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Review: Methicillin and Vancomycin Resistant Staphylococcus Aureus

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Abstract
Staphylococcus aureus is a Gram-positive bacterium that considered as an opportunistic pathogen responsible for great morbidity and mortality; human beings are its main reservoir. The organism is toxigenic and one of the effects of the toxin is reducing the efficacy of antibiotics. Before the discovery of antibiotics, mortality rate of *S. aureus* strains was more than 75 %. The over use as well as misuse of antibiotics in humans, nutritive and therapeutic antibiotic treatment of farm animals resulted in antibiotic-resistant bacteria. The first drug used to treat *S. aureus* was penicillin for which the bacteria becomes resistant in short time and oxacillin or methicillin was introduced as a drug of choice, but, the bacteria also became resistant to this drug. Methicillin resistant *S. aureus* has hospital-acquired and community-acquired phenotypes. Currently, vancomycin has been accepted worldwide as the last choice against methicillin resistant *S. aureus* infections and it's widely usage resulted in vancomycin resistant strains and also multi drug resistant *S. aureus*. Its main mode of transmission is by direct contact with colonized or infected individuals and objects or surfaces contaminated. Constitutional symptoms of the disease are unusual. Diagnosis of *S. aureus* infection is carried out by culturing organisms from a focal site of infection followed by drug sensitivity test by disc diffusion method. Multiplex PCR method also used to detect resistant genes. Preventing the emergence of multidrug resistant organism require a systematic and comprehensive approach that build up the health care and public health system.
Keywords: Staphylococcus aureus, Methicillin, Vancomycin, Resistance

1. INTRODUCTION

Staphylococcus aureus is also known as *Staph. aureus* or *S. aureus*. It means "golden cluster seed" or "the seed gold". *S. aureus* was discovered in 1880 by Dr. Alexender Ogston, who was a surgeon in Aberdeen, Scotland (Chukwunonso *et al*., 2018; Hajo *et al*., 2006; Murugaiyah *et al*., 2011). *Staphylococcus aureus* belongs to the family *Micrococcaceae* and is part of the genus *Staphylococcus*, which contains more than 30 species. Among the staphylococcal species, *S. aureus* is by far the most virulent and pathogenic for humans. *S. aureus* is a 1 µm, Gram-positive cell that in the laboratory may be observed as single cells, in pairs or as grape-like irregular clusters (Ghias *et al*., 2016; Murugaiyah *et al*., 2011; Stark, 2013).

It is characterized as coagulase- and catalase positive, non-motile, non-spore-forming and as facultative anaerobic. It grows in yellow colonies on nutrient rich media and is referred to as the yellow staphylococci (Hajo *et al*., 2006; Hasan *et al*., 2016; Stark, 2013). *Staphylococcus aureus* is considered an opportunistic pathogen responsible for great morbidity and mortality; man is its main reservoir. It can be present in several sites of the human body, including oropharynx, intestines, hands, skin, and nasal cavity, which is pointed as one of the areas where colonization occurs more frequently (Breves *et al*., 2015; Chukwunonso *et al*., 2018; El-Banna *et al*., 2015).

In health care settings, this pathogen may contaminate furniture, clothes and equipment around colonized or infected patients, which function as sources or reservoirs (Breves *et al*., 2015). The organism is toxigenic, and one of the effects of the toxin is reducing the efficacy of antibiotics. Methicillin resistance is seen in *Staphylococcus aureus*, and so many other antibiotics and including highly potent beta-lactam drugs. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been implicated as the main cause of nosocomial infection worldwide since the 1970s (Adhikari *et al*., 2017; Chukwunonso *et al*., 2018).

A person is infected with methicillin-resistant Staph. aureus or vancomycin-resistant Staph. aureus when his/her test culture is positive and has no signs and symptoms of infection caused by the organism. (Shobha *et al*., 2012; Stark, 2013; Thati *et al*., 2011).

The evolution of antibiotic resistance was assigned to a combination of microbial characteristics. They were categorized as the selective pressure of antibiotic use and social and technical changes that increased the transmission of resistant organisms(Askari *et al*., 2012). The use as well as misuse of antibiotics in humans, nutritive and therapeutic antibiotic treatment of farm animals resulted in antibiotic-resistant bacteria. These mutant bacteria could enter into human food supply; colonize human digestive tract thereby transferring resistance genes to human commensal bacteria's. The bacteria acquire the resistant genes from other bacteria when they joined together and transferred the genes to each other. Free plasmids were gathered by the bacteria which resulted in the resistance to a number of antibiotics. Once a resistant gene was localized in the bacterium DNA, the bacterium could dominate other bacteria and pass on the resistance gene to all of its descendants. The

antibiotic resistance was initiated by certain mechanisms: A) Antibiotic inactivation-direct inactivation of the active antibiotic molecule; B) Target modification-alteration of the sensitivity to the antibiotic by target modification; C) Efflux pumps and outer membrane permeability changes-reduction of the drug concentration without modification of the compound; or D) Target bypass-some bacteria become refractory to specific antibiotics by bypassing the inactivation of a given enzyme. There was a great diversity of antibiotic resistance mechanisms within each of these four categories and a single bacterial strain. The diversity exhibited was due to several types of resistance mechanisms depending on the nature of antibiotics, their target site, and the bacterial species and whether it was mediated by a resistance plasmid or by a chromosomal mutation (Gallagher *et al*., 2017; Hiramatsu *et al*., 2014; Islam and Shamsuzzaman, 2015)

Hospital acquired infection also known as nosocomial infection that spreads through hospitals and patients gets the infection from the hospital during the stay. Infections are said to be hospital acquired if they occur within 48 hours after admission to the hospital or within 30 days after discharge of the patient. These infections have many complications which increase the morbidity and mortality rate (Koupahi *et al*., 2016; Yousefi *et al*., 2017).

2. HISTORY AND OVERVIEW

2.1. Methicillin Resistant Staphylococcus aureus

After the introduction of antibiotics, the evolution of antimicrobial resistance accelerated rapidly over the last decade which focused attention on the sustainability of recent modern medical practices globally. *Staphylococcus aureus* caused wide spectrum of pyogenic lesions involving several organs, hospital outbreaks and community acquired infections(Srinivasan *et al*., 2002; Stark, 2013). In hospitals, *S. aureus* infections were lethal accompanied with resistance to several beta-lactam antibiotics. Since 1970, MRSA (Methicillin Resistant *Staphylococcus aureus*), classified as pandemic pathogen, was concurrent with several nosocomial outbreaks and life threatening cross infections (Abad *et al*., 2014; Adhikari *et al*., 2017; Hiramatsu *et al*., 2014). It was estimated that 2 billion populations globally might carry *S. aureus* on their skin and mucous membrane. The over usage of antibiotics in hospitals was associated in the development of in-hospital acquired MRSA strains. Furthermore, increased use of antibiotics in animal feed has resulted in emergence of a new MRSA with multiple non-beta lactam drug resistance (Chukwunonso *et al*., 2018; Mahadevan, 2017).

Before the discovery of antibiotics, mortality rate of *S. aureus* strains was more than 75 % (El-Banna *et al*., 2015; Van *et al*., 2012). At first, penicillin was used to treat *S. aureus* infections. Soon afterwards, resistance emerged when strains acquired a genetic element coding for β-lactamase production, and today over 80 % of all *S. aureus* strains are resistant to penicillins (Chukwunonso *et al*., 2018; Morales-Cartagena *et al*., 2015). The next drug to be introduced for treating infections with *S. aureus* was the semi-synthetic, penicillinase-resistant penicillin named oxacillin or methicillin, but shortly after its introduction the first isolate with resistance was detected (El-Banna *et al*., 2015; Rehm and Tice, 2010; Van *et al*., 2012). Naturally occurring strains of methicillin-resistant *Staphylococcus aureus* (MRSA) were first reported from England in 1961, within short period of time after the introduction of semi-synthetic penicillin. Within a decade, MRSA was reported in the United States, with 22 such strains isolated from 18 patients at Boston City Hospital, and by 1981, it had become endemic in virtually all US health care facilities (Hajo *et al*., 2006; Rehm and Tice, 2010).

MRSA strains are inherently cross-resistant to virtually all beta-lactam antibiotics, the most effective and widely used class of antimicrobials. Moreover, in many countries clinical strains are quite often multi-resistant, which significantly reduces the therapeutic options for treatment of staphylococcal infections (Hiramatsu *et al*., 2014; Yousefi *et al*., 2017).

Currently there are two MRSA phenotypes: hospital-acquired (HA-MRSA) and community-acquired (CA-MRSA). HA-MRSA as well as widespread throughout the world is responsible for at least one-third of all *S. aureus* infections, with an estimated mortality rate of 6.3 per 100,000 individuals. The risk for HA-MRSA infections is related to: chronic diseases, dialysis, malignancy, prolonged exposure to antimicrobial agents, especially cephalosporin, aminoglycosides and fluoroquinolones, age, insulin dependent diabetes, smoking, obesity, dermatitis and prolonged hospital stay. At the end of 1990s MRSA infections began to be observed in the community in healthy individuals without traditional risk factors for acquisition of MRSA infections. The phenotype responsible for such occurrences, CAMRSA has emerged as a new pathogen which diverges from the hospital phenotype genetically and epidemiologically (Abad *et al*., 2014; Chukwunonso *et al*., 2018; Rehm and Tice, 2010; Siqueira *et al*., 2017).

In contrast to HA-MRSA, for which the risk factors are well established, CA-MRSA can occur in healthy individuals suggesting that these have higher virulence than traditional HA-MRSA samples. Moreover, CA-MRSA strains are capable of rapid spread, which might explain the worldwide dissemination (DeLeo and Chambers, 2009; Siqueira *et al*., 2017).

CA-MRSA and HA-MRSA isolates have been found to be microbiologically distinct, suggesting that CA-MRSA did not originate from HA-MRSA isolates that escaped from the hospital setting; rather, CA-MRSA

seems to have emerged from established CA-MSSA isolates. In addition to the genetic differences, the infections caused by CA-MRSA and HA-MRSA are generally different; the CA- MRSA pathogen is most frequently associated with skin and soft tissue (abscesses, boils, and folliculitis), whereas pathogens acquired in health care facilities are more likely to infect the respiratory tract, bloodstream, urinary tract, and surgical sites. Moreover, CA-MRSA is more frequently susceptible to non–beta-lactam antibiotics (such as clindamycin, trimethoprim-sulfamethoxazole, and tetracycline), compared with HA-MRSA, it also tends to be more aggressive. CA-MRSA can cause highly invasive, rapidly progressive, life-threatening infections, such as necrotizing pneumonia, severe sepsis, and necrotizing fasciitis. (DeLeo and Chambers, 2009; Rehm and Tice, 2010).

LA-MRSA is the most recent form of MRSA to be discovered and is characteristic in farm animals such as cattle and pigs. LA-MRSA may be seen in who rear animal, butcher and who work in close contact with farm animals (Chukwunonso *et al*., 2018).

Methicillin resistance in MRSA is determined by the staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element that carries the mecA gene. The mecA gene codes for an additional penicillin-binding protein (PBP) that has a reduced affinity towards methicillin (PBP2a/PBP2'). This results in a reduced ability to bind to the bacterial cell wall and inhibit synthesis (Kluytmans, 2010).

2.2.Vancomycin Resistant Staphylococcus aureus

Currently, vancomycin has been accepted worldwide as the last choice against MRSA infections. With the emergence of resistance to the penicillinase-resistant penicillins, the glucopeptide agent vancomycin became the treatment of choice for infections with MRSA, and in 1996 the first isolate with intermediate vancomycin resistance was detected in Japan. So far, this has not emerged to be a major concern, but the resistance has been detected in different parts of the world and needs to be monitored (El-Banna *et al*., 2015; Mahadevan, 2017; Rehm and Tice, 2010; Stark, 2013; Van *et al*., 2012).

Glycopeptides, particularly vancomycin, have been considered to be the drugs of choice for treating MRSA bacteremia and sepsis since the prevalence of that organism surged during the 1980s. The high prevalence of MRSA infection has led to increased use of vancomycin in chronic and seriously ill patients and, in turn, to the emergence of multiple phenotypes with reduced susceptibility to glycopeptides. The emergence of *Staphylococcus aureus* isolates resistant to vancomycin and other antibiotics have been elevated MRSA into multidrug resistant which result in serious danger than ever in a hospital environment and also recently in the healthy community (Alogholi *et al*., 2008; Murugaiyah *et al*., 2011).

VRSA is thought to arise in a different manner, with resistance probably resulting from acquisition of genetic material from enterococci. In vitro transfer of the *vanA* resistance determination gene from vancomycin-resistant *Enterococcus fecaelis* to *S. aureus* has been demonstrated, and conjugative transfer from vancomycin-resistant *E. fecaelis* has appeared to be the mechanism of resistance in at least 2 unrelated clinical isolates of VRSA (Rehm and Tice, 2010; Thati *et al*., 2011). Most infections with VISA or VRSA have occurred after prior long-term use of glycopeptide antibiotics and in patients with chronic illness, such as preexisting chronic renal failure, diabetes mellitus, or vascular compromise with devitalized tissue (Rehm and Tice, 2010; Stark, 2013).

2.3. Transmission

Human are the major reservoir of the bacteria. Transmission of MRSA generally occurs through direct or indirect contact with a reservoir. Its main mode of transmission is by direct contact with colonized or infected individuals and objects or surfaces contaminated with the organism (Breves *et al*., 2015; Sarrafzadeh *et al*., 2016; Siqueira *et al*., 2017).

2.4. Clinical Disease

Constitutional symptoms are unusual; if lesions extend or are widespread, fever, malaise, headache and anorexia may develop. Lesions are usually uncomplicated, but when organisms are invasive then pneumonia, lung abscess, osteomyelitis, sepsis, endocarditis, meningitis or brain tumor may occur. Common MRSA clinical infections involve the skin and soft tissues, and mostly not beyond the upper layer of the dermis, for example, cellulitis, impetigo, however in some cases may involve deeper structures like soft tissue abscess (Ghias *et al*., 2016; Hiramatsu *et al*., 2014; Morales-Cartagena *et al*., 2015). In addition to primary lesions of the skin, staphylococcal conjunctivitis occurs in newborns and the elderly. Staphylococcal endocarditis and other complications of staphylococcal bacteremia may result from parenteral use of illicit drugs or be acquired nosocomially through the use of intravascular catheters and other devices. Embolic skin lesions are frequent complications of endocarditis and/or bacteremia (Chukwunonso *et al*., 2018; Siqueira *et al*., 2017).

2.5. Diagnosis

Diagnosis of *S. aureus* infection is easily made by culturing organisms from a focal site of infection (nose, throat, rectum, blood, open wounds, pleural fluids, and bone or catheter exit sites). The main medium used for the screening and growth of MRSA is mannitol salt agar (MSA). Enrichment broths have also been utilized, and this increases the sensitivity, as it permits small numbers of MRSA to grow overnight in incubation before using a screening agar medium. Methicillin resistance is determined by standard antimicrobial susceptibility test methods, including disk diffusion, broth dilution, and automated methods (Chukwunonso *et al*., 2018; DeLeo

and Chambers, 2009). The uses of multiplex PCR primers to detect genes that identify strains of *Staphylococcus aureus* and *mecA* have been the major method used (Chukwunonso *et al*., 2018).

2.6. Treatment, Control and Prevention

Staphylococcus aureus are the normal flora on human skin and can cause opportunistic infection in immune-compromised people. Infections caused by *S. aureus* are difficult to be treated due to its ability to destroy neutrophils. *S. aureus* causes the neutrophils to lyse after phagocytosis, thus kills the neutrophils. This ability is even more enhanced in community-acquired methicillin-resistant *Staphylococcus aureus* infections (CA-MRSA) (Hiramatsu *et al*., 2014; Morales-Cartagena *et al*., 2015; Murugaiyah *et al*., 2011). Despite being able to destroy neutrophils, *S. aureus* also shows antibiotic resistance which makes the infection difficult to be treated. Resistance in *S. aureus* is inducible due to the presence of inducible *mecA* gene in the resistant (mutant) strains of *S. aurues* which is responsible for the methicillin resistance (Morales-Cartagena *et al*., 2015; Murugaiyah *et al*., 2011).

Another line of drug that is used for community-associated MRSA is rifampin. However, rifampin should not be used alone because of increasing resistance to rifampin due to mutation. It can be used in combination with trimethoprimsulfamethoxazole or doxycycline for treatment of skin or soft tissue infections caused by CA-MRSA. Also, trimethoprim-sulfamethoxazole or tetracyclines are not recommended as sole empirical therapy for a non-purulent cellulitis because of resistance of group A *Streptococci* to these agents (Chukwunonso *et al*., 2018).

The MRSA/ VRSA can be controlled by prapering a framework for managing persons with MRSA in acute and long term care facilities, limitation of contact with a person who is exposed to an MRSA/VRSA case in a manner in which transmission can occur, proper surveillance for the organism should be made. Beside the above controlling measures MRSA can be prevented by Public education in personal hygiene, especially hand washing, regular cleaning with household disinfectants or bleach (one part bleach to nine parts water), garbage should be disposed of in proper manner, Infected persons who are ill should not allowed to visit hospitals or personal care homes (Murugaiyah *et al*., 2011)

Although recommended measures to control the spread of VRSA have been promoted for several years, it is still not appreciably slow the increasing rate of infection or colonization of the *Staphylococcus aureus* especially at the country like United States. Preventing the emergence of multidrug resistant organism require a systematic and comprehensive approach that build up the health care and public health system. The encouragement to the public health care system are very important to recommend prevention and control guidelines, conduct active surveillance and ensure vigorous antibiotic stewardship by health care provider (Murugaiyah *et al*., 2011).

3. CONCLUSION

Drug resistant *Staphylococcus aureus* is distributed worldwide due to overuse and misuse of antibiotics. Also, the strains of *Staphylococcus aureus* are always changing over the years, thus it becomes resistant to many drugs. Poor hygienic practice in and around the health care centers and hospitals, poor hospital facilities and infrastructures, workers carelessness, working for longer time, ratio of patient to physician, rules of the centers for patient visiting, absence of drug sensitivity test before prescribing medications and etc may contribute for the wide distribution of the problem specially in developing countries.

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