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Overview on Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Its typing tools

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Antimicrobial resistance (AMR):

Antimicrobial resistance (AMR) is now recognized as one of the most critical challenges being faced globally in combating infectious diseases. It is one of the major public health problems especially in developing countries where relatively easy availability and higher consumption of medicines have led to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries. Antimicrobial agents are widely used not only in human and veterinary medicine but also in animal husbandry and other agricultural activities. This has contributed to an alarming increase in antimicrobial resistance (Aarestrup, 2005).

Staphylococcus aureus:

There has been increased concern in the world about the pathogenic microorganisms which are resistant to commonly used antibiotics for their control. Among different multidrug resistant pathogenic organism Methicillin Resistant *S. aureus* (MRSA) is one of the most important bacteria that is resistant to most of the commonly used antibiotics and is called as super bug. *S. aureus* is a well-known commensal pathogen of large number of animal species, including humans. A wide variety of infections can be caused by *S. aureus*, from superficial skin and tissue infections to life threatening septicaemia (Graveland et al., 2010).

Morphology and its General Characters:

They are facultatively anaerobic Gram-positive cocci, non-motile and catalase and coagulase positive. Cells are spherical, single or paired cocci or form grape like clusters. They are ubiquitous and most common cause of localized lesions in human beings. They are resistant to dehydration and are stable for months in the environment. Up to 30-50 per cent of the human population are carriers of this organism. Staphylococcus species occur worldwide as commensal colonizers of the skin and mucous membranes of the respiratory and intestinal tract or on other body surfaces of the animals and humans and is usually

asymptomatic. In healthy people, carriage is associated with a minor risk of developing an infection, however when the integrity of the skin is broken, the risk of infection increases dramatically. It is the leading cause of nosocomial infections and is responsible for a wide range of human diseases, including endocarditis, food poisoning, toxic shock syndrome, septicemia, skin infections, soft tissue infections, and bone infections.

Methicillin Resistant *S. aureus* (MRSA):

S. aureus acquires antibiotic resistance with remarkable proficiency and hence the infections with *S. aureus* respond poorly to antimicrobial therapy. Methicillin was first introduced in human medicine in the late 1950's and it was used to treat penicillin resistant Staphylococcal infections. Staphylococcus isolates are frequently resistant to penicillinase resistant penicillins. Organisms exhibiting this type of resistance are referred to as Methicillin Resistant *Staphylococcus aureus* (MRSA). Methicillin resistance is conferred by the presence of the *mec A* gene, which encodes for the production of an altered penicillin binding protein (PBP, PBP2a or PBP2') that has a low affinity for all beta lactam antimicrobials like penicillins, cephalosporins and carbapenems (Kwon et al., 2006).

The *mec A* gene resides on a genomic island termed the Staphylococcal Cassette Chromosome *mec* (SCC *mec*). The discovery of the mobile genetic element Staphylococcal Cassette Chromosome *mec* (SCC *mec*) in MRSA strains of human origin further advances the theory that *mec A* could be shared among Staphylococcal species. The recent finding of *mec C* which is a new *mec A* homologue *mec A* LGA251, with only 70 per cent nucleotide homology to the conventional *mec A* gene has brought the routine testing for *mec A* as a confirmatory test for methicillin resistance into question (Stegger et al., 2011).

Methicillin-resistant *Staphylococcus aureus* has become a growing concern in companion and food-producing animals. The presence of multidrug-resistance with a wide range of extracellular enterotoxin genes, virulence factors, and Panton-Valentine leukocidin (pvl) cytotoxin genes confer life-threatening traits on MRSA and makes them highly pathogenic and difficult to treat. MRSA is a critically an important pathogen that is an emerging concern in veterinary medicine and agriculture. It is present in a wide range of animal species, including dogs, cats, rabbits, horses, cattle, pigs, poultry, and exotic species, both as a cause of infection and in healthy carriers. Identification of MRSA in various species and in food has led to concerns about the roles of animals, both pets and livestock, in the epidemiology of MRSA infection and colonization in humans (Nehru et al., 2025).

Transmission:

Transmission of such resistant bacteria from animals to humans can occur not only by contact with the animals but also through contact with, or ingestion of food products of animal origin. Depending on the virulence of the microorganism involved, this antimicrobial resistance can lead to further difficulty in treatment of human diseases. Additionally, ingested resistant bacteria can transfer their resistance genes

to bacteria of the normal micro flora (Aubry- Damon et al., 2004) (Figure 1).

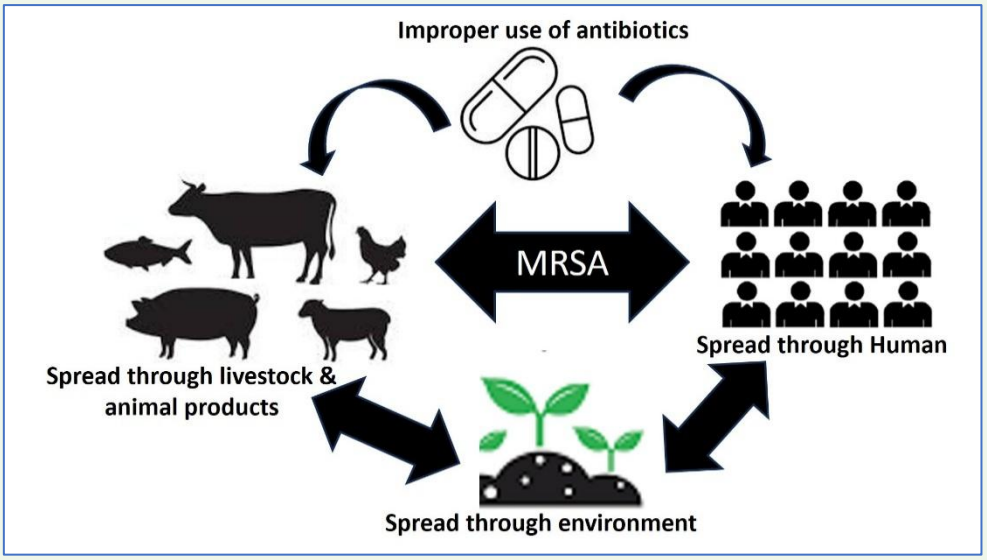

Figure 1: Transmission of Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Multiple antibiotics resistance by MRSA strains:

By the mid 1990s, MRSA had become a major problem because the strains generally exhibited multiple resistance to tetracyclines, aminoglycosides (gentamicin), macrolides, lincosamides and some other antimicrobial drug communities (Figure 2). Methicillin resistant Staphylococcal isolates exhibit phenotypic resistance to methicillin and related β lactam antibiotics, including cefoxitin and oxacillin. Today MRSA is one of the most important antibiotic resistant pathogens in hospitals and communities around the world.

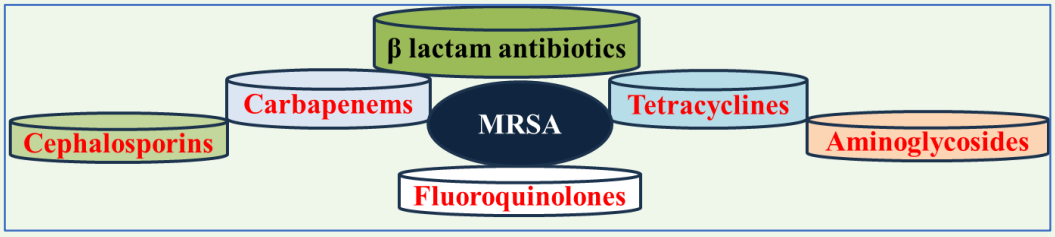

Figure 2: MRSA strains showing multiple antibiotic resistance development

Types of MRSA:

Various categories of MRSA based on epidemiologic characteristics are commonly used and include healthcare associated MRSA (HA-MRSA), community associated MRSA (CA-MRSA) and livestock associated MRSA (LA-MRSA). HA-MRSA infections are most commonly found in immune compromised people who have spent time in hospitals or healthcare centers, while CA-MRSA infections occur among otherwise healthy adults and children in the wider community. Livestock associated MRSA (LA-MRSA) refers to strains of MRSA in which animals, particularly production animals, serve as the main reservoir of infection in humans (Frana et al., 2013) Animal contact was the most important risk factor for colonization with MRSA in humans. The risk largely depends on the hygienic measures taken, the amount of MRSA present, and the ability of the strain to colonize the host. *S. aureus* is a common human pathogen that can

colonize the respiratory tract and cause infection. Nasopharyngeal carriage of macrolide resistant *S. aureus* was significantly more frequent in pig farmers which is transmitted from pigs.

Methods of Detecting the MRSA strains:

MRSA strains can be typed using both phenotypic and molecular methods. Phenotypic typing methods include the use of colony characteristics, biochemical reactions and antibiotic susceptibility pattern. The most important molecular typing methods that is currently in use includes the Pulsed Field Gel Electrophoresis (PFGE), Mutilocus Sequence Typing (MLST), Staphylococcal Chromosomal Cassette (SCC) mec and spa typing. These typing methods are useful for the comparison of the isolates from human and animals and helps in understanding the prevalence and extent of transmission of MRSA between the various species of animals and also in humans.

Isolation and Identification:

In most routine microbiological settings detection of methicillin resistance among staphylococci isolates is based on the phenotypic assays as it is easy to perform and interpret. But even with overall good sensitivity and specificity, the phenotypic methods have limitations in detecting staphylococcal isolates with borderline resistance or hetero resistance, as they are affected by variables, such as inoculum size, incubation time, temperature, media, pH, salt concentration of the medium, exposure to beta-lactam antibiotics and inter observer variability. Altered penicillin binding protein (PBP2a) encoded by *mecA* gene is mainly responsible for methicillin resistance in staphylococci. Therefore, its detection by genotypic method PCR is considered as “Gold Standard” (Sakoulas *et al*., 2001),

SCC*mec* typing:

A thorough understanding of the molecular epidemiology and evolution of MRSA is required to help detect, track, control and prevent human disease due to this organism. Full characterization of MRSA requires definition of not only the putative bacterial genetic background but also of the complex and heterologous SCC*mec* elements. SCC*mec* typing is an important molecular tool and its importance in community clonal outbreaks is increasingly being recognized (Sakoulas et al., 2001).

Pulsed-field gel electrophoresis (PFGE):

Pulsed-field gel electrophoresis (PFGE) is a powerful molecular typing method for MRSA that analyzes large DNA fragments to determine genetic relatedness and track outbreaks. It works by digesting the bacterial genome with a rare-cutting enzyme and then using an alternating electric field to separate the fragments, creating a unique "fingerprint" for each isolate. While PFGE was historically considered the "gold standard" due to its high discriminatory power and reproducibility, it is now often supplemented or replaced by faster, cheaper, and more easily shareable sequence-based methods like MLST and spa typing (Yeung et al., 2021).

Multilocus sequence typing (MLST):

Typing methods are useful for the comparison of the isolates from human and animals and help in understanding the prevalence and extent of transmission of MRSA between the species. Among various typing methods MLST is an excellent tool for investigating the emergence and clonal evolution of MRSA clones because it compares the 4 sequences of seven genes and hence more reliable. Multilocus sequence typing (MLST) is a highly discriminatory method of characterizing bacterial isolates on the basis of the sequences of 450- bp internal fragments of seven housekeeping genes. For each gene fragment, the different sequences are assigned as distinct alleles, and each isolate is defined by the alleles at each of the seven housekeeping loci. This results in an allelic profile or sequence type [ST] (Enright et al., 2000).

Spa typing:

Spa typing is an accurate DNA sequencing method for *S. aureus* typing, which is based on short sequence repeats of hypervariable X region in the spa gene. It is a single locus sequence typing method for *S. aureus* using the sequences of the polymorphic region X of *S. aureus* protein A (spa) gene. These regions have high degree of polymorphism and therefore are potentially suitable for discrimination in outbreak investigation (Moodley et al., 2006). A spa type refers to the composition of the VNTRs in the 3' end of the staphylococcal protein A gene (spa). The repeats that define a spa type are composed of 24 bp (the only exception being two new repeats found in a study, which were composed of 21 bp), and a total of 38 repeats have now been identified. Spa typing became very popular since it is based on sequencing of a single locus, less expensive and less time consuming than other methods. Moreover, it has more discriminative power compared to MLST

Conclusion:

The diagnostic typing tools contributes to understand the clonal diversity and transmission of MRSA in the community settings. It can be used in studying the genetic diversity among the strains of *S. aureus* for epidemiological tracing of source of infection and comparing the differences in virulent phenotypes among various strains. Therefore, understanding the interspecies transmission of MRSA strains by using these typing tools is of important significance, leads to formulate the preventive strategies to combat such AMR pathogens. Therefore, understanding the interspecies transmission of MRSA strains by using these typing tools is of great significance and helps in formulating preventive strategies to combat such AMR pathogens.

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