

# A Review on Pathogenesis and Regulatory Mechanisms of Infections from Staphylococcus Aureus

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**Abstract**— *S. aureus* is commonly found living on the outermost layer of human body which is the skin and in about 30% of individuals it is a permanent colonizer. This pathogen is blood borne infection and is the causative organism of commonly occurring infections like endocarditis and sepsis. This current review has effectively discussed the morphology and colonial characteristics of *Staphylococcus aureus* (*S. aureus*), its types and classifications, individuals who are at risk of getting infected, common skin infections caused due to the pathogen, resistance and the various managements available. The recent developments in managing this infections, are also discussed in this review. The most common and severe conditions caused by *S. aureus* are Food poisoning and Toxic Shock Syndrome, which elaborately discussed. The review presents the past findings and recent developments regarding *S. aureus* infection from all the aspects.

**Index Terms**— *staphylococcus, aureus, toxic shock syndrome, infection*

## I. INTRODUCTION

*S. aureus* is commonly found living on the outermost layer of human body which is the skin and in about 30% of individuals it is a permanent colonizer [1]. It is the most common causative agent of skin and soft tissue infection mainly affecting those individuals who have been already colonized by this bacterium [2]. The local skin infections are self limiting and self healing but sometimes this pathogen gains entry from the surface into the deeper tissues and into the main bloodstream causing bacteremia [3,4].

## II. MORPHOLOGY AND COLONY CHARACTERISTICS

*Staphylococcus aureus* (*S. aureus*) is a primary pathogens in a hospital/community setting leading to all sorts of infectious diseases, both mild to hazardous for e.g. 'mild skin and soft tissue infections, infective endocarditis, osteomyelitis, bacteremia, to life threatening pneumonia [5]. *Staphylococcus aureus* is a member of genus *Staphylococcus*, Firmicutes; It stains as Gram positive for a Gram stain, it is usually about ~0.8  $\mu\text{m}$  in diameter, and commonly arranged in clusters/ "string of grapes" under a microscope, it can be either aerobic or anaerobic; and optimal growth temperature is 37°C, at pH 7.4 [6,7]. When cultured on blood agar plate the colonies appear thick & shiny; exhibiting a circular shape having a diameter of 1~2 mm [8,9]. Majority of them form a hemolytic ring which is transparent (on blood agar plates) [9]. *S. aureus* is non-motile and non-sporulating. But a capsule is present; it is able to produce a pigment that has a golden yellow coloration, and it is able to decompose mannitol [10]. Other biochemical tests that stand positive and help in identification of *S. aureus* are 'plasma coagulase, lactose fermentation and deoxyribonuclease' [11].

## Types of *S. aureus* (usually found)

This bacteria can be divided into two groups methicillin sensitive and methicillin resistance; the latter is called as MRSA and in few years rapid evolution/mutations in the industrialized world cases of MRSA bacteremia have upsurged from 10-30 per,100,000 personal/ year [12]. This widely found variant of *S. aureus* called MRSA is a multi drug resistant variant which exhibits resistance to  $\beta$  lactum antibiotics, aminoglycosides, quinolones and macrolides [13]. In such kind of infections about 50% mortality rate has been experienced and so this organism is becoming a global problem [14]. It is also a major cause of nosocomial infections that are acquired after getting hospitalized in a health care system. Incidences of MRSA have been elevating since quite a few years particularly in the industrial regions but a decline has also been reported from the very same areas like USA [15, 16] Canada, UK etc. and it has been attributed to more developed and advanced methods of infection control. This decline is a specially evident in UK where MRSA bacteremia load declined to almost half during the time frame of 2004 to 2011 [17, 18] a similar situation was reported from US [19] Australia [20] and France [21].

The microscopic images of of *S. aureus* infections from the newly industrialized and the non-industrialized regions of the world is very cloudy and needs more customized studies to reveal the actual data and the risk associated [22-25].

## III. RISK GROUPS

People who are living at either extremities of life (infancy, early childhood and old-age people) are at more risk to *S. aureus* infection [26-29]. Chances of infection are much high during the first 12 months of life which gradually decrease in young adulthood and then again show an upsurge with

advancement in age [30]. A unique gender based fact associated with *S. aureus* is that male gender is consistently affected to a higher degree [30] as compared to the females and the male to female ratio is ~1.5; the probable reasons are still unexplained. The incidences of *S. aureus* infection have also been associated with ethnicity for example in United States the black population has twice the number of chances of getting an MRS infection then the white population per 100,000 person-years [16, 19]. In this similar vein in Australia the indigenous population is up to 20 times more prone of acquiring this infection then the non indigenous Australians [31] and in New Zealand people of Pacific Island have more chances then those of European ethnicity [32- 33].

#### Special risk group

People who are HIV positive have up to 24 times more risk than the non HIV infected cluster [34]. In this case it can probably be linked to the decreasing CD4 count. When homosexual men were compared to group that was injection drug users the homosexual group had most chances of nosocomial staph infection because of low CD4 count. In different areas around the globe the patients who are undergoing hemodialysis are at high risk group of acquiring this infection for example as in Taiwan [35] Ireland [36] United States [19]. The reason attributed is presence of and introvascular access device and a catheter for dialysis [36]. Some other factors which are associated with high risk of invasive type of *S. aureus* infection are improper functioning of neutrophil cells [37], overload of iron [38], diabetes [39], increased rate of colonization [39]. In dialysis patient where artificial kidney of large pore size [40-42] is used along with infrequent doses of vancomycin the patient is unable to maintain and sufficient trough level in high flux and it results in recurring infections of *S. aureus*.

#### IV. CLASSIFICATION OF TYPES OF INFECTION

Infections caused by *S. aureus* can be classified as complicated and uncomplicated and this typification is important in prognosis and determining the duration of antibiotic treatment. Complicated infection can involve central nervous system, cause metastasis, also cause relapse of infection along with acute systemic infections like vasculitis, infarcts, ecchymoses etc [43]. Another study stated that mortality within 1 month of bacteremia that does not have a focus is due to pulmonary infection or ineffective endocarditis is very high in contrast to catheter related *S. aureus* infections and other milder forms including UTI [44].

#### Steps involved for total recovery- Proper consultation

There has been suggested recommended guidelines with needs to be followed for the overall well being of the patient and which includes the following steps a. Getting results from follow up blood cultures to see the status of *S. aureus* infection [46, 47]. B. Getting an ecocardiograph test done [48, 49]. c. Identification and removal of infection foci, [47, 50] d. Appropriate use of beta lactams (those who have methicillin

sensitive *S. aureus*) [48]. Many studies have reported that which kind of timely consultation can surely reduce mortality rates [51].

#### Antibiotics duration

The most accepted recommendation for intravenous antibiotic treatment in cases of uncomplicated *S. aureus* infection is a minimum of 14 days. Studies have reported that if in the cases antibiotic therapy is not carried out for at least two weeks there is relapse rate of 8% and this relapse becomes 0% in cases those are treated for at least 14 days [52]. This relapse rate is in accordance with the 6% rate of complications that occur a bit slow including metastatic complications in case of catheter associated infections that are treated for less than 2 weeks [53]. According to a few studies one week treatment is adequate [45] but such cases have been categorized as investigational pending, robust generalized evidence. Patients suffering from right sided ineffective endocarditis and being treated with vancomycin must receive the treatment for more than 14 days. When talking of complicated *S. aureus* infections 1 month to 6 weeks of therapy has been the standard practice and is still recommended. Beta lactam antibiotics are preferred over glycopeptides for methicillin sensitive *S. aureus* [54-64]. In cases of methicillin resistant infection vancomycin and deptomycin are the first choices by clinicians [66, 70].

Endocarditis : *S. aureus* is the most common causative agent of ineffective endocarditis [71]. In US alone *S. aureus* cases were seen to upsurge from 24%- 32% during 1998-2009 [72]. Many studies have shown that the primary cause of endocarditis due to *S. aureus* is its spread through contact with healthcare professionals [71, 73] and these incidences have raised from < 10% to >25% [74]. In patients having a prosthetic valve the most common cause of endocarditis is *S. aureus* [76] which is responsible for 23-33% of cases [77]. The maximum chances of acquiring infection is 1 year after the replacement surgery [78] and the most likely reason is either inappropriate endothelialization or frequent close contact with healthcare professionals [75]. Surprisingly the risk of acquiring this infection is independent of both location (aortic/mitral) and composition of valve (mechanical/bioprosthetic) [79]. A damage caused in the cardiac endothelium provides the nidus where bacteria can colonize. Series of processes triggered by this causes the platelets to form sterile vegetations and when these get colonized by bacteria IT results in endocarditis [80]. It was also observed that left side valvular diseases (and of that of mitral valve) occur more frequently [81]. Any such kind of infection raised in alarm for proper antibiotic use [82] and daptomycin was the one that topped the chart [65] including MRSA infection s. Early surgery particularly in cases of heart failure and uncontrollable infection along with high risk of emboli is also one of the treatment here [83].

### Dermal infections

*S. aureus* is capable of causing a large variety of soft tissue infections and dermal outbreaks which maybe benign (cellulitis, impetigo) to fatal life threatening infections. It is among the commonest pathogen that has been ever isolated from infections caused at surgical sites. It is equally capable of causing epidemic episodes of community associated MRSA [84, 85]. Such kind of out breaks have been reported from various locations both geographic and populations specific [86], homosexual males, destitute and homeless people [87], army and military people [88-90] etc. The pathophysiology explains that on the advent of infection neutrophils and macrophages that migrate to the site of infection get attached by *S. aureus* in a variety of ways which include- chemotaxis of leukocytes gets blocked, antibodies of host are rendered ineffective, secretion of a biofilm and camouflage its identity; it is even capable of resisting its destruction even after it gets ingested by the phagocytes [91].

### Common skin infections of *S. aureus*

Children are mainly seen suffering from impetigo [92]. It starts with a bullous or papular lesions which later change to crusted lesions on exposed parts of body usually the face. It also causes cutaneous abscess [93, 94] also non purulent cellulitis. This kind of cellulitis usually occurs on lower regions of body but may also involve walls of the abdomen, face and upper extreme parts of body. When it occurs in combination with streptococcal it causes orbital cellulitis [95-97]. Necrotizing fasciitis is also a cutaneous syndrome; in a study from Taiwan involving 53 patients suffering from this disease it was revealed that in 38% cases it was caused by *S. aureus* and 60% of it was methicillin resistant *S. aureus* [98]. Another one called pyomyositis can be caused by both methicillin resistant and methicillin sensitive strains and accounts for up to 4% hospital admission in tropical countries and in 90% of such cases the causative agent is *S. aureus* [99]. It is rare in temperate region but if present can be identified in children, youth, [100, 101] and also in people infected with HIV [102]. Besides these *S. aureus* is the most generally found cause of post operative mediastinitis [103, 104]. Various kinds of topical solutions and antibiotics can be used in various proportions to treat *S. aureus*. In cases of impetigo topical antibiotics were found to be more effective than oral antibiotics [105]. Osteomyelitis and infection of bone can also be caused by *S. aureus*. There can be three types of osteomyelitis [106]. Type one hematogenous is found in long bones of children and adolescents; in case of a matured population the axial skeleton gets affected [107]. The third type usually occurs in diabetic patients and involves their foot and is a kind of peripheral vascular disease. *S. aureus* is the main causative agent in all these three kinds of osteomyelitis. The bacteria is also capable of causing septic arthritis [108]. Septic arthritis is usually monoarticular but in less than 10% cases can also be polyarticular. This infection if occurs in the pubic region, it can go under diagnosed [109, 110]. It is also

commonly found in prosthetic joint replacement surgery [111]. The risk factors commonly associated with it are obesity immuno separation and rheumatoid arthritis [112-114]. In prostatic infection *S. aureus* is commonly found associated with biofilm making generally used microbiological culture methods for identification as worthless [115]. Two treatments of choices are available in such cases involving long term and short term usage of vancomycin along with anti-staphylococcus penicillin and using or abolishing rifampin as combination therapy [116-117].

### Formation of biofilm

These bacteria form a biofilm on the outer surface of foreign devices whose eradication is impossible. A biofilm is a passive bacterial colony which is covered in an extracellular layer of water, nutrients, and polysaccharides along with DNA and proteins [118-120]. The biofilm is found to be resistant to antibiotics and immune system of the host [121-122]. Yet another type of Staphylococcus infection is intravascular catheter infection which can be caused during insertion or manipulation [123-125] along with Central line blood stream infection can also be caused by *S. aureus* [126]. Incidences of central line infection are more than three times in intensive care unit in developing countries and Europe as compared to US [126]. Catheter related infections are most commonly found in patients undergoing hemodialysis [127]. Possible reasons are recent bacteremia and immunosuppression of the patient body [127]. Beauty implants like breast prosthetics can also lead to staphylococcus infection [128-131]. The condition is represented by fever, pain, formation of pus, and erythema in the implanted breast region. Change in the shape of breast and capsular contraction can also be sometimes present [132].

## V. TYPES OF RESISTANCE

The resistance of *S. aureus* is of 2 types - intrinsic and extrinsic. The endogenous resistance can be attributed to following three aspects. In case of lower membrane permeability drug absorption by the bacteria gets reduced because the energy metabolism is being affected and thus drug resistance is obtained [133] for example resistance of this bacteria to aminoglycosides is achieved by lowering the membrane permeability [134].

### Efflux System

Many bacteria possess efflux system [135], and when it is introduced by substrates in the surrounding environment for a longer duration the genes responsible for encoding the efflux system become activated and express themselves enhancing the ability to efflux drugs causing drug resistance [136]. The protoplasmic membrane present in *S. aureus* has three kinds of multi drug pumping proteins and QacA from among them is an important feature of MRSA [137]. Third intrinsic factor is production of beta lactamase enzyme in surplus amount

which can nullify the effect of antibiotics by 2 mechanisms first by hydrolysis of beta-lactam antibiotics; second is by pinching -where beta lactamase binds with antibiotic present in the extracellular space making it unavailable to reach the target site [138].

#### **Extrinsic factors**

The external factors which can make this organism resistant to antibiotics include acquiring resistance by the process of mutations [139], plasmid mediated acquired resistance [140], resistance which is acquired due to biofilm production [141]. A yet unheard mechanism of acquiring antibiotic resistance is by persister cells which are a small cluster of cells that are phenotypically heterogeneous, grow at slow speed (may be remain dormant), and are able to withstand high concentration of antibiotics [142].

#### **Management of MRSA**

Now it has been understood that *S. aureus* that belongs to MRSA category is worrisome to treat not only by beta lactams but also by quinolones, aminoglycosides and even macrolides [143]. Outbreaks of MRSA from hospital ICU have also been in light [144].

A few management therapies can be briefed as follows-

#### **Quorum sensing**

It is the mechanism where bacteria regulate its population by self induced sensors. This is an important method where exchange of information occurs between bacteria and it includes biofilm bioluminescence and even expression of the toxic genes [145]. Any means which can disturb this mechanism of bacteria will result in to lowering of bacterial virulence, biofilm formation would not occur and resistance of bacteria will also come down [146].

#### **Lectin inhibition**

Lectin is a sugar binding protein which is not derived from the immune system and is capable of causing cell agglutination [147]. Lectins are capable of agglutinating RBC's, another types of cells including pathogens, germ cells and even cells of the immune system [148]. Lectins can be used in designing of new drugs that can obstruct the lock and key effect between pathogen and the recipient cell [147].

#### **Iron chelation**

Iron is an important component of all living forms including bacteria [149]. Iron acts as a catalyst and also is required in electron transport, synthesis of nucleic acid etc. [150]. By attaching the antibiotic molecule within iron carrier and reducing the permeability of outer membrane (through a complex process of reactions) the drug is given an entry inside the cell where it exerts its antibacterial action [151].

#### **Phage therapy**

Initially when the phages were discovered they were used to treat bacterial infection [152]. They lost their relevance when antibiotic became a household name but emergence of variety of drug resistant bacteria including MRSA compelled the scientist to return to phage research [153]. Many animal models have proved the efficacy of phages [154]. Phages are advantageous over antibiotics because they are highly specific, their self proliferation is fast, and development time is very less [155]. But there are some limitations with regard to *S. aureus* phages in the processes of preparation and storage [153]. Another disadvantage is that like bacteria become resistant to antibiotics they can even become resistant to *S. aureus* but as phages are diverse and variable in nature they present to the scientist immense resource pool for phage controlled bacteria. Limitation with phage therapy is proper inoculation time and appropriate dose should be determined; because if inoculated prematurely or in an inappropriate dose it can simply be eliminated out of the body before the bacteria reaches a certain threshold level to cause the disease [153].

#### **Nanoparticles**

Nanotechnology is preparing substances at Nanoscale for research and industrial uses [156]. Studies have revealed that nanotechnology can be a non invasive or minimally invasive medicine [157]. Inside the human body nanoparticles can facilitate fast delivery of drug [158]. Particles can effectively search and attack cancer cells or repair damaged tissues [159]. China has already developed Nano scale antibacterial drugs including those for *S. aureus* [160]. Nanoscale antibiotics have advantage of spectrum hydrophilic nature, environmentally safe and do not become resistant because they use natural minerals [161].

#### **Toxic Shock Syndrome**

Toxic shock syndrome is a condition caused by *S. aureus* and TSS t1 is the gene associated with it. It is able to cause both menstrual and non menstrual toxic shock syndrome; although the menstrual variety is common because of use of tampons by females. But surprisingly it was found that more number of men carried TSST-1 gene compare to females [162]. Study from France identified in over 100 patients identified the cause of circulatory failure and fever that happened in concordance with the monthly cycle of females (where other sources of sepsis were absent) and found out that it was due to menstrual toxic shock syndrome. All patients were reported to use vaginal tampons. All patients needed an ICU admission and non exhibited any kind of skin desquamation initially but it later developed in about 12% of the patients. At the time of ICU admission blood culture reports were negative and methicillin susceptible *S. aureus* was recovered from vaginal culture of 92 patients and 76 out of these exhibited the presence of toxin gene sequences with dominance of *tst-H* gene sequence (87% cases). The treatments that help the patients to recover included

antibiotics, intravenous immunoglobulins vasopressor therapy and even invasive mechanical ventilation with complete survival of victims [163].

A recent study by Taki et al 2022 revealed that toxic shock syndrome which is not related to menstruation can also be life threatening. This is because of production of super-antigen like staphylococcal enterotoxin A B and C along with toxic shock syndrome toxin-1 TSST-1. The growth media was provided with additional serum to test *tst* gene that encodes TSST-1, (the test were repeated in absence of additional serum also). And the results revealed that toxic shock syndrome which is caused by TSST-1 producing CC-5 strains exhibit slight trigger due to serum induction of TSST-1 and is regulated by 'mutation of putative SarA-binding site at *tst* promoter'. [164].

## VI. FOOD POISONING

*S. aureus* is a major cause of food poisoning which may be either in sporadic or epidemic form. Although self-limiting (getting resolved in about 2-3 days) it might be fatal for kids, the elderly, and immunocompromised individuals. Food sources vary from meat, other poultry products, fish, milk and related items (cream stuffed bakery items), salad from plants etc. dominant source of food contamination is unhygienic food handling. Enterotoxins that are produced by *S. aureus* are responsible for staphylococcal food poisoning. As toxins are already present at the time of consumption of contaminated food the incubation period of this bacteria is relatively short. Major symptoms include 'nausea, vomiting, abdominal cramps, and diarrhea'. To prevent food-borne intoxication by *S. aureus* proper hygiene needs to be maintained and food handlers should be educated [165].

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