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Immunoregulatory mechanisms of mesenchymal stem cell therapy in bovine mastitis

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Abstract

Bovine mastitis remains a significant constraint to dairy production worldwide, resulting in substantial economic losses, animal welfare concerns and growing limitations of antimicrobial-based therapies due to antimicrobial resistance and regulatory restrictions. Mesenchymal stem cell (MSC) therapy demonstrates consistent immunomodulatory, antimicrobial and regenerative effects that directly address the complex pathophysiology of bovine mastitis. Across experimental and early clinical studies, MSC administration results in a marked reduction in mammary inflammation, reflected by decreased somatic cell counts, attenuated leukocyte infiltration and suppression of pro-inflammatory cytokines. While bacteriological cure rates vary depending on the pathogen type and disease severity, MSC therapy consistently improves inflammatory resolution and clinical recovery, particularly in cases of acute mastitis. MSC-derived paracrine factors and extracellular vesicles support epithelial regeneration, angiogenesis and extracellular matrix remodelling, leading to faster restoration of milk yield, improved milk composition and reduced risk of fibrosis. Clinical studies have reported that both autologous and allogeneic MSCs are well-tolerated in dairy cattle, with no significant local or systemic adverse effects and minimal immunogenicity. Therefore, MSC-based treatments have the potential to reduce reliance on antibiotics and eliminate milk withdrawal periods, offering clear economic and public health benefits. However, therapeutic efficacy is influenced by cell source, route of administration, dosing strategy and mastitis phenotype, underscoring the need for optimized and standardized approaches. Collectively, the available evidence demonstrates that MSC therapy delivers reproducible anti-inflammatory and regenerative benefits in bovine mastitis, representing a viable antimicrobial-sparing strategy, particularly when integrated with conventional treatments in chronic or recurrent cases.

Keywords: Mesenchymal stem cells, regenerative medicine, stem cell therapy, inflammation

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Introduction

Bovine mastitis remains one of the most prevalent and economically devastating diseases affecting the global dairy industry (Morales-Ubaldo et al., 2023). Characterised by inflammation of the mammary gland, mastitis is primarily triggered by bacterial pathogens such as *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, *Escherichia coli* and coagulase-negative staphylococci, although fungal and algal infections have also been reported (Cobirka et al., 2020; Morales-Ubaldo et al., 2023). The disease manifests in both clinical and subclinical forms, the latter being particularly dangerous due to the absence of overt clinical signs while still significantly impairing milk quality and yield (Cobirka et al., 2020). From an economic standpoint, mastitis is responsible for substantial direct and indirect losses, including reduced milk production, discarded milk during treatment and withdrawal periods, increased veterinary costs, premature culling and replacement expenses (Morales-Ubaldo et al., 2023). Beyond economic considerations, mastitis poses a serious animal welfare concern. The inflammatory process can induce pain, tissue damage and systemic illness in severe cases, thereby compromising the well-being of affected animals. Recurrent or chronic mastitis can lead to irreversible mammary tissue fibrosis, impaired lactational capacity and heightened susceptibility to subsequent infections (Zhao & Lacasse, 2008).

Antimicrobial therapy remains the cornerstone of mastitis management in dairy cattle. Intramammary and systemic antibiotics are routinely employed during lactation and the dry period to eliminate bacterial pathogens and prevent new infections (Sharun et al., 2021). While these approaches have demonstrated efficacy against certain pathogens, their overall success is increasingly compromised by several biological, practical and societal limitations. The emergence and dissemination of antimicrobial resistance (AMR) represent a critical global challenge associated with the extensive use of antibiotics in food-producing animals (Boireau et al., 2018). Resistant mastitis pathogens have been increasingly reported, raising concerns about treatment failures, zoonotic transmission and the broader public health implications of antibiotic use in dairy farming (Boireau et al., 2018; Moradi et al., 2025). Regulatory pressure to reduce antimicrobial consumption in livestock, particularly in the European Union, has further constrained therapeutic options for mastitis management (More et al., 2022). Additionally, antibiotic therapy does not directly address the inflammatory and degenerative changes within the mammary gland. While bacterial clearance is the primary goal, residual inflammation often persists, impairing epithelial regeneration and milk secretion (Sharun et al., 2021; Nankemann et al., 2025). Antibiotics also necessitate milk withdrawal periods, resulting in economic losses and logistical challenges for farmers (Nankemann et al., 2025). These limitations underscore the need for alternative or adjunctive therapeutic strategies that can modulate inflammation, enhance host defence mechanisms and promote tissue repair without contributing to AMR (Soni et al., 2024).

Mesenchymal stem cells (MSCs) have emerged as promising candidates for regenerative and immunomodulatory therapies across human and veterinary medicine (Mamachan et al., 2024; Sharun et al., 2024a; Banu et al., 2025). Unlike conventional antimicrobial treatments, MSC-based therapies aim to harness and amplify endogenous repair and immune regulatory processes rather than solely targeting pathogens (Mamachan et al., 2024). This paradigm shift is particularly attractive for complex inflammatory diseases such as bovine mastitis, where host-pathogen interactions and dysregulated immune responses play central roles in disease progression and chronicity (Sharun et al., 2022a). MSCs possess a unique combination of properties that are highly relevant to mastitis therapy. These include the ability to modulate innate and adaptive immune responses, secrete a broad array of bioactive molecules with anti-inflammatory and antimicrobial effects, and support tissue regeneration and angiogenesis (Zaripova et al., 2023). MSCs exert their therapeutic effects primarily through paracrine mechanisms rather than direct differentiation, making them suitable for inflammatory environments such as the infected mammary gland. However, despite growing interest, significant knowledge gaps remain regarding optimal cell sources, mechanisms of action in the mammary microenvironment, dosing strategies and translational feasibility in commercial dairy settings. A critical and comprehensive evaluation of these aspects is essential to guide future research and clinical implementation.

Mesenchymal Stem Cells: Biological Basis for Therapy

MSCs, also referred to as mesenchymal stromal cells, are multipotent progenitor cells originally identified in bone marrow and subsequently isolated from a wide range of adult and perinatal tissues. The International Society for Cellular Therapy (ISCT) established minimal criteria to define MSCs, which have been broadly adopted in both human and veterinary research (Dominici et al., 2006; Sharun et al., 2024b). According to these criteria, MSCs must be plastic-adherent under standard culture conditions, express a characteristic set of surface markers, and possess the capacity for trilineage differentiation into osteogenic, chondrogenic and adipogenic lineages in vitro (Dominici et al., 2006). MSCs typically express surface markers such as CD73, CD90 and CD105, while lacking expression of hematopoietic markers including CD34, CD45 and CD14, as well as major histocompatibility complex class II, under basal conditions (Mafi et al., 2011). Although some interspecies variation exists in marker expression profiles, functional characteristics such as immunomodulatory capacity and paracrine activity appear to be conserved across mammalian MSCs.

Multiple tissue sources have been explored for the isolation of MSCs in cattle, each offering distinct advantages and limitations for therapeutic use in mastitis. Bone marrow-derived MSCs were among the first to be characterized in bovines and remain a well-studied source (Bosnakovski et al., 2005). These cells exhibit robust differentiation potential and immunomodulatory properties; however, bone marrow harvesting is an invasive procedure and yields relatively low cell numbers, which limits their scalability for widespread clinical application. Adipose tissue-derived MSCs have gained considerable attention due to their abundance, ease of collection and high proliferative capacity (Sharun et al., 2022b). Subcutaneous fat obtained during routine surgical procedures can serve as a practical source of autologous or allogeneic cells. Perinatal tissues, including umbilical cord blood, Wharton's jelly and placental tissues, represent an attractive alternative source of MSCs (Deus et al., 2020). These cells are typically more primitive, exhibit enhanced proliferative potential and display lower immunogenicity compared with adult tissue-derived MSCs (Witkowska-Zimny & Wrobel, 2011). Additionally, perinatal MSCs can be obtained without harm to the donor animal, aligning with the ethical considerations in veterinary regenerative medicine.

The therapeutic potential of MSCs in bovine mastitis is primarily attributed to their immunomodulatory, antimicrobial and regenerative functions (Fig. 1) (Li et al., 2023). MSCs interact dynamically with immune cells such as macrophages, neutrophils, dendritic cells and lymphocytes, modulating their activation and polarization states. Through the secretion of cytokines and mediators, including prostaglandin E2, indoleamine 2,3-dioxygenase, TGF-β and IL-10, MSCs can suppress excessive inflammation while preserving essential antimicrobial defences (Shi et al., 2011). In addition to immunomodulation, MSCs produce antimicrobial peptides, including cathelicidins, defensins and lipocalin-2, which directly inhibit bacterial growth (Ali et al., 2025). MSC-derived extracellular vesicles have also been shown to carry antimicrobial and anti-inflammatory molecules, contributing to pathogen clearance and immune regulation (Abreu et al., 2016). The regenerative effects of MSCs are mediated through the secretion of growth factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF) and insulin-like growth factor (IGF) (Mamachan et al., 2024). These factors support angiogenesis, epithelial cell proliferation and extracellular matrix remodelling, all of which are critical for restoring mammary gland structure and function following inflammatory injury. Collectively, these biological properties position MSCs as multifunctional therapeutic agents capable of addressing both the infectious and inflammatory components of bovine mastitis.

Mechanisms of Action of MSCs in Mastitis

The therapeutic effects of MSCs in bovine mastitis are mediated through a complex network of immunological, paracrine and cellular interactions within the mammary gland microenvironment (Peralta et al., 2020). Rather than acting through direct engraftment or differentiation into mammary epithelial cells, MSCs primarily exert their effects via dynamic crosstalk with immune cells, epithelial cells and stromal components (Sharma & Jeong, 2013). Understanding these mechanisms is essential for optimizing therapeutic strategies and predicting clinical outcomes in dairy cattle.

The innate immune response constitutes the first line of defence against invading mastitis pathogens. Neutrophils and macrophages are rapidly recruited to the infected mammary gland, where they mediate bacterial clearance through phagocytosis, oxidative burst and cytokine secretion (Wu et al., 2020). While effective pathogen elimination is crucial, excessive or prolonged innate immune activation can result in collateral tissue damage, epithelial barrier disruption and impaired milk secretion. MSCs have been shown to finely tune innate immune responses by modulating the recruitment, activation and functional polarization of key immune cells (Prockop and Oh, 2012). One of the most extensively studied mechanisms involves the interaction between MSCs and macrophages. In inflammatory environments, MSCs promote a phenotypic shift from classically activated pro-inflammatory macrophages (M1) toward alternatively activated anti-inflammatory macrophages (M2) (Zheng et al., 2018). This macrophage polarization contributes to reduced production of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-8, which are key drivers of neutrophil recruitment and mammary tissue damage (Thompson-Crispi et al., 2014; Peralta et al., 2020). At the same time, M2 macrophages support tissue repair by secreting anti-inflammatory cytokines and growth factors that facilitate epithelial regeneration. Neutrophils play a dual role in mastitis, acting as essential antimicrobial effector cells while also contributing to tissue injury through the release of reactive oxygen species and proteolytic enzymes (Wu et al., 2020). MSCs have been shown to modulate neutrophil function by enhancing their phagocytic capacity and bacterial killing while reducing excessive degranulation and neutrophil extracellular trap formation (Prockop and Oh, 2012). This balanced regulation helps maintain effective antimicrobial defence without exacerbating inflammation-induced tissue damage.

In addition to their effects on innate immunity, MSCs exert profound regulatory influences on adaptive immune responses (Prockop & Oh, 2012). T lymphocytes are increasingly recognized as important contributors to chronic and recurrent mastitis, particularly in infections caused by *Staphylococcus aureus,* where immune

evasion and persistence are common (Thompson-Crispi et al., 2014). MSCs suppress T cell proliferation and activation through both contact-dependent and soluble factor-mediated mechanisms (Prockop & Oh, 2012). B cell responses are also influenced by MSCs, although this area remains less explored in bovine mastitis (Merlo et al., 2022). Available evidence suggests that MSCs can inhibit B cell proliferation, differentiation and antibody production, thereby modulating humoral immune responses that may otherwise perpetuate inflammation in chronic disease states (Prockop & Oh, 2012). Through coordinated regulation of innate and adaptive immunity, MSCs help restore immune homeostasis within the mammary gland, creating an environment conducive to pathogen clearance, inflammation resolution and tissue repair.

MSCs regulate immune responses through multiple complementary pathways (Fig. 1). They secrete a broad spectrum of bioactive mediators, including metabolites, cytokines, growth factors, chemokines, extracellular vesicles and apoptotic bodies, which collectively shape the immune microenvironment. MSCs suppress the proliferation and activation of T lymphocytes and B lymphocytes, limit the production of IgM and IgG, and promote the differentiation of naive $CD4^+$ T cells into regulatory T cells (Tregs). In parallel, they direct macrophage polarization toward an anti-inflammatory, immunoregulatory phenotype. Additionally, MSC-induced apoptosis of activated T cells leads to the secondary activation of macrophages, resulting in enhanced TGF-β secretion and subsequent differentiation of Tregs, thereby reinforcing immune tolerance.

The concept of the MSC secretome has fundamentally reshaped our understanding of how these cells mediate therapeutic effects (Sharun et al., 2022a). The secretome encompasses a diverse array of bioactive molecules, including cytokines, chemokines, growth factors, lipids, metabolites and extracellular vesicles such as exosomes and microvesicles (Xunian & Kalluri, 2020). In the context of bovine mastitis, MSC-derived paracrine factors play a central role in orchestrating immune modulation and tissue regeneration (Alvites et al., 2022). Growth factors such as HGF, VEGF, FGF and IGF support angiogenesis, epithelial cell proliferation and restoration of mammary tissue architecture. These effects are particularly relevant following severe or recurrent mastitis episodes, where structural damage to alveolar and ductal epithelium can compromise lactational performance. Extracellular vesicles released by MSCs have attracted increasing interest as cell-free therapeutic agents (Sharun et al., 2022a). These vesicles carry

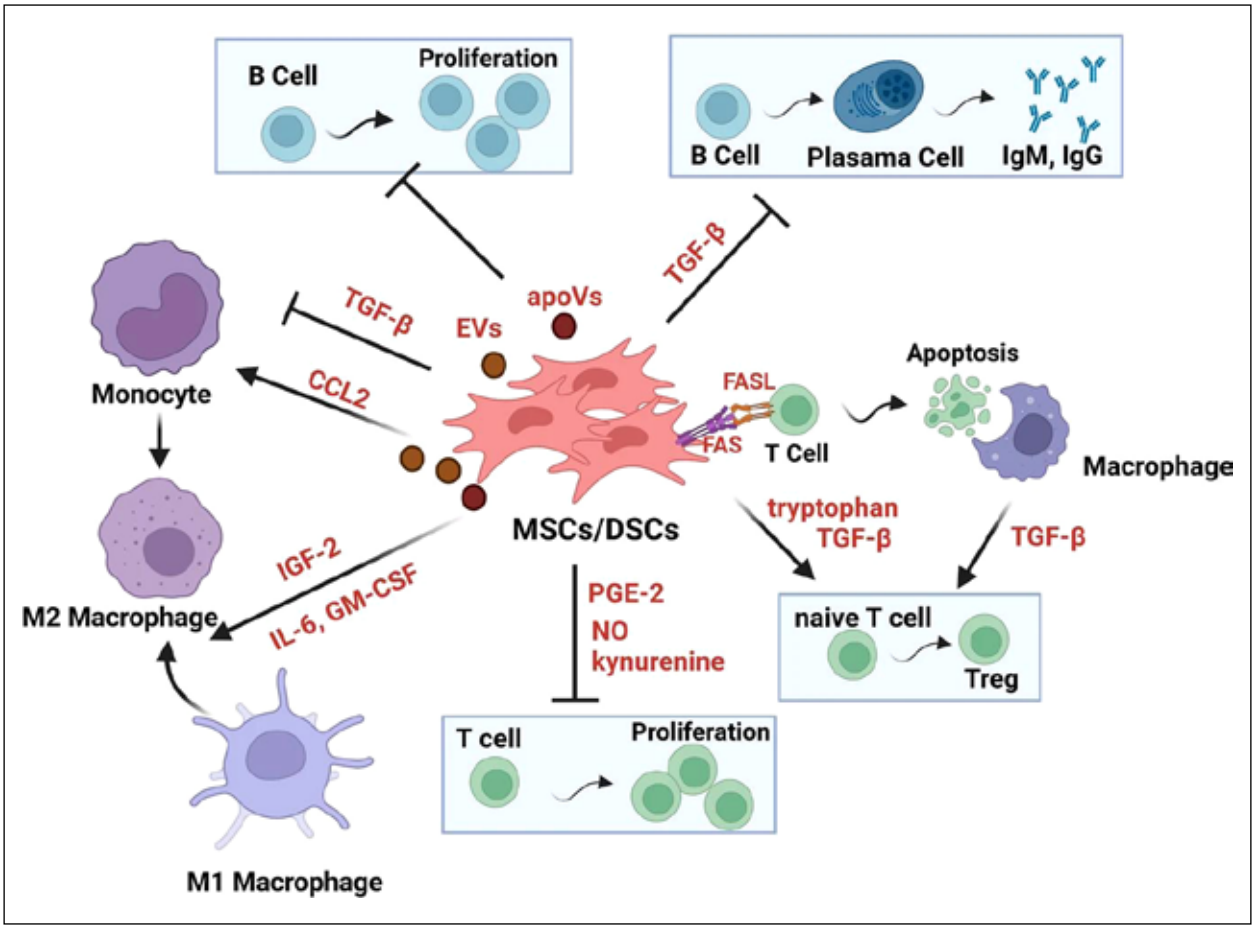

Fig. 1. Principal immunoregulatory mechanisms mediated by mesenchymal stem cells (©Li et al., 2023, CC BY).

proteins, lipids and regulatory RNAs that mirror many of the immunomodulatory and antimicrobial properties of parent MSCs. MSC-derived exosomes have been shown to suppress inflammatory signalling pathways such as NF-κB and MAPKs, which are central to mastitis pathogenesis (Wu et al., 2020; Homma et al., 2023). The secretome is highly responsive to the inflammatory milieu. Exposure of MSCs to pathogen-associated molecular patterns, inflammatory cytokines or hypoxic conditions can enhance the production of immunoregulatory and antimicrobial factors, a phenomenon often referred to as MSC priming (Sarsenova et al., 2022). This adaptive responsiveness may be leveraged to optimize therapeutic efficacy in mastitis by preconditioning MSCs prior to administration.

Beyond immunomodulation, MSCs possess intrinsic antimicrobial activity. Studies have demonstrated that MSCs secrete antimicrobial peptides such as beta-defensins, cathelicidins and lipocalin-2, which can directly inhibit the growth of mastitis-associated pathogens, including *Escherichia coli* and *Staphylococcus aureus* (Alcayaga-Miranda et al., 2017; Cahuascanco et al., 2019). MSCs also enhance host antimicrobial defences by stimulating phagocytosis and intracellular killing by macrophages and neutrophils (Li et al., 2018). This indirect antimicrobial effect is particularly relevant in the mammary gland, where efficient clearance of bacteria is essential for disease resolution. Collectively, these antimicrobial and anti-inflammatory mechanisms underscore the multifunctional nature of MSCs and their potential to address the complex pathophysiology of bovine mastitis in a manner that extends beyond pathogen eradication alone (Pokorska et al., 2024).

Clinical Evidence of MSC Therapy in Bovine Mastitis

The translation of MSC therapy from experimental immunology to clinical application in bovine mastitis has gained increasing attention over the past decade. While the body of evidence remains limited compared with human regenerative medicine, several preclinical studies, pilot trials and controlled experiments in dairy cattle have provided valuable insights into the feasibility, safety and therapeutic potential of MSC-based interventions (Table 1).

The route of MSC administration is a critical determinant of therapeutic efficacy in mastitis (Bagno et al., 2022; Pokorska et al., 2024). Intramammary infusion has been the most commonly employed route, as it allows direct delivery of cells to the site of inflammation and infection (Pokorska et al., 2024). This approach mirrors conventional intramammary antibiotic therapy and is therefore conceptually attractive for on-farm application. Intramammary MSC administration may result in transient cell retention within the mammary gland, allowing cells to interact with epithelial and immune cells in the local microenvironment. However, concerns remain regarding cell survival in the inflammatory and bacterially contaminated mammary lumen (Schouten et al., 2023). Systemic administration, typically via intravenous injection, has also been explored. Although systemically delivered MSCs primarily localize to the lungs and other filter organs, they can exert systemic immunomodulatory effects that indirectly influence mammary inflammation (Shokoohmand et al., 2025 Nov 15). Intravenous MSC therapy has been associated with reduced systemic inflammatory markers and improved clinical recovery in severe mastitis models, although its effects on local bacterial clearance appear less pronounced compared with intramammary delivery (Pokorska et al., 2024).

Assessment of MSC therapy efficacy in bovine mastitis has relied on a combination of clinical, microbiological and histological endpoints (Peralta et al., 2020; Pokorska et al., 2024; Hatipoglu et al., 2026). Reduction in somatic cell count is one of the most reported outcomes and serves as a proxy for inflammation resolution. Several studies have demonstrated a significant decrease in somatic cell counts in MSC-treated quarters compared with controls, particularly in acute mastitis models (Peralta et al., 2020; Pokorska et al., 2024; Hatipoglu et al., 2026). Milk yield and composition are critical indicators of functional recovery. MSC-treated animals have shown faster restoration of milk production and normalization of milk components such as fat and protein content. These findings suggest that MSC therapy may mitigate the long-term production losses associated with mastitis, although data from large-scale field trials remain scarce. Bacteriological cure rates following MSC therapy are variable and appear to depend on pathogen type and disease chronicity (Hatipoglu et al., 2026). While some studies report enhanced bacterial clearance, particularly in *E. coli*-induced mastitis, others indicate that MSCs alone may be insufficient to eradicate persistent pathogens such as *S. aureus* (Peralta et al., 2020). This has led to interest in combining MSC therapy with reduced-dose antibiotic regimens or other adjunctive treatments to achieve synergistic effects. Histopathological analyses provide further evidence of therapeutic benefit. MSC-treated mammary tissue typically exhibits reduced leukocyte infiltration, decreased interstitial oedema and improved preservation of epithelial structures (Schouten et al., 2023). These findings support the notion that MSCs promote tissue repair and limit fibrosis, which are critical for maintaining long-term mammary gland function.

Safety is a paramount consideration for any therapy intended for use in food-producing animals. Available evidence indicates that MSC therapy is generally well-tolerated in dairy cattle (Peralta et al., 2020). No significant adverse effects, such as local tissue necrosis, systemic illness or behavioural changes, have been reported in experimental studies. Immunogenicity concerns are mitigated by the low expression of MHC class II molecules on MSCs, particularly when derived

Table 1: Summary of major experimental and clinical investigations assessing mesenchymal stem cell (MSC) therapy in bovine mastitis.

Type	Organism	Stem cells	Dose and route	Outcome	Reference
Subclinical mastitis (SCM)	Not specified	Allogenic umbilical cord blood–derived MSCs (UCB-MSCs) and their extracellular vesicles (UCB-MSC-EVs)	UCB-MSC group: Two doses intravenously (jugular vein) and locally (intramammary) in infected quarters at a concentration of 5 x 10^7 cells / 2 mL PBS on days 0 and 7. UCB-MSC-EV group: Two doses intravenously and locally on days 0 and 7 with EVs equivalent to 500 µg protein / 2 mL injection.	Allogenic MSCs are immunologically safe for delivery in healthy cows. UCB-MSC and UCB-MSC-EV treatments markedly reduced milk somatic cell count (SCC) to safe levels compared to antibiotics. Leucocytes showed increased expression of anti-inflammatory cytokines, antimicrobial peptides, and angiogenic genes. Antibiotic and UCB-MSC-EV groups did not significantly downregulate pro-inflammatory cytokines.	Ghai et al. (2022)
Experimentally induced clinical mastitis (CM)	*S. aureus*	Allogenic foetal adipose tissue-derived MSCs (AT-MSCs)	Intramammary administration with a 2.5 x 10^7 suspension of bovine foetal AT-MSCs on experimental days 4 and 10	Repeated intramammary administration of AT-MSCs caused no adverse clinical or immune effects in healthy cows. In cows *with S. aureus*–induced clinical mastitis, AT-MSC treatment reduced milk bacterial load. The antibacterial effect appeared linked to host defence peptide activity, supported by the correlation between SCC and DEFß1 expression in mammary tissue.	Peralta et al. (2020)
Acute and chronic mastitis	Naturally occurring pathogens	Dulbecco's phosphate-buffered saline (DPBS) conditioned with amniotic membrane-derived MSCs (AMSCs)	10 mL conditioned-DPBS via intramammary injection	No significant differences in pH or titratable acidity between groups. Ionic calcium decreased from day 3 to 12 (DPBS group) compared to the antibiotic control. SCC is similar in both groups. Suggested as a potential antibiotic alternative.	Ting et al. (2020)
SCM	High level for *S. aureus* (including MRSA compared to Gram-negative bacteria (Enterobacteriaceae, *E. coli*, ESBL-*E. coli*)	Allogeneic MSCs derived from bone marrow (BMSC) and AT-MSC	50 million cells/mL intravenous; 4 million cells/mL intramammary suspended in physiological saline (IV + intramammary or intramammary alone)	MSC treatment reduced total bacteria, *S. aureus*, and Enterobacteriaceae, along with a decrease in SCC. Both IV + intramammary and intramammary routes achieved a therapeutic effect. BMSCs are more effective for MRSA, whereas AT-MSCs are effective against Enterobacteriaceae/*E. coli*.	Pokorska et al. (2024)
SCM and CM	Not specified	Xenogeneic human Wharton's jelly-derived MSCs (hWJ-MSCs)	2.5×10^7 hWJ-MSCs in 3 mL of DMEM were administered via intramammary infusion on days 7 and 14	hWJ-MSC treatment proved safe with no haematological toxicity and regulated immunity. SCC dropped ~30% (SCM) and ~70% (CM) by day 21. Most pathogens (*S. aureus*, *E. coli*) were cleared by day 21. Milk yield improved favourably post-treatment.	Hatipoglu et al. (2025)
Not specified	Not specified	AT-MSCs	1×10^6 cells in 2 mL physiological saline via intramammary and intramammary + IV route.	A marked decrease in SCC was observed in the intramammary group. Peak IL-6, IL-10, cathelicidin, lipocalin, cystatin, and angiopoietin expression on days 3 and 7 in the intramammary group. All animals completely recovered within 30 days.	Singh et al. (2021)

from perinatal tissues (Schu et al., 2012; Deus et al., 2020). Both autologous and allogeneic MSCs have been used without evidence of acute immune rejection (Colbath et al., 2020). However, long-term safety data, including repeated dosing and potential immunological sensitization, remain limited. Residue-related concerns are also relevant. Unlike antibiotics, MSCs and their secreted factors are biological entities that are metabolized or cleared by the host, potentially eliminating the need for milk withdrawal periods (Costa et al., 2024). Nevertheless, regulatory authorities require rigorous evaluation of food safety, including the absence of transmissible agents and unintended bioactive residues.

Despite promising findings, the current clinical evidence base for MSC therapy in bovine mastitis is characterized by several limitations. Most studies involve small sample sizes, short follow-up periods and experimentally induced disease models that may not fully capture the complexity of naturally occurring mastitis in commercial dairy herds (Peralta et al., 2020). Variability in MSC source, culture conditions, dosing and outcome measures further complicates the interpretation and comparison of results. Few studies adhere to standardized reporting guidelines, limiting reproducibility and translational relevance (Sharun et al., 2024b). Moreover, many investigations focus on acute mastitis, whereas chronic and recurrent cases represent a substantial clinical challenge in dairy practice. These limitations highlight the need for well-designed, large-scale clinical trials conducted under field conditions to establish the true efficacy, safety and cost-effectiveness of MSC therapy for bovine mastitis.

Translational and Practical Challenges

Despite the promising therapeutic potential of MSCs for bovine mastitis, several translational and practical challenges must be addressed before widespread clinical adoption in dairy practice can be realized. These challenges span biological, technical, regulatory, economic and logistical domains, particularly given the unique constraints associated with food-producing animals.

One of the foremost challenges in translating MSC therapy to the field is the identification of reliable, scalable and standardized cell sources. Autologous MSCs, while immunologically compatible, are impractical for routine mastitis treatment due to the time required for cell isolation, expansion and quality control (Pokorska et al., 2024). Mastitis often requires rapid intervention, rendering autologous approaches unsuitable for acute cases. Allogeneic MSCs derived from healthy donor animals represent a more feasible alternative (Colbath et al., 2020; Pokorska et al., 2024). Adipose tissue and perinatal tissues offer scalable cell sources with high proliferative capacity and relatively low immunogenicity (El-Badawy et al., 2016; Deus et al., 2020). However, donor variability, differences in tissue origin, and culture conditions can significantly influence MSC phenotype and therapeutic potency. Standardized protocols for cell isolation, expansion, cryopreservation and release criteria are essential to ensure batch-to-batch consistency (Sharun et al., 2024b). Potency assays that reflect relevant biological functions, such as immunomodulatory capacity or antimicrobial activity, are currently lacking in veterinary medicine. The development of functional assays linked to clinical outcomes in mastitis is a critical unmet need. Without such assays, regulatory approval and clinical reliability remain challenging.

Safety considerations are important for any cell-based therapy in food-producing animals. Although MSCs are generally regarded as safe, concerns regarding immunogenicity, ectopic tissue formation and tumorigenicity must be rigorously addressed. Current evidence suggests that MSCs exhibit low immunogenicity due to minimal expression of major histocompatibility complex class II molecules and co-stimulatory receptors (Machado et al., 2013). Nonetheless, inflammatory environments such as the infected mammary gland may alter MSC immunological profiles, potentially increasing immunogenicity (Ezzat Alnakip et al., 2014). While no neoplastic transformations have been reported in bovine MSC studies to date, comprehensive long-term surveillance data are lacking. Strict control of cell passage number, genomic stability assessment and exclusion of transformed cells are essential components of safety assurance (Torre et al., 2015). The risk of transmitting infectious agents through cell-based products is another critical consideration (Denys et al., 2020). Donor screening, pathogen testing and adherence to good manufacturing practice standards are crucial in mitigating this risk. These requirements, while essential, add complexity and cost to MSC production.

Regulatory frameworks governing the use of advanced therapies in food-producing animals are complex and vary across jurisdictions (Hernandez et al., 2022). In many regions, MSC-based products are classified as veterinary medicinal products or biologicals, subject to stringent regulatory oversight. Requirements typically include demonstration of safety, efficacy, quality and food residue safety. One major regulatory hurdle is the lack of harmonized guidelines specific to veterinary cell-based therapies. Unlike human medicine, where regulatory pathways for advanced therapy medicinal products are well established, veterinary regenerative medicine remains in a nascent regulatory landscape (Yoon et al., 2025). This uncertainty can discourage commercial investment and slow clinical translation.

Economic viability is a decisive factor in the adoption of any new therapy in the dairy industry (Richardet et al., 2023). The cost of MSC production, storage, transportation and administration currently exceeds that

of conventional antibiotic treatments. For MSC therapy to be competitive, it must demonstrate clear advantages in terms of reduced recurrence rates, improved milk yield, shortened recovery times, or elimination of milk withdrawal periods. On-farm feasibility also presents practical challenges. Intramammary administration of MSCs requires aseptic handling and appropriate training to prevent iatrogenic infections (Peralta et al., 2020). Cold chain logistics and storage infrastructure may not be readily available on all farms, particularly in low-resource settings. Cost-benefit analyses that incorporate long-term production outcomes, antimicrobial use reduction and animal welfare improvements are necessary to justify the integration of MSC therapy into mastitis management programs (Ruegg, 2025a). Hybrid approaches combining MSCs with reduced-dose antibiotics or cell-free secretome-based products may offer more economically feasible solutions in the near term.

Future Perspectives and Research Directions

A deeper understanding of the molecular mechanisms underlying MSC therapy in bovine mastitis is essential for rational therapy optimization (Ruegg, 2025b). High-throughput omics approaches, including transcriptomics, proteomics and metabolomics, provide powerful tools for dissecting MSC-host-pathogen interactions within the mammary gland microenvironment (Esener, 2025). Single-cell transcriptomic analyses could elucidate how MSCs influence specific immune and epithelial cell subsets during the resolution of mastitis (Ni et al., 2025). Similarly, profiling MSC-derived extracellular vesicles may identify key bioactive molecules responsible for immunomodulatory and antimicrobial effects, paving the way for cell-free therapeutic alternatives (Fig. 2) (Sharun et al., 2022a). The transition from experimental models to real-world applications requires robust clinical trials conducted under commercial dairy farm conditions. Such studies should include diverse herd management systems, naturally occurring mastitis cases, and extended follow-up periods to assess recurrence rates and long-term productivity outcomes. Standardized reporting guidelines and harmonized outcome measures will be critical for generating high-quality evidence. Comparative studies evaluating MSC therapy alone, antibiotics alone, and combination therapies will provide valuable insights into optimal treatment strategies.

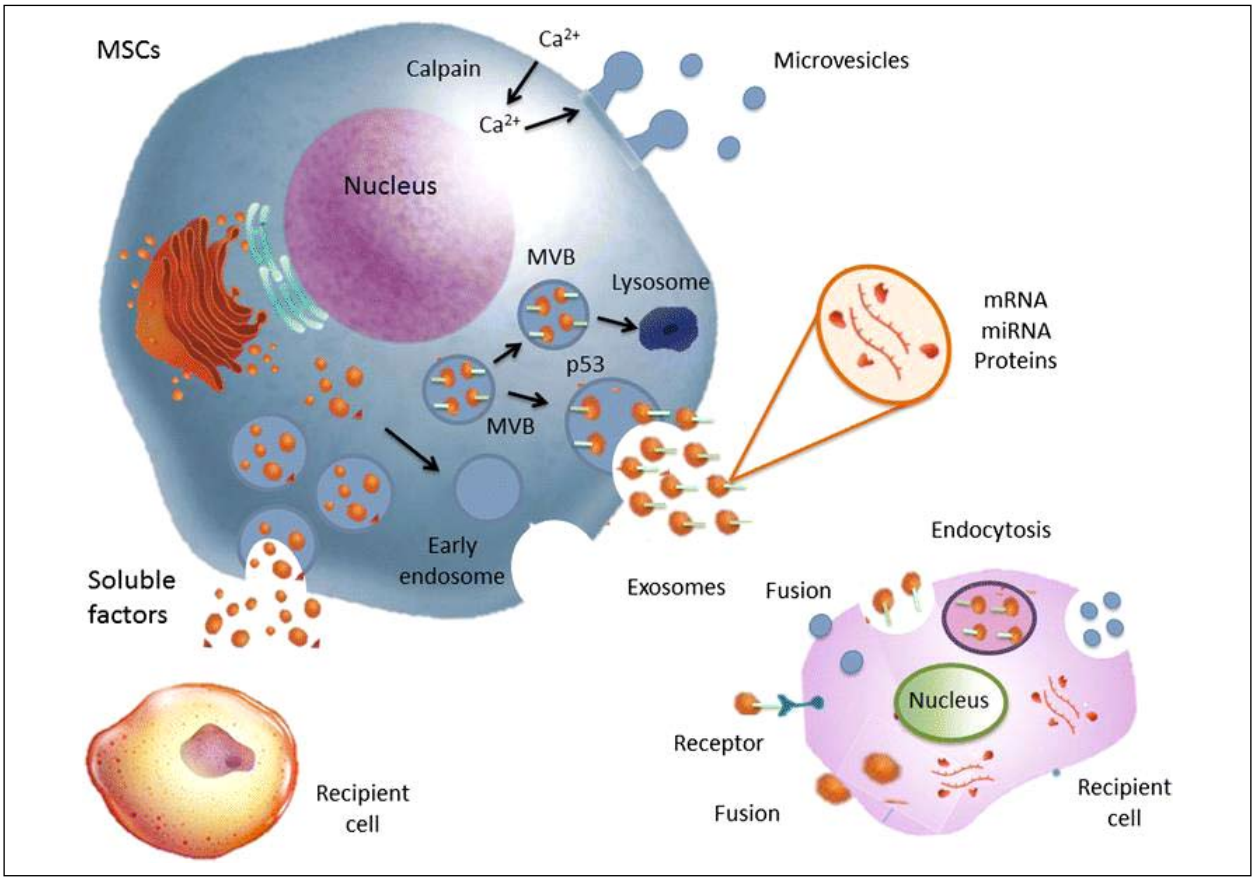

Fig. 2: Schematic overview of mesenchymal stem cell (MSC) extracellular vesicle biogenesis (© Abreu et al., 2016, CC BY). Extracellular vesicles arise through distinct intracellular pathways. Microvesicles are generated by direct outward budding from the plasma membrane, whereas exosomes originate from intraluminal vesicles formed by inward invagination of the limiting membrane of late endosomes, known as multivesicular bodies. Multivesicular bodies (MVB) are transported toward the cell surface and, upon fusion with the plasma membrane, release intraluminal vesicles into the extracellular milieu as exosomes. Reproduced from (Abreu et al., 2016) under Creative Commons Attribution 4.0 International License.

Advances in precision medicine offer exciting opportunities for tailoring MSC therapy to individual animals or herd-level risk profiles (Lloyd et al., 2016). Factors such as pathogen type, disease chronicity, host immune status and genetic background may influence therapeutic response. Integrating diagnostic biomarkers with regenerative interventions could enable more targeted and effective management of mastitis (Sharun et al., 2021). The development of off-the-shelf MSC products or secretome-based formulations customized for specific mastitis phenotypes represents a promising future direction. Such approaches may enhance efficacy while reducing costs and logistical complexity.

Conclusions

MSC therapy represents a novel and multifaceted approach to managing bovine mastitis, addressing key limitations of conventional antimicrobial treatments. Through immunomodulatory, antimicrobial and regenerative mechanisms, MSCs have the potential to reduce inflammation, support pathogen clearance and promote the repair of mammary tissue. While experimental and early clinical evidence is encouraging, significant translational barriers remain. Challenges related to cell sourcing, standardization, regulatory approval, cost-effectiveness and on-farm feasibility must be overcome before MSC therapy can be widely adopted in dairy practice. Continued investment in mechanistic research, well-designed field trials and innovative delivery strategies will be essential to unlock the full potential of MSC-based therapies. With careful development and integration into existing mastitis control programs, MSC therapy may contribute to more sustainable, welfare-oriented and antimicrobial-sparing approaches in the dairy industry.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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