

PATHOPHYSIOLOGY OF METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS AND DRUG RESISTANCE**Ataa Elias Karum**

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Abstract: Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most successful modern pathogens of community and hospital acquired bacterial infections. MRSA can lead to diverse infection such as bacteremia, endocarditis, skin and soft tissue infections, bone and joint infections and hospital-acquired infections. As well as genetically diverse, the epidemiology of MRSA is primarily characterized by the serial emergence of epidemic strains. MRSA still poses a formidable clinical threat, with persistently high morbidity and mortality. They are also becoming increasingly multi-drug resistant and have recently developed resistance to vancomycin, which has been used successfully to treat MRSA for many years. Successful treatment remains challenging and requires the evaluation of novel antimicrobials. In Conclusion the emergence of CA-MRSA and VRSA isolates is changing the management of clinical infections potentially caused by *S. aureus*. Rapid methods for accurate detection of MRSA are needed to promptly identify patients and implement contact precautions as well as appropriate treatment. Molecular genotyping techniques have an important role in evaluating possible outbreaks and for understanding of the emergence and evolution of MRSA strains

Keywords: methicillin, MRSA, bacterial infections, CA-MRSA & VRSA.

This is an open-access article under the [CC-BY 4.0](https://creativecommons.org/licenses/by/4.0/) license**Introduction**

Methicillin-resistant Staphylococcus aureus (MRSA) has been implicated as the main cause of nosocomial infection. MRSA is a bacterium that causes infections in different parts of the body. Staphylococcus aureus usually lives naturally on human skin, in the nasal cavity or in the respiratory

system. Approximately 20%– 30% of humans are presumed to be persistent carriers, whereas the remainders of the population are potentially intermittent carriers. It can be considered that most individuals are exposed to the bacterium transiently throughout lifetime. However, it can cause a range of diseases. MRSA is one of the most common causes of hospital acquired disease. And it is opportunistic pathogen responsible for many purulent infections in both humans and animals. The symptoms of MRSA depend on where you're infected. Most often, it causes mild infections on the skin, like sores, boils, or abscesses. But it can also cause more serious skin infections or infect surgical wounds, the bloodstream, the lungs, or the urinary tract (Mulcahy and McLoughlin, 2016) Staphylococcus aureus bacteria produces a number of toxins . MRSA It's tougher to treat than most strains of staphylococcus aureus – or staph – because it's resistant to some commonly used antibiotics. MRSA is a bacterium that causes infections in different parts of the body– have become resistant to antibiotics that once destroyed it. MRSA was first discovered in 1961. It's now resistant to methicillin, amoxicillin, penicillin, oxacillin, and other common antibiotics known as cephalosporins (Sabrina Felson, MD , 2019). The resistance to methicillin is conferred by the acquisition of the *mecA* gene, which is located on a large mobile genetic element called the Staphylococcal chromosome cassette *mec* (SCC*mec*) (Garza-González et al., 2010).Methicillin-resistant Staphylococcus aureus (MRSA) is a major cause of both nosocomial and community-acquired infections. Researchers delineated the epidemiologic patterns of MRSA infection in 2005, using data from nine predominantly urban areas around the country, comprising about 16.5 million people. They outlined the frequency of invasive MRSA infections, defined as the isolation of the organism from a normally sterile site, such as blood, cerebrospinal fluid, pleural effusion, or various tissues. (Cunha and Calsolari, 2008). The commonly associated risk factors for MRSA infection are prolonged hospitalization, intensive care admission, recent hospitalization, recent antibiotic use, MRSA colonization, invasive procedures, HIV infection, admission to nursing homes, open wounds, hemodialysis, and discharge with long-term central venous access or long-term indwelling urinary catheter. A higher incidence of MRSA infection is also seen among healthcare workers who come in direct contact with patients infected with this organism. Although advancing age by itself is not considered a risk factor for MRSA infection, age more than 65 years is a significant risk factor for hospitalization. Hence, advancing age is indirectly linked to MRSA acquisition. Living in an area with a high prevalence of CA-MRSA or admission to a hospital with a high prevalence of HA-MRSA also is considered a significant risk factor for MRSA colonization. (Hirschmann and Jan, 2007) . Evolution of methicillin resistance by *S. aureus* has been traced to the acquisition of the exogenous gene (*mecA*) which is part of the staphylococcal cassette chromosome *mec* (SCC*mec*) (types I– VII) and is under the control of *MecI* (a repressor) and *MecR1* (a transducer) and, when present, the regulatory/ signalling proteins of the *bla_Z* system .The *mecA* gene codes for additional penicillin binding protein (PBP2a), a peptidoglycan transpeptidase, can confer resistance to all β - lactam antibiotics (penicillins, cephalosporins, and carbapenems) .Other isolates containing a particular variant of SCC*mec* types II and III have expanded range of resistance due to the presence of additional resistance genes. NK cells, and lymphocytes), cytokines, chemokine, and various enzymes (Wallach et al., 2014) . Since the cardinal manifestations of sterile inflammation are redness, swelling, heat, pain, and loss of movement, all of which resemble the symptoms of common infectious diseases; some scientists believe that tissue damage during infection are mediated by the host immune response rather than other irritants (Wallach et al., 2014). The common theory suggests that a lot of harmful molecules are produced during the clearance of pathogens by host immune response. For example, the oxygen metabolite hydrogen peroxide is secreted because of its antimicrobial effects, but it can also cause host tissue injury by destroying connective tissue elements,

and harming tissue cells directly (Henson and Johnston 1987). Interferon and TNF α (Weiss et al., 1989) which are synthesized during infection can directly induce cell death. Additionally, inflammation can cause clogging and rupture of blood and lymphatic vessels. The blockage of local circulation, as well as hypoxia, pH change, ischemia reperfusion injury and other mechanisms can cause tissue destruction). Consequently, the pathogen (MRSA) itself and the host immune responses are the main components involved in tissue damage and pathogenesis. Under normal conditions, the activated immune responses were believed to be the major mechanism in causing tissue damage (Wallach et al., 2014). However, these two components always interact with each other. The persistence of MRSA can induce inflammation because of the presence of pathogen-associated molecular patterns (PAMPs); while the compromised immune system which cannot effectively eliminate the pathogen will then result in the persistence of a pathogen and the chronic inflammation. This study aims to how Methicillin-resistant Staphylococcus aureus (MRSA) one of the most successful modern pathogens of community and hospital acquired bacterial infections.

Methods

Microscopically Examination and Cultural characteristics:

MRSA diagnose by checking a tissue sample or nasal secretions for signs of drug resistant bacteria. The sample is sent to a lab where it's placed microscopic diagnosis and in a dish of nutrients that encourage bacterial growth. But because it takes about 48 hours for the bacteria to grow, newer tests that can detect staph DNA in a matter of hours are now becoming more widely available.

Biochemical reactions of MRSA:

It is coagulase positive, It is catalase positive, It is oxidase negative, MRSA ferments mannitol, sucrose, maltose, and trehalose under aerobic conditions, with the production of acid but no gas. It liquefies gelatin, hydrolyzes urea, reduces nitrate to nitrite, and is "Voges-Proskauer (VP)" and "methyl red (MR)" positive but indole negative. (Ziebuhr et al., 1997)..

Results and Discussion

Staphylococci show following features: They are Gram-positive cocci, measuring around 1 μ m in diameter, They are nonmotile, nonsporing, They are noncapsulated. They are cocci typically arranged in irregular grape-like Clusters (Ziebuhr et al., 1997).

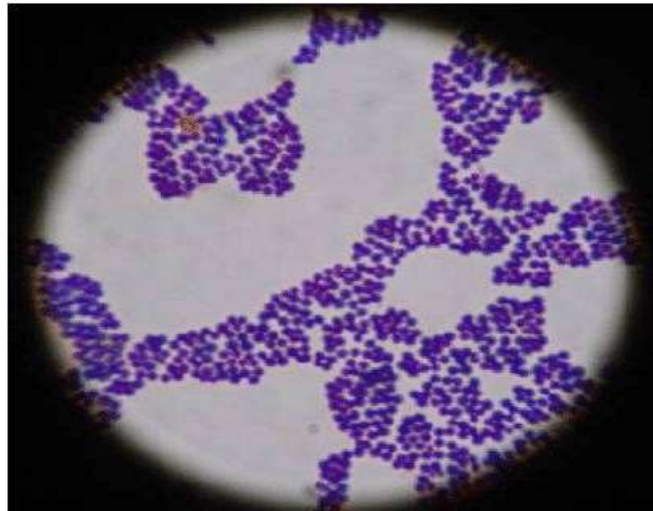


Fig. (1) MRSA slide

Staphylococci are aerobes and facultative anaerobes but can grow in the absence of oxygen also. They grow at a temperature range of 10–42°C (optimum temperature 37°C) and a pH range of 7.4–7.6 (optimum pH 7). Culture on solid media: Staphylococci can grow on a wide range of media including:

Nutrient agar: *S. aureus* produces round, convex, well defined colonies measuring 2–4 mm in diameter. *S. aureus* produces characteristic golden-yellow.

Blood agar: *S. aureus* produces a clear zone of hemolysis (beta-hemolysis) surrounding the colonies blood agar. Hemolysis is well marked on sheep or rabbit blood agar. Sheep blood agar is used for primary isolation. Human blood is not used, as it may contain antibiotics or other inhibitors. Other species of *Staphylococcus* do not produce hemolysis.



Fig. (2) Blood agar plate showing beta-hemolysis surrounding the colonies of MRSA

salt agar: Selective media, is the commonly used selective media for isolation of *S. aureus*. Mannitol salt agar contains 1% mannitol, 7.5% sodium chloride, and 0.0025% phenol red indicator. Most strains of *S. aureus* ferment mannitol with acid production, which gives rise to yellow zone formation around the colonies. (Kateete et al. , 2010).



Fig. (3) Yellow colonies of (MRSA) in Mannitol Salt Agar (MSA).

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This method has been recommended for screening colonies isolated on routine media and for confirmation of suspect resistance seen in disc diffusion tests. The method recommended by the NCCLS requires suspending the test organism to the density of a 0.5 McFarland standard and inoculating MH agar containing 4% NaCl and 6 mg/L oxacillin with a spot or a streak of the organism. Plates are incubated at 35°C or less for 24 h and any growth other than a single colony is indicative of resistance.(NCCL,2004).

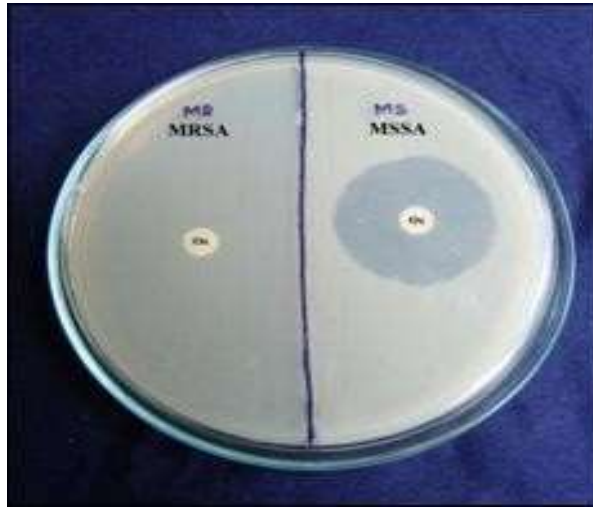


Fig (4) Oxacillin disc diffusion test

Polymerase chain reaction (PCR) testing is the most precise method for identifying MRSA strains. The *mecA* gene, which confers resistance to a number of MRSA (Schnellmann et al., 2006) .

Conclusion

It is clear that the emergence of CA-MRSA and VRSA isolates is changing the management of clinical infections potentially caused by *S. aureus*. Rapid methods for accurate detection of MRSA are needed to promptly identify patients and implement contact precautions as well as appropriate treatment. Molecular genotyping techniques have an important role in evaluating possible outbreaks and for understanding of the emergence and evolution of MRSA strains.

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