**Methicillin Resistant Staphylococcus aureus (MRSA)**

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**Abstract**

 *Staphylococcus aureus* is a Gram positive cocci arranged in clusters and is ubiquitous in nature. Penicillin was the drug of choice, to which *Staphylococcus aureus* developed resistance by producing enzyme beta lactamase. So, Methicillin was introduced in 1959. But, resistance to Methicillin emerged rapidly and in 1961 Methicillin resistant Staphylococcus aureus (MRSA) cases were reported3. Methicillin Resistant Staphylococcus aureus (MRSA) strains represent a worldwide threat because of their virulence and broad distribution in the hospital settings and community5. MRSA strains are often resistant to beta lactam antibiotics and also to Fluoroquinolones, Chloramphenicol, Clindamycin, Tetracycline and Aminoglycosides. In addition, resistance is also shown by the recently developed anti-staphylococcal agents including the Oxazolidione and Streptogramin6. MRSA is an emerging threat to the community owing its antibiotic resistance.

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

**I. INTRODUCTION**

 Cocci were first observed in the diseased tissues and in pus. It was isolated from human abscess around 150 years ago. Von Recklinghausen in 1871 named these organisms as “Micrococci”. In 1871, Billroth classified these organisms on the basis of their cell arrangements into *Monococcus*, *Diplococcus*, *Streptococcus*, and *Gliococcus*.

 Bergy’s Manual of Determinative Bacteriology includes (1923) ten numbers of species listed under genus *Staphylococcus*. In the sixth edition (1948), the *Staphylococcus* genus was deleted and all staphylococci were regulated to the genus *Micrococcus*. In the seventh edition (1957), the genus *Staphylococcus* was reintroduced. In addition, two species, *S.aureus* and *S.epidermidis*, were recognized on the basis of anaerobic utilization of mannitol and the production of coagulase by the former. In the eighth edition (1974), the genera *Staphylococcus*, *Micrococcus*, and *Planococcus* were included in the family *Micrococcaeceae*, and the genus *Aerococcus* was placed in *Streptococcaceae*1. In the nineth edition (1986), of Bergy’s Manual of Systematic bacteriology, the family *Micrococcaeceae* included four genera: *Planococcus*, *Somatococcus*, *Micrococcus*, and *Staphylococcus*[14]. In the road map of the latest edition of Bergy’s Manual of Systematic bacteriology, the genus *Staphylococci* is placed in the family Staphylococcaceae, genus *Planococci* in family *Planococcaceae*, genus *Micrococci* in family Micrococcaeceae, and the only member of genus *Stomatococci*, *Stomatococcus mucilaginous*, is placed in genus *Rothia*[2,3].

 In 1881, Sir Alexander Ogeston, a Scottish surgeon was the first to publish the observation of *Staphylococci* in abscess. He named it due to its typical occurrence of the cocci in grape-like clusters in pus and in culture (‘*Staphyle’* in Greek, meaning ‘bunch of grapes’; ‘*kokkos’* meaning a berry)[4].

 In 1884, German scientist Anton Rosenbach, grew the two strains, *S. aureus* (“golden staph,” for the golden colonies) and *S. albus* (white colonies), in pure culture.

 A French medical student, Ernst Duchesne, in 1886 accidentally found that *Staphylococcus aureus* colonies could be lysed by the mold *Penicillium notatum.*

 Alexander Fleming in 1929 published his observation on lysis of *Staphylococci* in the vicinity of Penicillium mold which contaminated his culture at St. Mary’s hospital laboratory[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**

 A large array of Superantigens can be found among different *S. aureus* strains. These factors play important roles in the disease process and in a host’s immune responses to an invading microorganism. Superantigen is defined by their ability to stimulate the release of small proteins called cytokines from various host defence cells such as T-lymphocytes and macrophages. Massive releases of cytokines by such host cells accounts for the most-severe effects of superantigen-associated illnesses. Staphylococcal superantigens include Staphylococcal enterotoxins (SEA-SEE), Staphylococcal enterotoxin-like toxins (SEG-SEQ) and nonmenstrual and menstrual toxic shock syndromes[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 quite evident that *S. aureus* can involve any organ system and the number of diseases that it causes is matched by no other single pathogen. *S. aureus* is a dynamic bacterial species, endowed with a wide array of adhesions and virulence factors that enables it to adapt to a variety of environments. *Staphylococcus aureus* causes a variety of diseases with clinical manifestations ranging from a single pus-containing lesion (pustule) to sepsis, and unfortunately death[10] The pathogen causes disease by a series of steps that include tissue invasion and the production of a number of exotoxins. *S. aureus* exotoxins are referred as “superantigens.” These poisons are grouped together on the basis of their unusual non-specific antigen activation of T-lymphocytes. Activated T-lymphocytes together with macrophages release massive quantities of cellular products that are responsible for causing staphylococcal toxic shock syndrome.

 It should be noted that 90% of *S. aureus* strains isolated from patients in the U.S. are resistant to penicillin due to the production of the enzyme penicillinase (beta-lactamase). The greater majority of isolates from both hospital and the community exhibit multiple resistances to antibiotics[46]

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

 The dawn of the antimicrobial era in the late 1930’s dramatically changed the focus of clinical medicine for the next several decades. With the introduction of the Sulfonamides and Penicillin, practicing physicians could effectively treat and cure many cases of infectious diseases. The early success of anti-infective treatment in the minds of many was taken as evidence that the battle against infectious diseases had been won. This ultimately proved to be misleading, largely because bacteria such as *Staphylococcus aureus* developed resistance to Penicillin soon after its introduction in the early 1940’s[13]. The resistance was due to the bacterium’s ability to produce the enzyme beta-lactamase also known as penicillinase. This enzyme converts the beta-lactam ring (chemical group central to all penicillin antibiotics) into harmless penicilloic acid. That led to the emergence of Methicillin Resistant Staphylococcus aureus. Methicillin, a penicillinase-stable beta-lactam antibiotic came onto the scene in 1961 to counter the problem of increasing penicillin resistance by *S. aureus*[8,9]

 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. MRSA infection is therefore classified into Hospital acquired Methicillin resistant Staphylococcus aureus (HA-MRSA) and Community acquired Methicillin resistant Staphylococcus (CA-MRSA).HA-MRSA infection is defined as infection occurring in a patient from whom MRSA was cultured 48 hours after admission or who has a history of hospitalization, surgery, dialysis or residence in a long term health care facility with six months prior to the culture date or had an indwelling intravenous line, catheter or any other percutaneous medical device present at the time of culture.

 CA-MRSA infection is defined as an MRSA infection in a patient who lacks specific risk factor for healthcare. CA-MRSA secrets a toxin Panton-Valentine leukocidin, which cause infection in healthy individuals. According to Centre for Disease Control and Prevention people who satisfy the following criteria, are said to be infected with CA-MRSA[14].

1. Diagnosed in the outpatient setting as MRSA infected.
2. Culture for MRSA must be positive within 48 hours of admission in the hospital.
3. No medical history of colonization, hospitalization, surgery, or dialysis.
4. No permanent indwelling catheters or medical devices passing into the body through the skin.

 Individuals who may be at greater risk of CA-MRSA infection include athletes, day-care attendees, those living in close quarters such as dormitories, military barracks and correctional facilities. Transmission of CA-MRSA occurs mainly by person to person spread but may also occur by contact with contaminated surfaces or items. CA-MRSA infection occurs both in healthy person and in those with known risk factors. The most frequent infections caused by CA-MRSA include skin and soft tissue infections (SSTIs) that typically present as boils, abscesses or purulent cellulitis. Early lesions are often described as appearing like spider bites. Less commonly, CA-MRSA can cause invasive infection such as bacteraemia, surgical site infections and pneumonia[44].

**XII. CARRIERS FOR MRSA**

 The spread of MRSA is also through healthy carriers who harbour MRSA in anterior nares, nasopharynx, throat, perineum and skin. It has been shown that in most cases the sources of *S. aureus* causing bacteraemia is the patient’s nose, and colonization with MRSA leads to autoinfection at a higher rate than colonization with methicillin susceptible isolates. It is estimated that about 30% patients colonize MRSA in nose[15]According to studies, 6-50% of health workers working in burns and intensive care units are nasal carriers[16]. Screening of carrier should be done as a part of MRSA surveillance protocols.

**XIII. GENETIC BASIS OF METHICILLIN RESISTANCE**

**a. mec-A gene:**

 The *Staphylococcus* genome consists of circular chromosome with prophage, plasmids, and transposons. Genes responsible for virulence and antibiotic resistance is found on the chromosome, as well as on extra chromosomal elements. These genes are transferred between staphylococcal strain, species or other Gram positive bacteria through extra chromosomal elements.The expression of methicillin resistance in *Staphylococcus aureus* is due to acquired *mec*A gene which encodes for altered penicillin binding protein called PBP2a. It is 78 K Da with 668 amino acids possessing both transglycosylase, transpeptidase enzymes involved in disruption of final steps of peptidoglycan synthesis of bacterial cell wall[17]. The gene mec A is carried on mobile genetic elements called Staphylococcal Cassette Chromosome (SCCmec), whose integration into and excision from the *Staphylococcus aureus* chromosome, are mediated by a unique set of recombinase genes cassette chromosome complex (ccrAabdccrB). SCCmec is classified into types I, II, III, IVa, IVb and V. Type I, II, III are found in nosocomial infections. Type IV is found in CA-MRSA. Additional type VI, VII are also found rarely. The *mec*A gene complex, cassette chromosome recombinases complex and junkyard variation results in characterization of SCCmec element[37].There are about 20 accessory determinants (fem ABC, fem B etc.) which are required for the expression of methicillin resistance. Any alteration in these elements decreases the expression of methicillin resistance in spite of the fact that PBP2a is present[18].

**XIV. DETECTION OF MRSA**

**a. Phenotypic detection:**

 Phenotypic expression of resistance can vary depending on the growth conditions, such as temperature, osmolarity and culture medium supplements with NaCl or sucrose.

**b. Agar dilution test:**

 A minimum of four to five colonies isolated from an overnight growth are transferred to sterile saline. The suspension is adjusted to a 0.5 McFarland standard (108cfu/ml). Spot inoculate on Mueller-Hinton agar plate supplemented with 2% NaCl and containing 0.125-256µg oxacillin/ml in serial doubling dilution. The oxacillin Mueller-Hinton plates are incubated at 35ºC for 24 hours. MIC of ≥2 µg/ml is considered resistant and MIC of ≤4 is considered susceptible[19].

**c. Disc diffusion test:**

 Cefoxitin disc diffusion test and Oxacillin disc diffusion test are used. 0.5 McFarland standard suspension of *Staphylococcus aureus* isolates is made and lawn culture done on Muller Hinton Agar plate. A 30µg of cefoxitin and1µg of oxacillin disc are placed and plates are incubated at 37°C for 24 hours and zone size is measured. Oxacillin disc diffusion test must be read in transmitted light[32].

 According to CLSI guidelines January 2007, Cefoxitin Zone diameter of ≥22mm is reported as methicillin sensitive and ≤21mm is reported as methicillin resistant and for oxacillin of ≥13mm is reported methicillin susceptible and ≤10mm is reported methicillin resistant[40]. Oxacillin is frequently misinterpreted as susceptible due to haziness. False susceptibility of 4.4% has been reported with oxacillin disc diffusion test[20].

 Environmental conditions like pH, temperature and salt concentration also decides the expression of methicillin resistance[41,42]. For detecting MRSA by both cefoxitin and oxacillin disc, the AST plated should be incubated between 35ºC-37ºC, but the temperature should not exceed more than 37˚C. Increasing the duration of incubation from 18 hours to 24 hours did not improve accuracy[32]. Incubation temperature of 37º C for 24 hours in disc diffusion is trustworthy[43].

 Cefoxitin is superior to oxacillin in disc diffusion method as it has higher sensitivity and specificity. Susceptibility or resistance to beta lactam antibiotics may be deduced from testing only penicillin and either cefoxitin or oxacillin[39,44].

 Oxacillin resistant strains are resistant to all penicillins, cephalosporins, monobactam other beta lactams/ betalactamase inhibitor combinations, and carbapenams. Penicillin Susceptible Staphylococcus is also susceptible to other penicillins, beta lactam/betalactam inhibitor combinations and carbapenem. Oxacillin Resistant Staphylococci is resistant to all currently available beta lactam antibiotics with exception of newer cephalosporins with anti-MRSA activity like Ceftaroline[44,45,46].

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

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

**f. Oxacillin screen agar:**

 Mueller-Hinton agar plate containing 4% NaCl and 6µg/ml of oxacillin are inoculated with 10µl of 0.5 McFarland suspension of the isolated by streaking in one quadrant and incubated at 35º C for 24 hours. Plates are observed carefully in transmitted light for any growth. Any growth after 24 hrs is considered oxacillin resistant. Induction with oxacillin requires an extended period for full expression. Hence, oxacillin-containing media achieve sufficiently high sensitivities only after 48 hours of incubation[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:**

 Media includes, 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. The chromogen in ChromID targets the α-glucosidase enzyme of S. aureus. Inhibition of competing flora is brought about by the incorporation of cefoxitin (4mg/litre), resulting in green coloured colonies of MRSA. ORSAB, a modified version of mannitol salt agar, is made selective by the addition of oxacillin (2mg/ml) to inhibit MSSA and polymyxin to suppress gram negative bacteria. This medium incorporates aniline blue as a pH indicator, giving MRSA colonies a characteristic blue colour.Colonies of MRSA on MRSA Ident agar are dusky pink or ruby colour due to a chromogenic phosphatase substrate and an antibiotic supplement including cefoxitin[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**

 Detection of mecA gene by PCR is considered as the gold standard. DNA extraction is performed on the isolate and mecA gene is amplified using specific primers. The master mix containing PCR buffer, dNTP mix, Taq DNA polymerase, and MgCl2 and template DNA is subjected to hot start PCR. This is followed by 30 cycles of denaturation at 94ºC for 45seconds, annealing at 50ºC for 45 seconds, and extension at 72ºC for 1 minute and final extension step at 72ºC for 3 minutes. PCR products are visualized on 2% agarose gel with ethidium bromide dye under UV transilluminator[22].

**XVI. OTHER METHODS FOR MRSA DETECTION**

 Latex agglutination test is a commercially available rapid test for the detection of MRSA. It makes use of monoclonal antibodies directed towards the PBP 2a antigen. Immunochromatographic test and DNA hybridization are other methods used in MRSA detection[36,41].

**XVII. RECENT DRUGS FOR MRSA**

 Ceftobiprole is effective against Vancomycin resistant MRSA. This new cephalosporin is the active form of the prodrug Ceftobiprole, emedocaril. It has been approved by FDA in 2010 in the treatment of MRSA[23].FDA has recommended Tedizolid phosphate and Dalbavan. Other upcoming antibiotics proposed to be active against MRSA are Telavancin, Oritavancin and Iclaprim are under development.

**XVIII. APPROCHES TO TREATMENT**

 Intravenous vancomycin is the mainstay of therapy for hospitalized patients with serious MRSA infections. Unfortunately, vancomycin can produce adverse side effects including allergic reactions such as anaphylaxis and “red man syndrome.” The incidence of red man syndrome varies from approximately 4 to 47%, with the more severe reactions occurring in patients more than 40 years of age[34]. The syndrome is infusion related and is characterized by severe itching and the presence of an erythematous rash. Treatment for patients with less severe infections or for those who can be treated with or switched to oral therapy is often complicated by a co-resistance on the part of the pathogen to other classes of antibiotics. The long-acting tetracycline derivatives, doxycycline, minocycline, and tigecycline, are considered to be reasonable oral treatment alternatives for patients with specific types of MRSA infections, especially those involving the skin and skin structures[24].

 Alternate for vancomycin in the treatment of MRSA infection includes linezolid and daptomycin for bacteraemia and dalbavancin for catheter-related blood stream infections. Linezolid, a member of the oxazolidinone family of antimicrobial agents, is active against almost all CA-MRSA isolates, as well as group A streptococci. The disadvantage of this agent includes the potential for the development of resistance among *S. aureus* strains[25]. Other combinations of antimicrobial agents also have been reported as promising treatment of patients with deep-seated infections. These include the oral administration of fluoroquinolone plus rifampicin. Fluoroquinolones should not be used for the treatment of skin and soft-tissue infections caused by CA-MRSA. Hence, resistance develops readily with *S. aureus*. Rifampicin is highly active against susceptible CA-MRSA isolates[35].There is need for new antimicrobial agents for MRSA. To be effective, must meet the therapeutic challenge. Along these lines, one promising drug is the investigational drug, telavancin. In 2008, the drug was found to be active against virtually all gram-positive bacteria including drug-resistant organisms such as MRSA, VISA and VRSA[26,27,28]. Telavancin has a multifunctional mechanism of action and includes inhibiting bacterial cell formation and disrupting bacterial cell membrane function. The drug is bactericidal in nature.

**XIX. VACCINES**

 *S. aureus* exerts a significant economic impact on health care. The emergence of antibiotic resistance has made treatment of staphylococcal disease difficult. The pressure to develop vaccines against *S. aureus* has been driven by the increasing spread of such antibiotic resistance. A variety of whole cell preparations, including live, heat-killed, and formalin-fixed of S. aureus has been studied as vaccines to prevent infections in clinical and veterinary trials. None of these experimental preparations produced an adequate immune response in animal models, or farm animals[29,30]. In 2003, D.L. Hu [36] and associates reported that immunization of laboratory mice with a mutant form of toxic shock syndrome toxin (toxoid).The immunized animals were protected against *S. aureus* infection. Pooled immunoglobulin preparation neutralises the number of staphylococcal toxins, and are commonly used in the therapy of patients with toxic shock syndrome.

**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 recognized as an important and universal hospital acquired pathogen causing epidemic and endemic infections in the health care centres. These organism became resistant to antibiotics because of unnecessary uses of antibiotics by humans, Antibiotics in food and water and Germ mutation. MRSA is resistant to all the groups of antimicrobial agents. So we in need of newer antibiotics to treat the MRSA. This chapter explained about the overview of MRSA and its detection methods.

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