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Methicillin resistance *Staphylococcus aureus* (MRSA) and Vancomycin Resistant *Staphylococcus aureus* (VRSA) problem in human and livestock and solutions

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Abstract

Staphylococcus aureus is an opportunistic bacterium of humans and other mammals that is becoming more clinically and veterinary important due to its fast development of antibiotic resistance. Some of these *S. aureus* varieties are methicillin-resistant *S. aureus* (MRSA), which is common in healthcare organizations, community settings, and livestock farms across the world. Beyond humans, MRSA has the potential to live in other animal species, which could result in the emergence and spread of antimicrobial agent resistance in various animal species. Vancomycin is a type of antibiotic classified as a final resort option, employed to address severe infections instigated by Gram-positive bacteria. Vancomycin remains among the primary choices for the initial treatment of MRSA infections. During the past few years, there has been an emergence of *Staphylococcus aureus* strains exhibiting strong resistance to vancomycin. The *vanA* gene cluster, obtained from vancomycin-resistant enterococcus, eases the transfer of vancomycin resistance in *S. aureus*. In terms of likely transfer routes, underlying mechanisms, and consequences of methicillin and vancomycin resistance from animals to humans and vice versa, this review aims to highlight the Methicillin resistance *Staphylococcus aureus* (MRSA)and vancomycin resistance *Staphylococcus aureus* (VRSA) issues

Key words: *Staphylococcus aureus*, MRSA, VRSA, human, animal.

Introduction

Staphylococcus

Staphylococcus is a genus of the Gram-positive cocci family staphylococcaceae, which contains more than 30 species of coagulase-positive and coagulase -negative staphylococci that culminate in a range of clinical symptoms. *Staphylococcus aureus* (*S. aureus*) is the most clinically significant species of opportunistic pathogen, colonizing between 30% and 50% of the human population as part of the typical commensal flora of humans and livestock (1). *S. aureus* is one of the principal organisms in hospital and community infections and can cause numerous infectious disorders, such as minor skin and soft tissue infections. Bacteremia, deadly pneumonia, osteomyelitis and infectious endocarditis (2) . Alexander Ogston, a surgeon in Aberdeen, Scotland, made the initial discovery of *Staphylococcus aureus* in 1880 while managing patients with open wounds. Under a microscope, *Staphylococcus aureus* appears structured like a "string of grapes" and is an element of the *Staphylococcus* genus of Firmicutes. It is Gram-positive, grows best around 37 ºC, and has a pH of 7.4 (3). *Staphylococcus aureus* has a wide range of metabolic capabilities and pharmic resistance, which let it adapt to a variety of situations. *S. aureus* colonizes the epidermis and nasopharyngeal membranes of around 25–30% of healthy people; this bacterium is a natural component of the human microbiota and does not harm individuals (4). *S. aureus* can result in a wide range of dangerous illnesses in people and cattle, from severe systemic infections to minor skin and soft tissue infections. (2). Six biotypes of *S. aureus* have been identified: human, -hemolytic human, bovine, caprine, avian-abattoir, and non-host specific. Animal isolates of *S. aureus* have been found to have distinctive phenotypic characteristics that differ depending on the host of origin (5). These biotypes have, for the most part, weathered the use of advanced characterization techniques; isolates from various hosts that are identified by multilocus enzyme electrophoresis group together (2). An arsenal of different toxins and virulence factors produced by *S. aureus* are thought to be responsible for its pathogenesis (6). According to the WHO's most recent global priority pathogens list (global PPL) of antibiotic-resistant bacteria, *S. aureus* is one of the most clinically significant multidrug-resistant concerns globally (7). Second on the priority list of the bacteria for the development of new antibiotics are methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate, and resistant *S. aureus* strains (8). This paper focus on MRSA & VRSA issues in human and animals with suggestion for solution.

Clinical significant of *S. aureus*

S. aureus infections can range from simple, superficial skin infections to harmful, fundamental illnesses like osteomyelitis and pneumonia that can enter the bloodstream and create septicemia in human. (9). *S. aureu*s causes various infections in human , including superficial skin diseases, surgical and trauma wound infections, urinary tract infections, and organ infections like pneumonia,

osteomyelitis, endocarditis, phlebitis, mastitis, and meningitis. People with chronic illnesses, diabetes, traumatic injuries, burns, or immunosuppression are more susceptible to these infections (10). Hospital infections caused by *S. aureus*, particularly is currently recognized as the most common cause of infective endocarditis in the industrialized world, have generated serious concerns in addition to food-borne diseases (11). *S. aureus* has been discovered in a variety of human physiological circumstances, including livestock, pets, food, and manufacturing processes. Since 1884, consuming tainted cheese has resulted in food-borne diseases. (12). A decade later, it was determined that a family experienced health issues brought on by eating meat from a cow that had passed away from a pyogenic staphylococci fever (8). Additional cases of food poisoning attributed to enterotoxin-producing *S. aureus* strains have been documented (7). As a result of these outbreaks, inspecting food items and production processes for bacterial contamination, particularly *S. aureus*, is more important than ever. (9).

The pathogen has also infected livestock resulting in the contamination of food products. This was demonstrated when a mastitis epidemic was noticed in a dairy herd that was very congested and was later determined to be brought on by a specific strain of *S. aureus* (13). In an examination of a variety of species of animals, including cows, goats, lambs, rabbits, chickens, and cats, *S. aureus* isolates carrying different staphylococcal enterotoxin genes was found. The incidence of outbreaks and the discovery of new genes predominating in *S. aureus* from animal hosts show that cattle constitute a major reservoir of staphylococcal infections (14). *S. aureus* is a challenging microorganism with the capacity to override humoral immune responses, release proteins that neutralize antimicrobial peptides, and avoid the immune system (15). To limit the prevalence and incidence of highly transmissible strains of the bacteria, strict cleanliness during milking, segregation of any cattle with *S. aureus* infections, and extensive culling of those infected might prove necessary (16). Regardless of the host, *S. aureus* isolates produce a variety of toxins that enable the bacterium to be a seriously dangerous pathogen (17).

Staphylococcal Toxins

When microbes make direct contact with a host, they discharge toxins, which are harmful substances. Panton-Valentine leukocidin (PVL), a notable toxin generated by *S. aureus*, is connected with numerous severe infections, which has been linked to a substantial number of *S. aureus* isolates that result in necrotic skin lesions, severe necrotizing pneumonia, and white blood cell destruction (10) . To understand what makes *S. aureus* isolates with PVL positivity, several research was carried out. In healthy children and young adults, PVL-producing *S. aureus* strains manufactured, hemorrhagic, necrotizing pneumonia with a high mortality rate (18). Another toxin generated by *S. aureus*, identified as an alpha toxin (α-toxin), plays a role in its pathogenesis as a virulence factor because it causes tissue necrosis and invasion while modifying macrophages' ability to eliminate

bacteria (19). The alpha-toxin was discovered to be a key component of the pathogenicity of opportunistic bacterial lung infections, where it significantly boosted bacterial growth and inhibited the acidification of bacteria-containing macrophages (phagosomes), lowering the efficiency of *S. aureus* destruction (20) . Additional toxins are involved in the pathogenesis of *S. aureus* in addition to the main toxins. Food poisoning and toxic shock are caused whenever the pyrogenic-toxin superantigens bind to the major histocompatibility complex II protein. This promotes substantial T-cell proliferation and the release of cytokines (18). The pathogen also makes a variety of other enzymes, such as proteases, lipases, and hyaluronidases, which break down host tissue and can assist in an infection spread through different tissues. The enzyme beta-lactamase inactivating penicillin (PBP2a), in particular, results in *S. aureus* that is resistant to antibiotics, Transpeptidase penicillin-binding proteins (PBPs) that Staphylococci manufacture decrease the action of -lactam antibiotics. (18). Reduced-affinity penicillin-binding protein 2a (PBP2a), which is produced by the mecA gene, was first discovered in 1981. Despite the presence of fatal doses of methicillin, the creation of the peptidoglycan cell wall of MRSA was allowed to continue because of the poor binding affinity of this PBP2a to -lactam antibiotics (12). It's interesting to note that a variety of virulence factors, such as toxins, cell-surface-associated adhesions, and secreted exo-proteins, are necessary for the pathogenesis of livestock-associated *S. aureus* (LA-SA), which is comparable to human-associated *S. aureus* (HA-SA) (21).

Antimicrobial resistance

Antibiotics are medications used to suppress or eliminate bacterial development, produced by living cells, by preventing the growth of challenging bacteria (22). However, more lately, Antimicrobial have been referred to be antibiotics that are also created entirely or in portion using synthetic methods (23). Several antibiotics have been approved for use in both humans and animals, categorized into five groups based on their actions (24):

1. Beta-lactam antibiotics (penicillins, cephalosproins, carbapenems, and monobactams) and vancomycin are examples of cell wall synthesis inhibitors with a bactericidal effect.
2. Protein synthesis inhibitors involve antibiotics that bind to either the 30S or 50S ribosomal subunits of bacteria (tetracyclines and aminoglycosides, for example).
3. The folate pathway inhibitors that hinder the synthesis of folic acid.
4. The DNA breakage-reunion step-interrupting quinolones, the RNA polymerase activity-inhibiting rifampicin, the DNA-gyrase or topoisomerase II and topoisomerase IV-binding inhibiting agents of nucleic acid synthesis.
5. The polymers and polypeptides that hinder the membrane of cells permeability.

The healthcare system faces challenges due to overuse and negligent prescribing of

antibiotics, often for viral illnesses that cure on their own. (17). Research indicates a lack of understanding about responsible antibiotic use and poor prescribing practices, leading to widespread, severe consequences in many nations. (16). Antibiotic resistance increases with increased usage, primarily due to novel selection, gene epidemics, and strain epidemics. These are caused by promoting entire species, mutations, and transferring resistance genes to mobile DNA (21). Antimicrobial resistance is a growing global concern, particularly in Europe, where it is becoming a significant public health issue due to the increasing use of broad-spectrum antibiotics. (25). Between 2000 and 2010, the global consumption of antibiotics increased significantly (35%) with 76% of the growth coming from Brazil, Russia, India, China, and South Africa (25). Multiple resistant proportions to various antibiotics were observed, including 87.1% of *Enterococcus faecium* to vancomycin, 56.8% of *Staphylococcus aureus* to oxacillin-methicillin, 39.7% of *Staphylococcus aureus* to clindamycin, 32.6% of *Pseudomonas aeruginosa* to fluoroquinolones, 31.3% of *E. faecium* to daptomycin (26).

Another significant factor contributing to antibiotic resistance, besides patients and doctors using medicines inappropriately, was the use of antimicrobials in animals (27). The use of these antimicrobial drugs, particularly antibiotics, is widespread. utilized in livestock production systems to protect their health and enhance their growth performance (28). Antimicrobial compounds in animal feed help reduce costs of meat, milk, eggs, and other animal products for human consumption, meeting the world's nutritional needs. (29). 78% of antibiotics in the USA are used on animals for food production, potentially leading to inaccurate use as preventative measures and nontherapeutic uses. (30). Antibiotic resistance will propagate across different cultures of bacteria when healthy animals are exposed to antibiotics for an extended period of period. It's possible that antimicrobial resistance cannot entirely be prevented and avoided.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Fleming launched the era of antibiotics for the management of infections in the 1940s with the discovery of penicillin (Figure1). *S. aureus*-related infectious illnesses were under control at the time, but as penicillin became more widely used in the 1950s, penicillin-resistant *S. aureus* started growing up in medical setting (31). Methicillin was used in the clinic in 1959 and was effective in managing penicillin-resistant *S. aureus* infections (32) . Only two years after the use of methicillin, in 1961, British scientist Jevons reported the isolation of an MRSA strain. This resistance was triggered by a gene (*mecA*) containing the penicillin-binding protein 2a or 2′ (PBP2a or PBP2′) which was integrated into the chromosomal element (SCCmec) of methicillin-sensitive *S. aureus* (33). Additionally, MRSA is growing rapidly as the most prevalent resistant infection found around the world, including Europe, the United States, North Africa, the Middle East, and East Asia (34). MRSA is divided into two categories,

community-acquired MRSA (CAMRSA) and hospital-acquired MRSA (HA-MRSA), according to its initial source (34). Livestock associated MRSA (LA-MRSA) was first described in 2005 (35). The fatality rate of MRSA infection exceeds that of AIDS and Parkinson's disease, according to the Centers for Disease Control (CDC) in the US (34) .

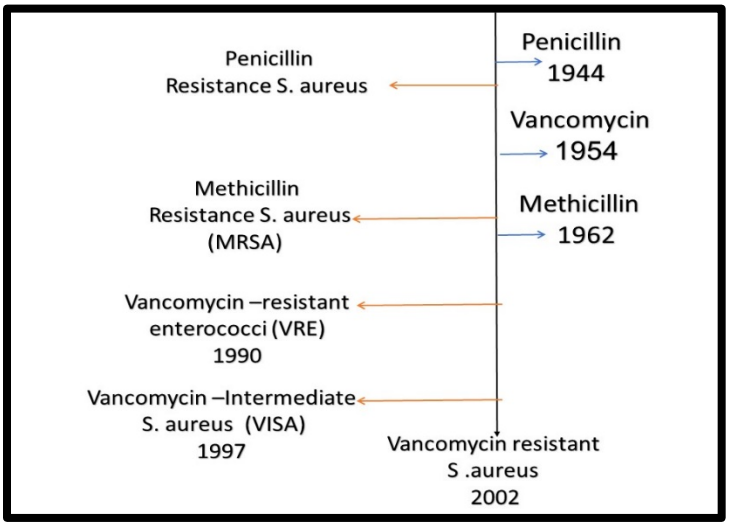

Figure 1: Demonstration the evolution of drug resistance in *S. aureus.*

Methicillin-Resistant and Beta-Lactamase mechanisms

Methicillin resistance is caused by the creation of a novel penicillin-binding protein (PBP) called PBP2a, which has low affinity for methicillin along with other Beta-lactams and precludes the antibiotic from accessing its target site, leading to resistance. Methicillin resistance is mostly caused by the *mecA* gene (32,36). The genomic region known as staphylococcal cassette chromosome *mec* (SCCmec) encodes this gene. Two genes, mecR1, which controls transcription, and mecI, which encodes the repressor protein, are required for the expression of the *mecA* gene. The most frequent PBP2a-encoding gene is the *mecA* gene; nevertheless, a novel mec gene has just been discovered. *mec C*, a component of the SCCmec type XI, has been found in samples from mammals and the environment in both *S. aureus* and CoNS. Although the *mec B* gene has just been discovered in *S. aureus*, two fewer *mec* genes (33) .

Beta -lactamase is a transferring enzyme that is conveyed by bacterial chromosomal genes that hydrolyzes an assortment of -lactam drugs, including broad-spectrum antibiotics like carbapenem (37). The studies revealed that beta-lactam antibiotics primarily eliminate bacteria through two main pathways: first, by binding to penicillin-binding protein (PBPs), which inhibits the

production of cell wall mucin synthase, disrupts the cell wall, and causes bacterial expansion and lysis; and second, by inducing the activity of the bacteria's autolytic enzyme, which causes autolysis and death (34). Antibiotic effectiveness is primarily decreased by excessive MRSA Beta-lactamase release via two processes, which results in MRSA resistance. The first is the hydrolysis process, in which Beta-lactam antibiotics were hydrolized and rendered inactive by Beta-lactamase; the second is the pinching mechanism, in which a significant concentration of -lactamase attaches quickly and permanently to target molecules. Two important processes through which MRSA's excessive -lactamase secretion diminishes the impact of antibiotics and results in extracellular drugs that are resistant to MRSA antibiotics are unable to enter the intracellular space and so cannot reach the target site (34) .

MRSA may be eradicated from hospitals by enforcing tight cleanliness and environmental controls. In several countries, search and destroy tactics were used to reduce the spread of both HA- and CA-MRSA in healthcare settings (38). Patients and health-care personnel are screened for MRSA transmission in these techniques. Following that, all MRSA-positive persons are separated and treated, wherever possible in order to eradicate MRSA carriage. However, since 2012, the rate of reduction in HA-MRSA cases has slowed (3). MRSA may infiltrate a farm through a variety of means. The most serious of these include the migration of MRSA-infected animals from one farm to another, direct contact with infected humans, and animal interaction with contaminated transport vehicles (39). During quarantine, animals should be checked for MRSA and only permitted to rejoin the main herd if they are MRSA-negative, before handling animals' farms should use a minimum of antimicrobials as possible. When MRSA first enters a farm, antibiotic usage aids in the selection of MRSA (40).

Vancomycin discovery and action mechanism

One of the earliest antibiotics, vancomycin has been utilized in healthcare for more than sixty years. In the tropical rainforests of Borneo, in 1957, Dr. Kornield, an organic chemist for Eli Lilly, discovered vancomycin from *Streptomyces orientalis* (3). Vancomycin acts successfully against Gram-positive bacteria such as *Listeria*, *Corynebacterium,* Staphylococci*,* Enterococci*,* Pneumococci*,* and *Streptococci.* Vancomycin is currently used to treat individuals who suffer from allergies to semi-synthetic penicillin or cephalosporins in addition to infections caused by MRSA (7). Its use was restricted due to the presence of chemicals that produced toxicities in previous formulations (3). Vancomycin's use grew starting in the 1980s when purer compositions were created in the late 1970s, but it was reconsidered after methicillin-resistant Staphylococci emerged in the 1970s (3). Vancomycin has supplanted conventional injectable medications as the preferred option for treating methicillin-resistant *Staphylococcus aureus* and drug-resistant *Enterococcus* species (41). Vancomycin eliminates bacteria by preventing the correct

creation of their cell walls in receptive bacteria. A cell wall structure that coats the majority of bacterial membranes prevents cells from growing and bursting owing to intracellular excessive osmolality (42). The peptidoglycan-containing cell wall structure has to be reinforced. Penicillin-binding proteins (PBPs) transglycosylate and transpeptide the precursor lipid II in order to incorporate it into the developing peptidoglycan. Vancomycin's hydrophilic molecule can engage via hydrogen bonds with the precursor lipid II's terminal D-alanyl-D-alanine (D-Ala-D-Ala) moieties. Vancomycin binding causes a conformational change that precludes the inclusion of the precursor to the developing peptidoglycan chain and the subsequent transpeptidation, resulting in bacterial lysis and cell wall breakdown (43. Vancomycin's intricate structure prevents it from traversing Gram-negative bacteria's outermost membrane, and it barely has a moderate bactericidal effect on bacteria (44).

The clinical and laboratory standards Institute divides the *S. aureus* isolates into three categories in accordance with their lower susceptibility to vancomycin. The three variants are vancomycin-susceptible *S. aureus* (VSSA) with MIC 2 µg/ml, vancomycin-intermediate *S. aureus* (VISA) with MIC 4-8 µg/ml, and VRSA with MIC 16 µg/m (43). Molecular techniques should be used to establish the presence of *vanA* or other van resistance determinants to determine when an isolate belongs to VRSA (43).

The heterogeneous vancomycin-intermediate *S. aureus* (hVISA), which is referred to as a *S. aureus* strain with a vancomycin MIC within the susceptible range (2 µg/ml) identified using conventional methods, and a cell subpopulation is in the vancomycin-intermediate range (4 µg/ml), has been proposed to be the origin of VISA strains (44).

VISA was believed to be generated by the progressive mutation accumulation of VISA-associated genes. Particularly significant are the genes for several-component regulatory systems, including WalKR, GraSR, and VraSR (43). Although their genetic lineages differed, VISA strains shared common phenotypes such as thickened cell walls, reduced autolytic activity, and decreased virulence (44).

The first vancomycin-resistant enterococci (VRE) were discovered in Europe and quickly spread to health care medical units. Vancomycin resistance in VRE was mediated by transposons determined mostly on plasmids, raising significant concerns about the possibility of vancomycin-resistant determinants spreading to generally susceptible bacteria of medical interest, particularly *S. aureus*. The effective transfer of the van element from *Enterococcus faecalis* to an MRSA strain in mix-infected rats validated this concern (46). In 2002, The first VRSA strain has been identified in Michigan, the second in Pennsylvania, and a total of 52 VRSA strains carrying van genes have since been noticed, including 14 isolated in the USA, 16 in India, 11 in Iran, 9 in Pakistan, 1 in Brazil, and 1 in Portugal (46).

Mechanism of VRSA resistance

Vancomycin resistance is classified into several gene clusters based on the DNA sequence of the ligase van gene homologues that encode the key enzyme for the synthesis of D-alanyl-D-lactate (D-Ala-D-Lac) or Dalanyl-D-serine (D-Ala-D-Ser). At least 11 van gene clusters confer vancomycin resistance, responding for VanA, VanB, VanD, VanF, VanI, VanM, and VanN phenotypes (47. Genes encoding D-Ala:D-Lac ligases, such as vanA, vanB, vanD, vanF, vanI, and vanM 9Figure 2), frequently result in high-level vancomycin resistance with MICs higher than 256 mg/ml, while genes encoding D-Ala:D-Ser ligases, such as vanC, vanE, vanG, vanL, and vanN, generally result in low-level resistance with MICs of 8-16 mg/ml (48).

Control of Resistance for Vancomycin

The development of preventive measures to control current resistance and prevent the development of resistant bacteria is critical for preserving the efficacy of antibiotics in both human and veterinary medicine. Studying the epidemiology of antibiotic resistance will allow us to devise preventative strategies to reduce current resistance and prevent the introduction of new strains of resistant bacteria (49. Hygiene methods to avoid cross contamination are used to control the emergence of resistance. and a reduction in antibiotic use are desirable. (50). Vancomycin use in animals should be limited to diseases that respond just to vancomycin and for which no other plausible options are available; when used in animals, it should be administered at the right dosage, dosing interval, and treatment duration (44).

Conclusions

Staphylococcus aureus is a bacterium that is found everywhere and is frequent in humans and animals. *S. aureus* may cause infections in hospitals and communities and has become the most common pathogen in hospitals across the world. The widespread use of antibiotics has resulted in an increase in bacterial resistance, beginning with the emergence of multidrug resistant strains such as MRSA, which has been regarded as a clinically important problem and has attracted extensive attention from domestic and international research. MRSA has become an obstacle in clinical therapy due to its features of simple infection, high mortality, and antibiotic resistance. Modern research has concentrated on how to successfully prevent and control MRSA. Science and technology have advanced throughout time, and medicine has continued to evolve.

For decades, vancomycin has been an effective treatment for MRSA infections. It is expected to maintain dominance as long as vancomycin resistance is under control and new antibiotics with higher performance are not available. Although the number of cases of VRSA infection is small, VRSA remains a potential hazard to public health. In health-care settings, intensive surveillance of vancomycin resistance, correct antibiotic usage, and adherence to infection control standards are critical.

The greatest strategy to control resistance in big groups of animals is to reduce the

demand for antibiotics. This can be achieved through proper vaccination against infectious diseases, the adoption of good hygienic practices in animal husbandry, the discontinuation of the use of antibiotics as feed additives for growth promotion in animals bred for food, the appropriate use of antibiotics for food animals, and the development of guidelines, codes of practice, and policies on the appropriate use of antibiotics.

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مشكلة مقاومة المكورات العنقودية للميثيسيلين (MRSA) والفانكومايسين (VRSA) في الانسان والحيوان وحلولها.

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الخلاصة

المكورات العنقودية الذهبية هي بكتيريا انتهازية تصيب البشر والثدييات والتي أصبحت أكثر أهمية من الناحية السريرية والبيطرية بسبب تطورها السريع لمقاومة المضادات الحيوية. بعض أصناف المكورات العنقودية الذهبية هذه مقاومة للميثيسيلين وتدعى بالمكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA)، وهو أمر شائع في منظمات الرعاية الصحية، والبيئات المجتمعية، ومزارع الماشية في جميع أنحاء العالم. وتعتبر MRSA ذات قدره على العيش في أنواع حيوانية أخرى، مما قد يؤدي إلى ظهور وانتشار مقاومة العوامل المضادة للميكروبات في مختلف الأنواع الحيوانية. الفانكومايسين هو نوع من المضادات الحيوية يُصنف من الحلول الأخيرة لمكافحة هذه البكتريا، يستخدم لمعالجة الالتهابات الشديدة التي تحرضها البكتيريا إيجابية الصبغة. يعتبر استخدام الفانكومايسين من بين الخيارات الأساسية للعلاج الأولي لعدوى (MRSA) خلال السنوات القليلة الماضية، كان هناك ظهور لسلالات المكورات العنقودية الذهبية التي تظهر مقاومة قوية للفانكومايسين. تعمل مجموعة الجينات (vanA) التي تم الحصول عليها من المكورات المعوية المقاومة للفانكومايسين، على تسهيل نقل مقاومة الفانكومايسين في المكورات العنقودية الذهبية. فيما يتعلق بطرق الانتقال المحتملة وعواقب مقاومة الميثيسيلين والفانكومايسين من الحيوانات إلى البشر والعكس، تهدف هذه المراجعة إلى تسليط الضوء على مشكلة المكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA)ومقاومة الفانكومايسين (VRSA) للمكورات العنقودية الذهبية المقاومة للميثيسيلين.

الكلمات المفتاحية: المكورات العنقوديه الذهبيه، مقاومة البنسلين، مقاومة الفانكومايسين ، الانسان ، الحيوان.