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Review article

Review on anti-microbial resistance patterns of *Staphylococcus aureus* isolated from mastitic cow's milk: Ethiopian context

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Abstract

Aim of this paper is to review antimicrobial resistance profile of *Staphylococcus aureus* (*S. aureus*) isolated from mastitic cow milk in Ethiopia between 2013- 2023. *S. aureus* causes chronic intramammary infections, causing financial losses and challenging antimicrobial therapy globally. In Ethiopia meta-analysis of the pooled prevalence of bovine mastitis was 47.6% showing *S. aureus* as the major isolates accounting for 13.4% and 16.5% of clinical and subclinical mastitis. In Ethiopia, there are indication of the misuse of antibiotics coupled with the rapid spread of resistant bacterial nature and inadequate surveillance, which contributed to the problem. According to this review resistance profile of *S. aureus* studied in Ethiopia, the bulk of tested isolates showed alarmingly high levels of resistance to widely used antimicrobial drugs for the treatment of mastitis, particularly penicillin G and tetracycline. Variuos studies warned low susceptibility of *S. aureus* to commonly used antimicrobials such as penicillin G and tetracycline as a great concern because this antibiotic represents the main antibiotic group recommended for staphylococcal mastitis infection in Ethiopia. If essential steps to stop the indiscriminate use of antibiotics are not implemented, the prevalence of antibiotic-resistant *S. aureus* could rise posing major risks to both animal and human health. Therefore, conducting regular antimicrobial sensitivity testing before treatment helps select effective antibiotics which reduce the development of resistance to commonly used antibiotics. Further studies should be conducted to detect antimicrobial resistant strains, continiuos surveillance and monitoring of *S. aureus* to prevent the spread of milk-borne drug-resistant strains throughout communities.

Keywords: Anti-microbial resistance, Bovine mastitis, Public health concern, *S. aureus*

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INTRODUCTION

Mastitis is a common disease of dairy cows and a major concern for the dairy industry because of economic losses due to decreased animal health and increased antibiotic usage (Marcondes et al., 2022). Besides Mastitis is one of the most frequent causes of antibiotic use in dairy cows; nonetheless, ongoing selective antibiotic pressure for the treatment and management of bovine mastitis may raise the possibility of bacterial strains resistant to certain antibiotics (Hossain et al., 2017). From the cow mammary gland, a total of roughly 140 microbial species, subspecies, and serovars have been isolated (Radostits et al., 2007). Among these *Staphylococcus aureus* (*S. aureus*) is a common cause of staphylococcal mastitis in dairy cows (Lalita et al., 2015). *S. aureus* are Gram-positive cocci with a size of 1µm that are grouped in irregular clusters or 'bunches of grapes'and usually characterized by catalase-positive, oxidase-negative, non-motile, non-sporulating, facultative anaerobes and having a white colony with regular edges (Markey et al., 2013).

S. aureus is one of the most common contagious mastitis pathogens in the world. It is known for producing chronic intramammary infections that do not react well to antimicrobial therapy and spreading throughout the herd, which results in significant financial losses (Molineri et al., 2020). *S. aureus* and its ability to cause persistent infection are associated with antibiotic therapy failure. Although antibiotics are the first choice to fight against bacterial infections, the emergence of multidrug-resistant pathogens and the presence of antibiotic residues in milk and milk products are major concerns (Pietrocola et al., 2017). *S. aureus* also exhibits several mechanisms or features that allow it to evade host defenses, such as the ability to build biofilms and create small colony variants (Kong et al., 2016). By reducing antibiotic diffusion inside the biofilm matrix and developing resistance to high concentrations of antimicrobials, biofilm formation makes *S. aureus* less susceptible to different antibiotics (Aslantas and Demir, 2016). As a result, alternative treatments that specifically target *S. aureus*' capacity to build biofilms are required (Asli et al., 2017).

The issue of antimicrobial resistance (AMR), threatens economic, social, and political implications internationally and places an additional burden on countries with limited resources, such as Ethiopia. The management of bacterial infections is threatened by rising AMR, according to studies on the topic; yet, prevention and control have gotten much too little attention up to this point. These conditions have negative effects on animals' productivity, including increased mortality, morbidity, and treatment expenses (Ibrahim et al., 2018). Studies conducted with the objective of revealing the AMR profile of *S. aureus* isolated from bovine mastitis in Ethiopia suggest an increase in the antimicrobial resistance of *S. aureus* to commonly used antimicrobials for treatments of bovine mastitis. According to the resistance profile of reviewed studies across Ethiopia, the majority of the tested isolates showed alarmingly high levels of resistance to widely used antimicrobial agents, particularly penicillin G, and tetracycline, suggesting a potential development of resistance to prolonged and indiscriminate use of those antibiotics (Regasa et al., 2019; Kalayu et al., 2020; Grima et al., 2021); the majority of the isolates were also susceptible to gentamycin, vancomycin, and chloramphenicol (Befikadu et al., 2017; Girmay et al., 2020; Grima et al., 2021).

S. aureus creates a serious financial issue for dairy farmers owing to protracted, expensive antibiotic treatments. The bacterium can cause long-lasting infections that can remain throughout lactation and into consecutive lactations and do not react well to antibiotic treatment (Zaatout et al., 2020). *S. aureus* is also regarded as a significant source of contamination for many dairy products and is ranked as the third most common bacterium responsible for outbreaks of food poisoning in humans (Dittmann et al., 2017). Foods contaminated with toxins or viable *S. aureus* cells are directly linked to inadequate sanitation practices. Although hazardous bacteria are frequently removed from human food, many poisons remain stable after heat treatment, especially when done over long periods (Babic et al., 2018).

Despite the significant economic effect and potential public health threat, the incidence of *S. aureus* isolates, as well as the phenotypic and genotypic antibiotic resistance characteristics of *S. aureus* isolates, has received less attention in developing countries such as Ethiopia. In these countries, there is scarce veterinary service, a shortage of a variety of drugs, and poor drug regulatory frameworks that could lead to underdosing medication that may end up with the development of antibiotic-resistant organisms. Additionally, poor housing and milking hygiene can spread *S. aureus* and other mastitis-causing infections among individual animals or farms (Marama et al., 2019).

To address the issues of antibiotic residue in milk and antimicrobial resistance, the control program must incorporate the strategic use of antimicrobials (Ruegg, 2017). Given the expense of treating mastitis and its potential benefits, judicious use of antibiotics should be practiced with sufficient knowledge, a scientific rationale for reducing antibiotic use, and legal requirements (Sharun et al., 2021). The antimicrobial susceptibility of udder pathogens should be periodically checked by the antimicrobial stewardship program since any exposure of bacteria to antibiotics for the treatment of mastitis may result in the selection of resistance. To guarantee the long-term effectiveness of antibacterial drugs, it is crucial to track developments in antibiotic resistance over time. Given that mastitis, therapy is frequently started before the pathogen has been tested for susceptibility, access to a recent repository of antimicrobial susceptibility data aids the veterinarian in choosing the best antibiotic for treating mastitis (de Jong et al., 2018).

In Ethiopia, although resistance *S. aureus* isolates are rising, adequate surveillance and monitoring systems are not undergoing, because fragmented studies on AMR that have been conducted in different regions of Ethiopia, and are not comprehensive, it might be difficult to acquire a complete picture of the scope of the problem. A collection of current data might help to determine the magnitude of the problem. As a result, the objectives of this review are to summarize the existing data and to provide information on *S. aureus*' antimicrobial resistance profile to commonly used drugs for the treatment of *S. aureus* mastitis in Ethiopia between the year 2013 and 2023. Aside from informing, future scientific efforts are needed to combat antibiotic resistance.

LITERATURE REVIEW

Staphylococcus aureus

Historical background of *S. aureus*

Although staphylococci have existed from the beginning of time, they weren't recognized as bacterial pathogens until the 19th century. Alexander Ogston discovered grape-like bacterial clusters in pus from a surgical abscess in a knee joint in 1880, and he gave them the scientific name Staphylococcus (from the Greek staphyle, "a bunch of grapes," and kokkos, "grain or berry"). German physician Friedrich Julius Rosenbach was able to cultivate the organisms in pure culture in 1884 and sorted them according to color they produced (Licitra, 2013). Staphylococci were distinguished from streptococci, which are organized in chains and can cause post-surgical infections, based on the description of the organization. By injecting staphylococci into the subcutaneous tissues of lab animals like guinea pigs and mice, Ogston performed experimental laboratory studies to study skin-associated infections caused by *S. aureus* and created abscesses (Thomer et al., 2016).

General characteristics of *S. aureus*

Staphylococci are gram-positive cocci with an average diameter of 0.8 to 1 µm, and they frequently form irregular clusters or "bunches of grapes" rather than pairs or tetrads. Colonies typically have white outlines with uniform borders. They lack both motility and sporulation, and the majority of species are fermentative facultative anaerobes. They are resistant to lysozyme (MIC 1000 g/ml), and bacitracin (0.04 unit disc), but sensitive to lysostaphin (12.5 g/ml) and furazolidone (100 g/disc) (0.5 mg). Typically, they are oxidase-negative and catalase-positive. Nutrient and blood agars both support growth, while MacConkey agar does not. Typically, they lack capsules or have a small number of capsules. The two major pathogenic staphylococci, *S. aureus* and S. *pseudintermedius* are coagulase-positive (Markey et al., 2013). *S. aureus* grow as smooth, circular, convex colonies of 0.5-1.5 µm in diameter with lustrous growth. The colony pigmentation may vary from grey, grey-white, and grey-white with yellowish to orange shades, and in blood agar typical β-hemolysis produced; depending on the growth condition (Jahan et al., 2015).

S.aureus and Bovine Mastitis

One of the most common ailments affecting dairy cattle, bovine mastitis is caused by intricate interactions between the host, environment, and infectious organisms**.** It has an impact on global dairy production by lowering the quantity and quality of milk produced (Hogeveen and Van, 2017). Bovine mastitis, is associated with many different infectious agents, commonly divided into those causing contagious mastitis (*S. aureus and Streptococcus agalactiae*), which are spread from infected quarters to other quarters and cows; those that are normal teat skin inhabitants and cause opportunistic mastitis (Coagulase-negative *staphylococci*), and those causing environmental mastitis (*S. uberis and S. dysgalactiae*, *S. equinus*, coliforms include *E. coli, Klebsiella species*. and *Enterobacter species*.), which are usually present in the cow's environment and reach the teat from that source (Radostits et al., 2007).

S. aureus is one of the most common contagious mastitis pathogens in the world. It is known for producing chronic intramammary infections that do not react well to antimicrobial therapy and spreading throughout the herd, which results in significant financial losses (Molineri et al., 2020). Because it is highly contagious, and able to induce long-lasting chronic infections, this microorganism is considered one of the major pathogens associated with bovine mastitis all over the world (Levison et al., 2016). *S. aureus* and its ability to cause persistent infection are associated with antibiotic therapy failure. Although antibiotics are the first choice to fight against bacterial infections, the emergence of multidrug-resistant pathogens and the presence of antibiotic residues in the milk and milk products are major concerns (Pietrocola et al., 2017).

In Ethiopia according to meta-analysis of the pooled prevalence of mastitis was conducted using data of 15,780 cows from 46 studies. The pooled estimate of the overall prevalence of bovine mastitis based on the random effect model was 47.6% (95% CI [42.4–52.9]). The analysis has shown that *S. aureus* was the major isolate accounting for 13.4% and 16.5% of the clinical and subclinical mastitis, respectively followed by *Streptococci* species, with a prevalence of 10.6% and 8.1% for clinical and subclinical mastitis, respectively (Tora et al., 2022).

Epidemiology of *S. aureus*

S. aureus causes mastitis, the major disease, which appears to have worldwide distribution and affects all species of animals. It is a sporadic disease and attains major economic significance in terms of its profound impact on the value and productivity of dairy animals (Eyob Eshetu, 2015). *S. aureus* is present in the normal flora of humans and animals and is an opportunistic pathogen that is widely distributed throughout the world (Tong et al., 2015; Dini et al., 2019; Pal et al., 2020). However, it is well recognized as an invasive human pathogen, resulting in significant morbidity and mortality. It has also been frequently isolated from animals and foods of animal origin (Tong et al., 2015; Wang et al., 2018).

Evidence of adaptation of mammary-associated isolates to host species comes from the acquisition of genes that encode proteins that target cattle-specific (and small ruminant-specific) molecules, the loss or decay of genes that encode proteins adapted to human targets, and the adaptation of *S. aureus* to its environment. Phenotypic diversity can result from the regulation of gene expression (Rainard et al., 2018). *S. aureus* can be transmitted from animal to animal, person to person, as well as from animals to humans, and vice-versa. Transmission usually occurs by direct contact, often via the hands, with colonized or infected animals or people and contaminated equipment and surfaces (Pal et al., 2020). The most common transmission pathways include the transfer from an infected mammary gland to an uninfected gland via fomites, such as milking equipment, or the milker's hands, uncontrolled animal traffic between different farms; and handling or eating food contaminated with *S. aureus*. *S. aureus* present in the nose and on the skin is shed into the environment by infected or colonized people and animals, indicating the possibility of airborne transmission as a possible route for infection (Gulzar and Zehra, 2018).

Anti-Microbial Resistance Profile of *S. aureus* in Ethiopia

Anti-microbial resistance (AMR) is an increasing threat to global health security that threatens economic, social, political ramifications globally and puts an extra burden on resource-poor countries. In Ethiopia, there are indications of the misuse of antibiotics by healthcare providers, unskilled practitioners, and drug consumers. These, coupled with the rapid spread of resistant bacteria and inadequate surveillance, contributed to the problem (Ibrahim et al., 2018). According to a meta-analysis conducted to evaluate the prevalence of inappropriate antibiotic utilization and resistance to antibiotics in Ethiopia, the pooled estimate of inappropriate antibiotic use was 49.2% (95% CI: 32.2-66.2). The pooled proportion of self-antibiotic prescription was 43.3% (95% CI: 15.7-70.9). Other reasons for inappropriate antibiotic use included a wrong indication, wrong duration, an improper route of administration, use of leftover antibiotics from a family member, and immature discontinuation of antibiotics. Thus inappropriate antibiotic use is a huge problem in Ethiopia, and many bacteria are resistant to commonly used antibiotics similarly, multidrug-resistant bacterial strains are numerous of which *S. aureus* and *Escherichia coli* are common (Muhie, 2019).

There have been studies conducted with the objective to reveal the AMR profile of *S. aureus* isolated from bovine mastitis in Ethiopia (Table 1), which suggest an increase in the antimicrobial resistance of *S. aureus* to commonly used antimicrobials for treatments of bovine mastitis. According to a study conducted by Marama et al. (2016) 33 *S. aureus* isolates were further tested for drug sensitivity to different antibiotics by disk diffusion method. Accordingly, gentamycin and amikacin showed high potency (100%), whereas penicillin-G showed the lowest potency *(0%)*. This study depicted the prevalence of antimicrobial-resistant *S. aureus* in the study farms. Also, another study conducted by Alemseged (2016) reported that out of 40 *S. aureus* isolates, all are resistant to penicillin G (100%), amoxicillin (100%), and all the isolates were found to be totally *(100%)* susceptible to gentamycin. 45.3% of the isolates were also found to be multidrug-resistant (MDR). Another study by Asmelash et al. (2016) has also demonstrated the existence of antimicrobial-resistant *S. aureus* at alarming levels to commonly used antimicrobial agents in the study area (farms). From 53 *S. aureus* grown on Muller-Hinton agar 25 (47.2%) were found to be resistant to cefoxitin which shows the prevalence of MRSA (Methicillin Resistant *S. aureus*). Out of the resistant *S. aureus* isolates, 24 (45.3%) were found to be Multidrug resistant (MDR*)* against 4 antibiotic discs primarily to penicillin G, amoxacillin, cefoxitin, and tetracycline.

Table 1 Descriptive statistics of meta-analysis database

Study area	No. of sample	*S. aureus* Isolates	Resistance Pattern	Susceptibility Pattern	Detection method and AMS Testing	Reference
Kombolcha	84	53	PenG, Amx, Cefx, TTC	Gen	PCR, and Disk diffusion	(Asmelash et al.,2016)
Afar	384	44	Pen G, Amp, Sxt	Chl, Gen, Str	Culture and Disk diffusion	(Beyene, 2016)
Holeta	216	33	Pen G	Gen, Amik	Culture and Disk diffusion	(Marama et al., 2016)
Asella	251	112	PenG, TTC, Cefx	Chl, Gen, Van,	Culture and Disk diffusion	(Kemal et al., 2017)
Bishoftu	177	110	PenG, Oxa, Ery, Amx	Gen, Chl	Culture and Disk diffusion	(Hika et al., 2017)
Adis Ababa	195	15	Amp, Pen G, Cefx	Gen, Kan	Culture and Disk diffusion	(Beyene et al., 2017)
W/Sodo	212	39	PenG, Cefox,TTC	Sxt, Chl	Culture and Disk diffusion	(Derib et al., 2017)
Mekelle	383	48	Pen G, TTC, Sxt	Dpt, Van, Rfp	PCR and Disk diffusion	(Kalayu et al., 2020)
Shire	64	21	PenG, Nal, Amp	Van	PCR, and Disk diffusion	(Girmay et al., 2020)
B/Gumuz	436	85	-	Pen G, TTC, Str	Culture and Disk diffusion	(Tassew et al., 2017)
Asella	230	107	Pen G	Kan, Van, Chl	Culture and Disk diffusion	(Seyoum, et al., 2017)
NW ET	240	52	TTC, Amp, Pen G	-	PCR, Broth microdilution	(Mekonnen et al., 2018)
Alage	444	27	Ery, Sxt, TTC, Cli	-	Culture and Disk diffusion	(Etifu and Tilahun, 2019)
Central ET	303	79	TTC, Amp, Sxt	Gen, Chl	PCR, and Disk diffusion	(Emeru et al., 2019)
Sululta	240	41	Pen G, Amx, Ery	-	Culture and Disk diffusion	(Regasa et al., 2019)
Sebeta	220	22	Pen G, OTTC	Van, SxT	Culture and Disk diffusion	(Tesfaye et al., 2019)
Sebeta	116	18	Pen G, TTC	Ery, Gen, Chl, Cip	Culture and Disk diffusion	(Grima et al., 2021)
Bulehora	240	11	Pen G, Cli, Spt	-	Culture and Disk diffusion	(Balemi et al., 2021)
Adama	384	37	OTTC, Sxt,	Kan, Str	Culture and Disk diffusion	(Tesfaye and Gizaw, 2021)
Addis Abab	255	52	Amp, Methacillin	-	PCR and Disk diffusion	(Lemma et al., 2021)
Adama	121	37	Oxa, Amx, OTTC	Kan, Str, Nal	Culture and Disk diffusion	(Yimana and Tesfaye, 2022)
Holeta	486	52	Amp, Amx, Oxa	-	Culture and Disk diffusion	(Gebremedhin et al., 2022)

Key: PenG: Penicillin G; TTC: Tetracycline; Sxt: Sulfamethoxazole Trimethoprime; Oxa: oxacillin; Amp: Ampicillin; Cefx: Ceftriaxone; Ery: Erythromycin; Gen: Gentamicin; Chl: chloramphenicol; Cip: Ciprofloxacin; Amik: Amikacin; Cli: Clindamycin; Kan: Kanamycin; Str: Streptomycin; Van: Vancomycin; Spt: Spectinomycin; Cefox: Cefoxitin; Dpt: Daptomycin; Rfp: Rifampicin; AMS: Antimicrobial sensitivity

According to a study by Kemal et al. (2017) 44.62% (112/251) of *S. aureus* isolates were identified from mastitic milk samples**.** Out of the 13 antibiotics used in this study, 65.18% of the isolate were MDR. Among all multiple antibiotic-resistant phenotypes of *S. aureus* isolates, 52.05% of them were resistant to three or four antibiotics, and 41.10% were resistant to five or six antimicrobials. Furthermore, 6.85% of them were resistant to seven or eight antibiotics. Highest rate of resistance among the isolates was against penicillin G (87.3%) followed by tetracycline Thus it is evident that MDR *S. aureus* was isolated from a mastitis milk sample.

Befikadu et al. (2017) also demonstrated that out of 42 *S. aureus* isolates subjected to antimicrobial susceptibility tests to seven different antimicrobial drugs by disk diffusion method. Thus, (4.3%) and (0%) of the isolates were resistant to tetracycline and penicillin G respectively. This study also warned that low susceptibility of *S. aureus* to commonly used antimicrobials such as penicillin G and tetracycline is a great concern because this antibiotic represents the main antibiotic group recommended for staphylococcal mastitis infection in Ethiopia. Another study has been conducted by Tassew et al. (2017) to evaluate *S. aureus* antimicrobial resistance patterns, and 63(74.11%) MRSA have been identified from a total of 85 *S. aureus* using cefoxitin through the disk diffusion method. The study showed a significant association of resistance pattern with *S. aureus* isolates, particularly to penicillin G (95.55%), cefoxitin (77.19%), and tetracycline (63.41%). This study revealed a higher prevalence of mastitis and the occurrence of MDR *S. aureus* specifically, which belongs to MRSA and is dependent on multiple associated risk factors.

Out of 212 samples collected and cultured, Derib et al. (2017) also showed that 71.8% of the *S. aureus* were resistant to cefoxitin, demonstrating the prevalence of MRSA. The study also suggests that regular antimicrobial sensitivity testing aids in the selection of efficient medicines and helps to prevent the emergence of drug resistance to widely used antibiotics In a study conducted by Regasa et al. (2019) to assess the antimicrobial susceptibility profile of *S. aureus*, its milk handling practices and associated risk factors in selected dairy farms, 42 samples were positive for *S. aureus*. The resistance profiles against penicillin and amoxicillin were 97.6 and 43.9%, respectively. The most frequent multidrug-resistant isolates were those exhibiting resistance to amoxicillin and penicillin, at a frequency of 21.95%. The study also demonstrated the existence of alarming levels of susceptibility of *S. aureus* to commonly used antimicrobial agents on the study farms. The study also revealed a prevalence of *S. aureus*, poor milk handling practices, and raw milk consumption behavior in the study area. Proper handling and hygiene decrease milk contamination by *S. aureus* and make it safe for human consumption.

Another study conducted by Kalayu et al. (2020) also indicated that isolates from dairy cows showed the highest resistance to penicillin (44/48, 91.7%) followed by tetracycline (17/48, 35.4%). No MRSA was isolated from the milk of the dairy cows in this study. In addition, no resistance was observed for vancomycin, daptomycin, or rifampin in both the milk and nasal isolates. Overall, 46/48 (95.8%) of the milk isolates were resistant to at least one of the nine antimicrobial agents, whereas 29/48(60.4%) were resistant to only one, 14/48 (29.2%) to two, and 3/48 (6.2%) were multi-drug resistant. A recently conducted study at Sebeta by Grima et al. (2021) showed that from a total of

116 milk samples collected, 18 *S. aureus* were isolated, and all the *S. aureus* isolates were found susceptible to erythromycin, gentamicin, ciprofloxacin, chloramphenicol, and sulphamethoxazole-trimethoprim. However, a high level of resistance was observed to common drugs such as penicillin and tetracycline. Out of the resistant *S. aureus* isolates, two were found to be MDR against three antibiotic discs, primarily penicillin G, tetracycline, and cefoxitin. The study also indicates the need to revisit our treatment guidelines for mastitis caused by *S. aureus*.

In study conducted by (Tegegne et al., 2021) *S. aureus* isolates were tested against nine commonly used antimicrobial agents, and large proportion (50–94.6%) of the *S. aureus* isolates were resistant to ampicillin, cefoxitin, penicillin, and streptomycin. Some of the isolates were relatively highly susceptible to ciprofloxacin and gentamycin. Similarly, low level resistance was observed against chloramphenicol. This study also demonstrated that isolates are characterized by MDR to commonly prescribed drugs in veterinary and human pharmacies. The study also showed that infection by multi-drug resistant *S. aureus* isolates, especially methicillin resistance A gene (*mecA*) may hold a serious threat to human and animal health (Table 1).

Resistance Mechanisms of *S. aureus*

Different strategies are used by *S. aureus* to develop antibiotic resistance. These strategies include restricting drug uptake, altering the drug target, inactivating the drug enzymatically, and active drug efflux. The use of one or more of these resistance mechanisms by the bacteria will depend on the antibiotic in question. For example, the horizontal transfer of resistance between bacteria is made easier by the location of resistance genes on transferable genetic components such as plasmids and transposons (Yilmaz and Aslantas, 2017).

S. aureus has a mobile genetic element that is surprisingly changeable and highly divergent. The staphylococcus cassette chromosomes (SCCs), bacteriophages, integrons, integrative conjugative plasmids, transposons, and Pathogenicity Island are just a few examples of the mobile genetic elements (MGEs) that make up more than 15% of the *S. aureus* genome. Antimicrobial resistance genes may be present in all of these MGEs, but not in bacteriophages. The majority of *S. aureus* clinical isolates have plasmids, which can be anywhere from 1 to 60 kilobases (kb) in size and are known to carry a variety of resistance genes. While large plasmids carry several drug resistance genes to aminoglycosides, beta-lactams, and macrolides, small plasmids carry drug resistance to tetracycline, chloramphenicol, and erythromycin. Additionally, larger plasmids combine with additional MGEs like transposons and impart resistance to beta lactams, trimethoprim, erythromycin, and spectinomycin (Haaber et al., 2017; Planet et al., 2017).

The resistance mechanism used by *S. aureus* to commonly used drugs for the treatment of bovine mastitis is described in the following sections.

β-lactam Resistance: penicillin

The β-lactam medication class is the most frequently utilized class of antibacterial agents. This drug class's members all have a core structure in common that is made up of a four-sided β-lactam ring. Three common pathways account for resistance to β -lactam medications: (1) inhibiting the interaction of the drug with the target PBP (Penicillin binding Protein), typically by altering the drug's capacity to bind to the PBP (this is mediated by alterations to existing PBPs or acquisition of other PBPs) (2) the medicine being hydrolyzed by β -lactamase enzymes; (3) the presence of efflux pumps that can extrude β -lactam drug (Bush and Bradford, 2016).

β- lactam antibiotics bind at the active site serine of the TransPeptidase in PBP2 by acting as structural analogues of D-Ala4-D-Ala5. The β-lactam bond is broken and a penicilloyl-O-serine intermediate is formed. The difference between this intermediate and the peptidoglycan acyl enzyme intermediate is that the former is extremely stable, taking 1–4 hrs for the addition of H_20 to regenerate the active site Serine and release the penicilloic acid product. This compares to the milliseconds it takes for the natural reaction to be completed. In essence, the active site of the transpeptidase enzyme is blocked and peptidoglycan biosynthesis ceases (Walsh, 2016).

Tetracycline Resistance

Tetracycline, which has bacteriostatic properties, prevents tRNA from entering the acceptor site and inhibits protein synthesis by attaching to 30s ribosomal subunits. Ribosomal protection and the efflux pump system are the two methods through which *S. aureus* develops resistance. *TetM* encodes for the ribosome's protection, whereas *TetK* specifies the efflux pump mechanism (Bitrus et al., 2018). The ribosomal protection provided by protein elongation and the activation of the efflux pump are the processes behind *S. aureus'* resistance to tetracycline. *TetK* and *TetL* genes are found on plasmids, while *TetM* and *TetO* genes are born on chromosomes and code for ribosomal protection and the efflux pump, respectively (Sheykhsaran et al., 2019).

Biofilm Formation

The creation of biofilm is a further process that has a substantial impact on the success of treating mastitis cases. By reducing antibiotic diffusion inside the biofilm matrix and developing resistance to high doses of antimicrobials, biofilm development lessens *S. aureus'* sensitivity to different antibiotics. The *S. aureus ica* locus contains the *icaA* and *icaD* genes, which are important for the development of biofilms. N-acetylglucosaminyltransferase is encoded by *icaA,* but *icaD* is essential for maximizing its expression, which results in the phenotypic expression of the capsular polysaccharide (Aslantas and Demir, 2016). A surface protein known as biofilm-associated protein *(*bap*)* has been shown to have a role in biofilm formation in addition to the genes indicated above by encouraging initial attachment and adhesion to inert and living surfaces (Figueiredo et al., 2017)

Public Health Importance

S. aureus is regarded as a significant source of contamination for many dairy products and is ranked as the third most common bacterium responsible for outbreaks of food poisoning in humans (Dittmann et al., 2017). Dairy products and raw milk are two items that *S. aureus* may grow in and are therefore suitable substrates for contamination. This indicates that there are several ways for the disease to get into dairy products intended for human consumption. These include dairy industry employees, the environment and milking equipment, or even directly from the animals because it may be found in filthy udders and nearby skin. One important additional possible source of milk contamination is when the dairy animals suffer from *S. aureus*-induced mastitis. It also causes food poisoning outbreaks, by ingestion of staphylococcal enterotoxins (SE); the common symptoms of these poisonings are vomiting, diarrhea, nausea, and abdominal cramps, which appear 2–6hr after SE-contaminated food consumption. In susceptible adults, just a few micrograms of SEs are required to produce Staphylococcal food poisoning, but 100 ng is adequate in children (Wu et al., 2016).

Foods contaminated with toxins or viable *S. aureus* cells are directly linked to inadequate sanitation practices. Although hazardous bacteria are frequently removed from human food, many poisons remain stable by heat treatment, especially when done over long periods. However, existing laboratory techniques to identify *S. aureus* contamination in samples like food or blood are time-consuming and require specialized resources. But detecting hazardous compounds, such as *S. aureus* toxins, in foodstuffs is of particular concern (Reddy et al., 2017). TSS-1 is a powerful toxin that causes toxic shock syndrome and causes 0.006 instances per 100,000 people. Hypertension, rash, fever, constitutional symptoms, multi-organ failure, and ultimately death are the hallmarks of TSS. TSS-1 stimulates T lymphocytes by boosting immunological activity, just like superantigens do. TSS-1 is a food poisoning risk factor whether it is present in humans, animals, or food, although its prevalence is less well documented than SEs (Babic et al., 2018).

Economic Significance

Contagious bovine mastitis is mostly caused by *S. aureus*, which creates a serious financial issue for dairy farmers owing to protracted, expensive antibiotic treatments. They can cause long-lasting infections that can remain throughout breastfeeding and into consecutive lactations and do not react well to antibiotic treatment (Zaatout et al., 2020). The analysis of mastitis-related financial losses is crucial. Three times higher production losses are caused by subclinical mastitis than by clinical mastitis, which accounts for 60–70% of the overall economic losses caused by all kinds of mastitis (Sharun et al., 2021). Subclinical mastitis is generally a more insidious form of the disease because it is invisible to the farmer, resulting in delayed diagnosis, and it spreads widely among dairy herds. Clinical mastitis, however, can cause serious harm to the udder and even systemic disorders leading to the culling of affected animals. As a result, the quality and production of the milk are lowered, which lowers both the income of the farmer and the value of the dairy sector (Pal et al., 2020).

Control and Prevention

To ensure the safety and quality of milk, the excessive use of antibiotics must be controlled. As mastistic milk obtained from antibiotic-treated dairy animals can be the source of antimicrobial resistance in humans. Control strategies must be adopted to avoid the use of antibiotics and greater losses in terms of culling. Control measures mainly rely on detailed screening and inspection of dairy farms, evaluation of welfare plans, and the use of prognostic diagnostic tests. These monitoring actions can identify animals at risk, and the spread of disease can also be controlled (Ashraf and Imran, 2020).

When milk is collected, processed, and stored, care should be taken to maintain a clean environment in all locations where contamination could occur. Along with maintaining milk quality and safety, a great deal of milk safety and quality measures should be put in place at any segment of milk production, handling, processing and storage to ensure the milk offered to the consumer is of high quality, safe and wholesome. Knowing the primary source of infection for each photogenic microbe is essential to prevent the quality of milk and milk products from degrading, since bacteria like *S. aureus* can cause major health issues. As a result, it's crucial to maintain herd health management, including vaccination, serological screening, tuberculin testing, tick control, mastitis control, feed hygiene and control, and regular screening tests on animal feed. Additionally, dairy farmers should implement the proper controls (pasteurization and safety precautions for personnel who are at risk) when the milk is processed and handled before being given to consumers (Merwan et al., 2019).

Milk quality tests are also intended to make sure that milk products adhere to the established requirements for chemical composition and purity as well as levels of a variety of microorganisms (Kavitha and Archana, 2015). The early detection of infection through an understanding of the pathogenesis, the development of new sensitive tests for early screening, the adoption of good management practices to lessen the likelihood of transmission, and the prevention of the uninfected ones is also necessary for an efficient and effective mastitis control program. To address the issues of antibiotic residue in milk and antimicrobial resistance, the control program must incorporate the strategic use of antimicrobials (Ruegg, 2017).

Given the expense of treating mastitis and its potential benefits, judicious use of antibiotics should be practiced with sufficient knowledge, a scientific rationale for reducing antibiotic use, and legal requirements (Sharun et al., 2021). The antimicrobial susceptibility of udder pathogens should be periodically checked by the antimicrobial stewardship program since any exposure of bacteria to antibiotics for the treatment of mastitis may result in the selection of resistance. To guarantee the long-term effectiveness of antibacterial drugs, it is crucial to track developments in antibiotic resistance over time. Given that mastitis therapy is frequently started before the pathogen has been tested for susceptibility, access to a recent repository of antimicrobial susceptibility data aids the veterinarian in choosing the best antibiotic for treating mastitis (de Jong et al., 2018).

CONCLUSION AND RECOMMENDATION

S. aureus has been the subject of intense investigations in the veterinary field and is probably the most studied causative agent of bovine mastitis, a disease with a huge impact on the dairy supply chain. Mastitis caused by *S. aureus* is also one of the major problems for dairy cows in milk production in Ethiopia. One of the largest problems in both global public health and veterinary care today is the development of antibiotic-resistant bacteria. The misuse and excessive use of antibiotics in the treatment and prevention of bovine mastitis contributes to the formation of antibiotic resistance among mastitis pathogens, particularly *S. aureus*, which carries a high number of resistant genes.

Studies conducted with the objective of revealing antibiotic resistance profile of *S. aureus* isolated from bovine mastitis in Ethiopia suggest an increase in the antimicrobial resistance of *S. aureus* to commonly used antimicrobials for treatments of bovine mastitis. According to the resistance profile of reviewed studies across Ethiopia, the majority of the tested isolates showed alarmingly high levels of resistance to widely used antimicrobial agents, the majority of the tested isolates showed alarmingly high levels of resistance to widely used antimicrobial agents, particularly penicillin G and tetracycline, suggesting a potential development of resistance to prolonged and indiscriminate use of those antibiotics, according to the resistance profile of reviewed studies across Ethiopia. Varying levels of resistance to Amikacin, Trimethoprim-Sulfamethoxazole, and ampicillin are also reported while majority of the isolates were also susceptible to Gentamycin and Chloramphenicol.

As a result, the diseases caused by multi-drug resistant *S. aureus* strains have a great economic impact on the animals by causing significant morbidity, mortality, and increased healthcare-related costs. And if the necessary action are not taken, against the indiscriminate use of antibiotics, the prevalence of antibiotic resistant *S. aureus* may increase further, leading to serious health hazards to animal as well as humans. Therefore, (1) examining the pattern of mastitis pathogen antibiotic resistance is a crucial requirement for the application of curative therapeutic guidelines and effective control. Besides, regular antimicrobial sensitivity testing helps select effective antibiotics that ultimately reduce the development of resistance to commonly used antibiotics. (2) Animal owners and dairy farm owners need to be advised to avoid the indiscriminate use of one type of antimicrobial for a long period of time and they need to consult animal health professionals for prescription and administration of drugs. (3) Implementation of an in vitro antibiotic susceptibility test before the use of antibiotics in both treatment and prevention of intramammary infections, which can be adopted as a long-term solution to control mastitis. (4) Continuous surveillance and monitoring of AMR *S. aureus*, to mitigate the emergence and spread of the milk-borne drug-resistant *S. aureus* strains across the high-risk pastoral communities. (5) New legislation about drug use or public awareness campaigns should be implemented to avoid drug abuse and the availability of drugs without prescription. (6) Further studies should be conducted to isolate the antimicrobial-resistant strains and genes of *S. aureus* in Ethiopia for the implementation of curable therapeutic guidelines and effective control of staphylococcal mastitis.

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