

THE EMERGENCE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*: THE PROBLEM TO CONTROL IT

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Abstract: *Staphylococcus aureus*, leading causes of nosocomial bacteremia, surgical wound infection, and urinary tract infection, are becoming resistant to many and sometimes all standard therapies. *Staphylococcus aureus* is notorious for its ability to become resistant to antibiotics. Infections caused by antibiotic-resistant strains often occur in epidemic waves initiated by one or a few successful clones. Methicillin-resistant *S. aureus* (MRSA) is prominently featured during these epidemics. Historically associated with hospitals and other healthcare settings, MRSA now has emerged as a widespread cause of community infections. So-called community or community-associated MRSA spreads rapidly among healthy individuals. Outbreaks of community MRSA infections have been reported worldwide and community MRSA strains are now epidemic in the United States. There is reason for concern because MRSA often are or can readily become resistant to multiple antibiotics, thus limiting treatment options. *Staphylococcus aureus* is the leading cause of bacterial infections in developed countries and produces a wide spectrum of diseases, ranging from minor skin infections to fatal necrotizing pneumonia. Although *S. aureus* infections were historically treatable with common antibiotics, emergence of drug-resistant organisms is now a major concern. Methicillin-resistant *S. aureus* (MRSA) was endemic in hospitals by the late 1960s, but it appeared rapidly and unexpectedly in communities in the 1990s and is now prevalent worldwide. This Review focuses on progress made toward understanding the success of community-associated MRSA as a human pathogen, with an emphasis on genome-wide approaches and virulence determinants. New rapid surveillance methods are highlighting the importance of examining enterococcal isolates at the species level. Most enterococcal infections are caused by *Enterococcus faecalis*, which are more likely to express traits related to overt virulence but--for the moment--also more likely to retain sensitivity to at least one effective antibiotic. The remaining infections are mostly caused by *E. faecium*, a species virtually devoid of known overt pathogenic traits but more likely to be resistant to even antibiotics of last resort. Effective control of multiple-drug resistant enterococci will require 1) better understanding of the interaction between enterococci, the hospital environment, and humans, 2) prudent antibiotic use, 3) better contact isolation in hospitals and other patient care environments, and 4) improved surveillance. Equally important is renewed vigor in the search for additional drugs, accompanied by the evolution of new therapeutic paradigms less vulnerable to the cycle of drug introduction and drug resistance.

Keywords: *Staphylococcus aureus*, nosocomial bacteremia, Methicillin-resistant *S. aureus* (MRSA).

1. INTRODUCTION

There are various bacteria living in this world. The most common one is *Staphylococcus aureus*. Almost everyone has heard of it. It is easy to find their habitats, such as hospitals, homes, parks, schools etc. Some of them are difficult to be eliminated because of drug-resistant mutations. Hence, lots of researchers devoted their efforts to eliminate them. This review illustrates the characteristics of the *Staphylococcus aureus* and the main threat of their drug-resistant strains, especially methicillin-resistant *S. aureus*. What's more, the article also highlights the plight in drug development.

2. WHAT IS *STAPHYLOCOCCUS AUREUS*?

Staphylococcus has caused diseases to human beings for centuries ^[1]. These bacteria were first defined as *Staphylococcus* (from the Greek *staphylos* “grape” and *kokkos* “berry or seed”) in 1882 by the Scottish surgeon Sir Alexander Ogston ^[2]. A German physician, Friedrich J. Rosenbach, described 2 pigmented colonies of staphylococci and classified them as *Staphylococcus albus* (Latin for “white”) and *Staphylococcus aureus* (from the Latin “gold”) ^[3]. From then on, *Staphylococcus aureus* (*S. aureus*) has surprised scientists and physicians continuously, because they killed millions of patients ^[4].

Staphylococcus aureus is a gram-positive coccal bacterium and the most common opportunistic pathogens of humans. They colonize on approximately 30% of the human population ^[5]. Furthermore, it refers to a large range of diseases from mild skin infections to life-threatening diseases ^[6]. Take the human skin as an example, the bacteria contribute to folliculitis, furuncles, and carbuncles, impetigo, mastitis, wound infections, and staphylococcal scalded skin syndrome. There are also many other existing infections, such as bacteremia, pneumonia, endocarditis, osteomyelitis, meningitis, urinary tract infection, septic thrombophlebitis, cellulitis, abscesses, and sepsis, necrotizing fasciitis, and toxic shock syndrome ^[6-8].

According to those diseases, it is easy to conclude that the infection site determines the type of disease. The capacity of *S. aureus* causing diseases depends on a lot of virulence factors which colonize, disseminate and evade the immune system of the hosts ^[9].

3. THE PECULIAR CHARACTERISTIC OF *S. AUREUS*: BIOFILM FORMATION

For keeping themselves away from hostile environmental effects, the agglomerate bacteria have been described as “biofilms”. And it is common to see the biofilms of *S. aureus*. They usually come into being surface-attached communities which embedded in an extracellular matrix ^[10]. There are 2 main advantages for *S. aureus*. First, it protects *S. aureus* from being washed or scraped away to enhance the survival rate. Second, it helps *S. aureus* to flee the host defense ^[11].

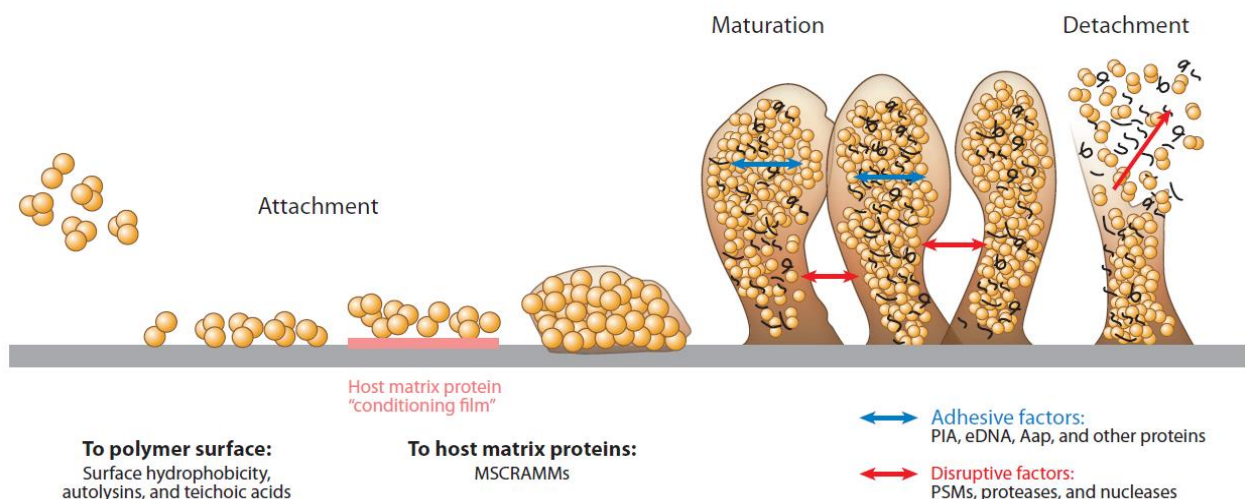


Figure 1^[11]

On the basis of figure 1, the biofilm formation contains 3 stages, initial attachment, maturation and final detachment. The first attachment occurs to a surface (like polymeric surface) or to a conditioning film (such as host matrix proteins). The procedure of maturation relies on those adhesive factors, while the process of detachment depends on disruptive factors. What's more, abbreviations in figure 1 are shown here: Aap, accumulation-associated protein; eDNA, extracellular DNA; SCRAMMs, microbial surface components recognizing adhesive matrix molecules; PIA, polysaccharide intercellular adhesin; PSMs, phenol-soluble modulins ^[11].

4. THE IMMUNE RESPONSE TO *S. AUREUS*: NEUTROPHILS

Neutrophils play an important role in phagocytizing cells so that they can defend the host against acute bacterial infection. If patients have congenital neutrophil deficiencies, bacterial infections will be fatal to them^[12]. Thus a healthy neutrophil-mediated killing system is the critical defense to eliminate gram-positive *S. aureus* in the host^[13].

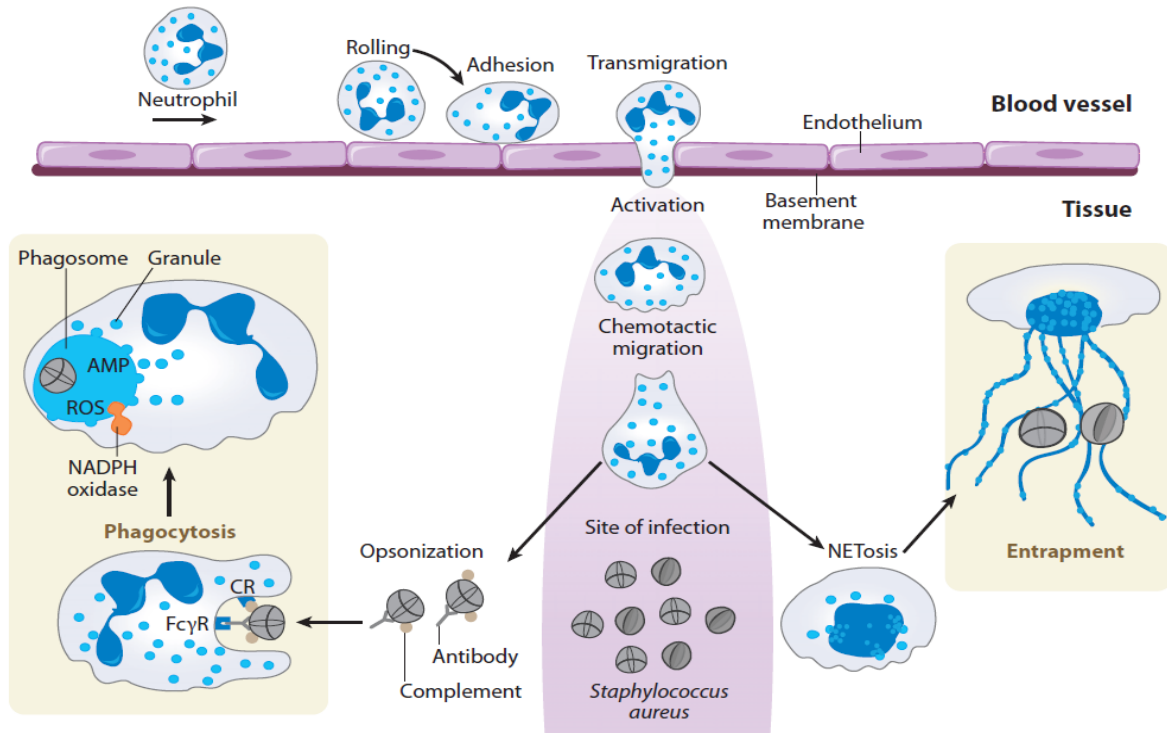


Figure 2^[13]

As is shown in figure 2, it illustrates how neutrophils can kill *S. aureus*. All things begin with the activation of the endothelium. There are some neutrophils which roll on the activated endothelium. Then they stop rolling and adhere to the activated endothelium firmly. After that, neutrophils transmigrate through the endothelium into the tissue, named as extravasation. Neutrophils keep migrating to an infected tissue in terms of a chemotactic gradient. When they arrive at an infected area, there are 2 directions for them to eliminate *S. aureus*. One of them is phagocytosis process to phagocytize *S. aureus* directly. Neutrophils with complement receptors (CRs) and Fc γ receptors (Fc γ R) are able to recognize and phagocytize *S. aureus* owing to attached antibodies and complements on the bacteria. Inside the neutrophils, the bacteria are sequestered by phagosomes. Subsequently, *S. aureus* is killed by granule fusion and NADPH oxidase, which release antimicrobial proteins (AMPs) and reactive oxygen species (ROS) respectively. The other one is called NETosis process for killing *S. aureus* extracellularly. Neutrophils expel their DNA which is decorated with histones and AMPs. Therefore, these special neutrophils have the ability to capture and kill the bacteria, namely, entrapment to *S. aureus*^[13]. Furthermore, in the process of phagocytosis, the apoptotic cell death (the neutrophils) follows eradication of ingested bacteria^[14].

The emergence of Methicillin-resistant *S. aureus*

As is known to all, *S. aureus* is famous for the pathogen causing numerous diseases to human. More seriously, its impact prominently enhanced by the antibiotic-resistant ability. Besides, one of the most common types is methicillin-resistant *S. aureus* (MRSA). The first appearance is in 1960. It has the capacity of causing serious healthcare-associated and community-associated infections, such as skin and soft-tissue infection (SSTIs), pneumonia, endocarditis and osteomyelitis^[15]. Actually, one of the most common causes of bone and joint infections is also MRSA^[16, 17]. MRSA is a great challenge for high mortality, limited therapeutic options and the heavy cost burden^[15, 18]. That is to say, compared with methicillin-susceptible *S. aureus* infections, patients with MRSA infections are easier to be seriously ill, and face a higher risk of death and more expensive costs^[19-21]. For example, recent years, researchers in the USA indicate that MRSA causes approximately 95 000 invasive infections and 19 000 deaths per year^[22].

By definition, MRSA is resistant to all β -lactam antibiotics, including oxacillin, nafcillin, dicloxacillin, and cefazolin [23]. Normally, we use oxacillin and/or ceftiofur for susceptibility testing. For methicillin-susceptible *S. aureus*, β -lactams are able to bind to the penicillin-binding proteins (PBP) which are essential for cell wall biosynthesis. Furthermore, the peptidoglycan crosslink formation is also inhibited. Therefore, this results in lysis of bacterial cells. However, MRSA has a mobile genetic element called staphylococcal cassette chromosome (SCCmec). The SCCmec carries the *mecA* gene to encode altered PBP(PBP2a) so that the affinity to β -lactam antibiotics is decreased prominently. Consequently, the inhibition of cell wall biosynthesis fails, and MRSA strains are capable of surviving even in the presence of β -lactam antibiotics [24].

MRSA strains are the most common bacteria among those healthcare-associated patients, and they are named as HA-MRSA [25-27]. Then, the first reports about community-associated MRSA (CA-MRSA) infections were published at the beginning of the 20th century, the infections happened on healthy individuals (with no risk factors of HA-MRSA infections), injection drug users, incarcerated people, and athletes [28-29]. HA-MRSA strains are genetically different from CA-MRSA, and one significant difference is the SCCmec. So far, 11 SCCmec types have been identified [30-31]. CA-MRSA strains are mainly related to SCCmec types IV and V, while researchers characterized SCCmec types I, II and III from HA-MRSA [32].

The attention of scientific literature and the lay press paid to MRSA has reduced the burden of hospital-acquired MRSA or healthcare-associated MRSA (HA-MRSA) infections, such as the infection of USA100 in hospitals [33-36]. Nevertheless, CA-MRSA is spreading rapidly throughout many industrialized regions of the world [37-39]. On the basis of some reports, the increasing trend of CA-MRSA indicates that these clones may ultimately replace HA-MRSA clones in hospitals [40]. Actually, USA 300 is now commonly found in both the healthcare setting and the community setting [41].

Dating back to the beginning of CA-MRSA, there were rare reports of it [42]. However, after the discovery of a unique MRSA clone in the community in Western Australia, the situation has changed [43]. Several years later, the CA-MRSA clones were recognized in Europe, the United States, Latin America, and Asia [28,44-46]. Thus, it is crucial to understand the epidemiology of CA-MRSA for controlling MRSA. According to most reports, the CA-MRSA infections are implicated in USA 300. CA-MRSA emerged, and the number of cases escalated, rapidly in the USA in the early 2000s. For example, a survey of 11 US hospitals confirmed that 97 percent of CA-MRSA isolates were the USA300 [47-48]. Not only are they popular in the US, but also they contribute to a global epidemic threat [49-50].

It is well accepted that the earliest cases of USA 300 occurred in a collegiate football team in Pennsylvania, then several outbreaks happened among prisoners in Mississippi and Los Angeles. The USA 300 strains originally have a close relationship with military personnel, prisoners, athletes, intravenous drug users, the homeless, urban populations, and men who have sex with men [38]. But it soon has expanded quickly to the general population [51]. It is easy to find the reports of USA300 from other countries besides the United States. For instance, USA300 was discovered in neighboring countries of Colombia since 2006 [52]. The predominant CA-MRSA clone, USA300, has become the primary cause of community-associated skin infection [48]. What is more, although they have strong virulence [53], little improvement was made for controlling them effectively.

Epidemiology of Methicillin-resistant *S. aureus*

There are a variety of reports related to MRSA. In 2011, approximately 80461 cases of MRSA infections occurred and caused over 11000 deaths in the USA [54]. MRSA also exists in Iran, and the prevalence is in the middle of Australia (lower) and the United States (higher) [55-56]. Over 9000 cases of *S. aureus* bacteraemia (SAB) happened per year in England, Wales and Northern Ireland, and 12.7% of these owed to MRSA in 2012 [57]. In Taiwan, the MRSA infection rate increased dramatically from 9.8% in 1999–2000 to 56% in 2004–2005 [58]. In addition, the MRSA infection rate in Europe is not high but rising day by day [59]. There are few reports about MRSA in developing countries, but it is certain that MRSA will lead to devastating consequences if it becomes prevalent there since resource-poor settings.

The mechanism of drug-resistant *S. aureus*

The penicillin G was introduced for improving prognosis prominently in the early 1940s, however, the resistance of *S. aureus* to it appeared 2 years later [60]. Penicillinase (β -lactamase enzyme) is the crucial reason which is responsible for the drug-resistant problem. These enzymes hydrolyze the β -lactam ring so that the drug is inactivated [61-62]. Besides, they

are encoded by blaZ, which exists on a large transposon on a plasmid. Unfortunately, the rate of drug-resistant in human *S. aureus* isolates is over 90%. That is to say, penicillin almost lost therapeutical effect ^[7]. Worse to come, *S. aureus* was capable of resisting other antibiotics such as erythromycin, streptomycin, and the tetracyclines ^[63-65].

In 1959, a semisynthetic antibiotic called methicillin was used to resolve the spread of penicillin-resistant dilemma. The methicillin-resistant *S. aureus* (MRSA) was isolated in 1960 ^[66]. The mechanism of MRSA resistance has already shown above (the part of the emergence of MRSA). Then MRSA keeps spreading in many countries, and it evolves to be a worldwide problem. In spite of useless methicillin, the term of MRSA is remembered by lots of people because of the remaining problem. Subsequently, MRSA shows drug-resistance to an entire class of penicillin-like antibiotics including penicillin, amoxicillin, oxacillin, meticillin, and others ^[67].

So far, vancomycin is considered as the perfect treatment choice for severe MRSA infections. With development, the susceptibility to vancomycin is decreasing in terms of some studies. In fact, full vancomycin-resistant *S. aureus* (VRSA) emerged clinically in 2002 ^[68]. And another kind of alternative antibiotic (daptomycin) has the drug-resistant problem too ^[4].

Table 1 summarizes the mechanisms between drug-resistant *S. aureus* and antibiotics. As is shown below.

Table 1: Representative Mechanisms of Staphylococcus Aureus Resistance to Antimicrobials ^[69-70]

Antibiotics	Resistance Genes	Gene Products	Mechanisms of Resistance
β-Lactams	blaZ	β-Lactamase	Enzymatic hydrolysis of β-lactam nucleus
	mecA	PBP2a	Reduced affinity for PBP
Glycopeptides	GISA: unknown	Altered peptidoglycan	Trapping of vancomycin in the cell wall
	VRSA: vanA	D-Ala-D-Lac	Synthesis of dipeptide with reduced affinity for vancomycin
Quinolones	parC	ParC (or GrlA) component of topoisomerase IV	Mutations in the QRDR region, reducing the affinity of enzyme-DNA complex for quinolones
	gyrA or gyrB	GyrA or GyrB components of gyrase	
Aminoglycosides (eg, gentamycin)	Aminoglycoside-modifying enzymes (eg, aac, aph)	Acetyltransferase, phosphotransferase	Acetylating and/or phosphorylating enzymes modify aminoglycosides
Trimethoprim-sulfamethoxazole (TMP-SMZ)	Sulfonamide: sulA	Dihydropteroate synthase	Overproduction of p-amino benzoic acid by the enzyme
	TMP: dfrB	DHFR	Reduced affinity for DHFR
Tetracyclines	Tetracycline, doxycycline and minocycline: tetM	Ribosome protection protein	Binding to the ribosome and chasing the drug from its binding site
	Tetracycline: tetK	Efflux protein	Efflux pump
Erythromycin	msrA	Efflux protein	Efflux pump
	erm (A, C)	Ribosomal methylase (constitutive or inducible)	Alteration of 23S rRNA
Clindamycin	erm (A, C)	Ribosomal methylase (constitutive or inducible)	Alteration of 23S rRNA
Linezolid	cfr	Ribosomal methyltransferase	Methylation of the 23S rRNA that interferes with ribosomal binding
Daptomycin	mprF	Lysylphosphatidylglycerol synthetase (LPG) synthetase	Increasing: synthesis of total LPG, outer LPG translocation and positive net charges on cell membrane

5. CONCLUSION

The most serious problem we are facing is the drug-resistant problem. The fundamental reason is that using antibiotics caused the drug-resistant problem. Furthermore, the chronic misuse and overuse of antibiotics have deteriorated the drug-resistant problem. The development of new antibiotics falls behind the urgent need for treatment. Hence, there is an urgency to develop novel drugs.

Besides, the way of developing novel drugs to resist the MRSA needs to be diversified. Some of the drugs should be used to eliminate the MRSA before the infection, some of the drugs ought to be utilized for treatment. To sum up, we have to create various ways to prevent infection and treat the patients at the same time so that we may get the chance to diminish the negative effect from MRSA and other drug-resistant *S. aureus*.

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