**Methicillin Resistant Staphylococcus aureus (MRSA)**

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**Abstract**

The gram-positive cocci, *Staphylococcus aureus* are found in abundance in nature and are grouped in clusters. The preferred medication was penicillin, but *Staphylococcus aureus* acquired a resistance to it by producing the beta lactamase enzyme. Methicillin was therefore made available in 1959. However, methicillin resistance quickly developed, and instances of methicillin-resistant Staphylococcus aureus (MRSA) were documented in 1961. Because of its aggressiveness and widespread dispersion in the community and clinical settings, Methicillin Resistant Staphylococcus aureus (MRSA) strains pose a hazard on a global scale. Beta lactam antibiotics, as well as fluoroquinolones, chloramphenicol, clindamycin, tetracycline, and aminoglycosides, are frequently ineffective against MRSA strains. Additionally, recently created anti-staphylococcal medications like Oxazolidione and Streptogramin6 exhibit resistance. Because MRSA is resistant to antibiotics, it is becoming a concern to the population.

**Key words:** MRSA, drug resistance, nosocomial infection, virulent

**I. INTRODUCTION**

Cocci were originally discovered in pus and the sick tissues. Around 150 years ago, it was isolated from a human abscess. These organisms were given the name "Micrococci" by von Recklinghausen in 1871. In 1871, Billroth divided these microbes into the Monococcus, Diplococcus, Streptococcus, and Gliococcus subgenera based on how their cells were organised.

In Bergy's Manual of Determinative Bacteriology, the genus *Staphylococcus* has classified into ten species (1923). The *Staphylococcus* genus was eliminated in the sixth edition (1948), and all staphylococci were moved to the genus *Micrococcus*. The genus *Staphylococcus* was reinstated in the sixth edition (1957). Additionally, two species, *S.aureus* and *S.epidermidis*, were identified based on the former's synthesis of coagulase and anaerobic consumption of mannitol. The genera *Staphylococcus*, *Micrococcus*, and *Planococcus* were added to the family *Micrococcaeceae* in the ninth edition (1974), and the species *Aerococcus* was added to the *Streptococcaceae*[1]. *Planococcus*, *Somatococcus*, *Micrococcus*, and *Staphylococcus* were the four genera included in the family *Micrococcaeceae* in Bergy's Manual of Systematic Bacteriology's ninth edition (1986)[14]. The genus *Staphylococci* is assigned to the family *Staphylococcaceae*, the genus *Planococci* to the family *Planococcaceae*, the genus *Micrococci* to the family *Micrococcaeceae*, and the only member of the genus *Stomatococci*, *Stomatococcus mucilaginous*, is assigned to the genus *Rothia*[2,3].

A Scottish physician named Sir Alexander Ogeston published the first account of staphylococci in abscess in 1881. He gave it that name because the cocci frequently form clusters that resemble grapes in pus and in culture (the Greek words "Staphyle" and "kokkos" mean "bunch of grapes" and "berry," respectively)[4].

The two strains of *S. aureus* (also known as the "golden staph," for its golden colonies) and *S. albus* (for its white colonies) were grown in pure culture by German scientist Anton Rosenbach in 1884.

Inadvertently, medical student Ernst Duchesne from France discovered in 1886 that the mould *Penicillium notatum* could lyse *Staphylococcus aureus* colonies.

In 1929, Alexander Fleming presented his findings on the lysis of *Staphylococci* near Penicillium mould that contaminated his culture in the lab at St. Mary's hospital[5].

Penicillin was manufactured in large scale in 1943.

Penicillin resistant staphylococcus was first described by Kirby in 1944[6].

In 1956 Erythromycin resistance came into existence[7].

In 1959, Methicillin was introduced into clinical practices.

Detection of Methicillin Resistant staphylococcus aureus was described immediately in 1961 by Jevons[8,9].

Vancomycin was introduced in 1958 for the treatment of MRSA.

In 1985, first case of community acquired MRSA was noticed.

In 1999, Quinipristin-dalfopristin was approved by FDA for MRSA treatment.

In 2000, Linezolid, the first oxazolidinone was approved by FDA.

In 2003, Daptomycin was the first lipopeptide approved by FDA.

In 2010, Ceftroline and Ceftobiprole was introduced and approved by FDA for treatment of MRSA.

In 2014, Oritavancin was introduced and approved by FDA.

**II. TAXANOMICAL CLASSIFICATION**

Domain : Bacterium

Kingdom : Eubacteria

Phylum : Firmicutes

Class : Bacilli

Order : Bacillales

Family : Staphylococcaceae

Genus : *Staphylococcus*

Species : *aureus*

The genus *Staphylococcus* has at least 30 species[1]. The three main species are *S. aureus*, *S. epidermidis*, *and S. saprophyticus*.

**III. MORPHOLOGY**

*Staphylococcus aureus* is a Gram positive cocci measuring 0.7 to 1.2µm in diameter. They divide randomly at three plane and the daughter cells do not separate completely giving them grape - like clusters in light microscope.

**IV. CULTURAL CHARACTERISTICS**

They are aerobes and facultative anaerobes. They readily grow on ordinary medium with a temperature range varying from 10ºC to 42ºC, the optimum temperature being 37ºC, and a pH of 7.4- 7.6. On nutrient agar plate the colonies are large about 2-4mm in diameter which are circular, convex, smooth, shiny, opaque and easily emulsifiable. They shows characteristic Oil-Paint appearance on nutrient agar slope. On Blood agar, some strains show zone of haemolysis, especially when incubated under 20-25% carbon dioxide. Some capsulated strains show large, convex, glistening colonies. On MacConkey or CLED agar *S. aureus* show similar colony morphology. The colonies are small and pink in colour due to lactose fermentation. The selective media available are Mannitol Salt Agar, Salt-milk agar, Ludlam’s medium, liquid salt mannitol agar, Phenyl ethyl alcohol agar and Baird Parker agar base[10,11].In Mannitol salt agar, colonies are of 1mm in diameter surrounded by yellow zone due to acid production from mannitol. Pigmentation is a characteristic of some species when grown aerobically at optimum temperature 22ºC. Pigment production is enhanced by addition of 1% glycerol monoacetate or milk in the medium.

**V. BIOCHEMICAL REACTIONS**

Slide catalase test and Tube catalase test is positive for *Staphylococci*. Modified oxidase test is negative and nitrates are reduced to nitrite by nitrate reductase enzyme. It ferments wide range of sugars including mannitol. Indole is negative, Methyl red and Voges Proskauer are positive. Urea is hydrolysed and gelatine is liquefied. It reduces tellurite to form black colour colonies in Potassium Tellurite agar. *Staphylococcus aureus* hydrolyses DNA and produces phosphatase[12].

**VI. HABITAT**

*Staphylococcus aureus* is ubiquitous in nature. This bacterium is the normal microbial flora of the skin, throat, gastrointestinal tract, and urogenital tract of approximately 25 to 50% of humans and lower animals[31]. *S. aureus* is commonly expelled into the air and onto the objects from infected persons and carriers.

**VII. COLONIZATION**

*Staphylococcus aureus* strains have been found to be commonly occupying certain anatomical body locations. Such colonization sites includes the anus, axillae, nares, pharynx, vagina, and vulva of healthy adults.

**VIII. VIRULENCE FACTORS**

Clumping factor (bound coagulase) –converts fibrogen to fibrin

Collagen binding protein

Fibronectin binding protein

Capsular polysaccharide adhesin

Protein A – bind to antibodies to prevent opsonization

α-toxin – membrane pore-forming hemolysin

Β-toxin (sphingomyelinase C) – hydrolysis of cell wall lipids

Gamma-toxin – wide spectrum of cytolytic activity

Delta-toxin – wide spectrum of cytolytic activity

Panton-Valentine leukocidin – membrane pore-forming

Exfoliate toxins – ETA and ETB – causes sloughing off of epidermis

Staphylococcal enterotoxins – SE-A, B, C1-3, D, E, G, H, I – gastrointestinal toxins

Toxic shock syndrome toxin – TSST-1 – causes leakage of endothelial cells

Coagulase – reacts with thrombin-like molecule to indirectly convert fibrinogen to fibrin

Deoxyribonuclease – hydrolyzes DNA

Hyaluronidase – hydrolyzes connective tissue

Lipases – hydrolyze lipids

Staphylokinase – lyses fibrin

**IX. SUPERANTIGENS**

Different *S. aureus* strains include a wide variety of Superantigens. These elements are crucial to both the development of the illness and the immunological responses of the host to an invading pathogen. The capacity of superantigens to induce the production of tiny proteins known as cytokines from different host defence cells such T-lymphocytes and macrophages defines them as antigens. The most serious symptoms of diseases linked with superantigens are caused by large-scale cytokine releases by such host cells. Staphylococcal enterotoxins (SEA-SEE), Staphylococcal enterotoxin-like toxins (SEG-SEQ), and nonmenstrual and menstrual toxic shock syndromes are examples of staphylococcal superantigens[10].

**X. PATHOGENESIS**

Steps involved are:

1. Colonization

2. Local infection

3. Systemic dissemination and/or sepsis

4. Metastatic infection

5. Toxinosis (toxin-caused disease)

It is clear that *S. aureus* may affect any organ system, and no other single bacterium causes as many disorders as it does. The virulence and extensive range of adhesions that *S. aureus* possesses allow it to adapt to a variety of situations, making it a dynamic bacterial species. Numerous infections are brought on by *Staphylococcus aureus*, and their clinical symptoms can range from a single pustule to sepsis and, sadly, death [10]. The pathogen injures tissue and produces a multitude of exotoxins as part of a chain of events that results in illness. Exotoxins from *S. aureus* are known as "superantigens." The peculiar non-specific antigen activation of T cells by these toxins serves as the foundation for grouping them together. Staphylococcal toxic shock syndrome is brought on by the enormous release of cellular components from activated T-lymphocytes and macrophages. Due to the development of the enzyme penicillinase (beta-lactamase), 90% of *S. aureus* strains isolated from patients in the United States are resistant to penicillin. The majority of isolates from hospitals and the general public show various antibiotic resistances.[46]

**XI. METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MSRA)**

The focus of clinical medicine throughout the following few decades was significantly altered by the advent of the antibiotic era in the late 1930s. Sulfonamides and Penicillin were developed so that practising doctors could treat numerous cases of infectious diseases. Many people believed that the fight against infectious illnesses had been won because of the early success of anti-infective treatments. This subsequently turned out to be false, primarily because *Staphylococcus aureus* and other bacteria quickly evolved resistance to penicillin once it was introduced in the early 1940s[13]. The bacterium's capacity to produce the enzyme beta-lactamase, commonly known as penicillinase, was what caused the resistance. The beta-lactam ring, which is the chemical building block of all penicillin antibiotics, is changed into the non-toxic penicilloic acid by this enzyme. Methicillin-resistant Staphylococcus aureus as a result emerged. Methicillin, a beta-lactam antibiotic that is penicillinase stable, was developed in 1961 to address the issue of rising *S. aureus* penicillin resistance.[8,9]

*Staphylococcus aureus* strains that are referred to as MRSA are those that are resistant to isoxazoyl penicillins like methicillin, oxacillin, nafacillin, and flucloxacillin. It was originally discovered in nosocomial settings before spreading widely over the neighbourhood. Methicillin-resistant Staphylococcus aureus (HA-MRSA) and community-acquired Methicillin-resistant Staphylococcus (CA-MRSA) are the two subtypes of MRSA infection. The term "HA-MRSA infection" refers to an infection that develops in a patient whose MRSA was cultured 48 hours after admission, who has a history of hospitalisation, surgery, dialysis, or residence in a long-term healthcare facility within the six-month period prior to the culture date, or who had an indwelling intravenous line, catheter, or any other percutaneous medical device present at the time of the culture. MRSA is defined as the strains of *Staphylococcus aureus* resistant to the isoxazoyl penicillins such as methicillin, oxacillin, nafacillin and flucloxacillin. It was initially found in the nosocomial settings which then became widespread in the community.

A CA-MRSA infection is characterised as an MRSA infection in a patient without a particular healthcare risk factor. A poison called Panton-Valentine leukocidin, which is secreted by CA-MRSA, infects healthy people. People who meet the following criteria are considered to have CA-MRSA infection, according to the Centres for Disease Control and Prevention (CDCP)[14].

1. Recognised as having MRSA infection in an outpatient environment.

2. Within 48 hours of hospital admission, MRSA culture results must be positive.

3. Lack of hospitalisation, surgery, dialysis, or colonisation in medical history.

4. No medical equipment or catheters inserted into the body via the skin permanently.

Athletes, nursery participants, and those who live in close quarters like dorms, military barracks, and prisons may be more susceptible to CA-MRSA infection. CA-MRSA is mostly transferred from person to person, although it can also be spread through contact with infected objects or surfaces. Both healthy people and individuals with established risk factors can get CA-MRSA. Skin and soft tissue infections (SSTIs), which frequently manifest as boils, abscesses, or purulent cellulitis, are the infections caused by CA-MRSA that occur most frequently. Early lesions are frequently compared to spider bites. Less often, CA-MRSA can result in pneumonia, surgical site infections, and invasive infections such bacteremia[44].

**XII. CARRIERS FOR MRSA**

Healthy carriers who have MRSA in their anterior nares, nasopharynx, throat, perineum, and skin can also transfer the infection. It has been established that MRSA colonisation causes autoinfection more frequently than colonisation with methicillin-susceptible isolates, and that the patient's nose is typically the source of *S. aureus* that causes bacteraemia. According to estimates, 30% of people have MRSA in their nose[15].Studies have shown that 6–50% of healthcare professionals who work in acute care and burn units are nasal carriers[16]. MRSA monitoring procedures should include screening of carriers.

**XIII. GENETIC BASIS OF METHICILLIN RESISTANCE**

**a. mec-A gene:**

The circular chromosome of the staphylococcus genome contains prophage, plasmids, and transposons. On the chromosome and other chromosomal components are the genes for virulence and antibiotic resistance. Through other chromosomal components, these genes can be shared between staphylococcal strains, species, or other Gram-positive bacteria. *Staphylococcus aureus* displays methicillin resistance as a result of acquiring the mecA gene, which produces the PBP2a altered penicillin binding protein. Both transglycosylase and transpeptidase enzymes, which are involved in disrupting the latter stages of the peptidoglycan production of the bacterial cell wall, are present in this 78 K Da, 668 amino acid organism[17]. The Staphylococcal Cassette Chromosome (SCCmec), which carries the gene mec A, is a mobile genetic element. Its integration into and excision from the *Staphylococcus aureus* chromosome are handled by a special group of recombinase genes termed the cassette chromosome complex (ccrAabdccrB). The kinds of SCCmec include I, II, III, IVa, IVb, and V. Nosocomial infections can have types I, II, or III of bacteria. Type IV of MRSA is present in CA. Rarely, type VI and VII are also seen. The SCCmec element is characterised by the mecA gene complex, cassette chromosomal recombinases complex, and junkyard variation[37].The expression of methicillin resistance requires roughly 20 accessory determinants (fem ABC, fem B, etc.). Despite the presence of PBP2a, any change to these components reduces the expression of methicillin resistance[18].

**XIV. DETECTION OF MRSA**

**a. Phenotypic detection:**

The growing circumstances, such as temperature, osmolarity, and culture media supplementation with NaCl or sugar, might affect the phenotypic manifestation of resistance.

**b. Agar dilution test:**

From an overnight growth, at least four to five isolated colonies are put into sterile saline. A 0.5 McFarland standard suspension is used (108 cfu/ml). Spot inoculate on a Mueller-Hinton agar plate that has been treated with 2% NaCl and has 0.125-256g of oxacillin per ml of serial doubling dilution of the antibiotic. The Mueller-Hinton oxacillin plates are incubated at 35 °C for 24 h. A MIC of 2 g/ml is thought to be resistant, whereas a MIC of 4 is seen to be susceptible[19].

**c. Disc diffusion test:**

Both the Oxacillin and Cefoxitin disc diffusion tests are employed. *Staphylococcus aureus* isolates are prepared into a 0.5 McFarland standard solution, and a grass culture is carried out on a Muller Hinton Agar plate. Plates are incubated at 37°C for 24 hours with a 30 g cefoxitin and 1 g oxacillin disc, after which the zone size is determined. Transmitted light must be used to read the Oxacillin disc diffusion test[32].

In accordance with CLSI criteria published in January 2023, a cefoxitin zone diameter of less than 22 mm is classified as methicillin sensitive, whereas a zone diameter of less than 21 mm is classified as methicillin resistant. Because of its haziness, oxacillin is commonly mistaken for being susceptible. With the oxacillin disc diffusion test, false susceptibility of 4.4% has been documented[20].

The expression of methicillin resistance is also influenced by environmental factors as pH, temperature, and salt concentration[41,42]. The AST plating should be incubated between 35 °C and 37 °C, but the temperature should not rise over 37 °C, in order to identify MRSA by both cefoxitin and oxacillin disc. Accuracy was unchanged when the incubation period was extended from 18 to 24 hours[32]. It is reliable to incubate disc diffusion at 37°C for 24 hours[43].

Cefoxitin has more sensitivity and specificity than oxacillin, making it better in the disc diffusion technique. Testing simply penicillin and either cefoxitin or oxacillin can determine if a person is susceptible to or resistant to beta lactam antibiotics [39,44]

All penicillins, cephalosporins, monobactams, various beta lactam/betalactamase inhibitor combos, and carbapenams are ineffective against oxyacillin-resistant bacteria. Possibility of Penicillin Other penicillins, beta lactam/betalactam inhibitor combos, and carbapenem are also effective against Staphylococcus. Except for newer cephalosporins like Ceftaroline that have anti-MRSA efficacy, all beta lactam antibiotics currently on the market are ineffective against Oxacillin Resistant Staphylococci[44,45,46].

**d. E test oxacillin MIC test:**

The inoculum is plated on Mueller-Hinton agar supplemented with 2% NaCl after being standardised to 0.5 McFarland turbidity. E-test strips are positioned and incubated for 24 hours at 35o C[39].

**f. Oxacillin screen agar:**

Mueller-Hinton agar plates are incubated at 35° C for 24 hours after being inoculated with 10 l of a 0.5 McFarland suspension of the isolated by streaking in one quadrant. The Mueller-Hinton agar plates contain 4% NaCl and 6 g/ml of oxacillin. In transmitted light, plates are carefully examined for any growth. After 24 hours, any growth is deemed to be oxacillin resistant. Full expression after oxacillin induction needs time to develop. So, after 48 hours of incubation, oxacillin-containing medium only reach suitably high sensitivities[21].

**g. Mannitol salt agar screening:**

Mannitol salt agar medium supplemented with 6µg/ml of oxacillin is used to detect MRSA. The presence of yellow colonies are suspected as MRSA and further confirmation of *Staphylococcus aureus* is done by repeating tube coagulase from yellow colonies[47,48].

**h. Chromogenic media for MRSA:**

ChromID, MRSA select, CHROM agar MRSA, Chromogenic MRSA/Denim Blue agar, ORSAB (oxacillin resistance screening agar base), MRSA Ident agar, and Chromogen oxacillin S. aureus medium are some of the media that are available. The S. aureus -glucosidase enzyme is the target of the chromogen in ChromID. Cefoxitin (4 mg/litre) is added to the mixture to inhibit competing microorganisms, which causes the MRSA colonies to become green. By adding oxacillin (2 mg/ml) to inhibit MSSA and polymyxin to inhibit Gram negative bacteria, ORSAB, a modified variant of mannitol salt agar, is rendered selective. Aniline blue, used in this medium as a pH indicator, gives MRSA colonies their distinctive blue colouring. Due to the presence of a chromogenic phosphatase substrate and an antibiotic supplement including cefoxitin, MRSA colonies on MRSA Ident agar appear dusky pink or ruby in color[38]. The chromogen in Chromogenic MRSA or Denim Blue agar detects phosphatase activity in *S. aureus*. The MRSA colonies will be in denim blue colour[40].

**XV. MOLECULAR METHODS**

The best method for finding the mecA gene is using PCR. The isolate is subjected to DNA extraction, and the mecA gene is amplified using certain primers. Hot start PCR is applied to the master mix, which includes PCR buffer, dNTP mix, Taq DNA polymerase, MgCl2, and template DNA. Following this, there are 30 cycles of 94°C for 45 seconds of denaturation, 50°C for annealing, 1 minute of extension, and 3 minutes of final extension. Ethidium bromide dye is used to visualise PCR results on a 2% agarose gel while using a UV transilluminator[22].

**XVI. OTHER METHODS FOR MRSA DETECTION**

A quick test for MRSA identification that is commercially accessible is the latex agglutination test. Monoclonal antibodies that are directed against the PBP 2a antigen are used. Other techniques for detecting MRSA include DNA hybridization and immunochromatographic tests[36,41].

**XVII. RECENT DRUGS FOR MRSA**

Ceftobiprole works well against MRSA that is resistant to vancomycin. The Emedocaril-based novel cephalosporin is the active ingredient of the prodrug Ceftobiprole. In order to treat MRSA, the FDA gave its approval in 2010[23].Dalbavan and Tedizolid phosphate are advised by the FDA. Telavancin, Oritavancin, and Iclaprim are three more antibiotics that are currently being developed and are said to be effective against MRSA.

**XVIII. APPROCHES TO TREATMENT**

The cornerstone of treatment for hospitalised patients with severe MRSA infections is intravenous vancomycin. Sadly, vancomycin can cause harmful side effects include allergic responses like anaphylaxis and "red man syndrome." Red man syndrome can occur anywhere between 4 to 47% of the time, with people over 40 years old experiencing the more severe reactions[34]. The infusion-related condition is characterised by intense itching and an erythematous rash. The pathogen's co-resistance to other classes of antibiotics frequently makes it difficult to treat individuals with less severe illnesses or those who can be moved to or treated with oral medication. For individuals with particular forms of MRSA infections, particularly those affecting the skin and skin structures, the long-acting tetracycline derivatives doxycycline, minocycline, and tigecycline are regarded as viable oral therapy options[24].

Linezolid, daptomycin, and dalbavancin are substitutes for vancomycin in the treatment of MRSA infections for bacteremia and catheter-related blood stream infections, respectively. The antibiotic drug linezolid, which belongs to the oxazolidinone family, is effective against practically all CA-MRSA isolates as well as group A streptococci. The possibility of *S. aureus* strains becoming resistant to this drug is one of its drawbacks[25]. There have been reports of other antimicrobial agent combinations as effective treatments for people with underlying infections. These consist of taking fluoroquinolone and rifampicin orally. When treating CA-MRSA-related skin and soft tissue infections, fluoroquinolones should not be utilised. As a result, *S. aureus* is easily susceptible to resistance. Rifampicin is quite effective against isolates of CA-MRSA that are prone to it[35]. For MRSA, new antibacterial substances are required. The therapeutic challenge must be met for treatment to be effective. Accordingly, telavancin, an experimental medicine, is one promising medication. Almost all gram-positive bacteria, including drug-resistant microorganisms like MRSA, VISA, and VRSA, were discovered to be susceptible to the medication in 2008[26,27,28]. Telavancin's multifaceted method of action involves preventing the development of new bacterial cells and interfering with the way their membranes work. The medication has a bactericidal effect.

**XIX. VACCINES**

*S. aureus* has a large financial influence on medical treatment. Treatment of staphylococcal illness has become challenging due to the development of antibiotic resistance. The rise of such antibiotic resistance has increased demand to create vaccinations against *S. aureus*. In both human and animal clinical and veterinary studies, a number of whole cell preparations, including live, heat-killed, and formalin-fixed *S. aureus,* have been investigated as vaccines to prevent infections. In animal models or farm animals, none of these experimental preparations elicited a sufficient immunological response[29,30]. In 2003, D.L. Hu [36] and colleagues reported that laboratory mice were vaccinated with a mutant variant of the toxoid that causes toxic shock syndrome.The animals that had received the vaccine were immune to *S. aureus* infection. For the treatment of individuals with toxic shock syndrome, pooled immunoglobulin preparations are frequently utilised since they neutralise a variety of staphylococcal toxins.

**XX. PREVENTION STRATEGY FOR MRSA**

Hand hygiene is recommended particularly in intensive care units.

* Active surveillance of colonization for patients
* Active surveillance culture for healthcare workers.
* Decolonization
* Environmental cleaning.
* Control of hospital overcrowding and understaffing.
* Early detection and appropriate treatment

**XXI. CONCLUSION**

Methicillin Resistant Staphylococcus aureus has been identified as a significant and common bacterium acquired in hospitals that causes endemic and epidemic illnesses in hospitals. These bacteria developed an antibiotic resistance due to human overuse, antibiotic contamination of food and water, and germ mutation. All categories of antibacterial drugs are ineffective against MRSA. So, in order to cure MRSA, we need newer medicines. This chapter provided an overview of MRSA and its techniques of detection.

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