DISINFECTION AND TREATMENT

OF

METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS

A MSc Dissertation report by :

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OF

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DECLARATION

I hereby declare that the literature review titled, “Disinfection and Treatment of Methicillin Resistant Staphylococcus aureus” has been carried out by me as part of my M.Sc. Biochemistry program in the Chemistry department, School of Chemical Sciences, Goa University. All the information derived from the literature review has been duly acknowledged in the text and a list of references is provided.

Date: 2/05/2022.

TANIA S GODINHO

CERTIFICATE

This is to certify that the literature review entitled, “Disinfection and Treatment of Methicillin Resistant Staphylococcus aureus” submitted by the student is the record of research work carried out by the candidate during the academic year 2021-22 under my supervision in partial fulfillment of the requirements for the degree of Master of Science in Biochemistry.

Dr Roshan R. Naik (Project Guide)

Prof. Vidhyadatta M. Shet Verenkar (Dean of SCS, Goa University)

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CHAPTER 1

INTRODUCTION

1. Introduction

A dangerous pathogen responsible for hospital-acquired and community-acquired infections is Methicillin resistance staphylococcus aureus (MRSA).It is a type of staph bacteria that becomes resistant to many of the antibiotics that is used to treat ordinary staph infections. The symptoms of MRSA depend on the place you are 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, in the bloodstream, the lungs, or the urinary tract. MRSA is usually spread in the community by contact with infected people or things that are carrying the bacteria. This includes through contact with a contaminated wound or by sharing personal items such as towels or razors, that have touched the infected skin. Even with the ongoing development of new antibiotics, active efforts and advances in infections prevention, MRSA still remains a prominent pathogen with persistently high mortality.

Staphylococcus aureus is one of the most versatile human pathogens. In the late 1930s, sulfonamides offered the first challenge to *Staphylococcus aureus* but they failed because of the presence of pus and the acquisition of resistance by the bacteria due to their poor clinical performance . The introduction of benzylpenicillin (penicillin G) in the early 1940s temporarily solved the problem of staphylococcal infections, but the use of this agent continuously caused the selection of the resistant strains, which produced β-lactamase (penicillinase) . By 1948 the prevalence of resistant strains had seriously reduced the value of benzylpenicillin [1].

Methicillin resistance has occurred in *Staphylococcus aureus* by mutation of a penicillin-binding protein, a chromosome-encoded protein. This type of resistance is transferred between *Staphylococcus aureus* organisms by bacteriophages. This is one of the only medically relevant examples of chromosome-mediated drug resistance by phage transduction [2].

A second type of MRSA of greater concern which appeared in the 1990s was known as community-acquired MRSA (CA-MRSA). It usually manifests itself as a skin infection in CA-MRSA which occurs outside of hospital settings.The CA-MRSA which can develop into a life threatening and more serious illeness where it tends to occur in conditions

where human are prolonged in physical activity for example in child care and long term facilities where skin to skin contact is involved such as in prisoners, soldiers and in athletes contact sports which leads to sharing personal items . Unlike hospital-acquired (HA)-MRSA the source of infection for CA-MRSA is often difficult to identify [3].

The colonization and infection with MRSA is a major health problem in hospitals and long-term care facilities. Although bacteriaemias with MRSA can be treated with vancomycin and other reserve antibiotics, 20% of patients cannot be successfully cured [4].

The growing concern is the emergence of MRSA in patients with no health care contact or apparent risk factors. The Community-associated MRSA infections which were initially found in children with infections in the blood streams and no prior health care exposure and have been increasingly reported as the cause of skin infections and abscesses among previously healthy adults and as the cause of bloodstream infections among patients in health care settings [5].

Vancomycin is still the recommended first-line antibiotic for all forms of serious infections ,despite the emerging resistance, for all MRSA suspected or confirmed. With the trial of trimethoprim-sulfamethoxazole, doxycycline, and clindamycin, uncomplicated skin and soft tissue infections can still be treated especially for the community-associated MRSA is suspected. Simple abscesses without surrounding cellulitis can frequently be treated with incision and drainage alone without adjunct antibiotics [6].

The first novel variant under investigation coronavirus was seen in UK on December 2020, Many countries since then have reported the spread of new rapid mutant viruses. The proposal of “environmental transmission,” a new alternation of transmission, has raised the requirements of environmental disinfection to an unprecedented level [7]. In medical institutions in high-risk areas, using disinfectants to disinfect “object surface and environment” is one of the core means to effectively control the iatrogenic infection [7]. However, if continuous sterilization with high concentration and high frequency is applied, it may increase disinfectant-resistant strains, especially MRSA [7].

Staphylococcus aureus continues to be a dangerous pathogen for both community-acquired as well as hospital-associated infections. *Staphylococcus aureus* resistant to methicillin were reported soon after its introduction in October 1960 and MRSA is now endemic in India [8].

The major sources of *Staphylococcus aureus* in hospitals are septic lesions and carriage sites of patients and personnel. Carriage often precedes infection. The anterior nares are the most consistent carriage site, followed by the perineal area. Skin contamination and aerial dissemination vary markedly between carriers and are most pronounced for combined nasal and perineal carriers. The principal mode of transmission is via transiently contaminated hands of hospital personnel. Airborne transmission seems important in the acquisition of nasal carriage. Infection control strategies include screening and isolation of newly admitted patients suspected of carrying MRSA or *Staphylococcus aureus* with intermediate resistance to vancomycin, implementation of an infection control program to prevent transmission of resistant strains between patients and hospital personnel, and institution of a proper antibiotic policy to minimize antibiotic resistance development [9].

For MRSA the culture media selective traditionally have been based on mannitol salt agar (MSA), blood agar, or Baird-Parker agar which contains oxacillin or methicillin alone or with the combination with other the antibiotics. Cefoxitin is a better agent for prediction of methicillin resistance in *Staphylococcus aureus* were shown in recent reports and disk susceptibility testing with cefoxitin now replaces the disk susceptibility testing with methicillin and oxacillin in a number of centers [10]. Some of the clones of *S. aureus* which evolved to MRSA by acquiring, through the transfer of horizontal genetic , the staphylococcal chromosomic cassette mec (SCCmec),which is a mobile genetic element which includes the mecA or mecC genes that gives resistance to most β-lactam antibiotics, which includes methicillin [11].

Not only to the β-lactams, MRSA has a great capacity to acquire resistance to any type antibiotic, which leads to important the implications to the present and future options for treatment of infections by this pathogen [12]. Although the risk of infection in dental clinics is lower than in hospitals [11]. In the beginning antibiotic was widely used, but

however, due to its toxicity, nowadays it is not commercialised for human use and later was replaced by more similar and more stable penicillins such as oxacillin. However, the term Methicillin Resistant *Staphylococcus aureus* is still used [13].

1.1 History of MRSA

MRSA are poorly understood as the evolutionary origins have no rational nomenclature which exists, and the number of major MRSA clones have no consensus or the relatedness of clones described from different countries.In 1959 Methicillin was introduced to treat infections caused by penicillin-resistant *Staphylococcus aureus*.

In 1961 the first MRSA strain NCTC 10442 was isolated in UK, harboured SCCmec type I, and spread around the world during the 1960s so-called archaic clone. A MRSA strain (N315) with SCCmec type II was discovered in 1982 in Japan, and this New York/Japan clone also spread worldwide; In New Zealand during 1985 the discovery of an MRSA strain (85/2082) harbouring SCCmec type II was discovered, in 1990s the MRSA strains harbouring SCCmec IV spread round the world and at the beginning of the 21st century, in Australia the first MRSA strain (WIS) with SCCmec type V was found [14]. Alexander Fleming discovered Penicillin in 1928. By the year 1942, penicillin was introduced for widespread use and hospital strains were resistant in 1946. Since 1950 the hospital resistant strains increased and then by 1960-70s it spread into the communities as there was no control by the year of 1980-90s it exceeded into hospital and community settings [15].

1.1.1. Antibiotic resistance

The treatment of infections caused by bacteria where done by the use of Antibiotics.when these medications no longer are able to kill the bacteria this is called antibiotic drug resistance. Since antibiotic drug resistance is a growing problem in the world because of overuse of antibiotics. MRSA this type of staph which is resistant to treatment of antibiotics such as methicillin and penicillin.

1.1.2 mecA gene

The genetic studies of MRSA is represented by the structural gene type. The gene for MRSA is mecA gene also known as staphylococcal chromosomal cassette gene SCCmec The bacteria strain that carries mecA is methicillin-resistant Staphylococcus aureus (MRSA).This are the genes which allow the bacteria to act resistant to the antibiotics such as methicillin,penicillin. mecA is involved in encoding PBP2a which is a penicillin-binding protein 2a as it has a lower affinity for beta-lactam antibiotics such as methicillin and penicillin.

CHAPTER 2

CHARACTERIZATION AND METHODS OF DISINFECTION AND TREATMENT

2 Characterization and Methods of treatment and disinfection

2.1 Types of MRSA

2.1 a.Hospital associated:

MRSA infections that are associated with health care settings such as nursing homes and hospitals.There is an increase of infections of MRSA in the hospitals settings. There were infections found in bloodstream and pneumonia for S.aureus which was found to be estimated around 125,969 hospitalizations in 1999–2000 by CDC investigators. Methicillin resistant were the isolates associated with these hospitalizations around 43.2%.In United States a large surveillance program of nosocomial bloodstream infections was showed that among all the S. aureus isolates and percentage of the MRSA isolates increased from 22% in 1995 to 57% in 2001.In which NNIS hospitals in 2003, where 64.4% of health care–associated S. aureus infections occurring ICUs were caused by MRSA, which was compared with 35.9% during 1992, representing a 3.1% increase per year .More recently, reported an increase in hospital on set MRSA bacteria cases, with an estimated 18,900 cases in 2005 [16].

2.1 b Community associated:

MRSA infections that occur to people who have not had a recent hospitalization or any other contact with the health care settings.The strain responsible for community associated MRSA infections differ from those of the hospital associated MRSA infections. They differ in their genetic and phenotypic features. The strains that CA-MRSA carries is type IV or V SCCmec elements which are PVL producing that is Panton- Valentine leukocidin and not a multidrug resistant .In the year of 1990s CA-MRSA infections were seen in the UK, New Zealand ,France ,US, Canada and Finland. Doxycycline, minocycline, clindamycin, trimethoprim-sulfamethoxazole, rifampin, and linezolid these are mostly susceptible to community-associated MRSA infections [17].

2.2 Methods for surface cleaning

Now the products that remove soil,dirt,organic matter and germs like viruses, bacteria and fungi are the cleaners or detergents . They play the role by lifting dirt and germs off the surfaces so then they can be rinsed away with water. To necessarily remove dirt the cleaning is done by the detergent which can prevent disinfectants from working. The cleaning agents have the disinfectants mixed in it.

The chemical products that are used to kill germs in health care settings are known as the disinfectants. Disinfectants which are effective against the *Staphylococcus aureus*, or staph, are also effective against the MRSA. There should be a list of germs that a certain given disinfectant product can kill which have an Environmental Protection Agency (EPA) registration number . These products are also sold at grocery and other retail stores and may be helpful when someone has an infected wound[18].

2.2.1 Disinfection procedures for handling community associated MRSA infections.

Laundry:

The routine laundry procedures, detergents, and laundry additives will all help to make clothes, towels, and linens safe to wear or touch. If items have been contaminated by infectious material, these may be laundered separately, but this is not absolutely necessary.

Equipment:

The shared equipment that comes into direct skin contact such as helmets and protective gear should be cleaned just after each use and kept to dry. Each equipment should be cleaned according to the equipment manufacturers instructions to make sure the cleaner will not harm the item.

Environmental cleaning: the use of disposable mops and cloths; keep lockers and tables clear of clutter to facilitate cleaning;and ensure the curtains are changed if applicable; to ensure the domestic staff to use Chlorine Based Product (CBP) for cleaning.

2.2.2 Disinfection procedures for managing hospital associated MRSA infections

Administrative procedures:

To perform assessment to check for the infection that is existing and if the patient is colonized with MRSA that is from the high risk area or history of recent hospitals. If the patient shows early symptoms IC team will take surveillance of incidence and MRSA strains.

Care delivery procedures:

The hand hygiene must be performed before and after direct contact with the patients regardless the use of gloves and to minimize the contamination the use of PPE should be initiated and once the task is complete remove and decontaminate.

Use of PPEs :

Before entering the patient's area Wear plastic apron and gloves ; ensure that PPE was worn for contact with patient, environment, and equipment; request visitors to wear PPE if visiting another patient; keep PPE on while removing/disposing of used equipment, and discard PPE in a clinical waste bin before leaving the patient's area [19].

2.3 Diagnostic assessment

Cefoxitin disk diffusion test:

In this test a better inducer of mec-A gene expression other than oxacillin or methicillin is the use of Cefoxitin which can be used for the screening of heterogeneous MRSA populations.

FDA approved assays:

There are FDA approved assays for the molecular detection of the mecA gene which are commercially available in chromogenic agars which are used for the detection of MRSA .

Anti-PBP2A monoclonal antibodies:

This is a method for detection of MRSA where the use of anti-PBP2A monoclonal antibodies are available as latex agglutination or immunochromatographic membrane assays [19].

2.4 Colonization with MRSA

The colonization with MRSA and other multi-resistant bacteria is a huge health problem that is often found in long-term care facilities and hospitals a. In Gran Canaria (Spain), 235 residents were examined in long-term care facilities ,whether they were carriers of multi-resistant bacteria or of MRSA .The report of the study showed that 36.2% of the residents with multi-resistant bacteria were colonized and about 10.2% were colonized with MRSA [20].

2.5 MRSA: a community-based prevalence survey

A prevalence survey of nasal methicillin-resistant Staphylococcus aureus (MRSA) carriage was undertaken on a random sample of adults aged over 16 resident in the community in Birmingham, UK in the year of 1998. The microbiological samples were taken from the anterior nares at the subjects general practice or in their home. The information about risk factors for the acquisition of MRSA was obtained via a self-completed questionnaire. A 58% response rate i.e 280/483 was achieved. The prevalence of nasal MRSA colonization was 1.5% i.e 4/274, 95% confidence interval (CI) 0.03–2.9. Twenty-three percent i.e 63/274 of subjects were nasal carriers of S. aureus. Six percent i.e 4/63 of S. aureus isolates were MRSA and 2 of the 4 MRSA carriers reported previous contact with health facilities. The prevalence of MRSA colonization in the general adult population in Birmingham appeared to be low [21].

2.6 Treatment of MRSA

2.6.a Impetigo

Treat complicated impetigo using systemic antimicrobial therapy with the choice of agent determined by susceptibility testing

For the prevention of antimicrobial resistance they considered an alternative to topical fusidic acid for example hydrogen peroxide 1% cream is a topical antiseptic , to treat the impetigo caused by the MRSA where there is a non bullous , localized disease and the patient is clinically well.we can consider the use of mupirocin or fusidic acid for second line option in this clinical settings only when the MRSA isolate is susceptible.

2.6.b Abscesses

Use antibiotics in combination with incision and drainage in patients with abscesses which is caused by the strain type USA300 of MRSA PFGE or where it is likely to be the most prevalent strain .

The use of oral clindamycin or co-trimoxazole for the oral treatment and where the MRSA isolate is known to be susceptible.

The use incision and drainage to treat abscesses that is caused by MRSA is a strong recommendation.But do not use any antibiotics routinely in patients with abscesses that is caused by MRSA that are drained,which are less than 5 cm in diameter, and where there is no systemic response (fever and/or cellulitis) and/or immunodeficiency, including neutropenia and defects of cell-mediated immunity.

2.6.c Other skin and skin structure infections

For severe cellulitis/soft tissue infection caused by MRSA use intravenous glycopeptides (vancomycin or teicoplanin) .

As an alternative when first- and second-line agents are contraindicated the use of tigecycline is considered, and the isolate is susceptible.

The use linezolid for oral or intravenous or daptomycin for intravenous is used as an alternative.

The recently licensed agents are considered such as telavancin ceftaroline, oritavancin, or delafloxacin, as an alternative options for the treatment of cellulitis/soft tissue infection which is caused by MRSA .

Clindamycin, doxycycline or co-trimoxazole are considered as oral agents specailly when the isolate is susceptible , for treatment of patients with mild skin and soft tissue infection caused by MRSA, or for oral stepdown therapy.

2.6.d Urinary tract infection (UTI)

For complicated UTI caused by MRSA consider intravenous glycopeptides (vancomycin or teicoplanin) as the first-line treatment.

There is recomendation for excluding the presence of bacteraemia of MRSA before the treatment of MRSA isolate is commencedfrom urine. Doxycycline, trimethoprim, ciprofloxacin, or co-trimoxazole, is consideredfor the treatment of a genuine lower UTI which is caused by MRSA with an oral agent.

Consider daptomycin as an alternative agent when a glycopeptide is contraindicated if intravenous therapy is required. Linezolid is not recommended for the treatment of MRSA UTI, given its poor excretion by the kidney [22].

CHAPTER 3

DISCUSSION

Discussion

The antibiotic susceptibility pattern is also changing with some community-acquired methicillin-resistant S. aureus having resistance patterns indistinguishable from that of hospital-acquired methicillin-resistant S. aureus. Thus the choice of antibiotics is becoming even more challenging in pediatrics, with an already-limited armamentarium of antibiotics [23]. Up to 2.3 million people are colonized with methicillin-resistant Staphylococcus aureus in the United States, causing well-documented morbidity and mortality. Although the association of clinical outcomes with community and hospital carriage rates is increasingly defined, less is reported about asymptomatic colonization prevalence among physicians, and specifically plastic surgeons.

The MRSA carriage prevalence of surgical staff is 4.5 percent. No prospective data exist regarding transmission and interventions for plastic surgeons. No studies were found specifically looking at prevalence or treatment of plastic surgeons [24]. In 2007, 27,711 episodes of MRSA BSIs were associated with 5,503 excess deaths and 255,683 excess hospital days in the participating countries, whereas 15,183 episodes of G3CREC BSIs were associated with 2,712 excess deaths and 120,065 extra hospital days. Excess mortality associated with BSIs caused by MRSA and G3CREC is significant, and the prolongation of hospital stay imposes a considerable burden on health care systems. A foreseeable shift in the burden of antimicrobial resistance from gram-positive to gram-negative infections will exacerbate this situation and is reason for concern. In the UK the incidence of MRSA has decreased considerably since the publication of the 2008 MRSA guidelines. Since the year of 2008 there has been a change in the clinical management of MRSA with the drugs linezolid and daptomycin which were available more widely.The community strains of MRSA, such as PFGE strain type USA300, have been remained uncommon in the UK. There was evidence was found to support the use of an antibiotic treatment in abscesses which was caused by USA300 , it may be necessary to recommend the adjunctive antibiotics for the management of abscesses [22].

In one study, however, multivariate analysis showed that age greater than 1 year and health care contact in the preceding month were significant risk factors for CA-MRSA. Skin and soft tissue infections are the most common manifestations, although serious

invasive infections and death may occur. Pneumonia has been reported more often in children with CA-MRSA than in those with CA-MSSA. Clindamycin is an effective therapy for CA-MRSA, but there is a risk for development of clindamycin resistance during treatment of a CA-MRSA that is clindamycin susceptible and inducibly erythromycin resistant. Trimethoprim-sulfamethoxazole is likely to be effective, and linezolid is a new option for treatment [25].

The exact burden of MRSA lung infection in peculiar populations such as patients with COVID-19There was important heterogeneity in the retrieved literature on the epidemiology of MRSA lung infection in patients with COVID-19, both when considering all other bacteria as the denominator (relative prevalence ranging from 2% to 29%) and when considering only S. aureus as the denominator (relative prevalence ranging from 11% to 65%). Overall, MRSA is among the most frequent causative agents of pulmonary infection in patients with COVID-19 [26]. A quantitative survey of reports of MRSA infections specifically in Brazil collaborates to point out how emergency it is to apply the objectives of national epidemiological inspection and control programs. It is evident that the spread of clones and the consequences they bring to patients were gradually increased over the years and that all regions of the country have already been notified, with the southeast region being the most affected in all decades, followed by the south and northeast. In all regions, SCCmec type IV is the most prevalent, followed by III, II, and I, demonstrating that the most prevalent in the country are the clones that circulate typically in the community which are followed by the hospital clones [27]. The prevalence of MRSA in India was relatively high which was at 27% with a higher proportion that was observed among men that aged by >18 years. In India necessitates the implementation of surveillance due to the high prevalence of MRSA infections and preventive measures to combat the spread of MRSA in both hospital and community settings [28].

4.Summary and conclusion

MRSA and *Staphylococcus aureus* evolve and adapt to the changing environment. Therefore, dissemination of MRSA should be continuously monitored for the molecular epidemiology and antibiotic susceptibility pattern, comprising hospital, community settings. In the diverse staphylococcal population the origin and dissemination of SCCmec are also important to be tracked with the advancement in molecular methods such as spread of the bacteria, the pattern of the genetic evolution, next-generation sequencing, and the resistance determinants which can be further understood and explored over the years.

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