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Antimicrobial Resistance in Staphylococcus Aureus and the Immunocompromised Child

Rashi Sharma¹, Namrata Gupta²

University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India, 140413

Abstract: *Staphylococcus aureus* is a gram-positive bacterium. Many antibiotics are tried in opposition to *S. aureus* infection but in the end they all fail because of the multidrug resistance in this bacterium. *Staphylococcus aureus* are also responsible for many infections like skin and shock syndrome. From that point forward Methicillin-safe *Staphylococcus aureus* strains (MRSA-Methicillin-resistant *Staphylococcus aureus*) were extremely normal which causes nosocomial diseases. Microorganisms for the need of the endurance goes through mutational changes either in their chromosomal DNA/RNA which gives the obstruction. One of the popular models is the obstruction against methicillin in *Staphylococcus aureus*.

Due to high morbidity and death rate antimicrobial resistance becomes very challenging. Antimicrobial resistance (AMR) takes place when microscopic organisms like bacteria, virus, parasites swap over some period of time and they have no response to any medicines. This disease is difficult to treat and it causes the risk of death, different illnesses and also major infections. In this review paper, the difference between antimicrobial resistance and multidrug resistance, antibiotic resistance drugs, classification of multidrug resistance, mechanism of penicillin and methicillin in *Staphylococcus aureus* are going to be discussed. Due to their frequent contact with the healthcare system, requirement for empiric antimicrobials, and immunological dysfunction, children with immunocompromising diseases represent a special category for the acquisition of antimicrobial resistant infections. These infections are made more difficult by the relative dearth of information on the clinical characteristics and treatment of *Staphylococcus aureus* infections in children with impaired immune systems. Review of the literature that is currently accessible on the clinical characteristics, antimicrobial susceptibility, and treatment of *S. aureus* infections in immunocompromised children. Children with HIV are more likely to develop *S. aureus* infections, which are linked to higher HIV viral loads and more severe CD4 T-cell suppression. Additionally, children with HIV frequently develop staphylococcal infections that show a multidrug resistant phenotype.

Keywords: *Staphylococcus aureus*, multidrug resistance, antimicrobial resistance.

I. INTRODUCTION

Multidrug resistance is the major concern in the medical field. *S. aureus* causes many infections like skin infection, soft tissue infection, various syndromes and some kinds of illnesses. Firstly, penicillin was used to fight against these infections caused by *S. aureus* but unfortunately it does not cause so much impact and then methicillin came into the picture to fight against the infection but this approach causes very little impact and then vancomycin became the last hope. Now methicillin and vancomycin are the two most used drugs against the resistance of *S. aureus*. Accordingly, the constant development of *S. aureus* strains was fruitful to deliver the vancomycin-safe strains also (VRSA). New medication improvement and medicines are applied to the *S. aureus* interceded contaminations which have ended up being the quick conceivable treatment for this. This section will assist the perusers with gaining extensive information in regards to the multi-drug resistance of *S. aureus* alongside the opposition component and potential medicines of Staphylococcal contaminations (Vivas et al ;2019).

A. Multidrug Resistance

Accidentally, Multidrug Resistance (MDR) is a worldwide worry that is gravely affecting medical services. Organisms are seeking impervious to antimicrobial treatments because of the consistent openness of antimicrobial medications. In the previous ten years, microbial diseases have risen immensely and this has prompted an expanded measure of obstruction. Multi-drug obstruction is the peculiarity whereby pathogenic creatures are impervious to numerous chemotherapeutic specialists (Tanwar *et al*; 2014). The development of MDR increases the mortality and horribleness rates for which they are known as 'Superbugs' (Nakaido ,2009). It is said that MDR is an exceptionally normal cycle among microorganisms yet the rising measure of this interaction is because of a few reasons like the utilization of unclear antimicrobial specialists, unhygienic clean circumstances, chronic weakness care offices.

The ubiquitous danger of anti-microbial safe microorganisms involves having not very many antimicrobial specialists for different contaminations.

B. Genetic Aspect of Resistance in *S. aureus*

Before examining the opposition of *S. aureus*, it is very important to gaze upon all the likely biochemical means of opposition that the bacteria show. Microorganisms have the strength to engage various habits to cultivate multi-drug fighting (Hiramatsu, et al; 2020). The opposition of all these antimicrobial powers against the pathogenic microorganisms is a rise in few subjects on account of extended use of the antimicrobial powers by these sufferers. Microorganisms for the need of endurance goes through mutational changes either in their chromosomal DNA/RNA that rewards the opposition. One of the legendary models is the opposition against methicillin in *Staphylococcus aureus*. The cell wall of a microbe plays an important role in the barrier and also helps in the being alive but due to changes in the chromosomal DNA the structure of the cell wall affects and this leads to encouraging the resistance phenomenon (Abbas, et al ; 2019). Drug Efflux Pumps are most of the major paths for MDR machines. ABC transporters (ATP Binding Cassette) are sheet proteins that are usually delimited as drug outflow pumps that expressly help in the transport of the drugs in the container (Bansal et al; 2006). The P-glycoprotein or multi-opposing protein (MRP) damages the permeability and influences the ATP-contingent outflow of the drugs that arrange dropping off the intracellular concentrations.

C. Mechanism of Methicillin Resistance *S. aureus*.

Methicillin is a beta lactamase resistance antibiotic and acts by inhibiting the synthesis of bacterial cell walls. Cell wall is very important for bacterial survival, it protects from environmental stress. Methicillin inhibits the cross linkage between the linear peptidoglycan polymer that make up the major cell wall of bacteria and it does so by competitively inhibiting the transpeptidase enzyme also known as penicillin binding protein. Methicillin-Resistant *Staphylococcus aureus* (MRSA) reached into the theme when the methicillin-susceptible *Staphylococcus aureus* (MSSA) begun adopting a particular deoxyribonucleic acid (methicillin-opposing deoxyribonucleic acid) chosen as *mecA* which is happened by a historical component named *Staphylococcus* cartridge deoxyribonucleic acid (SCC) and is moved into the MSSA by way of either combination or revolution (Horizontal deoxyribonucleic acid transfer). As SCC aspects are accomplishing the deoxyribonucleic acid *mecA* so, the complex is chosen SCC*mec*. The complex resides in the *mecA* and several different supervisory genes to a degree *mecR1*, *mecI*. There is likewise the vicinity of a particular complex chosen Cassette Chromosome Recombinase (CCR) that helps in the unification and extraction of the part from the deoxyribonucleic acid of the Staphylococcal class (Katayama et al; 2020). The region, inception of copy (*oriC*) in the *S. aureus* chromosomal factor is followed by a distinguished deoxyribonucleic acid chosen as *orfX* towards the coming after of the *oriC* (Novial et.al ; 2010). The deoxyribonucleic acid *orfX* is well-known for encrypting a distinguishing something which incites activity named ribosomal RNA methyltransferase and this deoxyribonucleic acid also has direct repeat sequences that help to defend the *Staphylococcus* cartridge deoxyribonucleic acid (SCC). In this way, diversified SCC components are established consecutively in a group that results in the establishment of the cluster of unfamiliar genes and forms a chromosomal domain whose name is *oriC*.

Now, chiefly two types of MRSA, one, the Community-Associated MRSA (CA-MRSA), and the other one is Hospital-Acquired MRSA (HA-MRSA). CA-MRSA has happened to receive sent between the public from cramped places and the CA-MRSA isolates are well opposing methicillin and medicine also. Minor skin questions, blush, scratching, and pain are the manifestations of the body concerned by CA-MRSA. HA-MRSA is seized from the clinic or some health management center. The *oriC* limit has many transposons and insert sequences (IS) that are adequate to encourage erasure, recombination, chromosomal transposition across *oriC* and this helps the *S. aureus* to uphold their continuation approach in accordance with the environmental condition.

Horizontal deoxyribonucleic acid transfer arbitrated by phage is the prime reason for the development of the *S. aureus*. It has happened to notice earlier studies that the Bacteriophages in the way that *Staphylococcus* Phage 80 α is a particular assistant bacteriophage are necessary for the group of *S. aureus* pathogenicity islands (SaPIs). SaPIs are known as traveling ancestral factors that are the accepted dwellers in the genome of *S. aureus* and are moved to different containers. These SaPIs are the reason for bearing various poison genes and again superantigen.

D. Mechanism of Penicillin Resistance *S. aureus*.

In the method of Penicillin, R plasmids encode the catalyst called as penicillinase. The plasmid quality that conveys the protein is *blaz*, and the organic entities that were impervious to penicillin were having this quality, which inactivated the anti-toxin by parting the β -lactam ring. Gradually, this turned into a danger and significant obstruction towards penicillin anti-infection arose overall. Utilization of methicillin began when penicillin neglected to fix the Staphylococcal diseases.

After significant disappointment of both these anti-infection agents, Quinolones were utilized. Quinolones annihilate the microscopic organisms by going after and restraining their bacterial topoisomerases which by and large facilitate the very curling of DNA and furthermore isolates DNA strands. Moxifloxacin and Gemifloxacin are helpful against the gram-positive microorganisms yet tragically *S. aureus* again created obstruction against quinolones.

S. aureus created opposition against fluoroquinolones by overexpression of the NorA efflux siphons. Essentially, point transformation is one more way by which this organic entity becomes impervious to quinolones (Gnanamani, et.al; 2017).

E. Mechanism of Vancomycin

Vancomycin is an antibacterial medicine in the glycopeptide class (Patel et al; 2020). Like penicillin, vancomycin forestalls cell divider amalgamation in vulnerable microbes. The primary distinction in the instrument of activity between the two anti-infection agents is in the limiting site of each. Beta-Lactam antimicrobials, for example, tie to the appropriately named "penicillin restricting proteins" to deliver their results (Nagarajan, 1991). Vancomycin ties to the acyl-D-ala-D-ala piece of the developing peptidoglycan cell divider, which is a gathering of amino acids and restricts various systems of activity (Livermore, 1990). In the first place, vancomycin utilizes its enormous size to obstruct the cross-connecting of the peptidoglycan divider. These cross-joints are important to keep the cell divider solid, and without them, the cell divider doesn't shape accurately. The bacterium recognizes that the cell divider isn't working ordinarily and endeavors to fix it by making more peptidoglycan building blocks. The cell produces overabundant peptidoglycan forerunners thus, which then, at that point, initiates a criticism circle where degradative catalysts that separate peptidoglycan are actuated. These compounds then, at that point, may likewise add to cell divider annihilation (Madani, 2003). Because of this action, both the beta-lactam antimicrobials like penicillin and the glycopeptide antimicrobials, for example, vancomycin are known as "bactericidal." Arriving at the uncovered cell divider in gram-positive microscopic organisms is genuinely simple for both penicillin and vancomycin. Penicillin and vancomycin contrast considerably in size and charge, notwithstanding.

While penicillin can traverse the lipid bilayer "safeguard" of gram-negative microbes, vancomycin is almost multiple times bigger and it has a net positive charge. Along these lines, vancomycin can't enter the gram-negative bacterial cell and thus the medication has no action against gram-negative infections (Gardete et al; 2014). Tragically for vancomycin, the size of the medication additionally restricts the viability of oral organization. Whenever given by mouth, oral vancomycin can't cross from the gastrointestinal lot into the blood in sums important to treat a fundamental contamination. This additionally implies that oral vancomycin doesn't cause similar secondary effects, for example, kidney harm (nephrotoxicity) or hearing misfortune (ototoxicity) that is conceivable with the intravenous form. Orally regulated vancomycin is utilized for *Clostridium difficile* (recently known as *Clostridium difficile* or *C. difficile*) diseases (Kohanski et al; 2010).

II. CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS\ACQUIRED IMMUNODEFICIENCY SYNDROME

Adults with HIV have been found to have greater rates of *S. aureus* colonization than the general population, with rates as high as 81 percent over the course of a year of research. (Gordon, et al, 2010) Additionally, invasive *S. aureus* infections, particularly bacteremia, are known to affect HIV-positive individuals more frequently than HIV-negative controls. (Senthilkumar et al 2010) Furthermore, *S. aureus* isolates with a multidrug-resistant (MDR) phenotype (Diep et al, 2008) frequently infect HIV-positive adults and kids. Resistance to clindamycin, macrolides, ciprofloxacin, tetracyclines, and mupirocin is a common trait of MDR-MRSA isolates. These MDR isolates include the resistance genes *ermC* and *mupA* on a large conjugative plasmid called pUSA03 (Gill et al, 2006). Antibiotic resistance is prevalent in *S. aureus* infections in HIV-positive children, with approximately 82 percent and 40 percent of isolates being resistant to methicillin and clindamycin, respectively. Additionally, the isolates had ciprofloxacin resistance in 47.6% of instances, which is consistent with an MDR phenotype. Even in the presence of persistent TMP-SMX prophylaxis, resistance to TMP-SMX in these staphylococcal isolates is rather uncommon in the United States (3%). In a series from Houston, Texas, 18 (85.7 percent) of the 21 isolates from HIV-positive children had the genes for PVL, and 19 of the 21 (90.5 percent) isolates were of the USA300 pulsed field gel electrophoresis type. The risk factors for *S. aureus* infection in the HIV community have been looked at in a number of research on adults. The risk factors for *S. aureus* infection in HIV-positive people are high-risk behaviors, injectable drug use, noncompliance with antiretroviral therapy, and higher HIV viral load. 30 Recent antibiotic exposure, a log₁₀ HIV viral load 3, a CD4 T-cell count 350 cells/mm³, and a higher Centers for Disease Control and Prevention (CDC) category of disease were all linked to *S. aureus* infections in univariate analysis, according to a single center investigation in children.

29 Another sizable multicenter study with more than 1,800 participants looked specifically at links with MRSA infection in young HIV patients. According to this study, living in a region with a high frequency of MRSA and having a log₁₀ viral load 3 were all independently linked to MRSA infection. Notably, MRSA infection in this sample was not related with behavioural HIV acquisition (i.e., high-risk sexual activity or injectable drug use). Although other invasive infections may happen, SSTIs are the most common type of *S. aureus* sickness among children who are HIV-positive (almost 80%). Studies on HIV-positive children in Africa have been somewhat different from those on kids in the developed world. In a research conducted at Tygerberg Children's Hospital in Cape Town, up to 24% of the 203 HIV-positive children had *S. aureus* colonization; more significantly, colonization was linked to a higher level of immunosuppression. 32 Other research from Johannesburg has demonstrated that *S. aureus* bacteremia is more common in South African youngsters than it is in the developed world and is particularly linked to HIV infection. 33 In addition, in a study of 150 South African children, *S. aureus* was more frequently the cause of pneumonia in HIV-positive patients (15 percent of cases) compared to HIV-negative patients (3 percent). 34 In a Cape Town research, almost 90% of the *S. aureus* isolates and almost 80% of those were MRSA. 32 Higher rates of antimicrobial resistance to a variety of medicines, including erythromycin, chloramphenicol, tetracycline, and gentamicin were observed in MRSA compared to MSSA in Gaborone, Botswana³⁵, confirming the presence of an MDR-MRSA phenotype in this group as well. (Lee et al, 2005)

While there does seem to be a link between *S. aureus* infection, viral load, and CD4 T-cell count, the relationship between *S. aureus* and HIV is complicated and still poorly understood (Sibberly et al, 2012). It's likely that HIV infection impairs granulocyte function and puts a person at risk for *S. aureus* infection due to CD4 T-cell depletion. Studies on the simian immunodeficiency virus's pathogenesis in nonhuman primates have shown that the loss of T helper 17 cells is correlated with the course of the illness. Interleukin (IL)-17-producing T-cell defective mice have been demonstrated to have decreased neutrophil recruitment, increased severity of cutaneous staphylococcal infections, and surgical site infections. Additionally, *S. aureus* nasal colonization has been demonstrated in mouse models to be a T-cell-dependent process,³⁹ indicating that HIV-mediated T-cell suppression may predispose individuals to *S. aureus* colonization and infection. (Cotton et al, 2008) Alternatively, as has been extensively documented for other infections like *Treponema pallidum*, one may postulate that at least some of the clinical findings of CD4 suppression are the result of transient changes in control of HIV illness caused by a concurrent infection.

Both the type of infection and the level of immunosuppression should be considered when treating bacterial infections in children with HIV. According to published standards, kids who don't have a substantial immune impairment (CDC category I) and aren't neutropenic should be treated the same as kids who don't have HIV. 41 In the Houston series, more than 50% of patients were successfully treated as outpatients with oral antibiotics, incision, and drainage. 29 For children who are neutropenic or have significant immunosuppression, the majority of specialists advise hospitalization and broad-spectrum empiric antimicrobials, including the use of bactericidal drugs. (Groome et al, 2008)

iii. TREATMENT AND FUTURE ASPECTS

Drugs that are talked about to be utilized for MRSA diseases are Daptomycin and Linezolid. Daptomycin is a manufactured medication that is the class of anti-toxins that obliterate the cell layer capacity by a calcium-subordinate restricting peculiarity which prompts bactericidal action in a fixation subordinate way. Among these, one of the broadly utilized anti-toxins and which shows great adequacy significantly more than methicillin and vancomycin. Hence, for any MRSA bacteremia, Daptomycin is viewed as exceptionally powerful (Gnanamani and Hariharan, 2017). There were numerous skin drugs utilized against the MRSA strains. These enemies of MRSA drugs were very compelling. Mupirocin, is one of the counter MRSA skin drugs which is applied on the skin for relieving skin diseases brought about by *S. aureus* (Dobie and Gray, 2004). The system of Mupirocin is, it ties to the isoleucyl t-RNA synthetase which represses the protein union of the living beings bringing about the obliteration of the life form (Dilworth et al; 2020). Fusidic corrosive is one more skin drug utilized against staphylococcal contaminations and ties to the factor G of microorganisms and slows down the movement interaction bringing about the restraint of the protein synthesis (Krishna et al; 2013).

Additionally, Linezolid which has a place with the oxazolidinones class prevalently represses the protein combination during the 50S ribosome of the phone. Linezolid shows a lot of viability against a few poison creating strains, for example, harmful shock condition poison, Panton-Valentine leukocidin, α -hemolysin (Sakoulas et al; 2014). In this way, the combinatorial hypothesis was considered. Combinatorial hypothesis assists with blending different mixtures to adjust the lacking states of different mixtures and increment adequacy of medications. The combinatorial hypothesis began with vancomycin and it shows synergistic connection with β -lactams. Concentrates on the fact that the limit free from clearing the MRSA disease causing strains was not high in sum when the patients were simply exposed to Vancomycin however in mix with β -lactams the leeway effectiveness was a lot higher in sum.

As indicated by the future viewpoint, there is a requirement for an elective system for treating the obstruction against *S. aureus*. Treatment techniques, like, utilizing nanoparticles are one of the productive approaches to conveying the medication straightforwardly to the patients. Under the nanoparticle treatment methodology, there is an interesting component of utilizing ligands that are target explicit for specific receptors in microbes. AuNPs were surface changed by vancomycin helps in decreasing the bacterial development and furthermore the iron oxide nanoparticles are adjusted with the porphyrin platinum and vancomycin which brings about warm corruption of the obstruction type of *S. aureus*. Another exceptionally intriguing perspective is the utilization of siRNA treatment which improves the MRSA restraint. Vancomycin nanocomplexes are demonstrated to have successful enemies of MRSA impacts which are exceptionally new to the investigation of elective systems (Vanamala et al; 2020). The significant impediment or disappointment that ascents is natural systems of bacterial opposition and the objective explicit antimicrobials or drugs have frustrated any helpful item. Another remarkable novel methodology has approached which consolidates the genomic data on the medication target and goes through substance alterations alongside viability testing (Franklin, 2003).

IV. CONCLUSION

Staphylococcus aureus is a significant reason for bacterial disease in people, which has had the option to secure protection from an assortment of anti-toxins. MSRA is an arising issue internationally on the grounds that separated from causing nosocomial contamination additionally arose as one of the critical causative specialists of local area gained diseases. Anti-microbial obstruction in *S. aureus* includes different components which are drug efflux, articulation, or change of target proteins, prompting its quick advancement which requires inventive ways to deal with foster novel treatment procedures. An extremely restricted measure of medicines is accessible for MRSA and this has turned into the justification for expanding the death rates. Fitting utilization of the antimicrobial specialists as the MDR is an extremely normal peculiarity and dealing with this kind of peculiarity needs additional consideration to limit the development pace of safe MRSA disconnects further from here on out. The advancement of new medications is additionally in progress with the goal that the obstruction can be decreased. MRSA skin drugs are widely being used for treating skin diseases. The new methodologies have been started by the utilization of Fusidic corrosive, Linzolid against Staphylococcal contaminations.

Children with immune system problems are a special population for the spread of *S. aureus* infections. While many of the symptoms of staphylococcal disease are comparable to those observed in juvenile populations that are healthy, there is a chance that complications could arise, especially in kids who already have cancer. Furthermore, infections in this population frequently show significant rates of antimicrobial drug resistance. These infections should be treated vigorously, with antibiotic selection influenced by local epidemiology, culture, and susceptibility information. There are still large knowledge gaps regarding the epidemiology and treatment of these illnesses, which need more research.

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