# *Escherichia coli*-Mediated Antimicrobial Resistance and Quorum Sensing in Bovine Mastitis: A Mini-Review

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**Abstract**
The dairy industry worldwide is facing great economic loss. One of the primary reasons is the inflammatory disease of the mammary gland of the cattle, more commonly known as bovine mastitis. A major causative agent for this disease among other implicated pathogens is *Escherichia coli*. It causes both clinical and subclinical mastitis in the dairy cattle. The pathogenesis of *E. coli* in the cattle occurs through quorum sensing (QS) mechanisms through the autoinducers signaling. The Autoinducer-1 (AI-1) pathway controls the main virulence factors of the bacteria that are biofilm formation, secretion of toxin and colonization of host tissue. The conventional management of bovine mastitis relies heavily on antibiotics, yet this practice has inadvertently driven the proliferation of antimicrobial resistance (AMR). The presence of multidrug-resistant *E. coli* in cattle milk highlights the zoonotic risk posed to consumers. This mini review seeks to provide an overview of *E. coli* quorum sensing mechanism in bovine mastitis and its growing threat of antimicrobial resistance.

**Keywords:** Bovine mastitis, *Escherichia coli*, Quorum sensing, Autoinducers and Antimicrobial resistance

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## Introduction

The importance of drinking milk and its derivatives is taught and known to everyone, due to their richness in nutritional value, and therefore, it has led to the success of the dairy industry. In recent years, this industry has been threatened by the deadly disease of the bovine udder, known as mastitis. It is primarily associated with the cattle production management and the rearing environment (Stanek et al., 2024). The disease progresses through the inflammation of the udder gland tissue of the cattle due to weakening of their defense mechanism caused by several pathogens, as well as physical trauma (Mramba & Mohamed, 2024). Mastitis can be of different types, namely clinical, subclinical, and etiological (non-infectious and infectious).

Clinical mastitis is classified into more types, where severe inflammation of the mammary glands and significant reduction in milk production along with systemic symptoms fall under hyperacute mastitis, acute mastitis is similar to but differ with fewer symptoms as well as fever or mild depression, whereas the subacute mastitis is derived of or have very few of these symptoms (Stanek et al., 2024). The appearance, composition and quality of milk are all affected in clinical mastitis, for instance, the milk may have traces of blood (Mramba & Mohamed, 2024). Subclinical mastitis is identified through a rise in the somatic cell count (SCC), and California Mastitis Test (CMT) (Stanek et al., 2024). The wide range of pathogens responsible for the infectious mastitis are yeast, fungus, virus, and bacteria (Morales-Ubaldo et al., 2023).

The most common pathogens that are responsible for bovine mastitis include *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, *Escherichia coli* and *Klebsiella pneumoniae*. All these bacteria are classified as environmental and contagious as they colonize and multiply under the udder skin (Morales-Ubaldo et al., 2023).

Bovine mastitis is causing huge losses to the global dairy industry by reducing the milk production and quality, along with the additional cost of treatment and labors (Stanek et al., 2024). The exact economic loss is uncertain, as it depends on several factors such as price, quantity, treatment, nutrition cost (Stanek et al., 2024). According to the article by Morales-Ubaldo (2023), a certain bacterium, the *Escherichia coli* has significantly contributed to the milk loss production by about 3.5 kilograms a day, compared to other bacteria which have yet, caused lower losses (Morales-Ubaldo et al., 2023).

There are certain preventive measures that can be applied as a primary initiative by the dairy farms to lower the susceptibility of the disease. For instance, maintaining milking hygiene, by using different cleaning towels for each cow, cleaning and drying the teat before and after milking, and cleaning the milking equipment routinely. The bedding conditions should also be inspected regularly and be kept clean. The arrangement for regular health checkups for the cattle should also be made available to check for infections, deficiencies, and other health issues. Keep the cow in a relaxed environment and away from dirt which can easily infect the udder.

The standard treatment practice for mastitis is the use of antibiotics, specific to the causative agent. In recent times, these drugs have become futile in curing diseases, due to the increase of antimicrobial resistance (AMR), that the World Health Organization (WHO) has termed as the “silent pandemic”, being in the top 10 global

public health threats (WHO, 2023). The reason behind this is mainly due to the overuse and misuse of antibiotics, for both humans and animals. The use of non-therapeutic antibiotics in animals have led to antibiotic resistance in humans (Martin et al., 2015). This global issue is termed “silent” because it is still not being discussed or brought to attention as much as it should be to raise awareness and act. Bacteria can adapt the therapeutic antibiotic function through chromosomal gene mutation or foreign DNA acquisition by horizontal gene transfer (HGT) (Salam et al., 2023). The mutations include mainly three types of genes, which are genes that encode for the antibacterial target, antibacterial transporters, and transporter expression repressor (Salam et al., 2023). Besides mutations and acquired resistance mechanisms, bacteria have intrinsic ability that causes them to become resistant to certain classes of antibiotics.

### *Escherichia coli as a Major Causative Agent for Bovine Mastitis*

*Escherichia coli*, a Gram-negative bacterium commonly found in the gastrointestinal tract, is a major environmental pathogen causing bovine mastitis (Smith & Fratamico, 2017). Its pathogenicity in the mammary gland is multifactorial, primarily driven by virulence factors such as lipopolysaccharide (LPS) (Zaatout, 2022). LPS binds to host Toll-like receptor 4 (TLR4), triggering a potent inflammatory response that leads to tissue damage and clinical signs of mastitis (Zhang et al., 2025). As a results, causing inflammatory responses through the teat by invasion of the udder of the cow (Cheng & Han, 2020).

Mastitis causing *E. coli* is seen in both clinical and subclinical mastitis. Mammary pathogenic *E. coli* (MPEC) is a class of extraintestinal pathogenic *E. coli* (EPEC) (Wang et al., 2021). EPEC binds to the dairy cattle udder epithelial cells. This leads to the production of biofilms, given the mammary environment is optimal for the bacteria to colonize (Wang et al., 2021). MPEC also ferments lactose once inside and utilizes the lactose as energy source (Goullart & Mellata, 2022). The main virulence factor (VF) triggering immune response if the host is the endotoxin (Goullart & Mellata, 2022). This VF exists on the lipopolysaccharide (LPS) outer membrane of the pathogen (Goullart & Mellata, 2022). The signaling pathway is initiated through the binding of this LPS membrane to TLR, mainly TLR4. Other molecules linked with the pathway include LPS-binding protein and cluster of differentiation 14 (CD-14) (Eckel & Ametaj, 2020). This binding triggers the myeloid differentiation factor 88 (MyD88). MyD88 then brings interleukin-1 receptor-associated kinases and tumor necrosis factor 6 (TNF-6). These activate the complex transforming growth factor beta-activated kinase 1 (TAK1). TAK1 complex inhibits nuclear factor kB (NF-kB) kinase. Then the inhibitor is phosphorylated, translocating NF-kB to the nucleus. TAK1 also phosphorylates mitogen-activated protein kinases (MAPK). This results in activator protein-1 nuclear translocation. The NF-kB protein binds to the DNA sequence and initiates transcription of mRNA which starts translation of inflammatory cytokines and inflammatory markers. Some examples of inflammatory markers include cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Fitzgerald et al., 2007; Khan et al., 2020). The host defense factor determined the severity of mastitis caused by *E. coli* (Goullart & Mellata, 2022).

Being an opportunistic pathogen, *E. coli* has a combination of VFs like toxins including- capsule production and resisting serum complement (Goullart & Mellata, 2022). These factors enable it to overcome the host selection pressure and survive within the bovine udder. *E. coli* can persist and cause recurrent mastitis due to them being strong biofilm producers (Goullart & Mellata, 2022).

### *Quorum Sensing in Escherichia coli*

Quorum sensing (QS) is a cell-cell communication system whereby bacteria secrete and detect specific signaling molecules called Autoinducers (AIs) to monitor population density and coordinate group behaviors accordingly. When quantities of these signal molecules reach a critical threshold, it will prompt relevant kinds of genes to be expressed synchronously. This could be anything from generating biofilms on a large scale or releasing all virulence factors at once. In *Escherichia coli* there are three main QS systems that have been recognized which known as autoinducer-1 (AI-1), autoinducer-2 (AI-2) and autoinducer-3 (AI-3). In *E.coli* and other Gram-negative bacteria, the AI-1 is primarily mediated by N-acyl homoserine lactones (AHLs).

In *Vibrio fischeri*, the canonical quorum sensing model holds the LuxI synthase that generates N-3-oxohexanoyl homoserine lactose (3OC6-HSL) which triggers LuxR to activate the operon responsible for bioluminescence (Bellissimo et al, 2024). In contrast, *E. coli* lacks this system and therefore, is incapable of AHL production on its own. It has a LuxR-type receptor, SdiA, to perceive and respond to AHLs (Cox et al., 2006). *E. coli* can make contact with other bacterial signals in polymicrobial environments with this system.

### *SdiA Receptor: LuxR Homolog*

The SdiA gene encodes a LuxR-family transcription factor and responds to exogenous AHLs synthesized by neighbouring species (Kendall & Sperandio, 2007). Unlike canonical LuxR proteins, SdiA does not consist of a linked LuxI synthase in the genome of the bacteria.

Structurally typical of LuxR proteins, but SdiA has an N-terminal ligand-binding domain and a C-terminal helix-turn-helix DNA-binding domain. In absence of the ligand, SdiA becomes unstable and can be degraded. The protein is stabilised through AHL binding which enables its dimerization and thereby, interaction with DNA (Yao et al., 2006). AHL molecules such as 3-oxo-C6-HSL or 3-oxo-C8-HSL act as both stabilizers and allosteric SdiA activators. These molecules are small and easily diffuse across bacterial membranes. When *E. coli* is in an environment with AHL-producing bacteria, the AHL signals diffuse into the cell and bind to SdiA. In a study by Cox et al. (2006), biosensor assay using *E. coli* strains with SdiA reporters confirmed that there was response to micromolar concentrations of exogenous AHLs (C6- and C8-AHLs).

The mechanistic hallmark of the AI-1 pathway in *E. coli* is ligand-mediated SdiA stabilization. This process can be hampered through endogenous signals known as indole produced by *E. coli,* which interferes with the SdiA activity (Lee et al., 2007). When activated, the SdiA regulates several genes. SdiA modulates the curli subunit gene (csg) D regulon that is responsible for controlling the production of curli fimbriae. Curli is critical for the formation of biofilm. Depending on environmental conditions, SdiA can repress curli expression in some *E. coli* strains but enhance biofilm development in others (Shimada et al., 2023). Recent studies have shown that SdiA is

involved in direct activation of carbon storage regulator (csr) B transcription. It is a noncoding RNA that opposes the global post-transcriptional regulator csrA (Shimada et al., 2023). SdiA has been demonstrated to exert a repressive effect on motility and adhesion through repression of flagellar gene expression, and has also been proposed as a repressor of biofilm formation, as *sdiA*-lacking strains show higher biofilm-forming ability (Mayer et al., 2025). In enterohemorrhagic *E. coli* (EHEC), it influences acid resistance genes (gadW and gadY). Thereby, enhancing survival in acidic conditions like the stomach of the bovine (Hughes et al., 2010). In EHEC, SdiA responds to AHLs in the rume. It also regulates the locus of the enterocyte effacement which affects the type III secretion system expression (Kendall & Sperandio, 2007). This directly connects AI-1 sensing to virulence.

The above transcriptional changes translate into crucial ecological and pathogenic traits. To summarize, biofilm modulation, motility suppression, survival in stress environments and virulence regulation. Thus, SdiA functions as an integrative regulator that adjusts multiple phenotypes in response to AI-1 signal to ensure *E. coli* can thrive in polymicrobial niches.

The SdiA system is able to intersect with AI-1 signaling through crosstalk with other signaling pathways. First is the indole signaling, where *E. coli* produces indole via tryptophanase (TnaA). Indole can counteract the expression of SdiA on curli and biofilm genes. This suggests antagonistic interplay between the endogenous and exogenous signals (Lee et al., 2007). Second is the CsrA/CsrB system, where SdiA positively regulates csrB that sequesters csrA, modifying biofilm and motility regulation (Shimada et al., 2023). Thirdly, there is indirect evidence that SdiA activity may intersect QseBC, which primarily responds to AI-3. Meaning, there might be co-regulation of virulence and motility. Lastly, AI-2 signaling, namely LuxS/AI-2. It is normally found in *E. coli* and together with SdiA, both AI-2 and AI-1 sensing provide a layered quorum sensing network (Surette & Bassler, 1998).

In the cattle, *E. coli* encounters a dense community of AHL-producing bacteria. In response to these AHLs, EHEC SdiA modulates the gene expression relevant for survival and colonization in the rumen (Hughes et al., 2010). Commensal *E. coli* in the cattle gut can identify AHLs from other *Enterobacteriaceae* or *Proteobacteria*, which opens cross-species communication (Ahmer, 2004). *E. coli* may co-exist with AHL-producing bacteria in mastitis or urinary tract infections of the cattle. One example of such a pathogen is *Pseudomonas aeruginosa*. *E. coli* can adjust biofilm formation and virulence through SdiA by perceiving their signals (Cox et al., 2006). These examples show that even though *E. coli* is unable to synthesize AHL, it can gain ecological intelligence from neighboring organisms. The AI-1 quorum sensing mechanism of *E. coli* represents the flexibility of bacterial communication. Their eavesdropping strategy provides critical information about their microbial landscape. It is an adaptive system that is central to its ability to survive and thrive in competitive niches. The gene regulatory outcomes of SdiA activation by exogenous AHLs, and the site-specific nature of this signaling along the bovine gut, are schematically represented in the following Figure 1A and 1B (Styles and Blackwell, 2021).

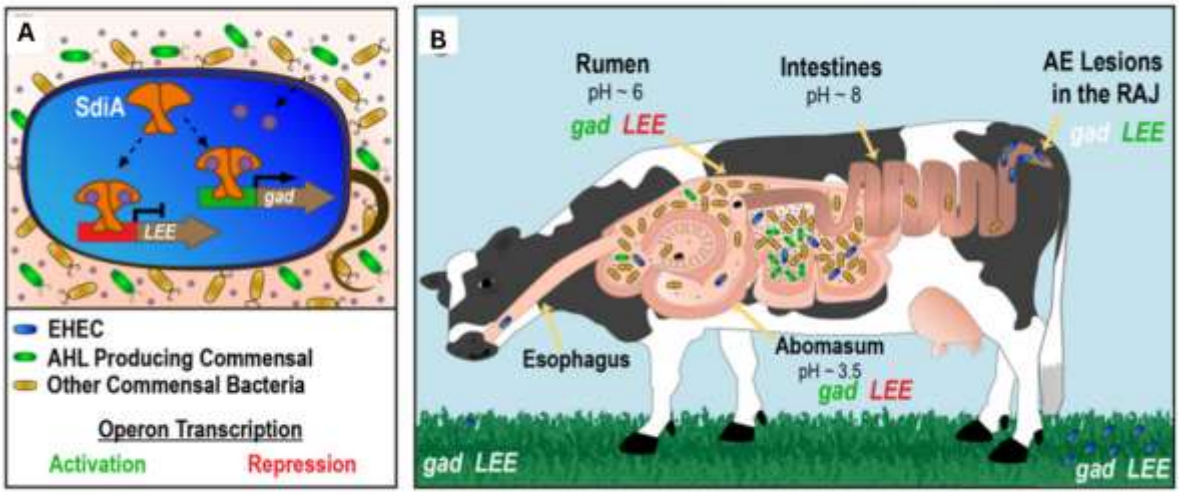


**Figure 1: (A) Schematic diagram production of AHLs. (B) EHEC colonization of cattle. (Adopted from Styles and Blackwell, 2021)**

### *Antibiotics for Bovine Mastitis*

The control measures for transmission of mastitis causing bacteria were periodic examination of the cattle milk, segregation and slaughter of the infected ones (Moreira et al., 2024). Sanitary hygiene has long been recognized as central to mastitis prevention, and antimicrobial therapy became widely adopted for treating bovine mastitis despite an incomplete understanding of its causative agents. Limitations of antimicrobial therapy have been recognized, but the use of antibiotics to treat cows affected with some pathogens remains an important tool for mastitis control (Ruegg, 2017). The antibiotic classes for Gram-negative bacteria were very limited in the past, therefore the now-banned drug chloramphenicol was used for therapy (Lees et al., 2021). Dry cow therapy (DCT) involves treating the disease after the lactation period ceases. This therapy uses pharmaceutical products made with antimicrobials (Moreira et al., 2024). It has certain elimination and absorption characteristics which can cure mastitis slowly during the drying process (Rowe et al., 2023). Mastitis is one of the major diseases in the dairy industry that requires antimicrobial therapy (El-sayed M et al., 2021). The common therapeutic drugs used in treating bovine mastitis include β-lactams, sulfonamides, tetracyclines, etc. (El-sayed M et al., 2021).

It is important to follow a therapeutic protocol when administering anti-inflammatories and antimicrobials to avoid the misuse of these drugs. The intensity of the symptom will determine the protocol required to be implemented (de Jong et al., 2023). When the mastitis infection is mild to moderate, a bacteriological analysis of the milk sample should be carried out following anti-inflammatories as proper treatment (Svennesen et al., 2023). During severe cases, both intramammary and systemic antimicrobials, preferably non-steroidal anti-inflammatory drugs, oral hydration, and intravenous hypertonic solutions are recommended (Ruegg, 2018). This will prevent septicemia or toxemia which are common for infections caused by Gram-negative pathogens of the Enterobacterales order (Ruegg, 2018).

Often, treatment without considering the consequences is adopted without veterinarian or specialized advice which disregard the necessary clinical diagnosis, animal history and, etiological agent (Sharun et al., 2021). Therefore, the same drugs are used for all cases without proper following of the recommended guidelines. The proper administration of therapeutics through intramammary route is not practiced, instead it is applied through intramuscular, intravenous, or subcutaneous routes (Ruegg, 2018). Eventually resulting in chronicity and spreading of antimicrobial resistance in dairy units (Ruegg, 2018).

***Antimicrobial Resistance through Escherichia coli***

The therapeutic drugs prescribed for bovine mastitis caused by *E. coli* are mainly antibiotics. Unfortunately, in recent times, antibiotic therapy has been futile in curing clinical or subclinical mastitis in cows. This is evidenced by the rise of antimicrobial resistance in bacterial isolates which is the same strain of *E. coli* for every case (Goullart & Mellata, 2022). It has been reported that mastitis associated *E. coli (*MAEC) is resistant to aminopenicillin, polypeptide, lincosamide, and macrolide (Goullart & Mellata, 2022). For instance, dairy farmers may not follow the withdrawal period for these drugs, or even overuse them without proper prescription. These are the reasons for conferring antimicrobial resistance (AMR) in the corresponding bacteria and it has become a global burden (Editorial, 2024). AMR has been responsible for 1.27 million global deaths leading to a significant increase in healthcare costs, reaching up to 1 trillion US dollars in 2019 (Patra et al., 2025). The spread of AMR is a unified consequence of human and veterinary practices alongside environmental reasons. From the misuse, overuse and improper prescribing of the therapeutic drug to prophylactic use in livestock agricultural settings, it has become extremely concerning.

*E. coli* is capable of forming biofilm on the tissue surface of the infected mammary gland. This may cause pathological modification in the area which later influences the distribution of the prescribed antibiotic in the parenchyma of the udder (Akers & Nickerson, 2011). Therefore, the antibiotic can no longer reach the site of infection, making the cow resistant to the treatment and get recurrent infections (Pederson et al., 2021). The history of *E. coli* as an antimicrobial resistance gene reservoir remains unchanged. It can confer these resistance genes through horizontal gene transfer to other pathogenic bacteria (Zhang et al., 2020). Previous studies have found several prevalent resistance genes in MAEC. It was investigated that MAEC encodes resistance to aminoglycoside, streptomycin, tetracycline, sulfonamide, and beta-lactams (Yu et al., 2019).

The major concern for antibiotic resistance in MAEC is the extended-spectrum β-lactamase (ESBL) enzymes (Yang et al., 2018). They hydrolyze penicillin, third and fourth generation cephalosporins and monobactam antibiotics (Bush & Jacoby, 2010). These enzymes are in the plasmids of *E. coli*. These ESBL *E. coli* are directly linked to multi-drug resistant bacteria and therefore, greater human mortality rates. Worldwide, there is an average increase of 1.2% per year or prevalence of ESBL producing *E. coli* in healthy individual gut microbiomes (Bezabih et al., 2021). Germany and Greece have reported the prevalence of these strains in mastitis infected cattle (Goulart & Mellata, 2022). Which means, the presence of ESBL-producing *E. coli* in milk raises concerns about the ingestion of that milk by humans who can have these genes transmitted to them (Goulart & Mellata, 2022).

A major concern for food safety is the presence of antimicrobial residues, from the treatment of cattle dairy disease. It is a threat to the health of the consumer of the dairy products and also responsible for economic losses due to faulty production (Virto et al., 2022). Antimicrobial residues in milk may lead to antimicrobial resistance, allergic reactions, and mutagenicity and even gut microbiome alteration of the consumer (Jeena et al., 2020). Possibilities of anaphylactic shocks in sensitive individuals due to the residues in milk cannot be eliminated from the consequences (Moreira et al., 2024). Many factors influence the persistence of the antimicrobial residues in milk. Some are-route of administration, dosage, and solubility. There should be proper information in the packages regarding withdrawal periods during lactation. In Brazil, High Performance Liquid Chromatography (HPLC) served as the official confirmatory test in the Brazilian Network of Milk Quality Control Laboratories (Moreira et al., 2024).

## Conclusion

The spread of antimicrobial resistance (AMR) through milk poses a major threat ro public health. Therefore, the development of effective alternative therapies for bovine mastitis is crucial to reduce antibiotic dependence and limit the emergence and spread of AMR. To date, several alternative approaches have been explored, including non-steroidal anti-inflammatory drugs (NSAIDS), antimicrobial peptides (AMPs), and vaccination but further research is needed to improve their efficacy. Emerging strategies such as stem cell technology, nanotechnology, nano therapy and plant-based products for quorum quenching should be explored to overcome this issue.

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