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Review on Staphylococcus Aureus

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Abstract

Staphylococcus aureus are Gram-positive, catalase positive cocci belonging to genus Staphylococcus in the family Staphylococcaceae, order Bacillales. They are approximately 0.5-1.5 µm in diameter, non-motile, non-spore-forming, facultative anaerobes that usually form in clusters. Staphylococcus aureus are uniquely resistant to adverse conditions such as high salt content and osmotic stress. Staphylococcus aureus are ubiquitous and are a part of the normal skin flora of animals and humans. This organism does not normally cause infections on healthy skin however, if it is allowed to enter the bloodstream or internal tissues, these bacteria causes a variety of potentially serious infections. In humans, Staphylococcus aureus causes various suppurative diseases, food poisoning, pneumonia and toxic shock syndrome. In animals, Staphylococcus aureus is considered one of the significant etiological agents of intra mammary infections in dairy ruminants causing both clinical and subclinical mastitis and resulting in substantial economic losses. Staphylococcus aureus produces many virulence factors, such as hemolysins, leukocidins, enterotoxins, exfoliative toxin. There is an evidence of bidirectional transmission of Staphylococcus aureus in humans and animals. Antibiotic resistance of Staphylococcus aureus is based on a wide variety of resistance genes. The most important is methicillin resistance mediated mainly by the mecA gene, which encodes for a penicillin-binding protein. MRSA strains have developed resistance to all beta-lactam antibiotics due to the overuse of these antibiotics. The increasing resistance to these antibiotics poses a great threat to the treatment of infections.

Keyword: MRSA, Pathogenesis, Staphylococcus Aureus and Virulence Factors

1. Introduction

Members of the genus Staphylococcus are Gram-positive bacteria that are cocci-shaped; tend to be arranged in clusters and described as "grape-like." The geniuses Staphylococcus are part of the normal skin flora of animals and humans. Although Staphylococcus is commensals of the skin, mucous membranes, alimentary and urogenital tracts of a diverse group of mammals and birds, they have been implicated in clinical infections of humans and animals [01].

Among the Coagulase-Positive Staphylococci isolated from clinical materials collected from humans, Staphylococcus aureus is the most important one [02]. In animals, the remaining species of Coagulase-Positive Staphylococci are far more common and clinically relevant [03]. Staphylococcus aurus is considered one of the significant etiological agents of intra mammary infections in dairy ruminants causing both clinical and subclinical mastitis and resulting in substantial economic losses due to reduced milk production and quality. In dairy cows, Staphylococcus aureus can be isolated from milk as well as from different other body sites. Transmission of Staphylococcus aureus intra mammary infections is believed to mainly occur during the milking process [04].

In humans, Staphylococcus aureus is associated with many diseases, from less serious skin problems to very serious infections such as bacteremia and pneumonia. Infections are common both in community-acquired as well as hospital-acquired settings. It does not normally cause infection on healthy skin; however, if it is allowed to enter the bloodstream or internal tissues, these bacteria may cause a variety of potentially serious infections [05]. Staphylococcus aureus causes various suppurative diseases, food poisoning, pneumonia and toxic shock syndrome. In addition, Staphylococcus aureus, especially MRSA, often causes serious problems via nosocomial infection in hospitals. Furthermore, community-acquired MRSA has recently emerged and has been reported to cause serious infectious diseases, sepsis, and pneu-

monia [06].

It is well known that Staphylococcus aureus produces many virulence factors, such as hemolysins, leukocidins, enterotoxins, exfoliative toxins, and immune-modulatory factors. The capacity of Staphylococcus aureus to cause infections is related to expression of these virulence factors. The agr system, known as the quorum-sensing system, is known to play a central role in the regulation of virulence factors. All these allow bacteria to adhere to tissues causing pathogenesis and invade the immune system causing toxic effect [07].

MRSA is a well-known pathogen of human and animals most commonly isolated from clinical cases. Emergence of multidrug-resistant livestock-associated MRSA has been increasingly reported worldwide. Problems arise during the treatment, in case MRSA strains occur. Despite all the measures taken in livestock breeding, the incidence of Staphylococcus aureus persists in the environment, in milk, on the animal's body, and also in humans [08].

From a public health perspective, there is concern about the risk of zoonotic transmission of livestock associated MRSA strains by direct contact of people working with animals including those working in dairy farms and also by their possible introduction in the community through the food chain [09, 10]. Once exposed to MRSA, animals become reservoir of infection for human beings [11]. Increased antimicrobial resistance of the organisms in animals treated with antibiotics is the most common health issue worldwide and to overcome this problem, many natural antimicrobial compounds have been attracting many researchers' attention in the development of novel therapies for infections caused by the multi-drug-resistant Staphylococcus aureus [12, 13].

In Ethiopia, since the use of antimicrobial drugs, both in humans and animals, is poorly controlled, multidrug resistant Staphylococcus aureus are frequently isolated from animals and humans [14]. In Staphylococcus aureus isolated from humans, there is a trend of increasing antimicrobial resistance [15]. Describing antimicrobial resistance patterns in both humans and animals may contribute to the knowledge on the importance of the issue in Ethiopia and to a more prudent and effective antimicrobial use. Therefore, the objective is to give general review on Staphylococcus aureus and to overview current situation in emergence of infections caused by drug-resistant Staphylococcus aureus.

2. Review Literatures

2.1. Description: Staphylococcus aureus are Gram-positive, catalase positive cocci belonging to the Staphylococcaceae family. They are approximately 0.5-1.5 μm in diameter, non-motile, non-spore-forming, facultative anaerobes that usually form in clusters. Many strains produce staphylococcal enterotoxins, the superantigen toxic shock syndrome toxin (TSST-1), and exfoliative toxins. Staphylococcus aureus predominantly colonizes the skin and nasal mucosa of healthy individuals globally [16].

2.2. Nomenclature and Classification

Staphylococcus aureus belongs to Genus Staphylococcus of Gram-positive bacteria in the family Staphylococcaceae, in the order Bacillales. Genus Staphylococcus includes at least 40 species of which 20 of them have veterinary importance. Ecological, epidemiological and virulence behavior, as well as the antimicrobial resistance profile, vary widely between species and even amongst strains of a given species [17].

One of the most important phenotypical features used in the classification of staphylococci is their ability to produce coagulase. However, while the majority of Staphylococcus aureus strains are coagulase-positive, some may be atypical in that they do not produce coagulase. Staphylococcus aureus is catalase-positive which makes the catalase test useful to distinguish staphylococci from Enterococci and Streptococci. Most reports characterizing animal-associated Staphylococcus aureus have demonstrated that strains affecting animals are distinct from those infecting humans, suggesting that there are host-specific lineages which only rarely cross species boundaries [18].

2.3. Epidemiology

Staphylococcus aureus is harmless and reside normally on the skin and mucous membranes of humans and animals. This pathogen is distributed worldwide. Rates of infection in community settings and residents of nursing home increased risk of acquiring MRSA [19].

2.4. Mode of Transmission

Transmission of Staphylococcus aureus through intramammary is believed to mainly occur during the milking process but this has been poorly researched in situations where hand milking is common. In humans, Ingestion of food containing enterotoxins and Person-to-person transmission occurs through contact with a purulent lesion or with a carrier unsanitary conditions and crowded community settings increase exposure to Staphylococcus aureus. Transmission of Staphylococcus aureus between animals and humans are known to occur. It was shown that infected animals can spread resistant strains not only in humans but also in raw food materials intended for further processing and for consumption [20].

2.5. Morphology and Growth Characteristics

Staphylococcus aureus stains purple by Gram stain and are cocci-shaped and tend to be arranged in clusters that are described as "grape-like." The colonies are often golden or yellow (aureus means golden or yellow). The yellow colour of the colonies is imparted by carotenoids produced by the organism [21].

On media, these organisms can grow in up to 10% salt, hence are uniquely resistant to adverse conditions such as high salt content and osmotic stress. The growth and survival of Staphylococcus aureus is dependent on a number of environmental factors such as temperature, pH, and presence of oxygen. These physical growth parameters vary for different

Staphylococcus aureus strains. The temperature range for growth of Staphylococcus aureus is 7–48°C, with an optimum of 37°C. Staphylococcus aureus is resistant to freezing and survives well in -20°C; however, viability is reduced at temperatures of -10 to 0°C. Staphylococcus aureus is readily killed during pasteurization or cooking [22]. Growth of Staphylococcus aureus occurs over the pH range of 4.0–10.0, with an optimum of 6–7. All species grow in the presence of bile salts. Staphylococcus aureus is a facultative anaerobe so can grow under both aerobic and anaerobic conditions. However, growth occurs at a much slower rate under anaerobic conditions [23].

2.6. Culture and Isolation

2.6.1. Mannitol Salt Agar Mannitol salt agar is used as a selective and differential medium for the isolation and identification of Staphylococcus aureus from clinical specimens. Mannitol salt agar contains peptones and beef extract, which supply nitrogen, vitamins, minerals and amino acids essential for growth. The 7.5% concentration of sodium chloride results in the partial or complete inhibition of bacterial organisms other than staphylococci. Sodium chloride also supplies essential electrolytes for transport and osmotic balance. Mannitol is the fermentable carbohydrate, fermentation of which leads to acid production, detected by phenol red indicator, aids in the differentiation of staphylococcal species. The inoculated mannitol salt agar with the sample of interest was incubated at 37 °C for 48 hours. Visual inspection of golden-yellow colonies on mannitol salt agar indicated the presence of presumptive Staphylococcus aureus due to mannitol fermentation. Colonies which showed consistent results of positive reaction for gram stain and catalase test and the tube coagulase test were phenotypically confirmed as Staphylococcus aureus [24].

2.6.2 Catalase Test: Catalase production and activity can be detected by adding the substrate H2O2 to an appropriately incubated (18 to 24-hour) culture. Staphylococcus aureus produce an enzyme catalase and able to convert hydrogen peroxide (H2O2) to water and oxygen and the resulting O2 production produces bubbles in the reagent drop, indicating a positive test. Organisms lacking the cytochrome system also lack the catalase enzyme and are unable to break down hydrogen peroxide, into O2 and water and are catalase negative. Catalase activity is very useful in differentiating between groups of bacteria. For example, the morphologically similar Enterococcus (catalase negative) and Staphylococcus (catalase positive) can be differentiated using the catalase test [25].

2.6.3. Coagulase Test

Most strains of Staphylococcus aureus produce one or two types of coagulase; free and bound coagulase. Free coagulase is an extracellular enzyme which reacts with prothrombin and its derivatives. Bound coagulase is localized on the surface of the cell wall and reacts with α- and β-chains of the plasma fibrinogens to form coagulate. Free coagulase is an enzyme that is secreted extracellular and bound coagulase is a cell wall associated protein. Free coagulase can be detected in tube coagulase test and bound coagulase can be detected in slide coagulase test [26].

2.6.4. Antimicrobial Susceptibility Test

The susceptibility of the Staphylococcus aureus isolates to different antimicrobial agents was done by disk diffusion method using commercial disks. The antimicrobial disks were as follows: ampicillin (30µg), streptomycin (10µg), kanamycin (30µg), erythromycin (10µg), chloramphenicol (30µg), cefoxitin (30µg), nalidixic acid (30µg), and novobiocin (30µg). Clinical strains were categorized as susceptible and resistant according to evaluation criteria developed by the Clinical and Laboratory Standards Institute guidelines. To identify VSSA and VRSA, MIC of vancomycin was determined by the microbroth dilution method using the Mueller-Hinton broth according to the Clinical Laboratory Standards Institute guidelines. Moreover, isolates with a zone of inhibition of ≤21mm to cefoxitin (30µg) were considered to be MRSA phenotypically [27].

2.7. Virulence factors

2.7.1. Toxins: Certain strains of Staphylococcus aureus produce the superantigen TSST-1, which is responsible for 75% of toxic shock syndrome (TSS) cases. Exotoxin TSST-1 causes' toxic shock syndrome by stimulating the release of large amounts of interleukin-1 (IL-1) by monocytes, interleukin-2 (IL-2), and tumour necrosis factor. Similarly, it induces the expression of IL-2 receptors and the proliferation of T lymphocytes. It does this by binding to MHC class II molecules and the exotonin is produced by most strains of Staphylococcus aureus. In general, the toxin is produced at the local site of an infection, and then enters the bloodstream [07].

Exfoliative toxins are the sole agents responsible for staphylococcal scalded skin syndrome, a disease predominantly affecting infants and characterized by the loss of superficial skin layers, dehydration, and secondary infections. Exfoliations are serine proteases with high substrate specificity, which selectively recognize and cleave (hydrolyses) desmosomes cadherins only in the superficial layers of the skin, which is directly responsible for the clinical manifestation of staphylococcal scalded skin syndrome [28].

Alpha-toxin secreted by Staphylococcus aureus binds to cell surface receptors and form the heptameric pores. This pore allows the exchange of monovalent ions, resulting in DNA fragmentation and eventually apoptosis. Higher concentrations result in the toxin absorbing nonspecifically to the lipid bilayer and forming large, Ca2+ permissive pores. This, in turn, results in massive necrosis and other secondary cellular reactions triggered by the uncontrolled Ca2+ influx. It is a highly conserved toxin that disrupts the tissue and endothelial barrier and enhances bacterial penetration [29].

Panton-Valentine leukocidin is a pore-forming protein exhibiting a cytotoxic nature which destroys leukocytes and causes tissue necrosis. The cytotoxin Panton-Valentine leu-

kocidin forms β-pores in target cells, causing necrotic lesions involving the skin or mucosa. More specifically, this cytokine assembles in the membrane of host defense cells, particularly white blood cells, monocytes and macrophages. The two subunits fit together and form a ring with a central pore through which cell contents leak and which acts as a superantigen [30].

Staphylococcal food poisoning is an intoxication that is caused by the ingestion of food containing pre-formed Staphylococcal enterotoxin. There are several different types of Staphylococcal enterotoxin; enterotoxin A is most commonly associated with staphylococcal food poisoning. Enterotoxins D, E and H, and to a lesser extent B, G and I, have also been associated with staphylococcal food poisoning [31].

2.7.2Enzymes

Nearly all strains of Staphylococcus aureus secrete several extracellular enzymes whose function is thought to be the disruption of host tissues and/or inactivation of host antimicrobial mechanisms. These enzymes include lipases, lecithin's, nucleases, hyaluronidase, and staphylokinase, coagulase and penicillinase. Coagulase (bound and free coagulase) is an enzyme which clots plasma and and coats the bacterial cell, probably to prevent phagocytosis. Hyaluronidase also known as spreading factor breaks down hyaluronic acid and helps in spreading it. Staphylococcus aureus also produces deoxyribonuclease, which breaks down the DNA, lipase to digest lipids, staphlokinase to dissolve fibrin and aid in spread leading to tissue damage and enhance bacterial invasiveness) and the beta-lactamase for drug resistance. Lecithinase hydrolyses the link between glycerol and phosphate in lecithin which is important component of cell membrane causing degradation and lysis of the cell [32].

2.7.3. Surface Protein A

It is abundant surface protein and a virulence factor which is released during normal cell division. Surface protein A is able to interact with the Fc portion of IgG and suppresses the adaptive immune response by limiting the antibody production by B-cells whereas it enhances the immune response if it binds with B-cell receptor allowing the activation of B-cells. Therefore, suppression of the IgG binding effects of surface protein A could be able to mount the immune response [33].

2.7.4. Capsular Polysaccharides

Capsules are the bacterial structure first recognized by the immune system. Staphylococcus aureus have been found to possess capsule composed of long polysaccharide chains known as capsular polysaccharides. Bacterial capsule is an extra-cellular material, which can be microscopically visualized [34].

2.7.5 Biofilm

Biofilm is a thick extracellular polysaccharide material produced by many organisms and its synthesis prevents many antibiotics from penetrating the bacterial cell and renders them resistant. The congregation of organisms embedded in an extracellular matrix allows the maintenance of an environment that is relatively impenetrable to standard antibiotic therapies and host defenses. Biofilm formation appears to be under complex genetic regulation, as numerous gene regulatory systems have been implicated in this process. The biofilm-forming ability of Staphylococcus aureus is well described, particularly as a component of chronic infections [35].

2.8. Infections

Staphylococcus aureus is main causes of subclinical mastitis in dairy herds that have successfully controlled major mastitis pathogens. Staphylococcus aureus does not normally cause infection on healthy skin; however, if it is allowed to enter the bloodstream or internal tissues, these bacteria may cause a variety of potentially serious infections. This pathogen is implicated in both community-acquired and nosocomial infections with considerable morbidity [36]. The infections are either minor as skin infections, soft tissues and urinary tract infection or more severe and even lethal such as endocarditis, meningitis, bacteremia, pneumonia and toxic shock syndrome [37].

2.9. Pathogenesis

Staphylococcus aureus is an opportunistic pathogen that can cause a variety of self-limiting to life-threatening diseases in humans and animals. Pathogenesis of Staphylococcus aureus involves colonization, local infection, systemic dissemination and/or sepsis, metastatic infections and toxicosis. The primary defense against Staphylococcus aureus infection is the neutrophil response. The clinical presentation of bacterial SSTIs can vary from superficial to highly invasive and/or disseminated disease [38]. When Staphylococcus aureus enters the skin, neutrophils and macrophages migrate to the site of infection. Staphylococcus aureus evades this response in a multitude of ways, including blocking chemotaxis of leukocytes, sequestering host antibodies, hiding from detection via polysaccharide capsule or biofilm formation, and resisting destruction after ingestion by phagocytes [38].

In addition to SSTIs, pyogenic bacterial abscesses can form in deeper tissues, such as underlying muscle, and bacteria can disseminate to form abscesses at distal sites and affect virtually any internal organ system. Staphylococcus aureus produces an array of potential virulence factors that play an important role on every level of host-pathogen interactions, including immune evasion molecules that allow bacteria to circumvent host innate and adaptive immunity. A multitude of these virulence factors protects Staphylococcus aureus from bactericidal activity of PMNs or directly alters neutrophil function [39].

Staphylococcus aureus have the ability to cause PMN lysis. Because PMNs contain numerous cytotoxic and proinflammatory molecules, uncontrolled lysis can have pivotal consequences to host health and additionally can promote dissemination of bacteria previously contained within phagosomes. Recent studies revealed that after PMN engulfment, Staph-

ylococcus aureus is able to divert PMNs from conventional apoptotic pathways and cause subsequent lysis of these host cells by means of a process termed programmed necrosis [40].

Notably, bacterial burden plays an essential role in directing PMNs toward programmed necrosis in addition to triggering programmed necrosis, Staphylococcus aureus secretes virulence factors that promote direct lysis of neutrophils. Among them are leukotoxins, such as Panton-Valentine leukocidin, leukocidin GH, or leukocidin DE, and α-type phenol-soluble modulins, γ-hemolysin, and δ-toxin [41].

Alpha- hemolysin/α-toxin is one of the earliest studied staphylococcal virulence factors. This pore-forming cytotoxin is freely secreted by Staphylococcus aureus as a water-soluble monomer, and then binds the surface of target cells, forming a heptameric transmembrane pore. Formation of functional pores generates ion imbalance, including efflux of potassium cations and ATP or influx of calcium ions, and ultimately leads to cell death [29].

Staphylococcus aureus produces a number of membranes damaging toxins capable of forming pores in the cytoplasmic membrane of host cells leading to cell lysis. Bi-component leukocidins form an octameric structure of alternating S and F subunits that form a β-barrel pore spanning the lipid bi-layer of the host cytoplasmic membrane resulting in lysis. Panton Valentine Leukocidin is a β-barrel pore-forming cytotoxin that binds to the complement receptors C5aR and C5L2 on the surface of neutrophils [42].

Enterotoxins released by Staphylococcus aureus is leading cause of food poisoning, resulting from the consumption of food contaminated with enterotoxins. Staphylococcal food intoxication involves rapid onset of nausea, vomiting, abdominal pain, cramps, and diarrhea. Symptoms usually resolve after 24 hours [31]. Scalded skin syndrome is caused by exfoliative toxins secreted on the epidermis resulting in conditions such as blisters, skin loss, pimples, furuncles, impetigo, folliculitis, abscesses, poor temperature control, fluid loss, and secondary infection [28].

2.10. Treatment

Knowledge of selection of the antibiotics for treatment is important as antibiotic responsiveness pattern of MRSA may vary. Systemic anti-MRSA drugs such as Vancomycin remained the mainstay of therapy against MRSA infections in hospitalized patients for decades. Numerous reports documented the clinical efficacy of vancomycin in treating various MRSA infections in hospitalized patients [43]. The problem of MRSA infections and lack of effective antibiotics other than vancomycin to treat them necessitated the discovery of novel anti-MRSA drugs. The continued efforts of researchers in discovering novel anti-MRSA drugs fructified resulting in arrival of number of newer anti-MRSA drugs for clinical use in the last 15 years [44]. These drugs include Ceftaroline, Telavancin, Tedizolid and Dalbavancin [45].

Anti-Virulence Agents which are not conventional antibiotics but able to inhibit the expression or function of the virulence factors, rendering the bacteria non-pathogenic is considered an alternative approach to tackle MRSA. Stripping microorganisms of their virulence properties without threatening their existence may offer a reduced selection pressure for drug-resistant mutations. Virulence-specific therapeutics would also avoid the undesirable dramatic alterations of the host microbiota that are associated with current antibiotics [46]. Accessory gene regulator (agr)-mediated quorum sensing system of Staphylococcus aureus plays a central role in pathogenesis of Staphylococci. Scientists identified small molecules which inhibited the agr system. Active and passive immunization strategies targeting the virulence factors of Staphylococcus aureus have also been explored [47].

Biofilm producing Staphylococcus aureus develops the ability to grow within the biofilm and survive phagocytosis and antibiotic action. Anti-biofilm compounds such as silver nanoparticles have emerged as novel antimicrobial agents in combination with existing antibiotics and have shown the most effective antimicrobial activity in vitro. Several recent studies have tested the efficacy of these silver nanoparticles in combination with antibiotics and they have been found to be a novel therapeutic strategy to treat infections caused by multi-drug-resistant organisms [48].

2.11. Antimicrobial Resistance

In recent years, antibiotic resistance among staphylococci is based on a wide variety of resistance genes. The most important is methicillin resistance mediated mainly by the mecA gene, which encodes for a penicillin-binding protein, PBP-2A. This gene resides on the staphylococcal cassette chromosome. Staphylococcal cassette chromosome is a large genetic mobile element which varies in size and genetic composition among the strains of MRSA. PBP-2A is an essential bacterial cell wall enzyme that catalyzes the production of the peptidoglycan in the bacterial cell wall. PBP-2A has a lower affinity to bind to beta-lactams (and other penicillin-derived antibiotics) when compared to other PBPs, so PBP-2A continues to catalyze the synthesis of the bacterial cell wall even in the presence of many antibiotics [49].

Among the isolates identified during routine diagnostics on milk samples in Germany the resistance situation is still favorable, but the number of resistant Staphylococci seems to be increasing [50]. The same situation is seen worldwide as documented for example for Europe. Among them, methicillin-resistant Staphylococcus aureus are seen frequently. Very commonly these MRSA belong to the clonal complex 398 (CC398), known as livestock-associated MRSA. MRSA strains were detected in humans and in animals, including those that are intended for the production of food, especially in pigs extremely limiting therapeutic options [51].

MRSA strains have developed resistance to all beta-lactam antibiotics including penicillin's, cephalosporins (except cef-

taroline and ceftobiprole), and carbapenems due to the overuse of these antibiotics, an increasing resistance continued to be reported and currently the resistance to these antibiotics pose a great threat to the treatment of infections [52, 53]. Penicillin-resistant strains of Staphylococcus aureus emerged shortly after the introduction of the Penicillin in the early 1940s. They expressed a β-lactamase that hydrolyzed the critical β-lactam bond and destroyed the drug's antibacterial activity [54].

MRSA are recognized as one of the most important risks for human and animal health. MRSA strains were detected in animals, including those that are intended for the production of food, especially in pigs [55]. It was shown that infected animals can spread resistant strains not only in humans but also in raw food materials intended for further processing and for consumption or as well as in the case of other raw materials, e.g. spices. The incidence of MRSA has been reported in cattle, horses, small ruminants, camels, poultry but especially pigs [08].

Multiple factors have been implicated in the development of antibiotic resistance, such as and misuse of antibiotics mostly in developing countries; however, biofilm-mediated drug resistance in bacteria is another major mechanism and it has been predicted that if the current treatment practice continues unchanged, the infections caused by antibiotic-resistant bacteria would be a major cause of death in 2050 where the expected number of deaths will be around 10 million every year [56].

3. Conclusions

Staphylococcus aureus has been recognized one of the most important pathogens for human and animal health. It is implicated in both community-acquired and nosocomial infections. There is bidirectional transmission of strains of Staphylococcus aureus between humans and livestock. The emergence of infections caused by drug-resistant bacteria is a serious and growing global health concern. Therefore, significant efforts should be made in the development of new antimicrobial compounds with improved efficacy and current research should be carried out on transmission and infection of Staphylococcus aureus.

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