**Chapter name:** Methicillin Resistant *Staphylococcus aureus* (MRSA): a versatile pathogen

*Staphylococcus aureus* is a Gram-positive, non-motile, coagulase-positive, coccoid bacterium belonging to the phylum Bacillota ([1](#_ENREF_1)). It was first detected by the Scottish surgeon Alexander Ogston in a leg abscess purulent sample during the 1880’s, soon after that, *S. aureus* was formally identified by Fredrich Rosenbach ([2](#_ENREF_2)). The *Staphylococcus* genus contains a large collection of species, estimated at about 52 species and 28 sub-species, however, *S. aureus* remains to be the most clinically important species in the genus ([1](#_ENREF_1)).

*Staphylococcus aureus* is commonly prevalent in human commensal microbiota, predominantly in the nasal mucosa, in fact, reports show that more than 20% of the general public commensally harbor *S. aureus* in the nasopharyngeal mucosa ([3](#_ENREF_3)). Moreover, other regions of the body can be colonized by *S. aureus* such as the axillae, gastrointestinal tract and the groin area; interestingly, extra-nasal carriage rates are positively proportional with persistent nasal colonization ([3](#_ENREF_3)). Evidently, persistent nasal carriers in general, possess larger clonal bacterial loads which often translated to higher dispersal events to various parts of the body ([3](#_ENREF_3)). Additionally, nasal colonization has been linked to persistent and recurrent staphylococcal infections ([4](#_ENREF_4), [5](#_ENREF_5)). It has been suggested that colonized areas may act as bacterial reservoirs in the body, from which *S. aureus* may be introduced to the bloodstream and other soft tissues, as a result of a breach or disruption in cutaneous or mucosal barriers due to wounds, compromised immune system, surgical intervention, or chronic skin condition ([1](#_ENREF_1), [4](#_ENREF_4)). Henceforth, *S. aureus* commensalism presents a major risk factor for future staphylococcal infections, and that is reflected by the globally reported high morbidity and mortality ([6](#_ENREF_6)). It is worth noting that *S. aureus* may survive on animate objects that come in contact with colonized areas of the body ([7](#_ENREF_7)). Such items like clothing, towels, furniture, or stationery may harbor *S. aureus* for weeks, though more investigations are required on the significance of fomites role in colonization and propagation ([7](#_ENREF_7), [8](#_ENREF_8)).

For many decades, *S. aureus* has been associated with nosocomial opportunistic infections, consequently, it is considered to be the leading cause of skin and soft tissue infections (SSTIs), bacteremia, endocarditis, and osteomyelitis ([7](#_ENREF_7)). In the early attempts to manage these infections, penicillin did provide an effective treatment, however, it was short-lived as 90% of hospital-borne strains demonstrated resistance mediated by the β-lactamase gene *bla*Z after few years of using penicillin ([9](#_ENREF_9)). Another short-lived success was attained by methicillin, a semi-synthetic, β-lactamase insensitive, anti-staphylococcal penicillin that was introduced in the late 1950’s, however, resistance to methicillin was documented in less than a year of clinical usage ([7](#_ENREF_7), [9](#_ENREF_9)). Initially, it was commonly prescribed in clinical practices but due to the resistance mediated by *mec*A gene and the later discovered human toxicity, methicillin has been replaced by other penicillins like oxacillin, dicloxacillin and flucloxacillin, yet the name methicillin-resistant *Staphylococcus aureus* (MRSA) is still widely used in clinical and scientific ventures ([1](#_ENREF_1)).

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## *Pathogenesis*

MRSA is implicated in a large spectrum of clinical conditions including necrotizing pneumonia, necrotizing fasciitis, skin lesions, pleural empyema, septic thrombophlebitis, septic shock, Waterhouse-Friderichsen syndrome and myositis ([8](#_ENREF_8), [10-14](#_ENREF_10)). It is also associated with facilitating pro-inflammatory responses and oxidative stress in the host, induced by neutrophil chemotaxis interruption and phagocytosis inhibition, complement system activation as well as promoting apoptosis and necrosis ([15](#_ENREF_15)). Indeed, the upregulation of many pro-inflammatory signals such as tumor necrosis factor α (TNF-α), IL-1β/4/6, macrophage inflammatory protein (MIP-1α), glutathione S-transferase (GST) among others, plays an important role in MRSA pathogenesis ([15](#_ENREF_15), [16](#_ENREF_16)).

Moreover, MRSA pathogenesis is further enhanced by the production of structural and secreted virulence determinants. In fact, a virulence determinant may facilitate multiple functions, and a pathological role may be induced by multiple virulence determinants, it is depended on by both virulence gene acquisition and expression ([4](#_ENREF_4), [6](#_ENREF_6)).

Adherence and localization of MRSA infection is often initiated by the expression and production of surface proteins called Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs), such as protein A, clumping factor A & B, fibronectin-binding protein A (FnBPA) and FnBPB, which facilitate adherence to host tissues and implanted prosthetic devices ([4](#_ENREF_4), [17](#_ENREF_17), [18](#_ENREF_18)). It is postulated that the production of MSCRAMMs in combination with wall teichoic acid (WTA) is obligatory in a many infections including osteomyelitis and endocarditis, owed to to their ability to bind to collagen, fibrinogen and fibronectin ([4](#_ENREF_4), [18-20](#_ENREF_18)). Upon adherence, *S. aureus* would be able to construct biofilms (e.g. PIA, PNAG and Bap) as well as antiphagocytic microcapsules (e.g. CP5 and CP8), as these structures would permit proliferation and evasion of host immune defenses and antimicrobial chemotherapy ([4](#_ENREF_4), [21-24](#_ENREF_21)).

In addition, MRSA expresses many degradative enzymes like lipases, proteases and elastases (e.g. metalloprotease SepA, V8 protease, triacylglycerol esterase, and phosphatidylinositol (PI)-specific phospholipase C, PIPLC) that enable invasion of host tissues and promote bacterial infiltration into other sites of the body, throughout the infection process ([4](#_ENREF_4), [25-27](#_ENREF_25)). Moreover, numerous toxin families (e.g. superantigens, hemolysins, leukocidins, and enterotoxins) are often expressed by MRSA during infection, these proteins are associated with clinical conditions like septic shock syndrome, bullous impetigo and food poisoning ([28-30](#_ENREF_28)). It is worth noting that some of these toxins modulate the immune responses of the host which plays a substantial role in complicating MRSA pathogenesis through inducing leukocytosis, neutropenia and cytokine storms ([1](#_ENREF_1), [4](#_ENREF_4)).

Interestingly, MRSA expression of virulence factors is highly regulated, for instance, MSCRAMMS are often produced during the exponential growth phase of the bacteria whereas toxins are often expressed throughout the stationary phase of the bacterial life cycle ([4](#_ENREF_4)). Many quorum sensing mechanisms are suggested to mediate such regulation, such as the accessory gene regulator (*agr*) system which decreases bacterial surface proteins expression and increases the expression of secreted virulence factors at the beginning of the stationary phase in response to signals in the microenvironment ([31](#_ENREF_31)). It also facilitates the expression of α-toxin, TSST-1 and phenol soluble modulins (PSMs), upregulation of fibrinogen-binding proteins, increased expression of *mec*A gene and effectively involved in SSTIs and invasive infections ([7](#_ENREF_7), [32](#_ENREF_32)). Other quorum sensing system have been investigated such as SaeRS system that downregulates bacterial adhesion and invasion, also, ArlRS system that counters agr system autoinduction by inhibiting the expression of hemolysins and exoenzymes ([33-35](#_ENREF_33)). Notably, the constellation of virulence factors produced by MRSA is not uniformed in all strains, some are influenced by the bacterial genetic background (e.g. clonal complex or sequence type) yet others are harbored via mobile genetic elements (MGEs) unrelatedly to the genetic background, all in all, there is limited information on the virulence gene expression during infection and remains incompletely understood, hence, more in-depth investigations into genome level research and virulence mobile genetic elements are warranted to better understand the complexity of MRSA evolution ([1](#_ENREF_1), [4](#_ENREF_4)).

## *Exotoxins*

MRSA harbors a plethora of exotoxins that play key roles in bacterial virulence ([28](#_ENREF_28)). They are associated with conditions like necrotizing pneumonia, toxic shock syndrome, deep-seated skin infections and staphylococcal scaled skin syndrome ([28](#_ENREF_28)). Most of toxin-encoding genes are propagated between strains through mobile genetic elements (MGEs) which explains the heterogeneity in toxin profiles expressed by MRSA strains ([36](#_ENREF_36)). These exoproteins may fulfill one or many functions including manipulating the innate and adaptive immune responses of the host, converting host cells into nutrients required for bacterial growth and damaging host tissues and inter-cellular junctions which enhances bacterial proliferation and propagation ([36](#_ENREF_36)). Three major groups describe exotoxins produced by MRSA, superantigens (SAgs), exfoliative toxins (ETs) and pore-forming toxins (PFTs) ([37](#_ENREF_37)).

Staphylococcal SAgs are a family of about 26 exotoxins that include toxic shock syndrome toxin (TSST-1), enterotoxins (SEs) and staphylococcal superantigen-like toxins ([28](#_ENREF_28), [38](#_ENREF_38)). SAgs induce the activation of T lymphocytes and the release of proinflammatory cytokines, and are associated with staphylococcal food poisoning (SFP) and staphylococcal toxic shock syndrome (TSS) ([28](#_ENREF_28), [38](#_ENREF_38)). They are encoded by MGEs like plasmids, staphylococcal pathogenicity islands (SaPIs), and prophages ([38](#_ENREF_38)). Exfoliative toxins (ETs) or epidermolytic toxins consist of 5 known exotoxins (ETA, ETB, ETC, ETD and ETE) ([39](#_ENREF_39)). They function as molecular scissors, as they cleave cell-cell adhesion arrangements in the epidermis as well as the keratinocyte junctions (desmoglein-1) ([36](#_ENREF_36)). This proteolytic activity facilitates bacterial skin invasion, skin peeling and blister formation, hence they are associated with bullous impetigo and staphylococcal scaled skin syndrome ([36](#_ENREF_36), [37](#_ENREF_37)).

Pore-forming toxins (PFTs) are the most common class of toxins amounting for about 30% of all characterized bacterial toxins ([40](#_ENREF_40)). They are associated with host cell lysis through damaging the cell membrane as well as through immune modulation ([40](#_ENREF_40)). PFTs can be categorized into hemolysins, leukotoxins or phenol soluble modulins ([37](#_ENREF_37)). They consist of a single subunit like α-hemolysin, or bi-component like γ-hemolysin, Panton-Valentine Leukocidin (PVL), LukED and LukAB ([41](#_ENREF_41)). These toxins may target leukocytes, natural killer cells, dendritic cells, T lymphocytes and erythrocytes, and are associated with necrotizing infections ([42](#_ENREF_42)).

### *Panton-Valentine Leukocidin (PVL)*

PVL is a staphylococcal bi-component exotoxin originally discovered by Panton and Valentine in 1932 ([43](#_ENREF_43)). It demonstrates a strong cytotoxic activity, targeting immune cells, like neutrophils, monocytes and macrophages, resulting in the formation of pores that span throughout the plasma membrane and ultimately, induce cell death ([42](#_ENREF_42)). PVL used to be strictly associated with CA-MRSA however, many epidemiological studies around the world demonstrated the uptake of this toxin by other MRSA lineages, making it a common fixture in MRSA pathogenesis ([44](#_ENREF_44)). It is associated with inflammatory infections, lung damage, necrotizing pneumonia, necrotizing fasciitis and SSTIs ([45-49](#_ENREF_45)). Because of its leukocytic properties, PVL is linked to the manifestation of thrombosis in association with osteomyelitis, also, many reports established a connection with life-threatening necrotic infections in children ([50](#_ENREF_50), [51](#_ENREF_51)). In fact, administrating purified PVL alone was sufficient to cause inflammation, localized lesions, weight loss and high rate of mortality in vitro and in a mouse pneumonia model as well as in a rabbit necrotizing pneumonia model ([52-54](#_ENREF_52)). Additionally, it was illustrated that incubating PVL with human neutrophils not only induced proinflammatory cytokines production and oxidative burst reaction, but it induced cell death within 20 minutes upon incubation which is much faster than incubating the cells with PVL-producing live bacteria (2-3 hours), which demonstrates a substantial cytotoxic potential upon release ([55](#_ENREF_55)).

PVL is released by the bacteria as inactive monomeric subunits that eventually oligomerize on the membrane of the target immune cell, forming a mature pore-forming complex ([42](#_ENREF_42)). The subunits of PVL (LukS-PV and LukF-PV) are secreted by *S. aureus* into the surrounding microenvironment which is prompted by receiving nearby signals when coming in contact with the host immune cells through the bacterial quorum sensory systems (e.g. SaeRS two-component regulatory system) ([42](#_ENREF_42)). The initial binding to the target cell membrane start with LukS-PV subunit binding with the chemokine receptor C5a anaphylatoxin chemotactic receptor 1 (C5aR1) or C5aR2 to lesser extent ([56](#_ENREF_56), [57](#_ENREF_57)). The formation of a functional β-barrel hetero-octameric pore-forming complex is prompted by the recruitment of LukF-PV subunits following the initial binding to the immune cell ([56](#_ENREF_56), [57](#_ENREF_57)).

Cell death mechanism mediated by PVL is not fully understood, but essentially, PVL pore-formation induces the efflux of cytoplasmic potassium ions (K+) which eventually activates NLRP3 inflammasome and leading to the production of IL-1β and other pro-inflammatory cytokines ([58-60](#_ENREF_58)). Consequently, IL-1β release would upregulate numerous proinflammatory components in the host tissue such as TNF, PLA-2, COX-2 and ICAM-1 among others, thus perpetuating the inflammatory effect of PVL ([61](#_ENREF_61)). Interestingly, this cellular stress caused by PVL may induce granulocytes to release additional proinflammatory mediators like leukotriene B4 (LTB4), histamine and IL-8 ([46](#_ENREF_46), [62](#_ENREF_62)).

### *Inflammasome Activation*

Cellular injuries prompted by pathogens, metabolic stress or DNA damage are identified by the host innate immune system through many receptors (e.g. nucleotide-binding oligomerization domain (NOD)-like receptors, NLRs) that aim to protect and repair damages presented by these cellular insults, triggering a range of inflammatory responses to resolve such injury ([63](#_ENREF_63)). Yet in instances where the damages are too great to be resolved, injured cells commit suicide via apoptosis or necrosis and subsequently removed by specialized immune cells ([63](#_ENREF_63)).

In the context of PVL pathophysiology, the inflammasome activation commences with the binding of PVL subunits with C5a receptors which are NLRs on the cell membrane of leukocytes ([42](#_ENREF_42)). These receptors are associated with chemotaxis, enzyme release and acute inflammatory responses, more specifically, the upregulation of IL-6, IL-8, IL-1β and HMGB1, as well as mediating cytokine storms in sepsis ([64](#_ENREF_64)).

The mechanism by which PVL facilitates cellular inflammation is yet to be fully elucidated, however, the postulated mechanism is through the activation of the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome ([63](#_ENREF_63)). It is a multiprotein complex that lead to the exocytosis of the proinflammatory cytokines IL-1β and IL-18 through the activation of caspase-1 as well as generation or ROS and alterations in Ca2+ and K+ ion fluxes ([63](#_ENREF_63)). Under healthy conditions, the NLRP3 pathway is auto-repressed, yet danger signals derived from pathogen invasion, pathogen-associated molecular patterns (PAMPs), pathogen-derived toxins, environmental irritants, damage-associated molecular patterns (DAMPs) and metabolic dysregulation would prompt activation ([63](#_ENREF_63)). Additionally, pathways by which NLRP3 activation ensues differ as well, events triggering NLRP3 like potassium ions efflux, lysosomal permeabilization, cathepsin B cleavage or ROS production all have been implicated in PVL mediated activation of NLRP3 inflammasome, yet more investigations are needed to fully understand the paradigm ([60](#_ENREF_60), [63](#_ENREF_63)).

## *Antibiotic Resistance*

Antimicrobial agents represent a group of substances that interfere with bacterial growth and persistence, with effects that can be described as bacteriostatic or bactericidal ([65](#_ENREF_65)). For many decades, these substances were used in treating bacterial infections, which prompted susceptible targets to develop mechanisms to evade the inhibitory effects of these agents ([65](#_ENREF_65)). Moreover, this resistance was fast-tracked as a consequence to the selective pressure imposed by inappropriate antimicrobial usage, especially, the liberal administration of broad spectrum antibiotics like β-lactams, tetracyclines, macrolides and aminoglycosides ([65](#_ENREF_65)). The widespread of resistance genes poses a major public health problem as affirmed by the World Health Organization recognizing this phenomenon as a major global health threat as well as in the legislative measures imposed by the European Parliament (EU Regulation 2019/6) to limit or eliminate the use of antibiotics especially in metaphylaxis and feed additives for livestock ([66](#_ENREF_66), [67](#_ENREF_67)).

Bacterial resistance to antimicrobial agents can be divided into two fundamental types, innate and acquired resistance ([65](#_ENREF_65)). Innate resistance, otherwise known as intrinsic or primary, describes a natural lack of susceptibility to a certain drug due to absence of receptor for the antibiotic, cell wall impermeability, low affinity or inhibitory enzyme production ([68](#_ENREF_68)). It can be manifested in genus-specific or species-specific manner ([68](#_ENREF_68)). This general insensitivity to certain antimicrobial groups has been manifested in *Mycoplasma* spp. resistance to glycopeptides and β-lactam antibiotics due to the absence of bacterial cell wall which disables the mechanism of action of in these groups of antimicrobial agents, similarly, enterococcal intrinsic resistance to folate pathway inhibitors (e.g. trimethoprim and sulfonamides) is carried out through exogenous folate dependency, thus, inhibiting folate synthesis pathways will not affect the viability of the bacteria ([65](#_ENREF_65)).

On the other hand, acquired resistance to antimicrobial agents occurs as a result of mutations in chromosomal target genes or due to the acquisition of foreign resistance genes ([65](#_ENREF_65)). These foreign genetic materials may be uptaken by the bacteria in the form of mobile genetic materials (MGEs) like plasmids, transposons, integrons and chromosomal cassettes, through mechanisms yet to be fully elucidated ([69](#_ENREF_69)). This category of resistance may follow many mechanisms such as enzymatic inactivation of the antimicrobial, decreasing intracellular drug accumulation or modification of target sites, establishing alternative metabolic pathways, among others ([70](#_ENREF_70), [71](#_ENREF_71)). It is worth noting that acquired resistance genes often propagated through horizontal gene transfer, making them available for a wider range of bacteria, pathogenic or commensal ([68](#_ENREF_68)).

Furthermore, β-lactam resistance in *S. aureus* is an example of acquired resistance, as Penicillin-Resistant *Staphylococcus aureus* (PRSA) strains are able to enzymatically inactivate penicillin through the production of β-lactamase through the expression of *bla*Z gene([65](#_ENREF_65), [72](#_ENREF_72)). Moreover, MRSA strains express additional resistance to virtually all β-lactam antibiotics with the exception of 5th generation cephalosporins ([1](#_ENREF_1)). This absence of susceptibility is mediated through the SCC bound *mec*A gene that encodes novel Penicillin-Binding Protein (PBP) called PBP2a which has low affinity for β-lactam antibiotics and ultimately facilitate the transpeptidase function in cell wall synthesis ([73](#_ENREF_73)). Interestingly, a new homologue of the gene *mec*A named *mec*C (*mec*ALGA251) has been detected in isolates recovered from farm animals, mainly belonging to the clonal complex 130, yet mechanism of action and regulation of this gene are yet to be fully understood ([65](#_ENREF_65)).

## *Healthcare-associated (HA) and community-associated (CA) MRSA strains*

Throughout a large part of the 20th century, MRSA was confined in the hospital environment, and known as a multidrug resistant pathogen mostly belonging to SCC*mec* type III single clonal type called phage complex 83A otherwise referred to as the Archaic clone ([74](#_ENREF_74)). Within decades, new MRSA clones emerged in the hospital settings (HA-MRSA) from different genetic backgrounds harboring a variety of SCC*mec* types, mostly I, II and III ([75](#_ENREF_75)). Further emergence of MRSA was reported in the 1990s, as MRSA started to infect individuals in the community void of conventional MRSA infection risk factors, and eventually causing epidemics in various regions around the world such in Aboriginal communities in Australia, Indian reservations in USA and African immigrant populations in Southern France ([75-78](#_ENREF_75)). Such outbreaks were attributed to lack of conventional personal hygiene measures, immense crowdedness and misuse of antimicrobial agents ([75](#_ENREF_75)). Eventually, genetically diverse clones of these community-associated MRSA strains (CA-MRSA) propagated into healthcare facilities and became the dominant clones in hospitals in many regions in the world ([7](#_ENREF_7), [79](#_ENREF_79)). It is suggested that this shift in strain dominance resulted from clone-specific genetic adaptations and variability, in combination with social, environmental and geographical factors, yet it remains to be fully understood ([7](#_ENREF_7)).

At the beginning of CA-MRSA emergence, it was assumed that these clones were initially nosocomial strains that had circulated into the community, however, multilocus sequence typing (MLST) and pulse-field gel electrophoresis studies disputed this notion ([9](#_ENREF_9)). Nowadays, it is postulated that CA-MRSA arose as a consequence of frequent co-colonization of MSSA and the SCC*mec* (type IV and V) donor Methicillin-Resistant *Staphylococcus epidermidis* (MRSE) which are common colonizers of human skin ([9](#_ENREF_9), [75](#_ENREF_75)). This notion is supported by the similarities in sequence types (ST30 and ST8) between MSSA in the skin flora and some epidemic CA-MRSA strains like Oceania clone and USA300 clone, yet these sequence types vary from commonly circulating HA-MRSA clones such as ST5, ST8, ST22, ST36 and ST45; it is worth noting that circulating CA-MRSA clones vary in different geographical regions ([9](#_ENREF_9), [75](#_ENREF_75), [80](#_ENREF_80)). Essentially, both HA-MRSA and CA-MRSA demonstrate resistance to all beta-lactam antibiotics with few exceptions (e.g. 5th generation cephalosporins ceftaroline and ceftobiprole), however, many differences between these two lineages still exist in contexts like resistance profile, virulence factors and clinical morbidity ([7](#_ENREF_7)). In definition, HA-MRSA infections occur in individuals with predisposing risk factors like compromised immune system, undergoing surgery as well as bearing indwelling medical devices, on the other hand, MRSA infection is considered to be caused by CA-MRSA when it is identified from an outpatient, or within 48 hours after admission to a healthcare facility; the patient should not have a recent history of MRSA infection, no history of long term admission to a hospital or nursing home, also, no history of dialysis, invasive medical devices and permanent indwelling catheters ([80](#_ENREF_80), [81](#_ENREF_81)). Additionally, individuals with higher risk of contracting CA-MRSA infections include military personnel, prison inmates, children in day-care centers, homosexuals and athletes in contact sports ([82-85](#_ENREF_82)).

In general, HA-MRSA strains tend to carry SCC*mec* types I, II and III, whereas, CA-MRSA carry the types IV, V and VI ([79](#_ENREF_79), [86](#_ENREF_86)). Also, HA-MRSA harbors a wide range of antimicrobial resistance genes and tends to be multi-resistant, CA-MRSA on the other hand, often express narrower range of antimicrobial resistance ([86](#_ENREF_86)). Additionally, CA-MRSA might express virulence factors like PVL and arginine catabolic mobile element (ACME) that are often absent in HA-MRSA strains ([86](#_ENREF_86)). In addition, differences in the clinical conditions associated with the two lineages have also been reported, as HA-MRSA is often associated with nosocomial infections and sepsis, whereas CA-MRSA is associated with necrotizing pneumonia, SSTIs and necrotizing fasciitis ([86](#_ENREF_86)). Recently, the differences between these two MRSA lineages became less pronounced as CA-MRSA strains propagated into healthcare facilities ([79](#_ENREF_79)). Multidrug resistant CA-MRSA strains have been reported in many regions, including resistance to antimicrobials like erythromycin, clindamycin, mupirocin, tetracycline, fusidic acid, gentamicin ciprofloxacin among others ([87-90](#_ENREF_87)). Also, the spectrum of clinical conditions associated with CA-MRSA has widened to include infections that were mainly associated with HA-MRSA like bloodstream infections, meningitis, prostatic abscess among others, so, the morbidity of CA-MRSA is no longer restricted to SSTIs ([91-93](#_ENREF_91)).

## *Epidemiology*

Historically, numerous HA-MRSA clones have been implicated in outbreaks and epidemics in healthcare facilities, and some of these clones were able to propagate internationally ([4](#_ENREF_4)). HA-MRSA clones like CC8-ST239 (Viennese/Portuguese/Brazilian clone, UK EMRSA-1) and CC5-ST5 (Pediatric clone, USA800) accounted for infections in hospitals in several regions like USA, South America, Southern and Eastern Europe, owing to their seemingly enhanced virulence and transmissibility ([94](#_ENREF_94)). The Brazilian clone for example, was the main culprit in nosocomial invasive infections in the 1990’s in Belem, Brazil, with a high prevalence of about 80% of all isolated *S. aureus* in healthcare facilities ([95](#_ENREF_95)). When compared with sporadic MRSA strains, it was found that this clone has higher adhesion capacity to bronchial epithelial cells and polystyrene as well as the ability to construct biofilms to higher efficiency, which could explain the enhanced ability of this clone to bind, invade and persist in human host ([4](#_ENREF_4), [95](#_ENREF_95)). Currently, two MRSA clones named CC22-ST22 (EMRSA-15) and CC30-ST36 (EMRSA-16) overtook the Brazilian clone to be the predominant HA-MRSA clones in healthcare facilities, since the turn of the millennium ([96](#_ENREF_96)). They have been reported in Asia, the Middle East, Australia, Africa, the Pacific and Europe, this immense distribution is owed to their enhanced ability to acquire antimicrobial and antiseptic resistance genes resulting in surviving many selective pressures within the healthcare environment ([7](#_ENREF_7), [97](#_ENREF_97)).

Similarly, various clones of CA-MRSA caused outbreaks in many regions, yet unlike HA-MRSA, these outbreaks were not confined in healthcare facilities ([4](#_ENREF_4)). During 1990s, a CA-MRSA clone, CC1-ST1 (MW2, USA400), was associated with aggressive MRSA infections in children in Minnesota and North Dakota, USA, these infections were fatal due to clinical complications with necrotizing pneumonia, sepsis and pulmonary abscesses ([98](#_ENREF_98)). Retrospective studies also, found that high prevalence of this CA-MRSA clone has caused infections in immunocompetent children with no predisposing risk factors in Chicago, USA during the period 1988-1995, causing conditions like cellulitis and abscesses ([99](#_ENREF_99)). This enhanced virulence was attributed to many factors such as unique staphylococcal enterotoxin H that can cause toxic shock-like syndrome, also, this clone harbors a plethora of superantigens, exotoxins and enterotoxins ([100](#_ENREF_100), [101](#_ENREF_101)). Interestingly, USA400 is a relative to another epidemic clone called WA-1 clone that was implicated in the first officially recorded CA-MRSA endemic outbreak that occurred in Western Australia among Aboriginal tribes in remote and sparsely populated areas, which may illustrate the expansive reach of community associated MRSA strains ([80](#_ENREF_80)). Additionally in the USA, outbreaks of staphylococcal skin and soft tissues infections in populations like prison inmates, homosexuals, contact-sport athletes and army forces affiliates were reported from the early 2000s to the present, however, the culprit clone was unrelated to USA400 lineage, it was a new PVL-producing clone called CC8-ST8 famously named USA300 ([102](#_ENREF_102)). One of the first reports of USA300 SSTIs outbreaks occurred in Pennsylvania, USA among football players, shortly after that, another outbreak was reported 1500 Kms away in Mississippi state prison where numerous inmates were complaining of aggressive skin infections that later determined to be caused by the same CA-MRSA clone ([7](#_ENREF_7)). USA300 is currently causing outbreaks throughout North America, indicating rapid replacement of USA400; moreover, the high morbidity associated with this clone is not only attributed to the expression of the exotoxin PVL, but also to the expression of ACME that enhances the persistence and virulence of USA300 via enabling survival in low oxygen and acidic niches ([80](#_ENREF_80), [103](#_ENREF_103), [104](#_ENREF_104)).

### *Global Epidemiology*

The burden of MRSA has a capricious geographical distribution, ranging from low prevalence in Nordic countries to very high in parts of Asia and America ([1](#_ENREF_1)). Variations in infection control policies as well as the stringency of antimicrobial administration are considered a driving force in manifesting these geographical variations in MRSA prevalence ([1](#_ENREF_1)).

In Europe, low prevalence of MRSA was sustained in most of the northern region of the continent in countries like Sweden, Denmark, Norway and the Netherlands, as 1-5% of invasive infections were attributed to MRSA, whereas higher prevalence at 25-50% were recorded in the Southern region of Europe in countries like Greece, Italy, Spain and Portugal ([105](#_ENREF_105)). This disparity is pronounced in country-specific reports from Europe, for example a German study on outpatients found that only 4% of SSTIs are caused by MRSA (ST8) and 40% of them were PVL-producing strains, on the other hand, reports from Turkey found that MRSA prevalence was 67% with only 18% PVL prevalence, which further illustrates the lack of uniformity in MRSA clinical dynamics ([106](#_ENREF_106), [107](#_ENREF_107)). MRSA in North America did not show substantial decline as MRSA is still the most common causative agent of SSTIs in the USA which is largely influenced by the emergence of USA300 ([1](#_ENREF_1), [108](#_ENREF_108)). Indeed, community-associated strains dominance was reported as more than 60% of MRSA isolates were characterized as CA-MRSA, 88% of them produce PVL ([108](#_ENREF_108), [109](#_ENREF_109)). Despite the efforts to manage this emergence, rates of bloodstream infections associated with HA-MRSA and CA-MRSA infections in the period from 2012-2017, remain high with only 7.3% reduction in HA-MRSA infections while no significant change occurred in CA-MRSA rates ([110](#_ENREF_110)). Similarly in Canada, in the period from 2007 to 2016, CA-MRSA rates increased from 21% to 56%, while HA-MRSA rates decreased from 79% to 44%, despite the overall reduction in MRSA rates from 28% to 18% ([111](#_ENREF_111)). Interestingly, PVL prevalence remained significantly lower than USA rates at 30% ([111](#_ENREF_111)). Moreover, MRSA reports from Asia and the pacific region vary from country to country, but in general, MRSA accounted for 50% of bloodstream infections in Asia ([112](#_ENREF_112)). Interestingly, even in relatively high income Asian countries, discrepancies in MRSA prevalence is seen, as MRSA prevalence in South Korea amounting for about 70% in 2011, yet in Japan the prevalence was 19% during the same period ([112-114](#_ENREF_112)). Additionally, MRSA prevalence in other countries in Eastern Asia (China, Taiwan, Philippines and Myanmar) ranged from 10% to 46%, while higher rates were reported in the Southeast Asian region (Nepal, Bangladesh, Pakistan and Afghanistan) ranging from 31% to 66% ([115-123](#_ENREF_115)). It is worth noting that despite HA-MRSA outbreaks in Taiwan in the 1990’s, prevalence of MRSA has declined substantially, yet CA-MRSA strains has replaced HA-MRSA at a high margin with PVL prevalence reaching 30% ([113](#_ENREF_113), [117](#_ENREF_117)). MRSA in Australia accounted 20-33% of clinical isolates in the early 2000’s, with PVL prevalence at 28% in the period 2012-2017 ([1](#_ENREF_1), [124](#_ENREF_124)). MRSA reports in Africa vary in coverage, in fact there is a major dearth in data from most African countries as most reports reflect data from single-center studies, yet MRSA prevalence is estimated to be about 50% in most reports with apparent increase since the early 2000’s ([1](#_ENREF_1), [125](#_ENREF_125)). This increase is characterized by a clear dominance in CA-MRSA with PVL prevalence reaching 100% in most reports ([126](#_ENREF_126)).

MRSA epidemiology in the Arabian Gulf region, a cosmopolitan area with high intercontinental traffic, shows an interesting paradigm ([127](#_ENREF_127)). Not unlike the global burden, regional MRSA epidemiology follows similar trends, with emergence and clonal shift to CA-MRSA, as well as increase in PVL prevalence, however, disparities in reported rates, even within a single country, is noticeable, which can be attributed to the lack of uniformed guidelines and MRSA screening programs ([127](#_ENREF_127)). In the Arabian Gulf region, MRSA prevalence among *S. aureus* isolates ranged from 21-31% in Kuwait, Qatar and UAE, however, higher prevalence at 37-67% was reported in Oman, Saudi Arabia and Iran, in fact, multiple studies from Saudi Arabia and Iran have reported high prevalence of MRSA in the range 39-55.3% and 45-67%, respectively ([128-135](#_ENREF_128)). Moreover, CA-MRSA comprised most of MRSA isolates in countries like Bahrain, Kuwait, Qatar, Oman and UAE, on the other hand, HA-MRSA remained to be the predominant lineage in most reports, as in Bahrain, Saudi Arabia, Iran ([129](#_ENREF_129), [132](#_ENREF_132), [134](#_ENREF_134), [136-142](#_ENREF_136)). Fluctuations in PVL prevalence between countries is noticed, studies from some countries reported a rate of 30-39% in Bahrain, Kuwait, Saudi Arabia and Iran ([134](#_ENREF_134), [142-144](#_ENREF_142)). Relatively higher PVL rates have been reported in Qatar, Oman and UAE 44-66%, yet more studies are need to ascertain this high prevalence ([129](#_ENREF_129), [137](#_ENREF_137), [138](#_ENREF_138)).

## *Management*

The high morbidity and mortality of MRSA infections are often predicated on inadequate treatment, underlying illness and complicated comorbidities ([145](#_ENREF_145)). Indeed, numerous scientific reports indicate that invasive staphylococcal infections might have modest probability of long term survival, regardless of the availability of initial treatment or the length of hospitalization ([145](#_ENREF_145), [146](#_ENREF_146)). Post-infection sequelae, like amputations and prostheses implantation, and toxicity and adverse effects of administered antimicrobials may also complicate the clinical management of MRSA infection ([1](#_ENREF_1)). Henceforth, intricate empirical therapy measures have to be implemented when managing MRSA infection.

Prevention measures such as hand hygiene practices, routine screening and precautious contact isolation, have shown mixed results in preventing MRSA transmission when applied individually, however, combined effect of these measures have reduced nosocomial infection rates by 40-60% ([147](#_ENREF_147), [148](#_ENREF_148)). Persistent MRSA colonization and colonization during hospitalization are associated with increased risk of infection, recurrent infections as well as MRSA propagation to other hosts ([3](#_ENREF_3)). It has been suggested that MRSA decolonization may present a way to control MRSA spread by inhibiting transmission and minimizing the risk of potential infections ([1](#_ENREF_1)). Reductions in surgical-site infections as well as nosocomial infections in the ICU have been attributed to effective targeted decolonization efforts ([149](#_ENREF_149), [150](#_ENREF_150)). Decolonization of MRSA is conducted through using topical agents applied nasally, this gel or cream often contains mupirocin as the principal agent, also it can be used in combination with chlorhexidine bathing for more effective restriction ([1](#_ENREF_1), [151](#_ENREF_151)). Nevertheless, it is recommended to use these agents judiciously, due to the emergence and propagation of resistance genes for mupirocin and chlorhexidine among MRSA strains ([152](#_ENREF_152)).

Various antimicrobial agents are used in treating MRSA, targeting different bacterial components ([1](#_ENREF_1)). The chosen antibiotic, the route of administration and the duration of therapy depend on the severity and site of MRSA infection (Table 1), also, continuing with the therapy or implementing adjustments is built around subsequent results of microbiological cultures and antibiotic susceptibility testing ([1](#_ENREF_1)).

For many years, vancomycin has been the cornerstone therapy for MRSA bacteremia, osteomyelitis, pneumonia and endocarditis ([153](#_ENREF_153)). However, challenges in dosing are influenced by obesity, the age of the patient and compromised renal function, especially when considering the potential risk of nephrotoxicity contingent upon vancomycin therapy ([153](#_ENREF_153)). Another FDA-approved first-line antimicrobial agent for MRSA bacteremia is daptomycin that has proven to be comparable with vancomycin in randomized controlled trials ([154](#_ENREF_154)). Nonetheless, some setbacks for daptomycin are well documented in the literature, such as being inactivated by the host’s pulmonary surfactant make it ineffective in pneumonia management, also the emergence of daptomycin-non-susceptible MRSA strains as a result of subtherapeutic dosing, persistent bacteremia and inadequate infection control measures ([155](#_ENREF_155), [156](#_ENREF_156)). In addition to vancomycin, the latest Infectious Diseases Society of America (IDSA) guidelines recommend the administration of clindamycin or linezolid for the treatment of MRSA caused pneumonia ([157](#_ENREF_157)). This recommendation is mostly influenced by the mode of action of clindamycin and linezolid as they inhibit bacterial protein synthesis which could result in reduction in toxin production, in particular, PVL ([157](#_ENREF_157), [158](#_ENREF_158)).

Many new antimicrobial agents have been developed for the treatment of MRSA infections, such as ceftaroline, ceftobiprole, tedizolid, delafloxacin, telavancin and dalbavancin, however, the safety, efficacy and dose adjustments are yet to be largely regulated especially for invasive MRSA infections ([1](#_ENREF_1)). These new therapy options may have potential advantages over current treatment options, for example, several case reports have reported positive clinical outcomes when administering daptomycin in combination with ceftaroline for MRSA bacteremia and endocarditis ([159](#_ENREF_159)). Also, ceftobiprole have shown promising antibacterial results superior to vancomycin, daptomycin and linezolid in endocarditis rabbit models ([160](#_ENREF_160)). Also, tedizolid have demonstrated several advantages over linezolid like lesser adverse effects, once-daily dosing and lower risk of development of spontaneous resistance, having the potential to effective agent in treating osteomyelitis and central nervous system infections ([1](#_ENREF_1)).

Table 1

Examples of antibiotics active against MRSA (Turner et al., 2019)

|  |  |  |
| --- | --- | --- |
| **Antibiotic** | **FDA-approved usage** | **Off-label use** |
| Vancomycin | Bacteremia, pneumonia, osteoarticular infection, SSTIs | - |
| Clindamycin | - | SSTIs, pneumonia, osteomyelitis |
| Daptomycin | Bacteremia and SSTIs | Osteomyelitis |
| Linezolid | Pneumonia, SSTIs | Bacteremia |
| Tedizolid | SSTIs |  |
| Trimethoprim-sulfamethoxazole |  | SSTIs and osteomyelitis |
| Ceftaroline | Pneumonia and SSTIs | Bacteremia and endocarditis |
| Ceftobiprole | - | Pneumonia and SSTIs |
| Telavancin | Pneumonia and SSTIs | Bacteremia |
| Dalbavancin | SSTIs | Bacteremia |
| Oritavancin | SSTIs | - |
| Delafloxacin | SSTIs | - |
| Quinupristin with dalfopristin | SSTIs | Pneumonia |
| Tigecycline | Pneumonia, SSTIs | Bacteremia |
| Omadacycline | SSTIs | - |
| Iclaprim | - | SSTIs |

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