enhancing the expression of antioxidant enzymes such as HO-1 and NQO1. Additionally, *Moringa* extract promoted casein protein synthesis, showcasing its potential as a therapeutic agent to manage udder inflammation and support antioxidant defences.

Immunotherapy: Leither *et al.* (2013) demonstrated the effectiveness of microbeads carrying specific antibodies against mastitis – causing bacteria, termed the Y complex, compared to antibiotics and NSAIDs. Additionally, interleukins-2 (IL-2) and immunostimulants like Saccharomyces cerevisiae yeast and egg yolk immunoglobins have shown therapeutic potential in managing mastitis by enhancing the immune response. These approaches offer promising alternatives to traditional antibiotic treatments and may help minimize the risk of new infection.These markers included somatic cell count (SCC), serum amyloid A (SAA), lactoferrin, N-acetyl-beta-D-glucosaminidase (NAGase) (Sharun *et al.,* 2021). Elevated concentration of milk markers indicated that IL- 2 activity on epithelial

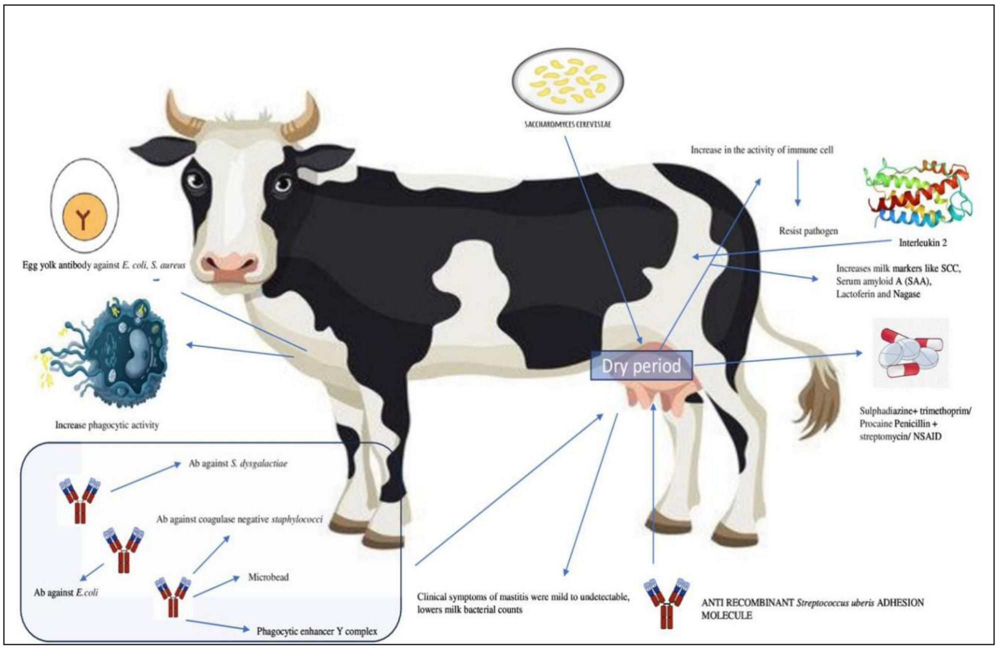

Fig. 3. Leveraging immunological methods to treat mastitis (Source: Adapted from: Sharun et al., 2021).

cells contributed to increase resistance against invading pathogens. Supplementing regular dry cow antibiotic treatment for *S. aureus* with IL- 2 enhance its effectiveness. However, 7.5% of COW treated with IL-2 experience abortion.

Nanoparticle- based technology: Nanoparticle technology is emerging as an innovative and effective delivery method for antimicrobial agents and various other drugs (Gomes and Henrique,2016). Different type of nanoparticle have been studies for its role in treating mastitis, showing promising results (Castelani *et al.,* 2019; Kalinska *et al.,* 2019; Orellano *et al.,* 2019; Pinheiro Machado *et al.,* 2019). Nanoparticle formulation can improve the uptake of active compounds by phagocytes, thereby enhancing their antimicrobial effectiveness (Gruet *et al.,* 2001). They have demonstrated effectiveness against several multidrug-resistant bacteria that pose significant threats to society (Yuan *et al.,* 2018; Castelani *et al.,* 2019).

Stem cell therapy: Bovine mammary epithelial stem cells are vital for maintaining under health and could be utilised to treat structural or cytological defects in udder caused by mastitis. Mesenchymal stem cells (MSCs) have been found to possess antibacterial properties, with studies showing their ability to inhibit bacterial growth and enhance bacterial clearance, particularly against methicillin-resistant *S. aureus* (Yuan *et al.,* 2014). This antibacterial activity is mediated by factors produced by MSCs, such as certain antimicrobial peptides. Additionally, MSCs have demonstrated the ability to modulate inflammatory responses, which could be advantageous in managing mastitis (Yuan *et al.,* 2014). However, the precise mechanism behind this modulation remains to be fully elucidated. It's noteworthy that there are species-specific differences in the antimicrobial activity of MSCs, with human MSCs showing broad-spectrum antimicrobial activity mediated by specific enzymes like indoleamine 2,3-dioxygenase (IDO), while murine MSCs lack IDO expression and hence antimicrobial activity. Studies have also explored the therapeutic potential of allogeneic adipose tissue MSCs in reducing bacterial counts in milk during clinical mastitis, indicating a promising avenue for mastitis treatment. These approach could improve milk production (Sharma and Jeong, 2013).

Acoustic pulse therapy (APT): Acoustic pulse therapy (APT) also refers to a shock-wave therapy is an innovative method for treating in dairy cattle. These technique employs hand held device that emits pulse pressure waves capable of penetrating deep tissue layers. These waves can help breakdown his scar tissue in chronic wounds and promote revascularization. Results showed that 70.5% of treated cows returned to normal milk production, compared to only 18.4% in the control group in sub clinical mastitis. In clinical mastitis, APT demonstrated a cure rate of 76.9% (n=13), significantly higher than the 18.7% cure rate achieved with traditional antibiotic therapy (**Leitner** *et al.*, 2018)

Management of Mastitis

Effective management of mastitis involves timely identification, appropriate treatment, and robust preventive measures to minimize its impact on animal health and milk production (Fig. 4). Clinical mastitis can be identified by observing visible alterations in milk, such as clots, flakes, or blood, as well as signs of udder inflammation, redness, or discomfort during milking. Subclinical mastitis, which lacks obvious symptoms, requires regular milk testing, such as somatic cell count (SCC) or milk culture, for detection.

Upon identifying mastitis, immediate steps include isolating the affected animal to prevent the spread of infection and consulting a veterinarian for a diagnosis and treatment plan. Diagnosis typically involves a physical examination of the udder for swelling, redness, or heat, along with milk sample testing to measure SCC and identify pathogens through bacterial culture. Treatment plans are based on culture results and may involve antibiotic therapy, administered systemically or directly into the udder via intramammary infusion. Anti-inflammatory drugs are used to alleviate pain and swelling, while supportive care, such as ensuring proper hydration, nutrition, and comfort, aids recovery.

Monitoring and follow-up are crucial to ensure successful treatment. Regular checks on the animal's progress, including improvements in udder health and milk quality, as well as repeat milk testing, help confirm the elimination of pathogens and resolution of infection. Preventive measures play a key role in reducing mastitis incidence. These include maintaining strict milking hygiene, using disinfectant teat dips post-milking, conducting routine milk testing for early detection, and considering the culling of chronically infected animals. Vaccination against specific pathogens may also be beneficial.

Training farm staff in mastitis recognition, treatment, and prevention ensures consistent and effective management practices. Additionally, maintaining detailed records of mastitis cases, treatments, and outcomes supports trend analysis and informed decision-making for herd health management.

Conclusion and Future Prospects

Conventional diagnostic techniques for mastitis often lack the sensitivity and speed required for efficient detection, limiting their applicability in modern dairy production. Although advanced diagnostic tools provide rapid and accurate results, their widespread adoption is constrained by high costs and technical demands. Antibiotics have long been the cornerstone of mastitis treatment; however, the rising challenge of bacterial resistance has diminished their effectiveness, necessitating the exploration of alternative therapies.

To address these challenges, there is an urgent need for innovative and sustainable approaches to mastitis management. Research should focus on developing universally effective therapeutic options that can replace antibiotics while maintaining efficacy. These alternatives could include immunomodulators, probiotics, or nanotechnology-based solutions. Additionally, advancements in affordable, rapid diagnostic techniques will be critical to enhancing early detection and treatment. By prioritizing these developments, the dairy industry can achieve more effective mastitis control, improving animal welfare, milk quality, and economic sustainability in the future.

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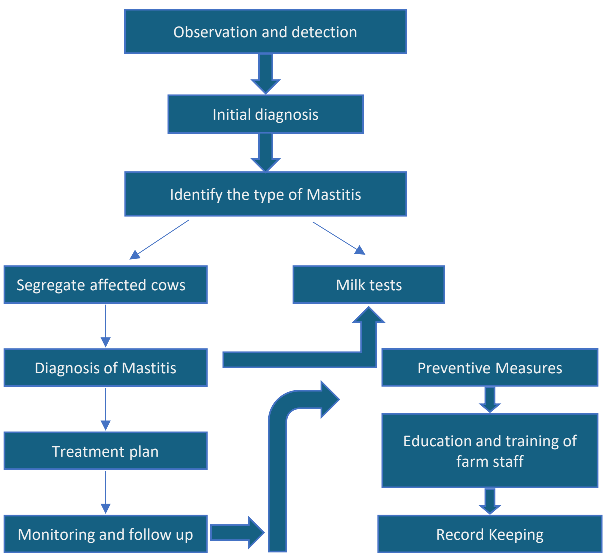

Fig. 4. Management strategies of controlling of mastitis in farm level.

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