AN OVERVIEW ON MULTIDRUG RESISTANCE OF *Staphylococcus Aureus*

Abstract

Both humans and domestic animals can get the sickness brought on by the bacterium. In certain animal species, it could lead to severe mastitis. *Staphylococcus aureus* is the cause of mastitis in cattle in around 30% of clinical and subclinical cases. The elderly, babies, and those with impaired immune systems are more susceptible to S. aureus infection than healthy individuals. S. aureus is the main source of nosocomial and community-associated infections, and it has become an issue due to the organism's rising incidence of antibiotic resistance. Numerous virulence variables were associated to its pathogenecity. Chronic inflammatory skin disease known as atopic dermatitis (AD) can be directly attributed to the presence of persistent bacterial infections such S. aureus. These diseases primarily affect newborns and children. According to data, the range might be between 18 and 22% in wealthy nations. Methicillin-Resistant Numerous illnesses, including infections of the skin and soft tissues, endocarditis, infections of the bones and joints, and others, are brought on by Staphylococcus aureus. The most prevalent and potentially fatal of these infections is MRSA bacteremia, which has a high death rate and several comorbidities. In this article we have focused on multidrug resistance of S. aureus and others pathogenic microorganisms.

Keywords: Staphylococcus aureus, MRSA, Chronic inflammation, Mastitis, Vancomycin

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I. INTRODUCTION

The pathogen can cause disease in both human and domestic animal. It may cause severe mastitis in animal species. Approximately 30% of cases of clinical and subclinical mastitis in cattle attributed by *Staphylococcus aureus* (Li et al., 2017). S. aureus are zoonotic pathogen. They are mainly gram positive bacteria, in which polysaccharide capsule may be present or absent. S. aureus can be divided into methicillin sensitive S. aureus (MSSA) and methicillin resistance S. aureus (MRSA) depending upon the sensitivity of antibiotic drugs. Now at the point of time, the drug resistance S. aureus has been increased due to excessive evolution of bacteria and abuse of antibiotics. The choice of therapy against such multidrug resistant S. aureus (MRSA) strains has been narrowed to a few antibacterial agents, among them the glycopeptide antibiotic vancomycin ,which has become the mainstay to therapy worldwide. MRSA strains with reduced susceptibility to vancomycin have been reported in clinical specimen since the late 1990s. In most of these so called vancomycin intermediate resistant S. aureus (VISA) isolate decrease in drug susceptibility, as expressed by the increase in the minimal inhibitory concentration (MIC) of vancomycin, is sufficient to cause complication in therapy and treatment failure. VISA type resistance has now been identified in each globally spread pandemic clones of MRSA.

Staphylococcus aureus is a pathogen which is responsible for various disease, it ranges from mild skin disease and soft tissue problems to life threatening problems such as Osteomyelitis Endocarditis and toxic shock syndrome (Reddy et al., 2017). S.aureus is the major cause of nosocomial and community associated infections and it has become the problem of growing prevalence of antibiotic resistance in the organism, the elderly, infants and immunocompromised people are more vulnerable to S. aureus infection. Its pathogenicity related to many virulence factors. The mode of action by which S. aureus Enterotoxin is responsible for food poisoning are yet not clear. S. aureus can pollute many food items such as; meats, fish, eggs, dairy products SEs in staphylococcus food borne disease was cleared and its causing problem in intestinal epithelium and vagus nerve. That causes stimulation in emetic center. (Rong et al., 2017). S. aureus can cause superficial and invasive infection of skin such as bacterimia and sepsis. The drug resistance of MRSA has moderately increased. It is evident that the resistant mechanism of s. aureus is very complicated especially for MRSA (U. Okwu et al., 2019).

S.aureus is also opportunistic human pathogen which generate the phenotype bifurcation of the cell into two genetically identical but different cell types during the tenure of the infection where the first type promotes the chronic infection and second type contributes to acute bacteremia (García-Betancur et al., 2017). S. aureus produce catalase and coagulase enzymes and they are non-motile bacteria and also non spore formed organisms which can survive in presence of oxygen. Infections such as food poisoning, scolded skin syndrome ,toxic shock syndrome occurs when S. aureus spread to the tissue from the wounds(Akanbi et al., 2017) .

Many antibiotics have been used for the treatment of infection which are caused by S. aureus, some infections like mastitis in dairy animal , so this resistance bacteria can spread in human being, when human consume the animal food product this is how this has been linked to the human (Massawe et al., 2019). S. aureus releases epidermolytic toxin which cause staphylococcal scalded skin syndrome when S. aureus colonize the human skin the proportion of methicillin resistant staphylococcus aureus (MRSA) strain is very high, so semi synthetic

penicillinase resistance penicillin or vancomycin , clindamycin are given for the treatment of staphylococcal scalded skin syndrome (Kong, 2018).

Synthesis of cell wall (beta lactam and glycopeptides) , synthesis of protein (aminoglycosides, macrolides) nucleic acid synthesis, are the important constituents part of the bacteria, so when antibiotics bind with this constituents part of the bacteria , it inhibits their synthesis. The penicillin binding protein 2a (PBP2a) has been encoded by mecAgene and they are present on the mobile gene element of staphylococcal chromosome cassette mac (ssmac) which has resistance for the S. aureus and has low affinity for the beta lactam antibiotics. (Akanbi et al., 2017). Huge formation of resistance to multiple antimicrobial agent may lead some problems during the treatment of the infection cause by S. aureus(Zhang et al., 2018).

The bacterial structure has high influence on multi drug resistance. More than 40% of antibiotics target the bacterial ribosomes. Ribosomes are cellular molecular machines that help in protein synthesis. Staphylococcus aureus contains teichoic acid glycopolymer which makes upto 60% of total cell wall mass in Gram positive bacteria. Teichoic acid can be present in two forms that are as lipoteichoic acid (LTA) in plasma membrane or in the form of wall teichoic acid (WTA) which is covalently linked to peptidoglycan. The LTA of S.aureus is composed of polymerizefd glycerol phosphate (GroP) subunits which can be modified either by D-alanine or α-N-acetylgluosamine (α-GlcNAc). WTA structure is present majorly in S.aureus lineages; it is composed of 40 ribitol phosphate (RboP) subunits modified by D-alanine and N-acetylgluosamine residues. WTA structure has great importance for S.aureus while interacting with human host. S.aureus adapts to its environment by regulating the structural composition and expression levels of WTA through a complex gene mechanism (van Dalen et al., 2020).

S.aureus possess highly cross-linked peptidoglycan (PG), which is a macromolecule containing glycan chains, synthesized by the FemXAB protein family. These glycan chains consist of N-acetylmuramic acid(Mur NAc) and N-acetylglucosamine(Glc NAc) sugars. A stem peptide attaches to Mur NAc and the peptide bridges crosslinks the glycan chains which envelops the cell by forming a mesh like structure surrounding it. These structural features provides strength and flexibility to the cell envelop allowing it to tolerate extreme pressure arising from the intercellular turgor. The presence of pentaglycine crosslinks makes Staphylococcal PG unique in nature. The efficient antibiotics mainly target the steps involved in biosynthesis of PG(Monteiro et al., 2019).To prevent this S.aureus has an ability to enter into a non-growing antibiotic tolerant state, called persisters. Persister reduces biosynthesis processes. The attractive antipersisters target is bacterial membrane because they can be disrupted independently of growth(W. Kim et al., 2019).

II. ATOPIC DERMATITIS

Atopic Dermatitis (AD) is a chronic inflammatory skin disorder can be caused directly by the presence of recurrent bacterial infections such as S. aureus. Mostly infants and children are affected by this disease. To put it in the terms of statistics it can differ between 18-22% in the developed countries. Some cases can be cured or resolved with time whereas some cases may leave adverse impact in our body which can lead to infecting our respiratory system and may cause diseases like asthma or allergic rhinitis. Many environmental factors

get affected by the severity of AD i.e food allergy, air pollution. In skins of AD patients (60-100%) are most likely to colonize my S. aureus as compared to healthy controls (5-30%).

One of the major challenges commonly encountered in the management of AD is when the S. aureus clusters in the skin. Impetigo is a frequent kind of superficial bacterial infection distinguished by irritated or infected epidermis. When MSSA levels rise, the rare variant bullous impetigo, which is characterized by fragile fluid-filled vesicles and flaccid blisters, is invariably caused by Staphylococcus aureus and is treated with tropical retapamulin for 5 days. The Infection Disease Society of America also suggests doxycycline, clindamycin, and trimethopric for MRSA-causing skin infections. These antibiotics may be less effective as the antibody resistance strain develops. Bleach bath or sodium hypochloride bath can also be helpful in treation AD patients. Bleach bath is not as effective as water bath alone. According to microbiome manipulation CON5 strains characterized by with antimicrobial activity reduced colonization of S. aureus in AD subjects (J. Kim et al., 2019).

Patients with slight to extreme atopic dermatitis go through a new remedy known as dupilumab. Which blocks IL-4/ IL-13 signaling and inhibits receptor signaling downstream the JAK-STAT pathway. by blocking this pathway three of major disease mechanism of atopic dermatitis can be affected

- The decrease of skin barrier function,
- The class switch to IgE
- TH2 differentiation.

In clinical trial phase 1-3, truthful or productive result has been shown by dupilumab. The study says dupilumab is supercilious to most commonly used immunosuppressor pills such as cyclosporine or methotrexate. Most relevant side effects are basically conjunctivitis and injection site reaction (Seegräber et al., 2018).

According to recommendations from the Clinical and Laboratory Standards Institute (CLSI), Mueller Hinton broth was used to determine the minimum inhibitory concentration (MIC), or the lowest concentration of an antimicrobial that will prevent a microorganism from clearly growing after an overnight incubation. Vancomycin's (MIC) value was among the lowest of all the tested antibiotics. Erythromycin and lincomycin were found to have the highest MIC90. The conventional antibiotics with the highest rates of resistance were ampicillin (58.5%), daptomycin (53.6%), lincomycin (38.2%), and erythromycin (32.0%). Fusidic acid resistance is around 10% in the general population and 50% in dermatology patients. A high in vitro activity against S. aureus has been found in fusidic acid (Błażewicz et al., 2018).

According to present study 15.5% of strains resistance to fusidic acid noted. As suggested by phenotypic analysis fusidic acid resistance was notibly co related with atopic dermatitis. The genotype constitution which is responsible for fusidic acid resistance were recognized, including obtained genes FusB and FusC and chromosomal mutations in FusA genes. FusB was the least frequent determinant found in 4%of cases compared to 20%of control (Harkins et al., 2018).

The ampicillin works on fragile organisms in two steps, much as any other beta lactum antibiotic (Figure 1):

1. In the first stage, the medication binds to membrane-bound penicillin binding protein receptors. The inactivation of penicillin-binding proteins by bound antimicrobial has an immediate arresting effect on their function, and these proteins play a significant role in the cell cycle.
2. Additionally, they have physiological effects that are brought on by the receptor ligand interlinkage that is created in the second stage. The penicillin-binding proteins are intricated at the last step of peptidoglycan production in the cell wall. Peptidoglycan, which is found in a hypotonic environment, maintains the integrity of the cell wall, and de-peptidoglycan arrangements lead to lysis and cell death

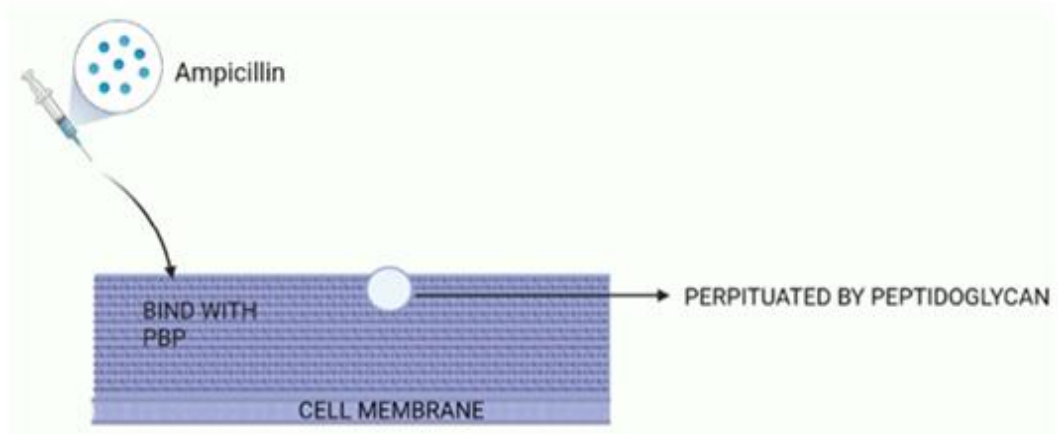

Figure 1: Ampicillin binds to primary receptors called PBP. Penicillin-binding proteins that are inactivated by bound antimicrobials due to morphogenic development of cell wall peptidoglycans have their activity immediately halted.

III. MRSA BACTEREMIA

MRSA or Methicillin-Resistant Staphylococcus aureus can cause broad range of diseases like skin and soft tissue infection, endocarditis, bone and joint infections and so on. Among these infections MRSA bacteremia is the most common and life-threatening disease due to its complications and high mortality rate. The complication increases with severe underlying conditions. The treatment provided to these patients mainly fail to cure the patients with underlying medical conditions like medical implant, presence of comorbidity and severe diseases or infections with non-susceptible strains. Patients with MRSA bacteremia have a mortality rate of 30% - 40% (H. J. Kim et al., 2020). It was observed that the MRSA strains develop its drug resistance capability in the duration of treatment of bacteremia which leads to failure of treatment and as a result the MRSA strains cannot be eradicated from bloodstream (Chen et al., 2020a).

The mechanism through which it causes bloodstream infection is when S.aureus enters the blood stream it takes over the host's coagulation system. If the endothelium is mechanically damaged then the collagen rich vessel's layer gets exposed which initiates the coagulation cascade and a clot consisting of fibrin and vWF is developed. It forms a binding site for S.aureus , so that its surface proteins and coagulase can interact with collagen, fibrin and vWF. If there is no mechanical damage then the inflammation activates the endothelium

and the cell surface display adhesion molecules like vWF, selectin and others. It engages immune cells (which bring intracellular bacteria to the site) and platelets. Platelets and vWF provides binding site for S.aureus. Once S.aureus binds to the vessel wall, it permits direct damage to the endothelium by the toxins secreted from the invading pathogens like alpha toxin and endothelium-activating superantigens (Kwiecinski & Horswill, 2020).

Anti-MRSA medications include a variety of antibiotics; however, MRSA strains are resistant to them. In a study (Chen et al., 2020b), it was discovered how MRSA strains changed as they became more resistant to routinely used anti-MRSA medications, reducing the efficiency of treatment for MRSA bacteremia. A middle-aged patient who had recurrent bacteremia for three years before passing away, after failing repeated regimens of antibiotic treatment, had 32 MRSA isolates found in his blood cultures. Despite being exposed to many antibiotics, the isolates were resistant to anti-MRSA drugs. The 32 strains were identified as ST5 by the first genotyping. The strains were cultured in liquid or on solid basic medium or tryptic soy broth, and they were kept at -80°C for storage. It showed resistance to linezolid as well as vancomycin and daptomycin. Etest (bioMe' rieux) determined the minimal inhibitory concentration (MIC) of linezolid, vancomycin and daptomycin.

After studying the evolution strategy of MRSA strains, as a result it was concluded that MRSA strains undergo certain mutations and they lose substantial genes by recombination to increase their non-susceptibility towards antibiotics. For example linezolid, a synthetic antibiotic which should bind in the peptidyl transferase center of large 50S ribosomal unit and prevent the bacteria from protein synthesis does not binds because of Cfr gene which encodes a methyl transferase (Shariati et al., 2020) that causes mutation in 23s rRNA site of 50S ribosomal unit. All of the linezolid resistant strains had 2 to 3 G2576T mutations in domain V regions of 23S rRNA (Chen et al., 2020c) (Figure 2).

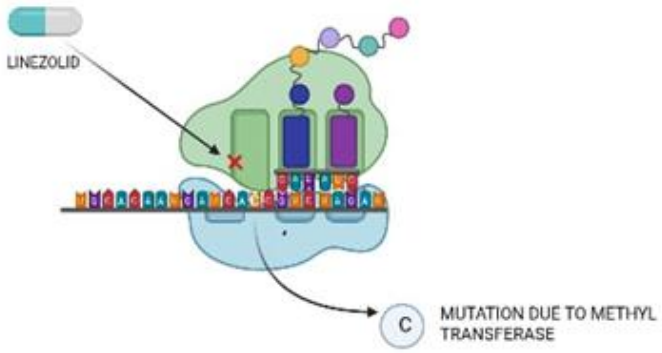

Figure 2: In MRSA bacteremia, Linezolid can't bind to 50S ribosomal unit because of gene mutation in mRNA caused by methyl transferase.

Regardless of these mutations, MRSA is sensitive towards Ceftaroline fosamil, a novel extended-spectrum cephalosporin and the only available beta-lactum antibiotic which is successfully effective against MRSA both in vitro and in vivo. Previously Vancomycin and Daptomycin was mainly used in MRSA bacteremia but recently rate of therapeutic failure has increased by using these antibiotics therefore Ceftaroline fosamil is used for complicated MRSA bacteremia. Ceftaroline is used as monotherapy to treat MRSA bacteremia associated with endocarditis and in combination with other antibiotics to treat persistent bacteremia. In a

report it was confirmed that ceftaroline can eradicate MRSA strains from blood stream and cure a patient with complicated MRSA bacteremia. For investigation few patients were selected with MRSA strains and two or more blood cultures were done. Treatment was done with Vancomycin, daptomycin, linezolid and after 4 days the blood culture was still positive for MRSA and persistent bacteremia. Then they were treated with ceftaroline. The ceftaroline dose was administered to the 6 patients was 600mg q12 and 2 patients was 200mg q12. As a result, after 7 days all 8 patients who had ceftaroline monotherapy were devoid of MRSA strains in their blood cultures and were showing signs of clinical improvement (Bhowmick et al., 2019).

In an in vitro experiment (Bhowmick et al., 2019), 1 strain of MRSA was cultured in a media of low concentration ceftaroline which demonstrated that neutrophils have enhanced their activity comparing to the strains whose media was lacking antibiotics. Monotherapy is possible with ceftaroline because of its increased innate bactericidal effect against MRSA. In another case study (Bhowmick et al., 2019) it was described that six patients had MRSA bacteremia where 3 patients were suffering from endocarditis and one patient had septic thrombophlebitis as well. All patients were treated with ceftaroline 600mg dose every 8 h for 2-3 weeks and the treatment was successful. Therefore it was concluded that Ceftaroline is an effective antibiotic against MRSA bacteremia (Bhowmick et al., 2019).

IV. OSTEOMYELITIS

Osteomyelitis is a chronic bone infection caused by the S. Aureus bacteria. It may result in bone necrosis and amputation and has a serious risk of deadly septicemia. The bone infection is related with diabetic foot ulcers,joint replacement etc. In every year, around 4million people are affected by osteomyelitis and 0.5 million people is in US and EU (Padrão et al., 2021). In antibiotic and surgical techniques, MRSA induced osteomyelitis remains a serious bone infection and it is difficult to cure bone infection. So, combination of multiple surgical debridements and antibiotic therapies are followed for treatment of osteomyelitis (J. Zhou et al., 2018).

In osteomyelitis, intracellular survival rate of S. aureus is maximum. The bacteria escapes cell death by evading lusosomal compartments preventing phagosomal fusion or persisting within vacuoles. S. aureus can also replicate intracellularly. They become metabolically inactive leading themselves to a persistent state. Antibiotic exposure to those persisters is unable to kill S.aureus completely. (Gimza & Cassat, 2021) (Fig.3)

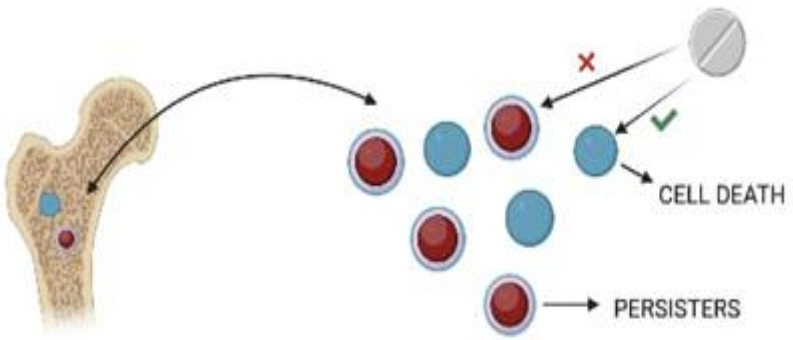

Figure 3: In Osteomyelitis, antibiotic is unable to eradicate all MRSA because most of them convert themselves into persisters.

Vancomycin, an amino-glycopeptide, is widely used to treat osteomyelitis and acts at the receptor level, blocking the adhesion of the bacteria. Vancomycin has standard antimicrobial therapy and depletion of microorganisms with elevated Vancomycin MIC is becoming more frequent. (D. & N., 2018)and (Lalikian et al., 2018). For bone infection therapy, there was synthesized a new antibacterial material. It is consist of SDECM means specific demineralized extracellular cancerous matrix in bone. This SDECM cross linked with vancomycin via electrostatic and chemical bond and named as VAN-SDECM. It is help to maintain the sustained bactericidal ability which is accompanied by degradation of scaffold. This infectious bone defect confirms the compressive anti-infective and osteogenenic ability of the VAN-SDECM (Fang et al., 2021).

Although, vancomycin have some side effects like drug allergies, pancytopenia of vancomycin which is discovered in childrens, pulmonary infection, rashes etc. For these reason, daptomycin, linezolid can be used instead of vancomycin. MRSA disjunct with vancomycin MICs often have elevated daptomycin MICs, rendering this alternative less attractive in cases where decreased vancomycin susceptibility is identified (Lalikian et al., 2018).

Also, erythromycin and curcumin has their roles in osteomyelitis is barely studied. Curcumin, an antioxidant, has an antibacterial activity as well as anti-biofilm activity and it is found to effective against S. Aureus. Activity of erythromycin and curcumin against chronical osteomyelitis induced by MRSA was discovered in rats. In case of rats, 4 week after bacterial inoculation, rats receives such treatments like erythromycin mono therapy, curcumin mono therapy, erythromycin plus curcumin combo therapy twice a day for 2weeks. Thus bacterial levels, bone infection status, inflammatory signals were evaluated and some side effects such as diarrhoea, weight loss were seen. The rats receive all treatment well. After the treatments, the results were seen. In case of erythromycin mono therapy, it did not inhibit the growth of bacteria and had no effect on bone infection. Also, in case of curcumin mono therapy, it slightly inhibits the growth of bacteria and alleviated bone infection a lot. But when the rats were given erythromycin and curcumin combo therapy, it was found that it markedly inhibit tha growth of bacteria and reduced TNF - alpha and IL-6 (Z. Zhou et al., 2017). So, the conclusion of the combo therapy of erythromycin and curcumin antibiotic is more stronger than mono therapy against MRSA induced osteomyelitis in rats.

V. TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) shows many symptoms like scarlet fever, diarrhea, erythroderma and high fever which leads to multiple organ failure. Both children and adults will be affected by TSS, the incidence of TSS in children is range from 2.5 to14% and mortality rate can rise to 50% , if proper treatment not don't within time (Matsushima et al., 2021).

S.aureus produces toxins which cause toxic shock syndrome. Release of Toxic Shock Syndrome Toxin -1(TSST-1) cause acute and fatal illness. S. aureus produce here resistant exotoxin which is TSST-1. Release of different cytokines such as Interleukin-1, Interleukin-2 and Tumor necrosis factor cause TSS, tst Gene encode TSST-1 which is a protein. 37 to 40 degree celcius temperature and low oxygen and glucose levels is a condition to cause mainly TSST-1 produce by S. aureus. In human, nasal mucous membrane and skin is the main site from were S. aureus spread in to the body surface. S.aureus also found in the axillary and

skin. tst Gene, of S. aureus which is present in nasal mucous membrane play important role in epimermology and pathogenesis of infection. In community and hospital S.aureus can easily be transmitted (Biglari et al., 2019). Hospital-associated or healthcare-associated pathogens are other names for Methicillin-Resistant Staphylococcus aureus. It has been seen that community acquired MRSA (CA-MRSA) strain cause infection are rapidly increase in the world. S. aureus toxin mainly exotoxin leads to multiple organ failure and known as Toxic Shock Syndrome (Sada et al., 2017a).

MRSA shows resistant to all beta - lactam antimicrobial but it does not show resistant to anti MRSA chephalosporin due to production of penicillin binding protein 2a (PBP2a) . It may cause risk factor for early mortality in a patient's due to inadequate antimicrobial for MRSA (D. Kim et al., 2019). In(Sada et al., 2017b) ,it was seen that a 40 year old woman having severe urinary tract infection and septic shock,on day 1 Dopamine infusion, intravenous ampicillin (2g,3 time daily) and gentamycin (120 mg once day) ,but she doesn't recovered and intensify diarrhoea. On day 2, she presented urine and vaginal discharge. S. aureus was detected and staphylococcus TSS or septic shock was suspected. Then the antibiotics are changed to Vancomycin (1g ,2 time daily, intravenously), Clindamycin (1g, 3 times daily, intravenously). Then on day 3 Community acquired S. aureus detected from vaginal discharge and urine. On day 9 STSS was diagnosed and on day 14 Vancomycin and clindamycin is given and patient shows full recovery. Clindamycin binds to P site of 23 rRNA of 50 s large ribosomal subunit and inhibits peptide chain elongation during protein synthesis and kill the bacteria (Sada et al., 2017a).

According to Matsushima et al., 2021, it was seen that patients with TSS due to nosocomial Methicillin Resistant Staphylococcus aureus (MRSA) infection with burn injury is due to MRSA or Methicillin Sensitive Staphylococcus aureus (MSSA). So, MRSA strains was cultured by oscillating the culture with brain heart infusion medium for about 18 hours. 736 patients having burn injury were admitted, among them 244 patients were diagnosed and shows nosocomial MRSA infection. Among 244 MRSA patients TSS occurred in 20 (8.2%) patients (Figure 4).

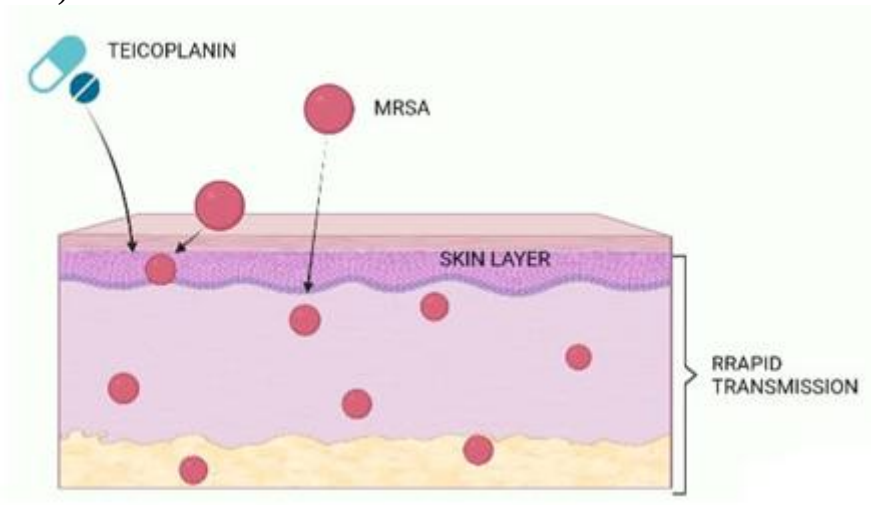

Figure 4: In TSS, Teicoplanin shows resistant due to rapid transmission of MRSA into soft tissue and skin.

Then the treatment was done with 20 patients at first Teicoplanin is used against MRSA, but it shows rapid spread of MRSA into soft tissue and in skin surfaces. Then Linezolid became the choice of drug to treat TSS. Linezolid is Oxazolidinone agent which inhibit the protein synthesis of bacteria by binding to the 50s ribosomal subunit,and then it blocks the formation of initiation complex. It Mainly bind to peptidlyl transferase centre on the ribosomal and inhibit protein synthesis and it also inhibit virulence factor and decrease toxin production by S.aureus in nasal mucous membrane from where it is spread into axillary and skin surfaces. Therefore it is a successful treatment (Azhar et al., 2017) (Figure 4).

In (Boudet et al., 2021), it was seen that a patient having TSS with Cystic Fibrosis (which is a genetic disorder and causes many oragns to function properly). Cystic Fibrosis contain a transmembrane ion channel known as Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) , when there is any change in this Transmembrane ion channel cause mucous membrane abnormal and thus low microbial clearance creat local condition for the bacterial persistent. Due to antimicrobial multi- drug resistance form of MRSA, the antibiotics are given for the management of MRSA infection by combining different antibiotics. For MRSA infection antibiotics are given that are Cortrimoxazole, Rifampicin, Fusidic acid, Minocycline and Vancomycin and Clindamycin used either alone or used in combination to treat patient. Therefore, MRSA strains shows resistance to Erythromycin, Lincomycin, Kanamycin tobramycin and susceptible to Gentamycin, Minocycline, Linezolid. For four Linezolid Resistance Staphylococcus aureus (LRSA), 2 strains co - isolated from 2 patient having TSS with Cystic Fibrosis, MIC of Linezolid are 16,24,32 and > 256mg/L ,were submitted to determine genetic determinant of Linezolid Resistance in a genome sequence. So, it was detected that mutation occur in the four LRSA strain. In some cases Intravenous Immunoglobin is also given to the patient and it is seen that among 20 patients given Intravenous Immunoglobin 17 patient recover by this administration (Boudet et al., 2021).

So, Bacterial MRSA strains shows resistance to Teicoplanin, Ampicillin, Gentamycin whereas bacterial MRSA strains shows sensitivity to Linezolid, Clindamycin combination with Vancomycin and Intravenous Immunoglobin.

VI. SEPTICAEMIA

Infection is the most frequent, costly, and fatal post-major surgical consequence. Despite employing antibiotics more often and in a wider range of dosages, surgical infections have continued to occur at unfathomable rates. Although the exact origin of these infections is unknown, the gut has been found to be a superior-level repository for antibiotic-resistant bacteria in people. However, it is still unclear precisely how pathogenic organisms in the stomach could influence postoperative infection. (Hyoju et al., 2019). Neonatal septicemia (NS) is one of the major problems that the humanity is facing and the most serious problem in special care neonatal unit (SCANU) and neonatal intensive care unit (NICU), resulting in significant disorders and deaths. It is evaluated that the protagonist pathogens and their drug sensitivity pattern in this study, which will certainly help in the choice of specific antibiotic during treatment of septicemic neonates. The purpose of this study is to segregate the contributory envoy of neonatal septicemia and to analyze antimicrobial susceptibility pattern of the detached (Islam et al., 2019). There were many competitive correlations between prevalence of resistance and countermeasures for unfamiliar combinations of antibiotics/bacteria and septicemia hospitalization/sepsis death rates in adults Out of 100

cases, 31 (31%) is confirmed as positive blood culture. Gram-negative exudes were 22 (70.97%) and gram-positive were 9 (29.03%). Klebsiella pneumoniae was the most common (41.9%), followed by staphylococcus aureus (29%) and E. coli (19.4%) among the detaches

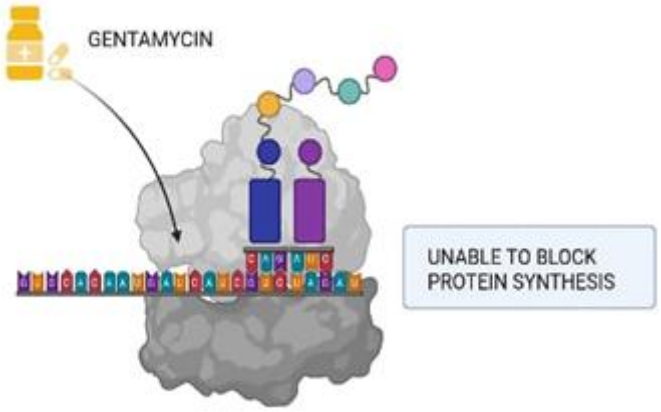

Figure 5: Gentamycin can't block the process of protein synthesis of Septicemia.

All of the three common detaches showed 100% resistance to ampicillin and very inferior level sensitivity to gentamicin. Gram-negative detaches were superiorly sensitive to amikacin and imipenem, whereas gram-positive detaches were superiorly sensitive to amikacin and vancomycin (Figure 5). Table 1 of the data shows the prevalence of neonatal septicemia. Out of the 516 blood samples collected from the affected newborns, 56 (10.8%) showed substantial bacterial growth, whereas 32 (6.2%) had contamination growth and 460 (82.9%) showed no bacterial growth at all. And of these 56 neonates, 32 (57.1%) were delivered inside, while the remaining 24 (42.8%) were born outside. Of these, 37 (66%) were confirmed boys, while 19 (33.9%) were girls, having a male to female ratio that was 1.9:1 in general. Compared to LOS 21 (37.5%) infants, the prevalence of the EOS phenomena was higher in 35 (62.5%) neonates (Thapa & Sapkota, 2019).

Table 1: Antibiotic Resistance

ANTIBIOTIC (µg/disk)	**RESISTANT, R (%)**	**INTERMEDIATE SENSITIVE, I (%)**	**SENSITIVE, S (%)**
Nalidixic acid (30)	22.0	26.5	52.0
Oxolinic acid (2)	8.0	23.0	71.2
Compound sulphonamides (300)	9.9	7.0	84.4
Doxycycline (30)	4.0	26.0	70.0
Tertracycline (30)	58.0	25.3	16.7
Novobiocin (30)	78.0	11.3	10.7
Chloramphenicol(30)	74.0	7.7	18.3
Kanamycin(30)	68.3	15.0	16.7
Sulphamethoxazole(25)	15.7	7.7	76.7
Flumequine(30)	12.3	14.3	73.3
Erythromycin (15)	37.7	22.3	40.0
Ampicillin (10)	77.0	18.7	4.3
Spiramycin (100)	74.7	7.7	17.7

Oxytetracyclin (30)	6.0	22.0	72.0
Amoxicillin (25)	69.2	12.1	19.8
Fosfomycin (50)	52.0	15.0	35.0

Hydrophila=Aeromonas hydrophila, E. tarda=Edwardsiella tarda (Lee & Wendy, 2017)

Table 2: Heavy metals and its resistance

HEAVY METAL	RESISTANT, R (%)
Hg^{2+}	22.4
Cr^{6+}	45.0
Zn^{2+}	68.1
Cu^{2+}	29.2

Table 2: Disease and their antibiotics

Sl.no	DISEASES	ANTIBIOTICS	
		Failed to kill MRSA	Succeed to kill MRSA
1.	Atopic dermatitis	Ampicillin	Dupilomab
2.	MRSA bacteremia	Linezolid, Vancomycin, Daptomycin	Ceftaroline
3.	Osteomyelitis	Vancomycin	Erythromycin & curcumin (combination therapy)
4.	Toxic shock syndrome	Teicoplanin	Intravenous immune globulin, linezolid, clindamycin & vancomycin (combination therapy)
5.	Septicemia	Vancomycin	Methicillin

VII. CONCLUSION

In this article, we discussed about the multidrug resistance of Staphylococcus aureus and the clinical impulse of risk factor (virulence factor) in patients with antibiotics. Antibiotics are used against the life threatening infectious diseases like atopic dermatitis, osteomyelitis, toxic shock syndrome, bacteraemia and septicaemia caused by S.aureus. Different types of Antibiotics are used for the treatments of various infectious disease. Some MRSA strains shows resistance to antibiotics and some shows sensitivity to antibiotics. Here in we described the mode of action of antibiotics against infectious disease-causing agents. The ampicillin which functions like any other beta lactam on delicate organisms, shows unsatisfactory results against Atopic dermatitis. After a certain point of time the genotype itself creates an antibody around it which cannot be penetrated by ampicillin. Thus it shows a result truly unsatisfactory. Whereas in case of dupilumab it blocks the signaling and inhibits the receptor signaling by blocking the pathway, so major disease mechanisms of A.D can be resisted. That's why in trial phase, productive result has been shown by dupilumab. In bacteraemia, MRSA strains has shown resistant towards Vancomycin, Daptomycin and

linezolid due to their multi-drug resistance capability but MRSA is sensitive towards Ceftaroline because of its bactericidal effect. In osteomyelitis, combination of antibacterial material SDECM and vancomycin, is able to supress the bacterial growth, means this combination is sensitive towards MRSA strain. In other hand, MRSA strains shows resistance towards erythromycin mono therapy and curcumin mono therapy but sensitive towards combination of erythromycin and curcumin therapy. In toxic shock syndrome S. Aureus shows resistance to Teicoplanin and shows sensitivity to linezolid, Clindamycin combination with Vancomycin. In septicaemia and osteomyelitis vancomycin is resistance to MRSA strain. So, the choice of drug is difficult for the different types of diseases caused by S. Aureus.

We accept that regardless of certain restrictions, our discoveries show a potential causal relationship between the utilization of penicillins, and the paces of sepsis hospitalization in the grown-ups matured between 50-84 years, recommending the possible advantages of anti-toxin stewardship. I trust that this biological examination would prompt further examinations of the connection between anti-infection recommending practices and sepsis in various settings, including singular level investigations of the connection between endorsing of various anti-microbials for the treatment of different conditions and resulting septicemia/sepsis results. Such examinations are expected to illuminate anti-microbial recommending rules, including the likely substitution of certain anti-toxins, especially penicillins in more seasoned grown-ups by different anti-infection agents in the treatment of specific conditions fully intent on alleviating the paces of septicemia, sepsis, and the related mortality. At last, we accept that a far reaching, long haul approach for controlling the paces of extreme results related with bacterial contaminations, including septicemia ought to incorporate not just the selection of suitable anti-infection recommending rehearses yet in addition the presentation of new anti-microbials.

VIII. ACKNOWLEDGEMENT

I personally want to acknowledge the effort and dedication of Anirban Ghosal, Amartya Ghosh, Md Kayem, and Souvik Mandal. and also the 3rd year BMLT students: Anirban Ghoshal, Amartya Ghosh, Md Kayem, and Souvik Mandal of Paramedical College Durgapur, West Bengal, India.

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