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Staphylococcus aureus and Antibiotic Resistance: Pathogenic Adaptations and the Role of Neutrophils in Host Défense

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ABSTRACT

Clinical implications include limitations in current antibiotic therapies, increased morbidity and mortality, and the need for novel therapeutics. Current and future approaches to managing antibiotic resistance include antibiotic stewardship programs, surveillance and monitoring, research and development, and innovative therapeutic approaches. Future directions include understanding resistance evolution in community settings, optimizing treatment strategies, and developing new antimicrobial agents. Aim of this review study to provide a comprehensive overview of the historical development of antibiotic resistance in *Staphylococcus aureus*, from the emergence of penicillin resistance to the rise of multidrug-resistant strains such as MRSA, VISA, and VRSA. Clinical ramifications include higher morbidity and mortality, restrictions on the use of existing antibiotic medicines, and the requirement for novel medications. Innovative therapeutic approaches, research and development, surveillance and monitoring, and antibiotic stewardship programs are some of the current and future strategies for managing antibiotic resistance. Prospective avenues of inquiry encompass comprehending the progression of resistance within community environments, refining therapeutic approaches, and creating novel antimicrobial substances. The purpose of this review study is to present a thorough overview of the evolution of antibiotic resistance in *Staphylococcus aureus* across time, starting with the advent of penicillin resistance and continuing through the emergence of multidrug-resistant strains like MRSA, VISA, and VRSA.

Keywords: *Antibiotic Resistance, Multi drug resistance, Morbidity and Mortality, MRSA, VRSA, Stewardship, penicillin resistance.*

1. INTRODUCTION

The worldwide growth of antibiotic resistance grants a danger to the efficacy of conventional medicines in treating common bacterial illnesses. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) study states that the prevalence of resistance in common bacterial diseases is startlingly high. There is significant worry about the median reported rates of 35% for methicillin-resistant Staphylococcus (MRSA) aureus and 42% for third-generation cephalosporin-resistant E. Coli across 76 nations. The vulnerability of E. Coli urinary tract infections to common antibiotics such ampicillin, co-trimoxazole, and fluoroquinolones decreased by 5% in 2020. WHO, the World Health Organization, 2023 As a result, properly treating common infections is becoming more difficult. Americans continue to be concerned about AR, as seen by the national death and infection statistics from the CDC's 2019 AR Threats Report. Approximately 2.8 million antimicrobial-resistant infections occur in the US each year, resulting in more than 35,000 fatalities. In July 2024, the CDC published Antimicrobial Resistance Threats in the United States, 2021–2022. These new findings show that, relative to the pre-pandemic period, the COVID-19 pandemic increased the prevalence of six bacterial antimicrobial-resistant hospital-onset infections by a total of 20%. In 2022, these illnesses were still higher than they were before the pandemic, having peaked in 2021.

Furthermore, from 2019 to 2022, there were almost five times as many clinical instances of Candida auris (C. auris), a form of yeast that can spread throughout healthcare facilities, is frequently resistant to antifungal medicines, and can cause serious

sickness (*2019 Antibiotic Resistance Threats Report*, 2024). These findings demonstrate the necessity of taking more measures to lessen the effects and spread of antibiotic resistance.

Apart from the documented cases involving illness and death, microorganisms resistant to antibiotics have a substantial financial impact. Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) was found to be associated with an annual cost burden of up to 13.8 billion dollars in the United States (Lee et al., 2013). The 1940s saw the first report of S. aureus resistance to penicillin, and infections with this resistant strain of the bacteria are still a concern today. In reality, the CDC currently classifies MRSA as a "serious threat." This category is based on seven characteristics, including transmissibility, clinical effect, occurrence, and accessible therapies. S. aureus is one of the six "ESCAPE bugs," or antibiotic-resistant bacteria that account for the bulk of nosocomial infections in the US, which is consistent with this conclusion (Pruett, 2010). With the introduction of penicillin resistance and the subsequent appearance of multidrug-resistant strains such as MRSA, VISA, and VRSA, the goal of this review study is to provide a comprehensive overview of the evolution of antibiotic resistance mechanism in *Staphylococcus aureus* across time.

S. aureus as a Leading Nosocomial and Opportunistic Pathogen

A wide range of host species' skin and mucous membranes are naturally habitat to staphylococci. Many bacterial species coexist peacefully or in association with their hosts; but, if the bacteria penetrate the host tissue through damage to the epidermal barrier, they may turn dangerous. The most important species in this genus is *Staphylococcus aureus* due to its flexibility as a pathogen that affects both people and animals (Jørgensen et al., 2005). S. aureus is the causative agent of numerous human ailments, from minor skin infections to serious illnesses. Furthermore, S. aureus is capable of producing strong superantigens and additional toxins that can lead to certain toxin-mediated illnesses such food poisoning, scalded skin syndrome, and toxic shock syndrome.

Animal mastitis, also known as intramammary infections (IMIs), frequently occurs by S. aureus (Keane, 2019). Every year, intramammary infections cause the dairy industry to suffer large financial losses on a global scale [(Morales-Ubaldo et al., 2023). Several opportunistic diseases in humans and animals are caused by other Staphylococcus species, which are collectively referred to as coagulase-negative staphylococci (CNS). Many of the species in this group are so commonplace that their clinical value has traditionally been disregarded. When obtained from clinical specimens, the bacteria have only been considered contaminants. However, this view is beginning to shift as other species have been identified as significant nosocomial infection sources, particularly in connection to infections associated with external devices and infections in patients with impaired immune systems (Forbes et al., 2018). Healthy humans and animals are colonized by the facultative anaerobic, gram-positive, catalase-positive bacterium *Staphylococcus aureus.* This bacterium is a significant opportunistic pathogen as well. Alexander Ogston identified S. aureus in pus from a leg abscess in the late 1800s. (Paniker, 2017). S. aureus is still common in the environment and in animals' natural flora. (Smith et al., 2009) It is both a pathogenic and commensal bacterium. It is consistently carried and is known to occur as normal flora in the skin of around 20% of the global population without causing any harm. Furthermore, 60% of people have it on occasion throughout their lives. If it has the chance to infiltrate tissue and the bloodstream, it is regarded as an opportunistic pathogen for both people and animals. Usually, it doesn't become contagious until it manages to penetrate the skin or mucous membrane through a puncture caused by a piercing item. It is discovered to result in several Illnesses ranging from minor skin conditions like boils, folliculitis, cellulitis, scalded skin syndrome, acne, furuncles, carbuncles, and abscesses to serious illnesses like pneumonia, osteomyelitis, meningitis, endocarditis, and septicemia. (Gurung et al., 2020).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a strain of *S. aureus* that has acquired resistance to β-lactam antibiotics, which include penicillins and cephalosporins (Krishnamurthy et al., 2014).MRSA strains are versatile and significant nosocomial pathogens, often causing postsurgical wound infections almost exclusively of hospital origin, as described in 1961 MRSA infections account for 20–80% of all nosocomial *S. aureus* infections in many centers across the world and lead to increased mortality, morbidity hospital stay and costs (Edlin et al., 2013). WHO has reported that 64% of MRSA-infected patients are more likely die than non-MRSA-infected patients.

It is now recognized that *Staphylococcus aureus* is a significant opportunistic pathogen. Because of its ability to form biofilms on materials like vascular catheters, prosthetic joints, and artificial heart valves, this bacterium has emerged as the primary source of infections associated with indwelling medical devices. These biofilms can lead to persistent or recurrent infections. Medical implant material infections are linked to significant morbidity and expense. Since bacteria in biofilms can be up to 1,000 times more resistant to antibiotic treatment than the identical organism developing planktonically, these illnesses are extremely difficult to cure (Bharti & Mathur, 2017).

Antibiotic Resistance in Staphylococcus aureus:

When penicillin and methicillin were first developed and used in the latter part of the 20th century, they were shown to be efficient against *S. aureus*. But S. aureus quickly developed resistance to these drugs, making infections with PRSA (penicillin-resistant *S. aureus*) and MRSA (methicillin-resistant *S. aureus*) harder to treat. Despite advancements, MRSA continues to pose a serious global risk to human health. For instance, isolates of S. aureus account for 29% of all bacterial

isolates reported in Europe, and in 2014, there were an estimated 72,444 cases of invasive MRSA infections in the US (ElSayed et al., 2018).

MRSA infections were first identified in the 1960s as a threat in adult patients, but became prevalent in children in the 1990s. Healthcare-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) were identified in the 1990s. Treatment methods include trimethoprim-sulfamethoxazole and clindamycin, but resistance to these has increased. Vancomycin, once considered the last resort, has been criticized for its resistance, especially for children. Ceftaroline, a cephalosporin, has shown good efficacy against MRSA, but has not been recognized as widespread(Romandini et al., 2021).

The staphylococcal chromosomal cassette carries the mecA or mecC gene, which confers methicillin resistance. The enzymes that crosslink the peptidoglycans in bacterial cell walls, penicillin-binding protein 2A (PBP2A) or PBP2ALGA, are encoded by this gene. Resistance to beta lactam antibiotics arises as a result of both enzymes' poor affinity for these medications (Hiramatsu et al., 1997). Vancomycin has been one of the first-line treatments for MRSA infections for a long time. However, clinical isolates of S. aureus that are fully and intermediately resistant to vancomycin have emerged throughout the past 20 years, posing serious health risks to the general public.

In the late 1980s, vancomycin was developed as a medicinal drug to treat serious infections brought on by MRSA ,However VRE(vancomycin-resistant enterococci) were identified in Europe almost at the same time(Uttley et al., 1988).

Table: Antibiotic Resistant History in *Staphylococcus aureus*

Year	Event
1928	Discovery of Penicillin
1940	Isolation of Penicillin
1944	Introduction of Penicillin
1946	Identify 1st Case of Penicillin resistant S.aureus
1958	Introduction of Vancomycin
1959	Introduction of Methicillin
1961	Identify 1st case of MRSA (Methicillin Resistance S.aureus)
1997	1st case of VISA (Vancomycin Intermediate Resistance S.aureus)
2002	Identify 1st case of VRSA (Vancomycin Resistance S.aureus)
2003	Introduction of Daptomycin
2005	Identify Daptomycin non susceptible S.aureus

When treating invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections or significant methicillin-susceptible *S. aureus* (MSSA) infections in individuals with beta-lactam allergy, daptomycin (DAP) is an substitute to vancomycin. The DAP non-susceptibility in *S. aureus* is an evolving problem, since multiple papers have noted the formation of resistance during DAP therapy (Sabat et al., 2018).

Mechanisms of Antibiotic Resistance in S. aureus

Kirby found that the action of a penicillinase, which is currently recognized as a form of b-lactamase, hydrolyzes the amide bond of the Beta-lactam ring of ampicillin and penicillin, which is the cause of *S. aureus* resistance to penicillin. While *S. aureus* strains differ in their penicillinase production, strains that produce more of the enzyme are more likely to be resistant to other antibiotics. Hospitals were the initial sites of isolation for penicillin-resistant *S. aureus,* which later spread to the

community and caused illnesses (Wyllie et al., 2011).

A pandemic was caused by the phage-type 80/81 strain, which was extremely virulent and spread. Methicillin is resistant to cleavage by *S. aureus* β-lactamase due to the presence of an ortho-dimethoxyphenyl group that sterically hinders the enzyme from hydrolyzing its target amide bond. Within a year after the introduction of methicillin, MRSA were isolated from hospitalized patients. The mecA gene, located on a mobile genetic element called staphylococcal cassette chromosome mec, encodes a transpeptidase known as PBP2a, an altered penicillin binding protein with low affinity for b-lactam antibiotics circumvents the ability of these antibiotics to inhibit cell wall synthesis. (Rungelrath & DeLeo, 2020)

MRSA (Methicillin-Resistant Staphylococcus Aureus):

Methicillin successfully suppressed the infection of penicillin-resistant *S. aureus* after it was introduced to the clinic in 1959 (Kanwar et al., 2017). But in 1961, just two years after methicillin was introduced, British scientist Jevons reported the isolation of an MRSA strain; this resistance was caused by a gene encoding the penicillin-binding protein 2a or 2′ (PBP2a or PBP2′) (mecA), which was incorporated into the methicillin-sensitive S. aureus chromosomal element (SCCmec). Furthermore, MRSA has quickly emerged as the most common resistant pathogen seen in a variety of regions across the globe, including North Africa, the Middle East, East Asia, Europe, and the United States (Lekshmi et al., 2018)

As per the MRSA's original source Hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) are the two categories into which it falls. The percentage of MRSA acquired in hospitals in China has risen to 50.4%. Furthermore, according to the US Centers for Disease Control (CDC), the fatality rate from MRSA infection exceeds that of AIDS and Parkinson's disease (Guo et al., 2020).

Historically, hospital-associated MRSA infections have primarily affected immunocompromised patients or those with predisposing risk factors, including prior infections, surgical incisions, indwelling medical devices, or surgery. The 1990s saw the first reports of true CA-MRSA infections, however, as well as reports of illnesses brought on by MRSA strains in otherwise healthy people that happened outside of a medical facility. In addition to being extremely virulent, CA-MRSA also spread quickly among a variety of healthy groups, exhibiting improved transmissibility and/or colonization capabilities. Infections with CA-MRSA have been documented in Asia, Australia, Canada, Europe, South America, and the United States, and they have quickly escalated to pandemic levels. (Rigby & DeLeo, 2011)

The total burden of MRSA has increased as a result of the pandemic expansion of CA-MRSA in the USA. Since CA-MRSA first appeared, there have been concurrent increases in staphylococcal burden seen all around the world. About 90% of CA-MRSA infections manifest as skin and soft tissue infections, with the majority being abscesses or cellulitis with purulent discharge. But the most common strains of CA-MRSA have also been shown to be capable of causing serious invasive illnesses including necrotizing fasciitis and necrotizing pneumonia, which were uncommon prior to CA-MRSA's ascent. Despite being comparatively rare, CA-MRSA-associated invasive infections were responsible for 14% of all invasive MRSA-associated deaths in the United States in 2005. (Laupland et al., 2008, Rigby & DeLeo, 2011)

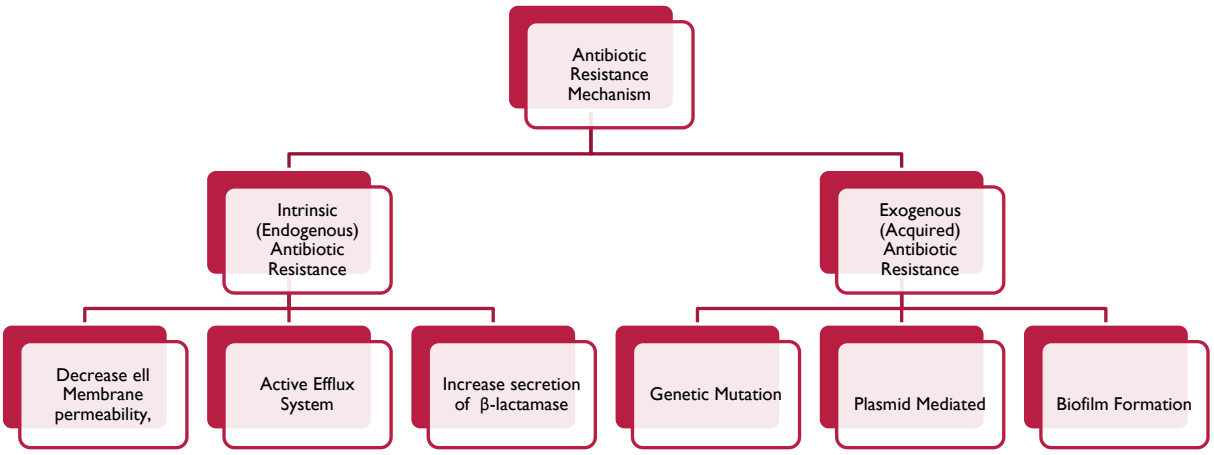

Fig: 1: Antibiotic Resistance Mechanism

A. **Endogenous Antibiotic Resistance Mechanism:**

The endogenous or intrinsic antibiotic resistance mechanism mostly include Membrane permeability, active efflux system and enhance production of β-Lactamase.

i. Drug resistance in bacteria is a result of lowered cell membrane permeability, which affects energy metabolism and reduces drug absorption (Anuj et al., 2018).

ii. The active efflux system, discovered in 1980, is a normal physiological structure of bacteria and exists in sensitive strains (Lee & Park, 2016). Genes encoding the efflux system are activated and expressed in response to environmental substrates, which improves the drug's ability to be effluxed. A factor in drug resistance to several medicines is active drug efflux mechanisms. Three different kinds of multidrug-pumping proteins are found in Staphylococcus aureus (MRSA), one of which is QacA, a proton kinesin that conducts material exchange via an electrochemical gradient (Hashizume et al., 2017).

iii. Two mechanisms—hydrolysis and pinching—are used by MRSA to reduce the effectiveness of antibiotics when they secrete excessive amounts of β-lactamase. Antibiotics β-lactams are hydrolyzed and rendered inactive by the hydrolysis mechanism, but MRSA resistance is caused by pinching, which stops antibiotics from reaching the target location. Bacterial chromosomal genes encode the transferable enzyme β-lactamase. MRSA resistance is caused by the overproduction of β-lactamase, which diminishes the effectiveness of antibiotics through two different processes (Harada et al., 2014).

B. **Exogenous (Acquired) Antibiotic Resistance:** Acquired antibiotic resistance can be develop by mutation, plasmid transfer, biofilm formation etc.

i. Drug accumulation can be inhibited in *Staphylococcus aureus* (S. aureus) via genetic mutation that modify the target DNA gyrase or decrease outer membrane proteins (Yang et al., 2019).

ii. One kind of plasmid-mediated resistance called acquired resistance arises when drug-resistant genes are inserted, transformed, and transduced through plasmids, producing abundant β-lactamase. Bacteria that are resistant to drugs, like MRSA, can acquire drug-resistant plasmids from Enterococcus, which increases and intensifies their resistance (Vestergaard et al., 2019) (Lazaris et al., 2017).

iii. Bacterial biofilms are an extracellular complex structure made up of a highly hydrated extracellular polymer matrix enclosing a microbial population adhered to the surface of a substrate. Because of their strong adherence and drug resistance, these biofilms enable bacteria to withstand host immunological reactions and avoid being killed by antibiotics. They are capable of becoming 1,000 times more resistant to antibacterial drugs (Kanwar et al., 2017).

iv. A tiny subset of phenotypically diverse but genetically similar bacteria are known as persisters; they develop slowly or dormantly and are resistant to high antibiotic doses. They grow slowly, are resistant to antibiotics, and can re-infect themselves after being treated with antibiotics. Though not mutants, persister cells are phenotypic variations (Fisher et al., 2017).The intricate process of bacterial persistence involves various interconnected signaling pathways, such as the toxins-antitoxin systems, the physiological reduction of energy metabolism in cells, the synthesis of proteins and nucleic acids, the protease systems, trans-translation, DNA protection and repair systems, and external pumping systems. (Michiels et al., 2016).

Vancomycin resistant *Staphylococcus aureus* (VRSA): In the late 1980s, vancomycin was developed as a medicinal drug to treat serious infections brought on by MRSA (*Staphylococcus Aureus Resistant to vancomycin--United States, 2002*, 2002). Vancomycin-resistant enterococci (VRE) were discovered in Europe almost simultaneously and swiftly spread throughout hospital intensive care units (Cong et al., 2019).

Vancomycin kills bacteria by preventing the vulnerable bacteria from synthesizing their cell walls properly. The cell wall structure that covers the majority of bacterial membranes prevents cells from swelling and rupturing as a result of intracellular excessive osmolarity. The peptidoglycan and other components of the cell wall must increase during propagation. The penicillin-binding proteins (PBPs) do this by trans glycosylating and transpeptiding the precursor lipid II into the developing peptidoglycan (Fig. 1a). Vancomycin's hydrophilic molecule can interact with the precursor lipid II's terminal D-alanyl-D-alanine (D-Ala–D-Ala) moieties to generate hydrogen bonds. Vancomycin binding results in a conformational change that stops the precursor from being incorporated into the expanding peptidoglycan chain and from transpeptiding, which causes cell wall breakdown and lysis of bacterial cell (Patel et al., 2023).

Mechanism involves in vancomycin resistance of VRSA:

The S. aureus isolates with reduced vancomycin susceptibility have been categorized into three classes by the Clinical and Laboratory Standards Institute. MICs of ~ 16 lg/ml for VRSA, 4–8 lg/ml for vancomycin-intermediate S. aureus (VISA),

and 2 lg/ml for vancomycin susceptible S. aureus (VSSA). VanA or other van resistance determinants should be detected by molecular methods in order to identify whether an isolate belongs to VRSA (Werner et al., 2008).The development of vancomycin resistance in bacteria is caused by van gene clusters, which are found in pathogens (such as E. faecalis, E. faecium, S. aureus, and Clostridium difficile), glycopeptide-producing actinomycetes (such as Amycolotopsis orientalis, Actinoplanes teichomyceticus, and Streptomyces toyocaensis), anaerobic bacteria of the human bowel flora (such as Ruminococcus species), and the biopesticide Paenibacillus popilliae (Kruse et al., 2014). Based on the DNA sequence of the ligase van gene homologues that encode the essential enzyme for the synthesis of D-alanyl-D-lactate (D-Ala-D-Lac) or D-alanyl-D-serine (D-Ala-D-Ser), vancomycin resistance is categorized into many gene clusters. Vancomycin-resistant VanA, VanB, VanD, VanF, VanI, VanM, VanC, VanE, VanG, VanL, and VanN phenotypes are attributed to at least 11 van gene clusters (Kruse et al., 2014).

Acquired vancomycin resistance is still rare in other pathogenic bacteria and is most frequently observed in Enterococci. The vancomycin-resistant mechanism has been demonstrated to be present in Enterococcus species, which are the main cause of acquired vancomycin resistance. Although 11 van gene clusters have been identified to give vancomycin resistance, only the vanA gene cluster is responsible for the isolated VRSA strains (Hollenbeck & Rice, 2012). The vanA gene cluster, together with VanS, VanR, VanH, VanA, and VanX, are necessary for vancomycin resistance. Native D-Ala-D-Ala precursors are converted into resistant D-Ala-D-Lac by these proteins. VanA ligates D-Lac to D-Ala to form the resistant D-Ala-D-Lac. On the other hand, modified D-Ala-D-Lac reduces the bactericidal activity of vancomycin on modified peptidoglycan precursors. These elements are intriguing targets for therapeutic development since they can restore vancomycin action when deleted. VanA and VanX are inhibited by phosphonate, hydroxyethylamines, phosphonate transition-state analogues, and substances such as sulfur-containing, covalent, and phosphate-based chemicals (Chen et al., 2018).

Daptomycin Resistant *Staphylococcus aureus*:

Gram-positive bacteria, including Staphylococcus aureus, have their cell membranes disrupted by the cyclic lipopeptide antibiotic daptomycin. It inserts into the lipid bilayer, attaches to bacterial membranes in a calcium-dependent way, and depolarizes the membrane, resulting in the loss of membrane potential, the suppression of vital biological functions, and the death of bacterial cells.

In clinical practice, daptomycin resistance in *Staphylococcus aureus* (*S. aureus*) is a major concern, especially when treating severe infections including osteomyelitis, endocarditis, and bloodstream infections. The activation of cell stress response pathways, modifications to the cell membrane and envelope, and decreased daptomycin entry into the membrane are important factors. Increased positive charges on the cell membrane caused by mutations in genes such as mprF, yycFG, and cls2 can lessen the electrostatic attraction of the daptomycin-calcium complex. Treatment tactics are complicated by treatment failure in cases of serious infections and cross-resistant strains. Rapid detection of resistance during therapy is essential to avoid ineffective treatments, and the emergence of daptomycin resistance highlights the need for new antimicrobial drugs or combination therapies to tackle resistant S. aureus strains (Bayer et al., 2012).

When treating invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections or severe methicillin-susceptible S. aureus (MSSA) infections in individuals with beta-lactam allergies, daptomycin (DAP) is a suitable alternative for vancomycin. S. aureus's DAP non-susceptibility is becoming a bigger issue, and numerous studies have detailed how resistance develops during DAP treatment (Jones et al., 2008). According to what is now known, S. aureus's DAP resistance is complicated and arises from mutations in several distinct genes. Up to now, the majority of clinical DAP-resistant S. aureus isolates (MICs >1 μg/ml) that have been studied include mprF mutations, usually in the form of single-nucleotide polymorphisms (SNPs). The positively charged phospholipid lysyl-phosphatidylglycerol is synthesized and translocated (flipped) within the cell membrane by a bifunctional membrane protein that is encoded by the mprF gene. Cell membrane phospholipid profiles are changed as a result of the amino acid changes in the MprF protein found in the strains exhibiting DAP resistance. It causes changes in the fluidity of the cell membrane and an increase in the positive charge of the membrane. The process by which D-alanine is added to teichoic acids in gram positive bacteria involves the dltABCD operon (Sabat et al., 2018).

Recent Development of Antibiotics for Multidrug-Resistant Staphylococcus aureus:

1. Multidrug-resistant S. aureus (MDRSA) strains of Staphylococcus aureus are difficult to treat because they have developed resistance to a number of drugs. resistant to methicillin . The most common type, Staphylococcus aureus (MRSA), is resistant to beta-lactam antibiotics like methicillin, amoxicillin, and penicillin. MRSA is a leading cause of infections in hospitals and the general population globally.
2. **Cresomycin:** Based on previous lincosamide compounds, cresomycin is a fully synthesized antibiotic that has demonstrated notable efficacy against MDRSA. It functions by attaching itself to the ribosomes of bacteria in a manner that circumvents typical resistance mechanisms. In mice models infected with resistant S. aureus, studies showed that it was effective, with full survival of infected animals compared to high mortality in untreated controls (*Designing a New Antibiotic to Combat Drug Resistance*, 2024).

3. **Antimicrobials based on Silver:** Studies have shown that silver compounds are useful against S. aureus. By interfering with several bacterial processes, these substances function as adjuvants for antibiotics, increasing the effectiveness of conventional antibiotics against resistant strains (Blechman & Wright, 2024).
4. Computer-aided antibiotic development: By examining the metabolic pathways and gene activity of S. aureus, researchers are employing computational models to map out its vulnerabilities. This could aid in identifying novel therapeutic targets and creating more specialized antibiotics (Barney, 2023).
5. **Derivatives of Eixobactin:** This naturally occurring antibiotic has demonstrated promise in treating resistant infections, such as methicillin-resistant S. aureus (MRSA). Teixobactin derivatives are being investigated to increase its stability and spectrum. (*Designing a New Antibiotic to Combat Drug Resistance*, 2024).

Role of Neutrophil in Bacterial Infection:

After developing and maturing in the bone marrow, neutrophils are discharged into the peripheral blood vessels. Neutrophils are the first innate immune cells that are quickly drawn from the circulation to infection sites once a pathogen has penetrated the epithelial barriers. Exogenous products like lipoproteins, peptidoglycan, or formyl peptides are released when pathogens enter and replicate in host tissues. Additionally, the invasive infection can harm bodily tissues that release inflammatory signals, such as cytokines and chemoattractant. (Naess et al., 2016)

Many of S. aureus's gene products, such as catalase, superoxide dismutase, and staphyloxanthin, specifically combat neutrophil reactive oxygen species. The significance of these interactions in the pathophysiology of S. aureus infections is illustrated by the fact that each of these gene products represents a distinct tactic for shielding the bacteria from oxidants produced by neutrophils.

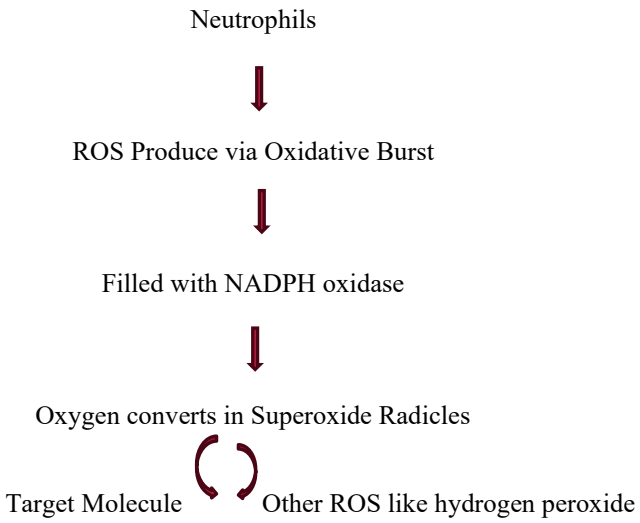

Fig: Role of ROS

Since the oxidative burst is primarily powered by oxygen consumption, neutrophils depend on fermentative glycolysis to produce energy during infections and actively consume glucose and glycogen to support their survival and effector activities. During an infection, airway metabolites significantly influence the airway's inflammatory tone. Macrophages emit succinate in response to Gram-negative substances such as lipopolysaccharide (LPS), which stabilizes HIF-1α and stimulates the production of interleukin-1β (IL-1β). Itaconate, a mitochondrial metabolite produced by immune response gene 1 (Irg1), inhibits this pro-inflammatory pathway. Itaconate inhibits glycolysis, limits succinate oxidation, stops inflammasome activation, and inhibits JAK signalling, among other mechanisms, to control macrophage-driven inflammation. (Tomlinson et al., 2023).

Conclusion and Future prospect: With the emergence of multidrug-resistant strains such as MRSA, antibiotic resistance in Staphylococcus aureus poses a serious threat to world health. Many traditional antibiotics are no longer effective due to S. aureus's capacity to evolve resistance mechanisms, such as enzyme synthesis and changes in drug targets. In both healthcare and community settings, this has resulted in a rise in infections that are challenging to cure. Ongoing study is essential for the future. There is hope because of the creation of novel drugs like cresomycin and silver-based antimicrobials. These initiatives concentrate on developing medications that can target bacterial ribosomes or interfere with several bacterial

processes in order to overcome resistance mechanisms. However, sustainable methods like enhancing infection control protocols, cutting back on needless antibiotic use, and investing in quick diagnostics to reduce overprescription are just as important for long-term success as drug research. To remain ahead of changing resistance, future breakthroughs should combine these strategies with ongoing study.

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