
# Immunity Response Against Methicillin-Resistant *Staph aureus* Infection (Literature Review)

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ABSTRACT

This articles highlight on the role Immunity Response Against Methicillin-Resistant *Staph aureus* Infection , the study showed that interleukin-6 (IL-6) regulates the immune system and mediates inflammation, This response will give you a rundown of interleukin-6, what it does, and how it's involved in many disorders .while the The chemokine interleukin-8 (IL-8), sometimes called CXCL8, plays a role in controlling immunological responses and inflammation. It is essential for attracting and activating neutrophils to infection and tissue damage sites. Macrophages, endothelial cells, fibroblasts, and epithelial cells all contribute to the production of IL-8 when exposed to pro- inflammatory stimuli such as cytokines, tissue damage, or bacterial or viral infections

**Keywords:** Immunity Response, Methicillin-Resistant *Staph aureus* Infection

## Introduction

the opportunistic pathogen *Staphylococcus aureus* can colonise the nasal mucosa and skin, leading to a host of infections that can range from relatively harmless skin blemishes to potentially fatal conditions like septic shock, endocarditis, osteomyelitis, and pneumonia .The identification of methicillin-resistant *staph aureus* (MRSA) increases the severity of the *S. aureus* infection (1 ). *Staphylococcal aureus* antibiotic resistance is linked to the production of penicillin-binding protein 2a (PBP2a), which is encoded by the mecA gene. This gene is found on a mobile genetic element called staphylococcal cassette chromosomal mec (SCC*mec*) . SCCmec can be categorised into many categories based on its gene structure and makeup. According to research (2), types I, II, and III are more likely to have resistance genes, which makes them connected with healthcare-associated MRSA (HA-MRSA). On the other hand, types IV and V are believed to be related to community-associated MRSA (CA-MRSA).Furthermore, *S. aureus*, which is resistant to antibiotics, is a highly adaptable pathogen capable of producing a wide range of virulence factors that can kill host cells and induce infections through multiple mechanisms (;). *Staphylococcus aureus* produces many virulence factors that trigger inflammatory reactions and tissue damage, as well as different cytokines, such as interleukin-6(IL-6). Although it is mostly a proinflammatory cytokine, IL-6 can also function as an anti-inflammatory cytokine by inhibiting TNF-α, and it is implicated in both inflammation and homeostatic processes. It is IL-6 that plays a pivotal role in T cell recruitment and B and T cell synthesis during inflammation and delayed T cell death . Furthermore, IL-8 plays a role in attracting T cells, Basophils, and Neutrophils (3). Research has demonstrated that TNF-α

triggers the production of IL-8, whereas IL-10 suppresses its production. IL-10 is a cytokine that is anti- inflammatory that plays a crucial role in controlling immunological responses.IL-10 inhibits the production of proinflammatory cytokines like IL-6 and decreases the expression of TNF-α, T helper type 1 cytokines, and Major histocompatibility complex (MHC) class II molecules (4 )

## 1. Staphyloccal cassette chromosome mec(SCC*mec*)

Compared to *S. aureus* strains that are susceptible to methicillin, MRSA strains exhibit unique patterns related to microbiology and therapy . The acquisition of the mecA gene is responsible for methicillin resistance. The presence of this gene in the *S. aureus* genome is not natural, and its expression is a result of the development of a unique penicillin-binding protein known as PBP2a. PBP2a has a lower affinity for β- lactam antibiotics compared to other PBPs. One mobile genetic element known as the staphylococcal cassettes chromosome mec (SCCmec complex) typically carries the mecA gene, which is present both in coagulase-positive as well as -negative staphylococci( 4). At its core, SCCmec is made up of two gene complexes: *ccr* and *mec*. In addition, the *ccr* genes complex, which produces site-specific recombinases and open reading frames, makes SCCmec mobile. According to, the *mec* gene complex can incorporate many unrelated resistance determinants through insertion elements, as well as the *mec*A gene and the mecR1-mecl regulatory genes. Thirteen (I–XIII) SCCmec types have previously been established based on the combination of ccr allotypes and the mec gene complex( 5). The two most common types of methicillin-resistant Staphylococcus aureus (MRSA) strains are those found in hospitals and those in the community . HA- MRSA infections have been linked to longer hospital stays and higher healthcare expenses . A high morbidity and mortality rate is related to infections attributed to HA-MRSA strains, according to clinical research. These strains typically exhibit resistance to multiple drugs, which can restrict the choice of an appropriate antibiotic for treating staphylococcal infections . Panton-Valentine leukocidin is one of the virulence factors that an increasing number of CA-MRSA strains are expressing; this protein is linked to devastating conditions including severe necrotic infections. CA-MRSA bacteria typically exhibit reduced susceptibility to non-β-lactam antimicrobials in comparison to other classes of antimicrobials (6 ). HA-MRSA isolates are commonly classified as SCCmec types I to III, whereas types IV and V are typically linked to CA-MRSA isolates . HA-MRSA isolates in the United States predominantly possess SCCmec type II, but in other countries, these isolates typically possess SCCmec type III SCCmec typing has yielded compelling evidence supporting the existence of a different genesis of HA-MRSA strains apart from CAMRSA strains (7).

## 2. The role of Immune System toward *Staphylococcus aureus*

Human immune systems identify and eliminate infections. The immune system has innate and adaptive parts. The initial line of defence is the innate immune system, which detects and eliminates infections . Pattern recognition channels that recognize non-specific bacterial illness signals rapidly induce innate immune reactions, the main defence against bacterial infections . The activation of neutrophils and macrophages is a prominent effect ( 8). Toll-like Receptors activate innate immune cells that boost antimicrobial responses, inflammation, and effector cells. This produces interferons, proinflammatory, and cytokines. Fever is caused by local host cell pro-inflammatory cytokines . Acquired (adaptive) host immunity, the second type of immunity, is more developed than natural immunity and developed with each infectious agent encounter and repeated pathogen exposure, increasing its defence storage capacity and features . This immunity is faster and stronger and responds differently to each environmental influence. The adapted host immune response targets specific microbial antigens via T cell activation and B-cell antibody production, with memory for that pathogen in recurrent bacterial infections(9 ).

## 3. Innate immune responses toward *S. aureus*

Body's largest organ, skin, defends itself from surrounds. Tissue that transports extraterrestrial antigens causes immune reactions(10). T lymphocytes, Langerhans cells, melanocytes, and keratinocytes are important skin cells. Langerhans DCs collec *S. aureus* t skin antigens prior to maturation. Nucleotide-binding oligomerization domain NOD-1, NOD-2, Toll-like Receptors (TLRs), and CD36 in keratinocytes detect Pathogen-associated molecular patterns (PAMPs) and microbial pathogens first . The receptors trigger transcription factors including the AP1, NF-kB, and CREB, which create the chemokines cytokines, and antibacterial effectors such as Antimicrobial peptides (AMPs) and inducible nitric oxide synthase (iNOS) . Peptidoglycan and lipopeptides are tracked by TLR-1, TLR-2, and TLR- 6( 11). Various stages of *S. aureus* infection involve this TLR. Defensins, cathelicidin LL-37, and neutrophil antimicrobial peptides are released by keratinocyte TLR-2 when it recognizes bacterial infections; these molecules cause the bacteria's membranes to become permeable( ). White phagocytic neutrophils with chemotaxis are another line of unspecific immunedefense Acute reactions and *S. aureus* depend on neutrophils. Inflammation, phagocytic effector reactions, antimicrobial peptide synthesis, and the intracellular Pattern recognition receptors (PRRs) that recognize microbial peptidoglycan are all caused by NOD-1 and NOD- 2(12). NOD-2 compounds detect *S. aureus* muramyl- dipeptide( ).Immature bloodstream macrophages are monocytes. Dermal macrophage cells effectively ingest and kill *S. aureus* by creating reactive nitrogen and oxygen species, antimicrobial peptides, and removing proteins that deprive microbes of essential micronutrients . Dermal macrophages also produce chemo-attractant molecules that recruit neutrophils via MyD88 and IL-1-R . Since it quickly apoptoses, neutrophil immune cells must be eliminated from the infection site. To hasten neutrophil mortality, *S. aureus* cells release toxins like Panton-Valentine leukocidin, α- toxin, phenol-soluble modulins, and γ-hemolysin. These toxins cause necrosis and release danger-mediated molecular patterns(13). S. aureus-specific responses are triggered by PAMPs in Langerhans cells that swallow pathogens and migrate to draining lymph nodes, according to Dejani.. Many skin dendritic cell subtypes may not fight *S. aureus* infection . C3b and IgG opsonin-coated *S. aureus* cells show different antibacterial activities . Neutrophils can eliminate infections with toxins . Defensins, cathelicidin- related peptide, and antimicrobial peptide LL37 are all produced during degranulation. Proteinase-3, elastase, lactoferrin, lysozymes, cathepsin, and azurocidin are all released during degranulation. *S. aureus* is contained in the host skin by Neutrophil Extracellular Traps (NETs) DNA constructs released by neutrophils via TLR2 and MyD88 to prevent bacteremia . NET degradation and 2'-deoxyadenosine enhance macrophage death, allowing *S. aureus* cells to survive in abscesses . Cathelicidin, RNase7, dermcidin, beta-defensins, and HNPs interact with cutaneous *S. aureus* cells. Glenthøj et al. found that neutrophils release high rates of HNPs, one-half of which include peptides within their granules. (14 ) found that keratinocytes, the macrophages and DCs produce four human β-defensins (hBDs). Cathelicidin, or LL-37, is a 37- amino acid derivative of the 18 kDa cationic antimicrobial protein that has strong action against *Staphylococcus aureus*( ). RNase 7, another human keratinocyte AMP, targets *S. aureus* . Dermacidin is produced by eccrine sweat glands that are active against *Staphylococcus aureus*( ). When the innate immune system's complement system is activated, it triggers cytolytic and severe inflammatory responses. Host adaptive immune defenses were manipulated . According to Parnham and Ross ( ), the complement can be activated through traditional, alternative, and lectin recognition routes. All methods create bacterial C3 convertase complexes . C3 convertase labels high-C3b and iC3b microbial antigens . Opsonize is absorbed by phagocytic complement receptors . The staphylococcal complement inhibitor is a distinct component that is produced by *Staphylococcus aureus* cells. It attaches to the surface of staphylococci and inhibits their C3 convertases( 15).

*S. aureus* protection in mice is not dependent on T lymphocytes . The activities of various types of

T lymphocytes vary, and mouse evaluations and HIV patients' susceptibility to staphylococcal infections have shown these differences . Most CD4- and CD8-positive T cells have long been identified as the host's principal adaptive immune weapon . CD8-positive T lymphocytes destroy intracellular microbial infections by cytolyzing infected human cells . There has been no discernible role for CD8 (positive) T lymphocytes in S. aureus infection or staphylococcal super-antigen exposure, which is in line with the idea that S. aureus cells were an early extra cellular bacterial pathogen. Naive CD4+ T cells are polarized against diverse effector functions by the cytokine milieu that stimulates their TCR receptor. Cytokine formation profiles determine Th lymphocyte function. Humans will have a rate of polarized lymphocytes that are memory lymphocytes waiting for antigen stimulation. In addition to CD4 positive and CD8-positive positive T lymphocytes, new types of T lymphocytes named γδ T lymphocytes, NK cells, as well innate lymphoid cells have been identified. These cells primarily participate in innate immune responses at mucosal sites rather than antigen- specific memory. However, recent research has suggested that γδ T lymphocytes may be able to participate in memory reactions under certain circumstances ( 16).

**4. Interleukin-6 (IL-6)**

Among its many important roles in health and disease, interleukin-6 (IL-6) regulates the immune system and mediates inflammation. It has been the subject of substantial research since its 1986 discovery. This response will give you a rundown of interleukin-6, what it does, and how it's involved in many disorders, with sources to back up each claim.

1. T, B cells, monocyte/macrophage, fibroblast, and endothelial cells generate interleukin-6 in normal and pathological situations (17 ).
2. Both of membrane-bound and soluble versions of the IL-6 receptor (IL-6R) are present, and they are responsible for IL-6's action. Hepatocytes and certain immune cells contain the membrane-bound IL-6R receptor, however cells devoid of this receptor can be activated through trans-signaling by producing the soluble version.
3. The acute phase response includes IL-6, which stimulates hepatocytes to produce C-reactive protein (CRP) and other acute-phase proteins. According to Tanaka et al. ( ), it further promotes B cell development into plasma cells that produce antibodies.
4. IL-6 works both physiologically and has been linked to the development of several illnesses. For instance, IL-6 is known to increase rheumatoid arthritis symptoms, such as joint damage and inflammation.
5. IL-6 plays a role in the initiation and advancement of some cancers. According to Grivennikov et ( ), it has the potential to enhance angiogenesis, tumor cell proliferation, invasion, and survival.
6. It has been found that dysregulated IL-6 signaling is linked to cytokine release syndrome (CRS), a severe immunological response that can occur during specific immunotherapies such as chimeric antigen receptors T- cell(CAR-T) therapy .
7. In different situations and through different signaling pathways, IL-6 can have either pro- or anti-inflammatory effects. Can enhance immune response amplification by promoting the production of additional pro-inflammatory cytokines including IL-1 as well as tumor necrosis factor- alpha (TNF-ί). Contrarily, IL-6 can suppress pro-inflammatory signals and have anti-inflammatory effects through increasing the synthesis of soluble TNF receptors and IL-1 receptor antagonists (IL-1Ra)(18).

Inflammatory bowel disease (IBD), systemic lupus erythematosus ( (SLE), and multiple sclerosis (MS) are only some of the autoimmune illnesses that have been linked to the presence of IL-6 in their aetiology. In these diseases, a malfunction in its synthesis and signaling might exacerbate chronic inflammation and harm tissues .

9. IL-6 levels are elevated in a number of inflammatory chronic disorders, including psoriasis, Crohn's disease, and rheumatoid arthritis. According ( ), IL-6 has a role in these disorders by prolonging inflammation and tissue damage.

10. A significant role for IL-6 has been found in the cytokines release syndrome (CRS), an illness that can be fatal marked by an overabundance of immune response. High levels of IL-6 are related to CRS, which can develop as a reaction to medicines such as CAR-T cell therapy and immune checkpoint inhibitors (19 ).

11. The effects of IL-6 on different disorders have been studied as potential treatment targets. The IL-6 receptor can be blocked by monoclonal antibodies, and medications like sarilumab and tocilizumab have been authorized in the management of inflammatory disorders including rheumatoid arthritis.
Tanaka et al. found that these antibodies helped reduce inflammation and improve symptoms.

12. The process of hematopoiesis, the creation of blood cells, is greatly influenced by IL-6. It promotes the development of specific immune cell types, such as plasma cells, B cells, and T cells. IL-6 effects on hematopoietic stem cell differentiation and maturation as well( ).

13. The role of interleukin-6 in the development of cardiovascular illnesses has been suggested. Heart failure, unfavourable remodeling of the heart, and atherosclerosis are all worsened by elevated IL-6 levels. IL-6 causes inflammation, problems with capillary function, and the growth of vascular smooth muscle cells, all of which can lead to heart problems (20 ).

14. The modulation of metabolism is a role of IL-6. It plays a role in the onset of insulin resistance, a hallmark of diabetes type 2 mellitus. Insulin signaling can be impaired by IL-6, which can lead to chronic low-grade inflammation and insulin resistance. These are critical factors in the development of metabolic dysfunction and insulin resistance .

15. Neuroinflammation and neurodegenerative disorders have both been linked to IL-6. Conditions like multiple sclerosis, Alzheimer's disease, and Parkinson's disease are associated with elevated IL-6 levels. IL-6 activates microglia and induces central nervous system pro-inflammatory processes, which damage and malfunction neurons .

16. Exercising and physical activity have been the settings of IL-6 studies. It has favorable effects on metabolism, immunological function, and muscle adaption; it is released by skeletal muscles during exercise. As a myokine, IL- 6 encourages the regeneration and repair of muscles .

**5.Interleukin-8 (IL-8)**

The chemokine interleukin-8 (IL-8), sometimes called CXCL8, plays a role in controlling immunological responses and inflammation. It is essential for attracting and activating neutrophils to infection and tissue damage sites. Macrophages, endothelial cells, fibroblasts, and epithelial cells all contribute to the production of IL-8 when exposed to pro- inflammatory stimuli such as cytokines, tissue damage, or bacterial or viral infections .It binds to neutrophils' CXCR1 and CXCR2 receptors to attract them to inflammatory areas( 21).When neutrophils are activated by IL-8, they release inflammatory mediators such as reactive oxygen species, antimicrobial peptides, and more It has been linked to several autoimmune and inflammatory disorders, such as Chronic obstructive pulmonary disease (COPD) , inflammatory bowel disease (IBD), asthma, and rheumatoid arthritis ( ). Breasts, colorectal, lung, and pancreas cancers are among those that have linked IL-8 to tumour growth and metastasis, in addition to its inflammatory functions( 22).IL-8 promotes endothelial cell migration and proliferation, which helps generate new blood arteries .IL-8 is a key target for treating inflammation, immunological responses, and disease processes ( ). 1. IL-8 is an example of a chemokine that belongs to the CXC family. Its N- terminus is defined by a conserved amino acids motif called Cysteine-X-Cysteine. This motif binds receptors and activates signaling (23 ).

2. In addition to neutrophil chemotaxis, IL-8 can attract and activate T, B, natural killer, and monocyte (24).

3. Tumour, fibroblast, and epithelial cells produce IL-8 as well as immune cells. Inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1, microbial products, and hypoxia can stimulate its synthesis (25).

4. Many disorders are linked to IL-8 dysregulation. Rheumatoid arthritis, psoriasis,

and chronic inflammation can all be brought on by an overabundance of interleukin-8 (IL-8) (26).

5. Many respiratory disorders are linked to IL-8. Asthma and COPD are lung diseases where IL-8 is involved in neutrophil recruitment and activation, which in turn causes inflammation of the airways and tissue remodeling (27).

6. IL-8 promotes cancer growth and metastasis. It boosts tumour cell survival, angiogenesis, and migration and invasion( 28).

7. Therapeutic IL-8 and receptor targeting ongoing. To combat the pro- inflammatory effects of IL-8-mediated signalling, several strategies have been developed, such as gene therapies, small chemical inhibitors, and monoclonal antibodies (29 ).

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