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Emergence of UTI Causing *Staphylococcus aureus* as a Superbug: has the Pathogen Reduced the Options of Antimicrobial Agents for Treatment?

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Abstract

S. aureus is a Gram positive cocci shaped bacterium and is associated with a variety of human related infections ranging from skin, nasal infections to food poisoning, bacteremia and urinary tract infection (UTI). The bacterium is naturally associated with the nasal membrane which accounts to 30% in humans and is capable of resisting β-lactam antibiotics like penicillin and ampicillin. In fact, recent years has witnessed the emergence of highly virulent strain of *S. aureus* for antibiotics like methicillin resulting in the development of MRSA strains which has increased the use of vancomycin to counteract the infection. However, studies claim the existence of *S. aureus* strains capable of resisting the potency of vancomycin has reduced the available options of managing the pathogen. The current review attempts to provide the insights of the resistance capabilities of *S. aureus* against the commonly employed antibiotics and the factors contributing towards the resilience of the pathogen. The review briefly highlights the role of *S. aureus* in conferring urinary tract infection and the emergence of resistance among the UTI causing *S. aureus.* However, the prime aim of the review is to provide the insights of the antibiotic resistance exhibited by UTI causing *S. aureus* and the significance of various genetic elements in making the pathogen tough. In addition to genetic variants, the review also briefly attempts to illustrate the importance of biofilms and quorum sensing mechanism in making the pathogen resilient. The review focuses on MRSA, VRSA and related genetic elements contributing towards the pathogen's resistance.

Keywords: *S. aureus; UTI; MRSA; VRSA; antibiotic resistance; empirical treatment; Biofilms and antibiotic resistance; Biofilms and quorum sensing*

Abbreviations: UTI: Urinary tract infection; MDR: Multidrug resistance; MRSA: Methicillin resistant *S. aureus*; MSSA: Methicillin sensitive *S. aureus*; VISA: Vancomycin intermediate *S. aureus*; VSSA: Vancomycin sensitive *S. aureus*; VRSA: Vancomycin resistant *S. aureus*; CA-MRSA: Community associated MRSA; HA-MRSA: Hospital acquired MRSA; PVL: Panton-Valentine leukocidin; PVL-SA: Panton-Valentine leukocidin *S. aureus*; MIC: Minimum inhibitory concentration; MATE: Multidrug and toxin extrusion family; MFS: Major facilitator super family; pETB: exfoliative toxin B; SCC*mec*: Staphylococcal cassette chromosome *mec*

Introduction

The preface of microbiology and microorganisms dates back to the 16th century when the first microorganisms were observed by AntonVan Leeuwenhoek who is regarded as the first microbiologist. His attempts have indeed introduced the creatures referred as "Animalcules" which are known as microbes to the present world. Since then many scientific explorers and investigators have endeavored to understand the role of microorganisms and their significance towards the mankind. Despite the fact, of their beneficial aspects which has revolutionized the industrial sector, their darker side towards the mankind cannot be denied. The current review focuses on one such microorganism which is regarded as a pathogen and is responsible for conferring human related infections leading to death under severe

circumstances. Nevertheless, the term pathogenicity is more often associated with Gram negative pathogens, the current review attempts to disclose the role of *Staphylococcus aureus* in conferring human related infections as a consequence of increased resistance to antimicrobial agents. *Staphylococcus* is genus comprising of Gram positive bacteria and the pathogen's name was derived from a Greek word which signifies a bunch of grapes due to its appearance (cocci shaped). *S. aureus* is generally associated with the respiratory tract and skin in humans and is an affiliate of the phylum firmicutes which are known to generate spores capable of surviving extreme environmental conditions. The pathogen is commonly found in the skin and nasal passages of humans and about 20% of human population serve as long term carriers which in turn enhance proximity of the pathogen with humans and are responsible for staph infections which range from food poisoning, conjunctivitis to sepsis. Though, the pathogen is known for its pathogenicity and is responsible for a wide range of human related infections, the current review attempts to illustrate the role of *Staphylococcus aureus* in conferring urinary tract infection (UTI) among humans and the extent of antimicrobial resistance exhibited by the pathogen which is a consequence of empirical treatment.

S. aureus belongs to the genus *Staphylococcus* and demonstrative studies have been carried out since decades in order to reveal the insights of the pathogen. It is a widely accepted fact that around 80% of UTI is a consequence of *Escherichia coli* [1] but the recent studies on *S. aureus* confirms their contribution toward the infection among humans [2]. There has been an increase in community associated and hospital acquired infections over the past two decades and enhanced antibiotic resistance exhibited by the pathogen is regarded as one of the prime reasons [3]. As a consequence of scientific explorations and demonstrative studies, 47 species and 24 sub species of Staphylococci has been illustrated and the capability of *S. aureus* to produce coagulate differentiates it from the other species of the same genus. S. aureus capable of exhibiting multidrug resistance has been problematic in terms of treatment and has challenged the medical field [4,5]. Demonstrative studies have confirmed the presence of the organism in the nostrils which serves as the major reservoir of *S. aureus* in humans but the association of the pathogen in the other human body parts cannot be denied [6].

Human skin and perineum are considered as major ecological niche for the pathogen [7,8] and research studies have even disclosed the presence of *S. aureus* in vagina (in females) and gastrointestinal tract [9]. Several studies have also confirmed the prominent presence of the organism in the throat of humans which is contrary to the research studies claiming the human nostrils to be the major ecological niche [10-13]. The research studies and experimental analysis carried out in the past as well as the ongoing research have disclosed the significance of *S. aureus* in affecting animals apart from humans which includes livestock and domestic animals like cats and dogs [14]. Another major issue that has gained the interest of the researchers is the extent of resistance exhibited by the pathogen to commonly employed drugs and has in turn become an issue of concern. Demonstrative studies carried out by scientific investigators has revealed the presence of methicillin resistant *S. aureus* (MRSA) among the ST398 strains of the pathogen isolated from pigs and are known to colonize the human tissues [15]. However, pathogens of human lineage are not usually found in animals as the existence and persistence of the pathogens relies on the host specificity which in turn depends on the genotype and gene combinations [16].

The above schematic representation depicts the various factors responsible for the colonization and infection which ranges from genetic to environmental factors and the most vital aspect is the host proximity which enables the pathogen to survive and multiply which as a consequence causes the infection. The virulence of the pathogen in combination with the pathogen's enhanced capacity to tolerate the commonly employed antibiotics makes it a difficult contender to tackle. However, there are several factors ranging from the pathogen's genetics to its environment which makes them tough to deal with.

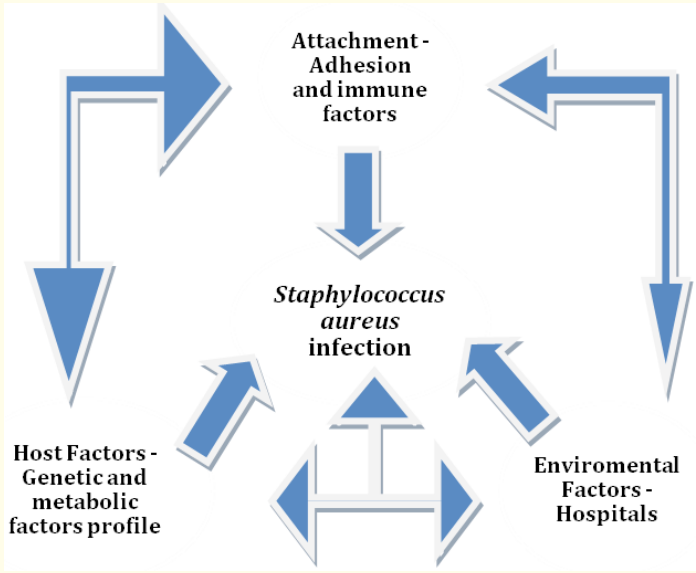

Figure 1: *Staphylococcus aureus colonization and infection [17].*

What is Urinary Tract Infection (UTI)?

Before we proceed in to the insights of the pathogen and the factors responsible for their antimicrobial tolerance, there is a need to address one of the infections caused by *S. aureus* which is gained a lot of medical attention over the last few decades. Despite the fact, that *S. aureus* is known to cause a variety of human related infection, urinary tract infection (UTI) has its own significance in terms of prevalence among men and women. The higher incidence of the infection among the females has indeed drawn the attention of several researchers and scientists in order to explore the hidden facts. Urinary tract infection usually abbreviated as UTI is a common infection among men and women and affects the lower and the upper urinary tract. The occurrence of the infection is higher in women due to their shorter urethra and pregnancy enhances the prevalence of the infection [18]. The infection affects the lower and upper parts of the urinary tract which includes bladder, kidney and other related parts of the urinary tract. The lower tract infection is referred as cystitis otherwise known as bladder infection and the infection of the upper tract is known as phylonephritis which affects the kidneys. The UTI among men and women is further broadly classified in symptomatic and asymptomatic based on the presence or absence of the symptoms [19]. Though the patient does not show any kind of clinical symptoms during asymptomatic condition, the symptoms related to symptomatic UTI considerably varies depending on the clinical condition (cystitis or phylonephritis) which varies from painful to recurrent urination during cystitis and flank pain and high fever during phylonephritis [20]. Medical analysis and demonstrative studies claims the role of bacteria in the occurrence of the infection. Despite the fact that virus and fungi have their part in contributing the contagion, it is considered to be a rare phenomenon [21,22]. Though the initial stages of the infection can cause no harm, lack of proper treatment can lead to dire outcomes leading to death under severe condition. UTI is regarded as the most common form of bacterial infection which involves the role of Gram positive and negative bacteria [23,24]. Many scientific investigators have indeed made attempts to explore the insights and research studies confirm the consequences of poor diagnosis can lead to UTI and as a result UTI is also considered as common hospital acquired infection and patients admitted for long term treatment are prone to UTI but this relies on the eternal environmental conditions as lack of hygiene is one of the prime reasons for the invasion of the pathogen [25,26]. The bladder infection as a consequence of cystitis under untreated conditions can lead to kidney and blood borne infections. However, the infection includes a diverse group medical pattern that relies on epidemiology, etiology, location severity of the condition [27]. Nevertheless, the

extent of infection also vary in expressed local symptoms, frequency of recurrence, extent of damage caused, presence of complicating factors and the risk from their reiterate occurrence. Infection of the upper urinary tract can be a consequence of untreated lower tract infection which affects the kidneys and enhances the occurrence of blood borne infection. Hence, UTI is capable of claiming lives under severe clinical conditions and is considered as the second most common form of bacterial infection after blood borne infections [28]. Studies have disclosed the higher occurrence of the infection among women of varying age groups and pregnancy enhances the onset of the infection and reaches the peak during the second trimester of pregnancy.

Prevalence UTI among women during pregnancy

UTI in common in women due to their reproductive anatomy and pregnancy enhances the scope of infection when compared to non pregnant women. Analysis of urine sample is an appropriate method to trace out the infection and the associated perpetrators. Several demonstrative studies have claimed the role of *S. aureus* in conferring UTI among women and pregnancy is considered as a crucial period which enhances the scope of the infection. UTI during pregnancy can lead to consequences like Perinatal and maternal morbidity and mortality in turn complicating pregnancy. The nature of infection can either be symptomatic leading to cystitis or phylonephritis or the infection could be asymptomatic where the patient does not show any clinical symptoms. The significance of UTI and its association with perinatal complexities has been illustrated by several studies [29,30]. The occurrence of UTI among women during pregnancy ranges from 2-10% globally [31,32]. Parity is regarded as one of the prime factors associated with the prevalence of UTI and studies reveal the higher prevalence of infection among women with higher parity [30]. Though there are several factors related to the infection, but few studies have cited the significance of economic status of the individual and demonstrated the wide spread of the infection among the indigent patients [33]. In addition to socioeconomic condition, other factors like increased age, parity, previous history of UTI, diabetes, bladder retention, urinary tract abnormalities and frequency of sexual activity are related to the prevalence of the infection. Clinical conditions like urethral dilatation, urinary stasis, reduced immune function and presence of urinary reflux as the consequences of UTI among pregnant women [34,35]. Despite the fact that several studies claim the occurrence of UTI among pregnant women during the first antenatal visit, the prevalence is less than 1% in women after a negative screening in the earlier stages of pregnancy [34]. Phylonephritis as a consequence of maternal complication accounts to 25-40% among women with asymptomatic bacteriuria as pregnancy progresses. However, such complications in women without asymptomatic bacteriuria constitute to 1-2% [36]. The prevalence of symptomatic and asymptomatic bacteriuria significantly varies in women during pregnancy as research studies claims the prevalence of symptomatic and asymptomatic bacteriuria around 1-2% and 2-13% in women respectively [37]. Hormonal activities and anatomical changes during pregnancy leads to conditions like urethral dilatation and urinary stasis which enhances the risk of UTI in women [38]. These conditions as a result of UTI in pregnant women allow the spread of bacteria from the bladder to kidneys enhancing the risk of kidney disorders [39]. Demonstrative studies have revealed the significance of appropriate treatment to counteract the consequences of asymptomatic and symptomatic UTI as untreated UTI can result in post birth complications like premature delivery, low birth weight and still birth [40]. Despite the fact that UTI is not a life claiming contagion, untreated or inadequate medical treatment could lead to clinical conditions like acute cystitis and phylonephritis. The later condition under severe circumstances leads to renal failure resulting in death. Women diagnosed with acute cystitis as a consequence of UTI experience clinical symptoms like dysuria (painful urination) [41].

***S. aureus* as a perpetrator of UTI**

It is a widely accepted fact that UTI as a consequence of *E. coli* colonization accounts to 80% but the involvement of Gram positive bacteria in relation to the infection cannot be ruled out and one such pathogen of scientific significance is *S. aureus*. Nevertheless, *S. aureus* accounts to 0.5-6% of the infection [42] it cannot be underestimated as untreated infection can lead to severe health threatening conditions [43,44]. Though research studies have regarded the isolation of *S. aureus* as secondary from urine samples, cases of *S. aureus* colonization and infection have been demonstrated by scientific investigators. Medical instruments such as indwelling catheters enhance the scope of *S. aureus* infections in the urinary tract [45,46]. Several studies have revealed the prevalence of *S. aureus* infection at an ascending rate among patients after urological procedures involving urinary catheters and researcher have revealed the significance

of bacteremia resulting in bacteriuria among the patients [47]. However, researchers illustrate the prevalence of pathogen among the elderly patients as a consequence of catheters and this rule out the condition of bacteriuria due to UTI. Nevertheless prolonged use of indwelling catheters can result in UTI, but a clear differentiation between the asymptomatic bacteriuria and UTI among elderly patients is yet to be understood [48,49]. However, the scope of *S. aureus* bacteremia among the patients positive for *S. aureus* bacteriuria is not clear [50]. In addition to S. aureus, Gram positive bacteria like *S. saprophyticus* and Enterococcus faecalis contributes to 5-15% of UTI. The occurrence of UTI due to fungal infection had been demonstrated through scientific studies and is usually considered to be a rare phenomenon. Patients with history of diabetes and immune compromised patients are prone to such infections [51]. Researchers have validated the presence of *S. aureus* from primary UTI or due to bacteremia resulting in kidney infections [52]. The scope of secondary bacteremia among the patients with Staphylococci UTI accounts to 5.5-8.3% under untreated conditions. The primary UTI due to *S. aureus* infection can be counteracted by oral medication but secondary bacteremia due to S. aureus is harmful and involves the use of intravenous antibiotics with multiple investigations to avoid complications like endocarditis and septic shock [53]. However the use of antibiotics relies on the patient's medical history like the frequency of recurrence of the infection, antibiotic therapy and the occurrence of resistant pathogens to the employed antibiotics [54]. Several studies have attempted to understand the kinetics of S. aureus infection and its role in conferring UTI and the ability of the pathogen to survive hostile environmental conditions has concerned the scientific community and the development of resistance of the pathogens towards the antimicrobial agents is a global issue. Many researchers have attempted to explore the antimicrobial pattern of *S. aureus* among women during pregnancy [55]. Demonstrative studies have confirmed the role of the pathogen in conferring UTI through colonizing the intestines and vagina. Scientific investigations have also associated the role of S. aureus in causing uncomplicated skin infections in addition to asymptomatic UTI. The prevalence of UTI up to 6.9% and 7.7% in pregnant and non pregnant women has been reported by demonstrative studies as a consequence of Staphylococcal infection. This confirms the presence of multidrug resistant *S. aureus.*

Over 30 species of *Staphylococcus* have been recognized of which the pathogenicity of *S. aureus* have been established since a long time and is regarded as the most virulent strain of the genus [56,57]. The role of *S. aureus* in conferring the infection was demonstrated by several researchers and the ability of the pathogen in causing the nosocomial and community associated infection was validated [58,59].

Kinetics of UTI

UTI occurs in the lower and upper urinary tract which together forms the urinary system and is common in both males and females. However, the reproductive anatomy of the females makes them more vulnerable towards the infection due to shorter urethra which in turn enables the invasion of the pathogens in to bladder and kidneys [60]. It is a widely accepted fact that kidneys which are vital organs of the upper urinary tract plays an important role in the disposal of water soluble waste and allows the re absorption of essential nutrients and amino acids. The collected waste from the kidneys is passed on to the bladder through ureter which is a tubular structure. The accumulated waste from the bladder is flushed out from the genitals through urethra. This is a systemic process and UTI hinders the smooth functioning of this system which in turn results in health threatening clinical conditions [61]. UTI can be classified as complicated/uncomplicated and primary and recurrent based on the factors responsible for it and nature of occurrence of infection respectively. Though UTI is not life threatening in the initial stages, untreated condition can lead to renal failure resulting in severe clinical consequences. Women are 10 times more prone to the infection compared to males and the available reports on UTI claims the incidence of the infection in 50% of women with a scope of recurrence that accounts to 30%-40% within 6 months of earlier incidence [62]. Several studies have revealed the association of recurrent UTI with morbidity during pregnancy and they are regarded as symptomatic UTI which occurs after an earlier incidence usually after appropriate drug treatment. The recurrent UTI may be due the infection of the same pathogen that the patient has previously encountered or a second bacterial isolate may serve as the perpetrator. However, most recurrent UTI are due to the invasion of the same pathogen involved in the previous incidence of the infection. Younger women with normal anatomical and physiological urinary tract are prone to recurrent UTI [63,64]. The prevalence of recurrent UTI

significantly varies among women of different age groups. Scientific reports postulate the prevalence of the infection in older women and younger women to be 55% and 36% respectively within a year after the initial occurrence of the infection [65]. UTI is further classified as symptomatic and asymptomatic which relies on the symptoms exhibited by the patients. Despite the fact that, asymptomatic UTI is harmless, untreated condition could result in symptomatic leading to bladder and renal disorders [66]. According to researchers, asymptomatic bacteriuria accounts to about 70% of cases of symptomatic UTI among unscreened women during pregnancy. A microbial population of > 10^5 bacteria/ml in a single sample of mid stream urine or presence of same amount of bacteria in two consecutive clean catch urine samples in the absence of clinical symptoms confirms the presence asymptomatic UTI which ranges from 2-10% during pregnancy [67].

Antimicrobial resistance among UTI causing *S. aureus*

It is a widely accepted fact that *S. aureus* is responsible for a variety of human related infections ranging from nasal to skin and internal tract infections which under severe clinical conditions can claim lives. Though there are several other pathogens, *S. aureus* has gained a special interest and research studies have confirmed an increase in the prevalence of UTI as a consequence of *S. aureus* infection [68,69]. Scientific studies have revealed a higher prevalence of the infection among men and women which accounts to over 150 million cases annually [70,71]. Researchers regard *S. aureus* as an opportunistic pathogen that is capable of influencing the immune competent and immune compromised individuals as the pathogen is known to compromise an individual's immune system. This is one of the reasons that patients after surgery are prone to *S. aureus* infection [72]. In addition to surgical patients, new born babies and patients with diabetic history are highly prone to *S. aureus* infection [73,74]. Apart from the virulence of the pathogen, its ability to tolerate the affectivity of antimicrobial agents has gained the attention of the researchers and scientific investigators. This is indeed an issue of serious medical concern as it becomes difficult in terms of managing the pathogen and demands the requirement of novel practices to counteract the infection. Studies have confirmed the ability of *S. aureus* to develop tolerance to the employed drugs globally and this in turn has challenged the medical sector [75,76]. Existence of multidrug resistance *S. aureus* (MRSA) strains has reduced the available options of managing the pathogen which in turn requires innovative means of counteracting the pathogen and the infection.

There are several factors that make the pathogen resilient to these drugs which ranges from the type of environment in which the pathogen is embedded to molecular and genetic factors. It is a widely accepted fact that *S. aureus* is known to produce external polymeric matrix referred as biofilms which offers the protection against several antimicrobial agents by preventing their penetration in to the microenvironment of the pathogen. However, the role of genetic factors cannot be denied and the pathogen to known to possess extracellular genetic material referred as plasmids which favors the horizontal transfer of genes responsible for this tolerance of the pathogen against the commonly used drugs [77]. Despite the fact that, *S. aureus* is susceptible to a variety of antimicrobial agents the evolution among the pathogen as a consequence molecular and genetic factors has made the pathogen resilient and the phenomenon of horizontal gene transfer can be regarded as a prime reason for this modified state of the pathogen. Nevertheless, the chromosomal mutations as well as the choice of antibiotic are vital [78]. For instance, penicillin which was regarded as the wonder drug during the 1950s has no affect on *S. aureus* and the current scientific studies performed on the clinical isolates of *S. aureas* reveals the higher level of resistance exhibited by these isolates. Existence of *S. aureus* strains resistant to other powerful drugs like methicillin has reached epidemic proportions worldwide which is an issue of serious concern and this problem is encountered at healthcare centers and recent research findings have revealed the spread of community based infections [79,80].

Methicillin resistant *S. aureus* (MRSA)

S. aureus is regarded as one of those pathogens which are highly adaptive to the external environment and are capable of developing high levels of tolerance against the antimicrobial agents. It is a well accepted fact that about 90-95% of *S. aureus* strains are resistant to penicillin and the first methicillin resistant strain emerged in the 1960s and there are there are over 60% of *S. aureus* strains

that are tolerant to methicillin [81-83]. Scientific studies discloses the increase in the prevalence of skin and soft tissue infection due to community associated MRSA (CA-MRSA) in the United States and there is a remarkable increase in the outbreak of the infections caused by CA-MRSA [84,85]. These strains were also found in countries other than the United States which includes Canada and other European countries and are highly virulent and are capable of causing tissue destructive infections which includes necrotizing fasciitis and fulminant, necrotizing pneumonia and demonstrative studies confirm the association of these infections with the CA-MRSA strains [86,87]. Several demonstrative studies have validated the existence of MRSA as a consequence of constant exposure to health care centers and long term hospitalized condition among patients is prone to such infections. However, the MRSA accounts to around 1-3% of the total population [88,89]. Methicillin resistant strains of *S. aureus* is clinically significant and has gained the attentions of global scientific researchers due to the fact that a single genetic element offers resistance against the beta lactam antibiotics like penicillin, cephalosporins, carbapenems [90]. The MRSA strains have been known to the mankind over the last 3 decades as the hospital acquired MRSA (HA-MRSA) and are the prime perpetrators in causing the hospital acquired infections where as the CA-MRSA has gained the clinical significance in the late 1990s [91]. Scientific investigations confirm the distinctive nature of CA-MRSA and HA-MRSA at the genetic and phenotypic levels. The CA-MRSA strains capable of producing Panton-Valentine leukocidin (PVL), is highly virulent and is frequently associated with hospitalized infections [88]. Demonstrative studies have substantiated the role of Panton-Valentine leukocidin positive *S. aureus* (PVL-SA) in causing repetitive skin and soft tissue infections. However, prevalence of invasive infections such as necrotizing haemorrhagic pneumonia as a consequence of PVL-SA cannot be denied [92,93]. The discovery of the toxin was made by Panton and Valentine in 1932.

S. aureus with PVL genes produces the PVL toxin which makes them highly virulent and 14 such strains have been discovered. This gene is found in *S. aureus* strains which accounts to < 2% isolates and is found in MRSA and MSSA strains (Methicillin sensitive *S. aureus*) [94,95]. PVL-SA strains are generally associated with community acquired infections among the healthy individuals including children and adults. Most of the research studies in the UK reports the association of these infections with PVL-MSSA. Nevertheless, studies also confirm that the community acquired MRSA is most liable to produce PVL in contrast to hospital acquired MRSA. On the contrary, studies have confirmed the presence of virulence factors in addition to the PVL, which are essential for the up regulation of the toxin synthesis *in vivo* [96,97]. A scientific survey in the UK has revealed the presence of 20% of PVL positive *S. aureus* isolates from the skin and soft issues of the infected individuals and the recorded prevalence was 2% higher when compared to the data reports collected earlier [98].

Vancomycin resistant *S. aureus* (VRSA)

Vancomycin is a glycopeptides antimicrobial agent which was initially used against penicillin resistant *S. aureus* but eventually became the first line drug for treating MRSA infections [99,100]. Vancomycin abbreviated as "van" is considered as the drug of last resort and is in use over the last three decades and drug is commonly used against the MRSA strains. Though the existence of vancomycin resistant *S. aureus* (VRSA) is rare there are certain strains of the pathogen that have ability to tolerate the efficacy of the drug. With the outbreak of MRSA strains, vancomycin has been used as the only option to counteract the activity of these MRSA strains but certain studies have reported a reduced efficacy of vancomycin against the MRSA strains [101]. Though vancomycin is considered as the most effective drug against the MRSA strains for almost three decades, it's efficacy under the *in vitro* conditions has been a concept of constant debate. Researchers claim the empirical use of vancomycin to be a vital reason for the emergence of less susceptible strains or in other words the experimental use of the drug has in turn resulted in the existence of more resistant strains. The studies also report an increase in the minimum inhibitory concentration (MICs) of the drug against the MRSA strains [102]. Clinical studies have revealed the presence of MRSA and VRSA strains among the hospitalized patients. These virulent strains are commonly associated with enhanced rates of morbidity and mortality among the infected patients. Clinical studies also claim the existence of vancomycin intermediate *S. aureus* strains (VISA) which is a consequence of constant use of the drug and the prolonged usage of the drug can transform the VISA to VRSA (vancomycin resistant S. aureus) [103]. It is a widely accepted fact that *S. aureus* is associated with a variety of human related infections including nosocomial infections, skin, nasal infections and the urinary tract infection. These infections as a consequence of

S. aureus invasion require proper on time treatment which is possible through the exact diagnosis of the condition. But experimental usage of antimicrobial agents has given rise to these resistant strains which are problematic in terms of treatment. Due to the rapid rise of MRSA isolates, vancomycin is used as the first line drug for treating the patients. This constant administration of the drug among the hospitalized patients has reduced the potency of the drugs against the MRSA. The first strain of vancomycin with reduced susceptibility rate to vancomycin was first reported in Asia [104-106]. Ever since, there has been a rise in the cases of VRSA and VISA which has in turn got the attention of the medical community due to the ability of the pathogen to cause life claiming condition among hospitalized and non hospitalized individuals [107]. However, certain findings illustrate the susceptibility of most strains of *S. aureus* and the MICs (minimum inhibitory concentration of the drug) are taken as a scale to reveal the extent resilience exhibited by the pathogen towards the drug. S. aureus isolates exhibiting an MIC of 8-16 μg/ml for vancomycin are considered to be VISA strains in contrast to isolates with a MIC of 0.5-2 μg/ml which are considered to be VSSA (vancomycin sensitive *S. aureus*). The isolates of S. aureus which exhibits a MIC ≥ 32 μg/ml are considered to resistant strains (VRSA). The other class of glycopeptides antibiotics includes teicoplanin but the strains resistant to vancomycin cannot exhibit the same level tolerance to teicoplanin. However further studies are required to provide the insights on the extent of resistance or susceptibility exhibited by the pathogens towards the antimicrobial agents.

Genetics of *S. aureus*: Vital factor for conferring multidrug resistance (MDR)

Multidrug tolerance among the strains of *S. aureus* can be due to the over expression of certain genes capable of producing the relevant proteins that confer the pathogen to resist more than a single antimicrobial agent. Investigations in the past as well as ongoing research have validated this nature of the pathogen with appropriate scientific data and reports. Research studies have illustrated the significance of efflux mechanism exhibited by the pathogen which is considered to be a vital process in the removal of substances like toxins, neurotransmitters and antimicrobial agents. Studies have also confirmed the importance of this mechanism and its role in making the pathogen tolerance against many drugs [108]. The proteins belonging to the multidrug and toxin extrusion family (MATE) are regarded as efflux proteins which are responsible for the multidrug resistant behavior of the pathogen. Extensive studies were carried in order to explore the insights of these protein and role in making the pathogen resilient against many drugs. The multidrug efflux is a significant means of antimicrobial resistance among bacteria [109,110]. The mechanism is mediated by distinct families of membrane based proteins and researchers have confirmed the significance of major facilitator super family (MFS) which comprises of such efflux proteins. Demonstrative studies have disclosed the role of multidrug resistance (MDR) pump also referred as MDR efflux proteins in conferring tolerance to antimicrobial agent among the strains of *S. aureus* [111,112]. Significance of plasmids in relation to the ability of the pathogen to tolerate drugs has been validated by several researchers and presence of genes responsible for multidrug resistance on plasmids has been reported. The plasmid encoding the exfoliative toxin B (pETB) has been known to possess the genes for multidrug resistance [113]. The exfoliative toxin is an exotoxin produced by Staphylococcal species and they are responsible for blisters on human and animal skin. These toxins are referred as accessory proteins, but they do not contribute towards the growth and cell division but investigative studies reveal their association with genetic elements like phages, plasmids and pathogenicity islands [114,115]. ET related to human infections are further divided in a, b and d subclasses and these are respectively located on the *eta* gene of the temperate phage, *etb* gene on a large plasmid and *etd* gene is confined to pathogenicity islands [116-118].

In addition to these exotoxins and related genes coding for special proteins responsible for making the pathogen resilient towards drugs, there are certain genes that makes the pathogen to overcome the efficacy of first line antimicrobial agents like methiccillin and vancomycin. *S. aureus* strains resistant to isoxazoyl penicillins such as methicillin, oxacillin and flucloxacillin are regarded as MRSA strains and demonstrative studies have reported that the MRSA strains are cross resistant to β-lactam antibiotics that are currently in use. The expression of penicillin binding protein PBP2a encoded by *mec* A gene in *S. aureus* enables the pathogen to resist the potency of methicillin and offers resistance against all the β-lactam antibiotics [119]. Several genetic elements are essential for the regulation of the factors responsible for the expression of methicillin resistance. Regulatory elements like *mec I* and *Bla I* gene play a vital role in the expression of methicillin resistance in *S. aureus*. These genes (*mec I* and *Bla I*) are in turn controlled by *mec* RI and bla RI transducers.

In addition, the expression of methicillin resistance in *S. aureus* also relies on the stimulation of the other genetic elements like the *fem* (factors essential for methicillin resistance) and *aux* (auxiliary) genes. Many of these genetic factors are on the verge of identification and their contribution towards the formation of the cell wall in *Staphylococcus* is under study. Though the origin of the *mec* A is unknown, genomic analysis of *S. aureus* has revealed it location with the larger chromosome called as the staphylococcal cassette chromosome *mec* (*SCCmec*) region which stretches from 21-67 kbps (kilo base pair) [120]. *SCCmec* is a mobile genetic element and its sequences comprises of *mec A* gene along with *mec RI, mec I, pbp2 and ccr A*. Since the region is mobile, it gets accumulated on a plasmid or a transposon which in turn result in the expression of factors responsible for the development of multidrug resistance. Five types of *SSCmec* have been discovered of which type I, II and III are found in healthcare associated MRSA (HA-MRSA) where as type IV SSCmec is commonly associated with community associated MRSA (CA-MRSA) [121]. Of all these types, the type IV SSCmec is small and can be transferred through the process transduction where as the other types (I, II, III) cannot be transferred through this means (strain to strain like in case of type IV SSCmec) but they spread from one individual to another as they are mostly associated with hospital acquired infections otherwise known as nosocomial infections [122]. The genetics of *S. aureus* and the associated factors have not only resulted in MRSA strains but the emergence of VRSA strains of the pathogen has alarmed the scientific community. Though the existence of vancomycin resistant bacteria was reported in the late 1980s in the isolates of *Enterococcus faecium* the prevalence of VRSA strains were first reported in 1997 in Japan. Expression of several gene clusters has imparted this property to the pathogen [123]. Since then the emergence of virulent strains of *S. aureus* like the MRSA and VRSA have emerged and this has in turn challenged the scientific community due to the issues of serious health concerns. Molecular analysis has revealed the presence of nuc gene responsible for coding thermo stable nuclease highly specific to *S. aureus*. Studies have reported higher resistance of VRSA against the β lactam drugs. However drugs like gentamicin which is an aminoglycoside and ciprofloxacin which is fluoroquinolone were effective against S. aureus. The VRSA strains comprised of large plasmid which stretches over 53 kbps and the PCR (polymerase chain reaction) amplification of the region confirmed the presence of *vanHAX* gene cluster which consists of *vanH, vanA* and *vanX* which are 969 bp, 1032 bp and 609 bp respectively. In addition to these gene clusters, the VRSA isolates were positive to mecA gene which confers resistance against methicillin [124]. Despite the fact that, the research studies claim the existence of VRSA isolates to be a rare phenomenon, the rise in their prevalence over the last few years cannot be denied. This in turn demands the requirement of appropriate screenings and medical evaluations among the infected patients. Recurrent usage of vancomycin against the MRSA strains have in turn enhanced the pathogen's ability to tolerate the glycopeptides and this condition was observed among the patients who were subjected to constant vancomycin administration to counter act the MRSA infection. Research investigations have reported the higher prevalence of VRSA infection among the patients who were previously treated with vancomycin [125,126].

Evolution of *S. aureus* as a Superbug (Horizontal Gene Transfer)

The mechanism of antibiotic resistance among bacteria is not a new term as it has been known to the mankind since decades but as the time progressed, it has resulted in the discovery of pathogens capable of resisting more than one drug and such pathogens are known to exhibit multidrug resistance. However, there are instances where a single organism has the potency of tolerating many antimicrobial agents which are scientifically referred as "superbugs" due to their resilience against many drugs. Investigations have confirmed the role of MRSA in hospital associated infections and the options of fighting the contagion are limited due to the emergence of superbugs that exhibit resistance against the prevailing antibiotics [127,128]. The development of superbugs can be due to genetic mutations that are spontaneous or induced. In addition, possession of genes responsible for multidrug resistance from another bacterium through horizontal gene transfer can result in the emergence of superbugs which occurs by means of conjugation, transformation or transduction. Plasmids serve as the reservoir of the genes responsible for making the pathogen resilient and demonstrative studies have reported that a bacterium gaining resistance to a particular drug will not be able to revert back to its previous state [129]. Many demonstrative studies have claimed the importance of horizontal gene transfer in *S. aureus* and its role in transforming the pathogen in to a superbug as a bacterium resistant to a particular drug is capable of passing on those genes to its offspring by means of different

gene transfer methods. Studies on population genomics of *S. aureus* has revealed the ability of the pathogen to adapt to host conditions due to the expression of certain genes achieved through horizontal gene transfer [130]. Genome of *S. aureus* is highly diverse and researchers have performed genome sequencing methods for the identification of major clone carrying the genes achieved through horizontal gene transfer. The most interesting aspect was the presence of mobile genetic elements (MGE) that encode proteins responsible for antibiotic resistance, virulence and host adaptation. Research studies has provided sufficient scientific evidences to validate the significance of horizontal gene transfer (HGT) mechanism in making the pathogen resilient to antimicrobial agents and also confers the pathogen with host adaptation ability [131,132]. It is understood that bacteria obtain genetic difference as a consequence of mutations which are spontaneous or induced and HGT is a vital mechanism that allow the transfer of genes responsible for a variety of factors and contributes towards the success of the pathogen. In fact, this mechanism has enabled the bacteria to take up the genes from another bacterium and the process is much rapid among the isolates of the same strain. However, this is not just limited to the isolates of the same strain as the HGT can even occur between distantly related species so that one species is benefitted from another. Hence, the pathogen does not have to rely on random mutations for valuable gene variant [133]. The extent of antibiotic resistance however varies among the strains of the pathogen and studies claim the varying degree of tolerance level to antimicrobial agents among the hospital associated and community associated strains of *S. aureus*. In addition, studies also confirm that hospital isolates are highly tolerant to the employed antimicrobial agents due to their constant exposure to them and hygiene is another vital factor for the prevalence of the infection.

Horizontal Gene Transfer

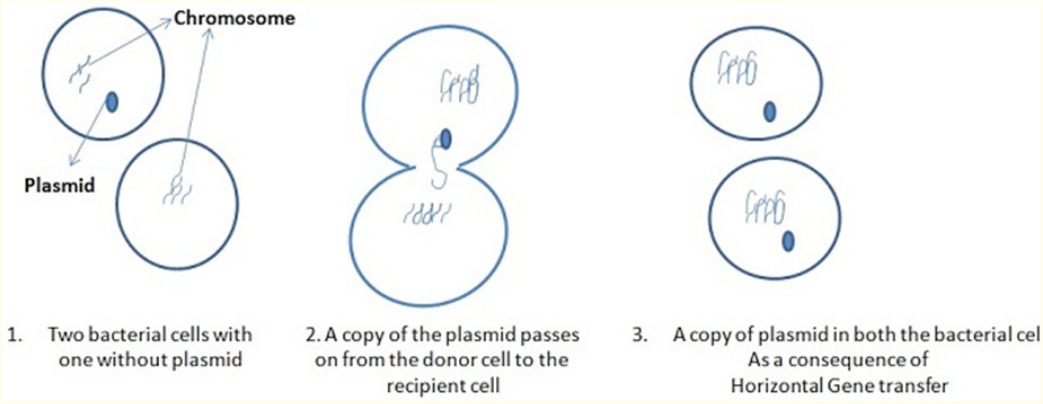

Figure 2: *Diagrammatic representation of horizontal gene transfer via plasmid.*

The diagrammatic illustration depicts the mechanism of the uptake of a copy of plasmid from one bacterium to the other followed by the integration of the plasmid in the genome of the recipient. Emergence of novel genetic variants in a population as a consequence of mutation has indeed enhanced the ability of pathogen to survive and reproduce. The gene variants pass on from the parent cell to the daughter cells and this result in the development of complex traits that makes the pathogen resilient. The plasmids are known to contain several genes and each of these confers the resistance to different antibiotics. Studies have confirmed the ability of MRSA plasmid to offer resistance against penicillin and streptomycin families of antibiotics [134]. Experimental analysis were performed to substantiate the mechanism of uptake of *mecA* gene under *in vitro* conditions from a MRSA to a MSSA (methicillin sensitive *S. aureus*) and molecular biological techniques were employed to confirm the presence of the transferred gene in the recipient bacterium as a consequence of horizontal gene transfer. The transfer of *mecA, ccrA3, ccrb2* genes between the *S. aureus* strain of close proximity under

in vitro conditions advocates the possibility of horizontal gene transfer among the clinical isolates [135]. Researchers regard the MRSA strains as superbugs due to their ability to resist a variety of antibiotics as a consequence of horizontal gene transfer (HGT) and mobile genetic elements (MGEs). Demonstrative studies in the past confirmed the role of plasmid in the emergence of resistant strains of *S. aureus* whereas the recent study signifies the importance of HGT in offering resistance against the antibiotics [136]. Studies also claim the key role of *mecA* in enabling the pathogen to overcome the potency of the β lactam antibiotics and the transfer of this vital gene responsible for resistance is facilitated by the SSCmec which are mobile genetic elements [137,138]. However, the origin of *mecA* gene is yet to be explored.

Relationship between biofilm formation and multidrug resistance in *S. aureus*

Researchers regard *S. aureus* as the perpetrator associated with broad spectrum of diseases and they are known for their ability to overcome the potency of a variety of antimicrobial agents. It is a widely accepted fact that the genetics of the pathogen plays a vital role in offering the resilience characteristic but there are studies where the scientific investigators have attempted to reveal the importance of biofilms in offering resistance to drugs. Biofilms are complex structures comprising of a variety of biological molecules ranging from nucleic acids to lipids, proteins and extra polymeric substances which serve a vital purpose towards the resilience of the pathogen and studies have confirmed the abilities of *S. aureus* in producing intricate biofilm network. Data in relation to biofilm analysis has reported the presence of a variety of pathogens enclosed within the extra polymeric matrices which could be of a single or different species. Researchers also validated the role of biofilms in conferring the bacterium with specialized functions ranging from antibiotic resistance to virulence and enhance the survival abilities of the bacteria. In fact, such specialized functions are not exhibited by non biofilm producers or free floating planktonic bacteria [139]. Several researchers and their demonstrative studies have regarded these biofilms as an integral part due to its role in promoting the regulatory and metabolic activities which is beneficial to the bacteria. Demonstrative investigations have exemplified these extra polymeric matrices as bacterial communities attached to a living or a non living entity. The altered properties of the enclosed bacteria with the extra polymeric matrices distinguish them from the other non biofilm producers and free floating planktonic bacteria [140]. Clinical studies claim the role of biofilms in human related infection accounting up to 60%. These extra polymeric matrices are responsible for the outbreak of severe infections and their prevalence is common among patients with medical devices. Patients with urinary catheters and orthopedic devices are prone to biofilm infections [141,142]. A vital factor that has concerned the researchers is the degree of virulence exhibited by the pathogens enclosed with the biofilms and studies have illustrated the relation between the biofilms and enhanced virulence of the pathogen. Recent studies have disclosed the relation between the biofilms and the extent of multidrug resistance exhibited by the *S. aureus* isolates. Scientific studies have attempted to demonstrate the extent of biofilm forming capacity of *S. aureus* among the patients by exposing the patients to MDR *S. aureus* [143]. It is a globally accepted fact that the emergence of multidrug resistance strains of *S. aureus* has triggered the issue of public health concern and the problem is aggravated in the regions of the globe that lack the provision of systematic antibiotic susceptibility testing. This condition prevails in the sub Saharan African regions and the lack of knowledge on the usage of appropriate antibiotic has in turn resulted in empirical treatment which is regarded as one of the main reason for the emergence of multidrug resistance among the strains of *S. aureus*. The condition is more prevalent in the hospitals as the prospects of transmission of the infection are high among the patients [144,145]. Studies confirm the lack of proper hygiene has enhanced the faster rate of the occurrence of the infection among the hospitalized patients.

Demonstrative studies have reported an increase in the rise of strains of *S. aureus* resistant to methicillin which is an indication of the organism to resist many drugs which in turn has reduced the option of treating the infection due to the property of multidrug resistance as a consequence of inherent and acquired mechanisms [146-148]. Mutations that are either spontaneous or induced play a vital role in conferring the pathogen with antibiotic tolerance and complex genetic elements coding for mec and vanA genes are responsible for the emergence of superbugs as the organism acquire these genes through the process of horizontal gene transfer [149,150]. Scientific investigators have illustrated the significance of pathogen's resistance pattern which is a vital means for drug usage guidelines and

susceptibility examination of *S. aureus* in the regions devoid of routine antibiotic testing. The complicated biofilm network of *S. aureus* enables the organism to resist the conventional drug therapy. In addition, the biofilms also assist in the passing of the vital resistant traits among the nosocomial pathogens as a consequence of mutations resulting in multidrug resistance [151,152]. The expression of adhesion antigens known as polysaccharide intracellular adhesion antigens (PIA) are responsible for cell to cell attachment and they play a vital role in the regulation of biofilm formation. However, existing data on biofilm research confirm the clinical significance of biofilm producing *S. aureus* which are difficult to control due to their enhanced resistance to a variety of antibiotics when compared to the strains of *S. aureus* not involved in biofilm production. Nevertheless, demonstrative studies have illustrated the importance of understanding the relation between the biofilm production and antimicrobial pattern in *S. aureus* as it enhances the scope of counteracting the infections that are hospital acquired [153].

Biofilms: A major barrier that reduces the potency of antibiotics

Biofilms are the extra polymeric substances that enclose the microbial communities within it and act as a major barrier by preventing the entry of antibiotics which allows the pathogen to escape the efficacy of the employed drug. Factors like inactivation of the antibiotic, alteration of the target site and exclusion of the antibiotics enables the pathogen to survive the activity of the drugs [154]. These actions involve the accumulation of specific genetic factors like the genes encoding β-lactamase or efflux pump. These extra cellular matrices known as biofilms not only confers resistance to antibiotics, but they enable the pathogen to overcome the periods of stress and also make the pathogen resilient towards the host's defense mechanism which in turn makes them a difficult perpetrator to tackle [155]. The non biofilm producers otherwise referred as free living bacteria are susceptible to the antibiotics as well as the defense mechanism exhibited by the host while the scenario is different in case of biofilm producers. The extent of resistance shown by these biofilm produces has increased up to 100-1000 folds when compared to planktonic bacteria (free floating) which are susceptible to the employed drugs. The studies have shown an increase in the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the antibiotic against the pathogen [156].

In spite of years of demonstrative studies and scientific investigations, very limited information on the mechanism of antibiotic resistance in biofilms is available and the reason behind the modified efficacy of the antibiotics on the microbial communities embedded within the biofilms is yet to be explored. However, scientific explorers have attempted to understand this behavior of the microbial communities within biofilms by segregation of the resistance factors as innate and induced [157]. The biofilm developmental pathways contribute towards the innate factors responsible for the resistance against the drugs. These innate factors are also known as intrinsic factors. Researchers over the years have disclosed the significance of these internal factors as a prime means of antibiotic resistance and several such factors have been identified. For instance, the diffusion barrier as a consequence of biofilm matrix results in the obstruction of the drug which enables the pathogen to escape the potency of the drug. The microenvironments within the biofilms play a vital in altering the physiology of the pathogen by introducing oxidative stress and studies claim that these extra polymeric matrices comprises of different strains of the same species or pathogens of different species so the scope of developing resistance through horizontal gene transfer is possible. Scientific explorations also confirm the degree of physical obstruction caused by the biofilms as they are composed of a variety of biological molecule and the employed antibiotic has to penetrate the thick layers of exopolysaccharides, DNA and proteins in order to reach the embedded microbial cells [158, 159]. These physical and chemical barriers have in turn reduced the effective concentrations of the antibiotics and have resulted in the emergence of multidrug resistance pathogens of clinical significance. Despite the fact that, demonstrative studies performed by researchers has claimed the efficacy of antibiotic on the outer layers of the bacterial cells resulting in their death, this in turn stimulates the bacterial population embedded within the biofilm matrix which adapts to the altered environment resulting in antibiotic tolerance [160]. However, the reduced level of antibiotic penetration in the bacterial biofilms may not be common behavior exhibited by all bacterial biofilms and scientific investigators are attempting to understand the relation between the biofilms and antibiotic resistance [154]. The altered microenvironment within the biofilms also contributes towards the resilient nature of the bacteria. One of the vital factors in relation to the altered microenvironment of biofilms

is the depletion of the nutrients which results in a slow growth of the bacteria. Researchers have confirmed the importance of the oxygen concentration and the extent of nutrient intake. The oxygen concentration is usually high at the surface of the biofilms when compared to the inner portions and this in one of the prime reasons for higher activities at the surface region. The reduced metabolic activities within the inner regions of the biofilm matrices results in the slow growth and this enables the bacteria to escape the efficacy of the antibiotics [161,162]. Increased antibiotic efficiency on the actively growing cells has been demonstrated by researchers as the mortality rate is directly proportional to the growth rate. For instance, antibiotics like penicillin and ampicillin will be effective at specific cell densities and will not be able to counteract the pathogen at lower growth rates. Despite the fact, that the β-lactam antibiotics are capable of killing the non-growing cell, their activity is higher among actively growing cells. Therefore, reduced growth rate within the biofilms certainly contributes to the resistance of the bacteria [163].

Quorum sensing and antibiotics

Bacterial communication is a vital mechanism which favors a range of metabolic processes encouraging the growth of the bacteria and is referred as quorum sensing. Quorum sensing is a vital phenomenon that enables cell to cell contact and enhances the survival abilities of the pathogen and also contributes to the virulence of the pathogen. Quorum sensing and antibiotic efficacy are closely related and numerous attempts have been carried out to illustrate the significance of quorum sensing and their role in serving as suitable targets to the employed antibiotics [164]. The significance of biofilms towards the pathogen's resistance has been validated by several research studies and the importance of quorum sensing in biofilm formation cannot be denied as demonstrative studies have signified the importance of quorum sensing in biofilm formation. A desired population of cells results in the production of auto inducers which in turn triggers the quorum sensing mechanism enabling the cell to cell communication. The mechanism regulates the expression of vital transcriptional factors which initiates a cascade of metabolic activities that favors the pathogen [165].

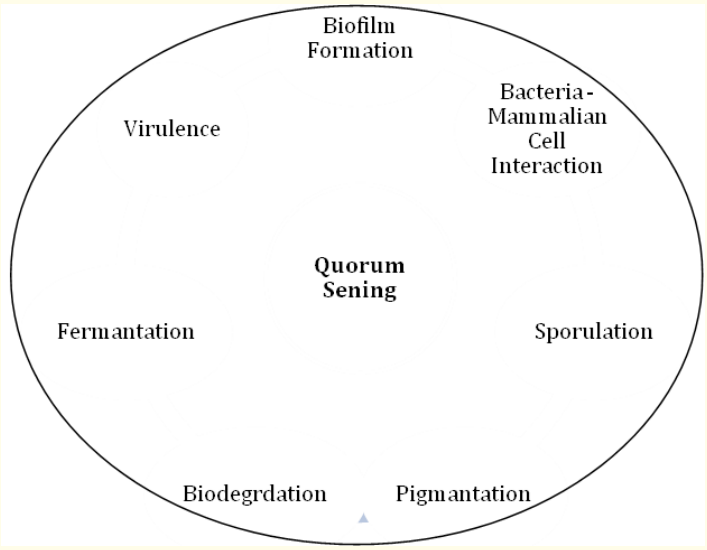

Figure 3: *Quorum Sensing and its associated metabolic functions.*

The above schematic representation depicts the various vital processes favored by the quorum sensing mechanism. However, the mechanism of quorum sensing very among the Gram positive and negative bacteria as the signaling molecules involved on the initiating the process significantly differs. Studies also confirm the significance of quorum sensing in enhancing the pathogen's ability of adjusting to the surrounding and maintain the flow of nutrients which in turn makes the pathogen highly competent [166].

Experimental studies at the molecular and genetic level has been performed to validate the importance of quorum sensing mechanism and several studies carried out on the mutant strains have claimed the importance of the quorum sensing. Studies carried out on the mutant strains have confirmed that the pathogens devoid of quorum sensing have resulted in the formation of weaker biofilms which in turn enhances the vulnerability of the pathogen to the antibiotics [166]. The mutant strains lacking the vital genes responsible for the production of signaling molecules have shown a higher degree of susceptibility against the employed drugs. Several studies have exemplified the importance of signaling molecules and knowledge on these molecules and their relevant genes enhances the scope of altering the quorum sensing mechanism which in turn results in weaker biofilms. As a consequence, the pathogen's susceptibility to the drugs increases [167]. Nevertheless, further studies are essential to substantiate the importance of quorum sensing in bacterial biofilms production and their role in contributing towards the antibiotic resistance.

Discussion

The current review focuses on aspects ranging from the prevalence of UTI among women as a consequence of *S. aureus* infection and attempts to disclose the vulnerability among women during pregnancy followed by the development of antibiotic resistance exhibited by the pathogen. The crux of the review endeavors to illustrate the extent of resilience shown by the pathogen towards a variety of antimicrobial agents and the related factors that enables the pathogen to overcome the efficacy of the employed drugs. It is well known fact that UTI is common among men and women but the anatomical physiology of the reproductive tract enhances the scope of prevalence among females. Factors like physiological changes during pregnancy, patients with history of diabetes, age and indwelling catheters augments the prevalence of the infection. Women encounter the infection at any point of their life time and several studies have demonstrated the occurrence of the infection among children and elderly population. The incidence of UTI among pregnant women during the second trimester accounts to 50% as a consequence of lack of adequate and appropriate treatment during pregnancy [168]. UTI is regarded as the most common hospital acquired infection accounting to 35% of nosocomial infection and is regarded as a vital factor for the occurrence of bacteremia among long term hospitalized patients [169]. The percentage of women encountering any form of UTI during pregnancy is estimated to be 2% to 8% [170]. Though several studies claim the involvement of *E. coli* up to 80% in causing, another etiological agent in relation to the prevalence of UTI is *S. aureus*. The role of *S. aureus* in conferring UTI has been validated by numerous demonstrative studies and a count of 10^5 CFU/ml is considered to be significant for symptomatic UTI [171,172]. The significance of *S. aureus* in invading the perineum of the women during pregnancy has been illustrated by scientific investigators and the development of resistance among the pathogen against the antimicrobial agents has been an issue of clinical concern [51]. Researchers assume the frequent use of antimicrobial agents among patients has led to the emergence of resistance among the pathogen [173].

Scientific investigations have revealed the ability of the pathogen to pass on the genes responsible for the resilience of the pathogen between different genera by means of plasmids [174]. The extent of antimicrobial resistance is quite common in hospitals due to frequent use of antimicrobial agents. However, the pathogen's role in community acquired UTI cannot be denied [175,176]. The emergence of multidrug resistance bacteria has been an issue if clinical concern and the research studies over the last decade have witnessed an increase in the population of such microbes. The health issues associated to community and hospital acquired infections as a consequence of multidrug resistance *S. aureus* has challenged the scientific community. *S. aureus* is a Gram positive pathogen and is known to colonize nasal and skin regions and accounts to 25-30% of infections among health individuals. Several studies have illustrated the prevalence of MRSA in hospitals and healthcare centers. Presence of HA-MRSA (hospital associated- MRSA) among the discharged patients has been reported by several researchers however, certain studies claim that these infection are not life threatening. Nevertheless, lack of proper diagnosis and treatment can aggravate the condition among the infected patients [47,48]. Significance of a single genetic element in conferring the resistance among MRSA has been an interesting aspect for research and many scientific

investigators have attempted to disclose the facts [49]. Patients with indwelling catheters and other medical devices are highly prone to MRSA infection and the infection is also common in patients after surgery. Clinical analysis over the years has attempted to reveal the various symptoms associated with MRSA infections and claims the presence of chronic illness among elderly patients. The prevalence of the infection is high as a consequence of surgical wounds and urinary catheters [177]. Appropriate diagnosis and treatment is essential to counteract the MRSA infections. Research studies have demonstrated the importance of preventive measures and their role in preventing the spread of the infection. Molecular biological methods like the PCR can be employed to find out the presence of specific genes responsible for conferring the resistance and this method has been used to trace the mecA gene which is known to offer resistance against methicillin resulting in MRSA strains [178]. Attempts are being made to design appropriate means of managing the MRSA infections and cost effective methods of treating the infections is under progress at the hospitals and healthcare centers. However, further experimental studies are essential to work on the development of cost effective methods to counteract the MRSA infection [179, 180]. The prevalence of S. aureus infections is not just limited to nasal and skin regions but studies have revealed it role in causing bone infections. *S. aureus* is regarded as one of the most common bacterium associated with healthcare associated infections. *S. aureus* exhibiting multidrug resistance is usually associated with infections with an increase in the rate of morbidity and mortality among the infected patients. However, studies have signified the importance of screening procedures in order to reduce the nosocomial infections among the hospitalized patients [62]. In addition, to hospital acquired and surgery related infections *S. aureus* is responsible for bacteremia and pneumonia. Studies confirm that normal individuals are known to possess these strains of the pathogen asymptomatically and the occurrence infection is endogenous which relies on the load of the pathogen and its colonization [181,182]. Scientific investigations also claim the outbreak of MRSA as a consequence of constant exposure to antibiotics. This in turn has resulted in the surfacing of the strains resilient to the methicillin.

However, the tendency of these strains to worsen the infection has been validated by several studies due to the ability of the pathogen to colonize the individuals for months or even years. Scientific data and reports authenticate the constant exposure of antibiotics as a prime reason for the development of such resistant strains. For instance the constant administration of cephalosporins has resulted in the development of resistance in *S. aureus* strains. Since the emergence of the first strains of MRSA in the early 1960s, several studies have attempted to reveal the clinical significance of the these strains and an increase in the global epidemic as a result of multidrug resistant *S. aureus* has been illustrated by research studies [49,183]. Prevalence of MRSA increased as the use of the antibiotic became regular and scientific investigators illustrate this as a consequence of repeated administration of the drug. This in turn exemplified the antibiotic stress as a main factor responsible for the surfacing of such resistant pathogens. Though the emergence of first MRSA strains dates back to 1960s, there has been an increase in MRSA since 1980s [184,185]. Development of MRSA and its role in human related infections is a globally accepted fact, but the emergence of other resilient strains tolerant to drugs belonging to the glycopeptides family has concerned the scientific society and gained the attention of the researchers. Vancomycin is one of the antibiotics that belong to the family of glycopeptides. The emergence of VRSA has become the interest of scientific investigators and several studies over the last two decades have validated the prevalence of VRSA. Though the existence of VRSA is considered to be a rare phenomenon, their prevalence cannot be denied. Vancomycin is commonly used to manage the methicillin resistant strains which have reduced the options of antibiotics against *S. aureus*. Despite the fact that most of the strains of *S. aureus* are susceptible to vancomycin, the minimum inhibitory concentration of the drug is taken as a scale to differentiate the resistant and susceptible isolates of *S. aureus*. Several demonstrative studies have hypothesized different concentration levels of vancomycin against S. aureus and the isolates capable of tolerating a concentration of 32 µg/ml are regarded as resistant strains (VRSA). In addition, studies have validated the presence of intermediary resistance among S. aureus strain to teicoplanin which belongs to the family of glycopeptides. VISA strains have exhibited intermediary resistance to the drug. However, this degree of resistance was not observed in all the VISA strains [186]. Nevertheless, several research studies have confirmed the significance of various factors that contributes to the resilience of *S. aureus*. Despite the fact that empirical use of antibiotics have contributed towards the development of resistance among *S. aureus* there are several other which cannot be denied. Though the constant exposure and selective antibiotic pressure has resulted in antibiotic tolerance, the genetics of the pathogen is very vital. The genetics of the pathogen comprises of several genetic variants responsible for specific genes that confer the pathogen

with resistance. In addition, biofilms play a vital role in the resilience of the pathogen by obstructing the entry of the employed drug. When the genetics of the pathogen is considered, several genes play a significant in offering the resistance towards a variety of drugs. The genome of *S. aureus* is highly diverse and is known to possess plasmids comprising of genes conferring resistance and these plasmids contributed towards the development of multidrug resistance thorough horizontal transfer mechanism which enhances the process of gene transfer between different strains of the pathogen.

Many researchers have claimed the presence of mobile genetic elements which play a significant role in passing the genes of resistance and studies have highlighted the importance of *mecA* gene which offers resistance to antibiotics like methicillin and penicillin and other β-lactam antibiotics as the gene codes for modified penicillin binding protein. Methicillin is a β-lactam antibiotic like the penicillin and is intended to act on the penicillin binding proteins which hinders the cell wall formation eventually leading to the death of the pathogen [187,188]. Though, research studies have demonstrated the efficacy of methicillin against the bacteria producing β-lactam, their potency in counteracting the bacterial infection is reduced during the secondary resistance of the bacteria towards the antibiotic. This is one of the prime reasons of these strains to get the attention of global scientific leaders and has become a topic of research interest. Researchers have confirmed the resilience of MRSA to several antibiotics. High replication abilities in combination with the horizontal gene transfer results in enhanced antibiotic resistance and also allows the gene transfer from one cell to the other. Studies also confirmed the significance of conjugation in favoring horizontal gene transfer. Emergence of penicillin resistance among 80% of S. aureus strains has provoked the use of first line antibiotics like methicillin and vancomycin. This degree of resistance among the S. aureus strains was observed in less than two decades after the emergence of the first strain resistant to penicillin [189]. However, the pathogens' exposure of these antibiotics has resulted in the development of resistance which in turn has reduced the option of drugs to fight the pathogen. Several studies have demonstrated the clinical importance of MSSA, MRSA and their association with food poisoning and toxic shock syndrome. Though, MSSA and MRSA are clinically significant, the reports and available scientific data derived from various studies highlights the difficulties in counteracting MRSA when compared to MSSA which are susceptible to β-lactam antibiotics. In contrast, MRSA and vancomycin resistant *S. aureus* are highly resistant to β-lactam antibiotics and this enhances the probability of bactereamia among the infected patients resulting in long term hospitalization which in turn increases the cost of treatment [190]. The action of vancomycin is similar to other antibiotics as it causes the death of the pathogen by attacking the cell wall and this mechanism been validated by research studies. However certain strains of *S. aureus* are known to counteract the efficacy of vancomycin by producing a thick layer of peptidoglycan. This mechanism has been reported in the *S. aureus* strains of Mu50 where the elevated amounts of peptidoglycan layer in the cell wall of the pathogen have been beneficial. Biochemical and transmission electron microscopy (TEM) have confirmed this phenomenon in the *S. aureus* strains of Mu50 which has made the pathogen resilient to vancomycin [191]. Though research studies in the past have demonstrated the efficacy of vancomycin against *S. aureus*, the current scenario is not same as it was a decade ago. Vancomycin was used for treating the infections of MRSA but the constant exposure of the pathogen to the drug has resulted in the emergence of vancomycin resistant strain. However, the prevalence of VRSA strains are usually considered to be a rare phenomenon but their existence cannot be ruled out. The extent of antibiotic resistance or susceptibility of the pathogen is based on the minimum inhibitory concentration which differentiates the susceptible, intermediary and resistant strains of *S. aureus*. Nevertheless, the mechanism of resistance among the intermediary and resistant strains of *S. aureus* is not same and is yet to be explored.

Demonstrative studies have claimed the significance of thickened cell wall in VISA strains for resistance against vancomycin. The thickening of the cell wall entraps the antibiotic which in turn prevent the drug to reach the target cite within the cytoplasmic membrane. In contrast, *vanA* gene is regarded as a crucial factor for the development of resistance among VRSA strains of the pathogen. The cases of vancomycin intermediary and resistant strains are relatively low and the epidemiology associated with these strains is yet to be disclosed. However, repeated administration of vancomycin among the MRSA infected patients has enhanced the potency of the pathogen to resist vancomycin [192-195]. In addition to these intrinsic genetic elements, the role of extra polymeric matrices known as biofilms also contributes towards the resilient behavior of the pathogen to antibiotics.

Conclusion

UTI is a common contagion encountered by males and females but the anatomy of female reproductive tract makes them highly vulnerable due to the shorter length of the urethra. Women of all age groups are prone to the infection and pregnancy enhances the scope of the infection. The examination of urine sample is an appropriate method of diagnosing the infection and colony forming unit count serves as an indicator to differentiate the asymptomatic and symptomatic UTI. The infection usually leads to bacteriuria but lack of appropriate treatment can lead to bacteremia which results in dire clinical conditions. Though *E. coli* is considered to be the most prevalent pathogen, the role of Gram positive bacteria cannot be denied and *S. aureus* is one such etiological agent that is capable of invading the urinary tract. *S. aureus* is capable of resisting the commonly employed drugs and several internal and extrinsic factors associated with the pathogen offers this property of resilience towards the antimicrobial agents.

Emergence of multidrug resistance *S. aureus* has been a threat to humans due to limited options of managing the infection. Several studies have confirmed the prevalence of infection among community and healthcare centers. However, the occurrence of such infections is high in hospitalized conditions where patients undergoing long term treatment are highly prone. Surgical wounds and indwelling medical devices enhances the scope of *S. aureus* infections and a variety of intrinsic and extrinsic factors are responsible for conferring the resistance to the pathogen. Though penicillin and other β-lactam antibiotics were effective against the pathogen, the constant selective pressure as a consequence of repetitive administration of the drugs has resulted in the emergence of drug resistance among *S. aureus* and the current scenario reports the existence of resistance to penicillin among 80% of *S. aureus* strains. As a consequence, the usage of methicillin against these resistant strains of *S. aureus* was an alternative and was effective in counteracting the pathogen. However, constant exposure to methicillin has resulted in the emergence of MRSA strains which was capable of resisting several drug.

This increased the use of vancomycin which is regarded as the drug of last resort but there are cases confirming the existence of VRSA strains. The genetics of *S. aureus* is an important factor responsible for making the pathogen resilient against several drugs due to the presence of genes like mecA and vanA. Studies confirm the prevalence of VRSA is considered to be a rare phenomenon and MIC of the drug against the pathogen is taken as a scale for classifying *S. aureus* as susceptible, intermediary and resistant strains. Nevertheless, the mechanism of resistance in VISA and VRSA strains are different as the cell wall plays a vital role in entrapping the employed drug in the former strains (VISA) and vanA gene is responsible for conferring resistance in the latter (VRSA). However, epidemiology of these strains is yet to be understood and further research studies are necessary to understand the mode of antibiotic resistance in *S. aureus*.

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