Methicillin-resistant *Staphylococcus aureus*: The Deadly Superbug

Elizabeth C. Lee

1Department of Biological Sciences, The George Washington University
Methicillin-resistant *Staphylococcus aureus*: The Deadly Superbug

Elizabeth C. Lee

1Department of Biological Sciences, The George Washington University
2023 G St. NW, Washington, D.C., 20052
elee314@gmail.com

*Current address: Laboratory of Immunogenetics, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, USA

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA), often referred to as the "deadly superbug" by the media, is currently a major epidemiological threat on a global scale. The adaptability of *S. aureus* to antibiotics led to the emergence of MRSA in 1961 in a hospital ward in the United Kingdom. *S. aureus* developed resistance to β-lactam antibiotics through the acquisition of the *meca* gene, which is situated on a mobile genetic element known as staphylococcal cassette chromosome *mec* (SCCmec). The *meca* gene encodes penicillin-binding protein 2a (PBP2a), which has a significantly reduced affinity for β-lactam antibiotics, thereby conferring β-lactam resistance. Although the first MRSA clones were hospital-associated (HA-MRSA), community-associated MRSA (CA-MRSA) clones are now increasingly found throughout the world, affecting normally healthy individuals. MRSA accounts for greater than 50-80% of *S. aureus* isolates. The global emergence of MRSA has raised concern among public health officials. In fact, in year 2005, Centers for Disease Control and Prevention (CDC) estimated that the number of MRSA fatalities in the United States surpassed the number of deaths from AIDS and hurricane Katrina combined. Several preventative measures have been suggested, including: covering wounds, maintaining good personal hygiene, and avoiding sharing personal items that could facilitate the transmission of MRSA bacteria. As MRSA continues to affect individuals worldwide, it is essential that further research be conducted on the epidemiology of this deadly superbug. Although progress has been made, our current knowledge of the pathogenesis and the molecular evolution of MRSA and the number of available treatments for MRSA infections are limited. This review describes our current understanding of the key determinants of multidrug resistance, worldwide dissemination, and modes of transmission of MRSA bacteria. Also, this review highlights some of the most recent research findings, which could lead to the development of novel anti-MRSA therapeutics. In addition, some of the challenges that researchers currently face are also discussed.

INTRODUCTION

*Staphylococcus aureus*, discovered in the 1880s, is a major human pathogen that is commonly carried on the skin or nose of 20 to 30% of the healthy human population. Also known as “the golden staph,” *S. aureus* is a facultative anaerobic and gram-positive coccus characteristically identified by notable round, golden-yellow colonies. *S. aureus* is one of the most common causes of skin infections in the United States, and it has been shown to cause a wide range of illnesses, ranging from pimples and boils to bloodstream infections and pneumonia (Deurenberg, R. and Stobberingh, E., 2008; Gantz, N. et al., 2003). The remarkable success of *S. aureus* as a human pathogen could be attributed largely to its ability to develop antimicrobial resistance. Just two years after the introduction of penicillin for medical use, in 1942, the first penicillin-resistant *S. aureus* isolate was observed in a hospital. Since 1960, approximately 80% of all *S. aureus* strains have been found to exhibit penicillin-resistance (Deurenberg, R. and Stobberingh, E., 2008).
Over the last decade, a menacing strain of *S. aureus* known as methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a pernicious pathogen. MRSA (Figure 1), often referred to as the "deadly superbug" by the media, first developed in the United Kingdom in a hospital setting in 1961 two years after the introduction of methicillin, a beta-lactam antibiotic of the penicillin class (Cohen, P., 2007; Deurenberg, R. and Stobberingh, E., 2008).

Since its discovery in 1961, various hospital-associated methicillin-resistant *S. aureus* (HA-MRSA) clones have spread worldwide. Although MRSA infections were previously mostly limited to immune-compromised individuals in health care facilities, MRSA infections are now increasingly found amongst normally healthy individuals (Paintsil, E., 2007). In 1982, the first case of MRSA acquired outside of a health-care setting, known as community-acquired MRSA (CA-MRSA), was described amongst intravenous drug users in Detroit, Michigan in the United States (Cohen, P., 2007).

Today, MRSA dissemination poses a serious, worldwide threat. Given its ubiquitous prevalence, infection caused by MRSA is considered to represent a rapidly evolving epidemic, affecting countries in: Africa, Asia, Europe, North America, Oceania, and South America (Kirkland, E. et al., 2008; Cohen, P., 2007). Currently, the prevalence of MRSA is 50-80% of *S. aureus* isolates (Appelbaum, P., 2006; Chen, Z. et al., 2010). Thus, MRSA has spread far beyond local outbreaks to a mounting epidemic of global proportions (Table 1).

**Figure 1. Methicillin-resistant *Staphylococcus aureus* bacteria.** (A) Image of magnified (9,560x) MRSA by a scanning electron microscope (SEM). (B) MRSA on blood agar. (C) A deadly new breed MRSA PVL (Panton-Valentine-leukocidin). (D) SEM image (20,000x). (Source: (A) Department of Health, Social Services, and Public Safety. (2008) Northern Ireland Regional Infection Control Manual, 1-8. (B) Childs, D. (2008) Docs Fear Deadly Combo of Flu, MRSA. ABC News.com. (D) National Institutes of Allergy and Infectious Diseases.)

**Table 1. Nations in which community-acquired methicillin-resistant *Staphylococcus aureus* has been reported.**

<table>
<thead>
<tr>
<th>Nations</th>
<th>CA-MRSA has been reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFRICA:</strong></td>
<td>South Africa</td>
</tr>
<tr>
<td><strong>ASIA:</strong></td>
<td>China, Hong Kong, India, Israel, Japan, Saudi Arabia, Singapore, Taiwan, Turkey</td>
</tr>
<tr>
<td><strong>EUROPE:</strong></td>
<td>Austria, Belgium, England, Finland, France, Germany, Greece, Italy, The Netherlands, Poland, Portugal, Spain, Switzerland, UK</td>
</tr>
<tr>
<td><strong>NORTH AMERICA:</strong></td>
<td>Canada, Mexico, USA</td>
</tr>
<tr>
<td><strong>OCEANIA:</strong></td>
<td>Australia, New Zealand, Samoa</td>
</tr>
<tr>
<td><strong>SOUTH AMERICA:</strong></td>
<td>Argentina, Brazil, Chile, Colombia</td>
</tr>
</tbody>
</table>

**Table 1. Nations in which community-acquired methicillin-resistant *Staphylococcus aureus* has been reported.**

This list of countries with CA-MRSA was generated from a study conducted in year 2006. (Source: Cohen, P. (2007) Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* Skin Infections: Implications for Patients and Practitioners. Am J Clin Dermatol 8, 259-270.)

**KEY DETERMINANTS OF BETA-LACTAM RESISTANCE**

MRSA is able to resist the bacteriostatic effects of most β-lactam
antibiotics, such as methicillin, because it bears a horizontally transferred mecA gene. The mecA gene, which is 2.1 kb in length, is located on staphylococcal cassette chromosome mec (SCCmec), which is a mobile genetic element, a DNA molecule that one bacterial strain acquires by interacting with other strains of bacteria (Ito, T. et al., 2003). The mecA gene encodes an altered 78-kDa protein called penicillin-binding protein 2a (PBP2a), which has a much lower affinity for β-lactam antibiotics compared to the wildtype penicillin-binding protein (PBP) found in non-methicillin resistant strains. In MRSA's counterpart, methicillin sensitive S. aureus (MSSA), the β-lactam antibiotics bind to the native PBPs that are present in the cell wall of S. aureus, thereby disrupting the synthesis of the peptidoglycan layer. Hence, MSSA will not survive in the presence of methicillin. In contrast, in MRSA, foreign PBP2a is present, so the the β-lactam antibiotics do not bind, and the synthesis of the peptidoglycan layer is not disrupted. As a consequence, MRSA has the ability to survive in the presence of methicillin. Hence, mecA confers β-lactam resistance by encoding a protein with an altered site that inhibits normal methicillin binding (Deurenberg, R. and Stobberingh, E., 2008; Cohen, P., 2007; Chen, Z. et al., 2010; Lim, D. and Strynadka, N., 2002; Chongtrakool, P. et al., 2006).

Currently, seven main types of SCCmec (types I to VII) are recognized, ranging in size from 20.9 to 66.9 kb. SCCmec type I (34.3 kb), IV (20.9-24.3 kb), V (28 kb), VI (20.9 kb), and VII (35.9 kb) cause resistance only to β-lactam antibiotics. However, SCCmec type II (53.0 kb) and III (66.9 kb) cause resistance to multiple classes of antibiotics due to the integration of plasmids harboring additional drug resistance genes. For instance, the integrated plasmid pUB110 contains the ant(4') gene, which encodes resistance to kanamycin and other aminoglycosides. In addition, tetracycline resistance is encoded by pT181, and resistance to penicillins and metals, including mercury, is encoded by pl258. By using SCCmec typing, as well as other molecular typing methods, such as: pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), and spa typing, scientists can study the molecular evolution of MRSA and investigate MRSA outbreaks (Deurenberg, R. and Stobberingh, E., 2008; Chongtrakool, P. et al., 2006).

GLOBAL EMERGENCE OF MRSA

Since its identification almost five decades ago, MRSA has become a source of significant morbidity and mortality on a global scale. After the first MRSA was isolated in the United Kingdom in 1961, MRSA began to spread to other European countries. Thereafter, in the 1970s, MRSA proliferated worldwide, including to the USA. Today, MRSA causes the majority of nosocomial infections throughout the world (Grundmann, H. et al., 2006). According to the SENTRY Antimicrobial Surveillance Program, between the years of 1997 and 1999, MRSA prevalence was 23% in Australia, 26% in Europe, 32% in the USA, 35% in Latin America, 40% in South America, and 67% in Japan (Diekema, D. et al., 2001; Bell, J. and Turnidge, J., 2002).

The statistics surrounding HA-MRSA are sobering (Figure 2).

![Figure 2. Estimated methicillin-resistant Staphylococcus aureus-related hospitalization rates in the United States from 1999 to 2005. The rates are the number of MRSA-related hospital discharges per 1,000 hospitalizations. There has been a steady increase in hospitalization rates for MRSA-related infections in the United States from 1999 to 2005.](image-url)

Figure 2. Estimated methicillin-resistant Staphylococcus aureus-related hospitalization rates in the United States from 1999 to 2005. The rates are the number of MRSA-related hospital discharges per 1,000 hospitalizations. There has been a steady increase in hospitalization rates for MRSA-related infections in the United States from 1999 to 2005.
increase in the rate of MRSA-hospitalizations throughout the years. (Source: Klein, E. et al. (2007) Hospitalizations and Deaths Caused by Methicillin-Resistant Staphylococcus aureus, United States, 1999-2005. Emerging Infectious Diseases 13, 1840-1846.)

A 2007 study from the CDC estimated that the incidence of HA-MRSA more than doubled from 127,000 in 1999 to 278,000 in 2005. Moreover, deaths due to HA-MRSA infections increased from 11,000 in 1999 to 17,000 in 2005 (Klein, E. et al., 2007). In fact, the number of HA-MRSA fatalities in 2005 surpassed the number of deaths from hurricane Katrina and AIDS combined, and it is substantially greater than the number of fatalities at the peak of the US polio epidemic. The death rate, length of stay, and cost of treating patients with MRSA are more than double than that of other hospital admissions (Klein, E. et al., 2007). It is estimated that MRSA places a $4 billion to $30 billion burden on the U.S. economy each year. (Lodise, T. and McKinnon, P., 2007).

There are three main reservoirs for HA-MRSA in hospitals and other healthcare settings: staff, patients, and objects, such as beds, linen, and utensils. Most health professionals who are carriers of HA-MRSA do not develop infection, and if they do, many spontaneously clear the infection without any treatment. Patients, however, have a 30-60% risk of infection following exposure. This could be attributed to an illness-related immunodeficiency that impairs their ability to clear or control the invading bacteria (Cohen, P., 2007).

Although the propagation of HA-MRSA is alarming, what is far more disquieting is the proliferation of CA-MRSA worldwide, not only in the community but also in healthcare facilities. In general, CA-MRSA is more virulent compared to HA-MRSA due to the presence of various virulence factors. Furthermore, CA-MRSA has the potent ability to infect unsuspecting, healthy individuals (Deurenberg, R. and Stobberingh, E., 2008; Chambers, H., 2001; Etienne, J., 2005).

The first report of CA-MRSA was in 1993 from Western Australia, and it described the infection of CA-MRSA in Aboriginal patients in remote communities (Udo, E. et al., 1993). Recently, the prevalence of CA-MRSA in healthcare facilities has increased, especially in the USA and Taiwan (Kleven, R. et al., 2006; Maree, C. et al., 2007; Moran, G. et al., 2006; Otter, J. and French, G., 2006; Seybold, U. et al., 2006). A study performed in emergency departments in 11 cities in the USA found that 78% of the isolates were MRSA, and among these, 98% were CA-MRSA USA300, one of the most common strains of MRSA (Moran et al., 2006). The USA300 clone and other CA-MRSA clones have even recently been found in countries that have, traditionally, a low prevalence of HA-MRSA, such as Denmark and Norway (Deurenberg, R. and Stobberingh, E., 2008).

Today, community outbreaks have been reported among various individuals, including: child-care attendees, prison inmates, military recruits, and athletes (Gantz, N. et al., 2003). Although close physical contact is critical to the propagation of CA-MRSA infections, CA-MRSA has also been found to cause infections among athletes when there is little skin-to-skin contact; in this case, infection is likely to spread by contact with commonly shared equipment (Gantz, N. et al., 2003). What makes containment of CA-MRSA infections particularly difficult is that MRSA can be present on the skin of and within an individual without causing any signs of illness. In this way, CA-MRSA can be passed from one individual to another unknowingly (Cohen, P., 2007).

Moreover, CA-MRSA carries a unique virulence factor called Panton-Valentine leukocidin (PVL), which is not found in HA-MRSA. The PVL cytotoxin destroys leukocytes by creating pores in the cell membrane, and it inflicts severe tissue damage, including necrotic skin lesions and severe necrotizing pneumonia, in both...
children and adults, which can lead to death within 24 hours after infection. The dynamic combination of the mecA gene and PVL in CA-MRSA creates super-adaptable bacteria capable of spreading rapidly throughout the community (Cohen, P., 2007).

In addition to PVL, CA-MRSA also differs from HA-MRSA phenotypically and genotypically in several other respects. It has been found that CA-MRSA and HA-MRSA lineages are not related to each other (Groom, A. et al, 2001; Naimi, T. et al., 2001). Unlike HA-MRSA isolates, the majority of CA-MRSA isolates are susceptible to non-β-lactam antibiotics. Moreover, CA-MRSA has a larger clonal diversity than HA-MRSA, which implicates that more S. aureus lineages have the ability to become CA-MRSA. The majority of CA-MRSA isolates have SCCmec type IV, V, or VII (Deurenberg, R. and Stobberingh, E., 2008). Hence, these SCCmec types and PVL are genetic markers for CA-MRSA (Tristan, A. et al., 2007).

ACQUISITION AND TRANSMISSION OF MRSA

The most common mode of transmission of MRSA involves direct skin-to-skin transmission between infected and uninfected individuals. MRSA transmission has also been associated with compromised skin surfaces caused by cuts and abrasions. Openings in the skin could provide a pathway of entry for bacteria when the compromised skin comes into contact with potentially infected surfaces. In addition, MRSA can be spread by the sharing of contaminated personal items, such as clothing, razors, and sports equipment. Humid environments, crowding, and lack of cleanliness have all been correlated with the spread of MRSA infections. Thus, covering wounds, avoiding the use of shared personal items, frequent handwashing, and maintaining good personal hygiene are important measures to take in the prevention of MRSA transmission (Ward, T., 2008). However, it is important to avoid excessive sanitation with antibacterial agents, as there is increasing evidence that the multiple-antibiotic resistance of MRSA may be attributed to over-prescription and improper use of antibiotics. Indeed, a plethora of researchers believe that the development of MRSA has most likely been accelerated by the overuse of broad-spectrum antibiotic treatments (Klein, E. et al., 2007).

Although MRSA has exhibited multiresistance, in the case of cutaneous infections, a few antibiotics, such as vancomycin and teicoplanin, may be used to treat MRSA. When these antibiotics fail, however, more invasive procedures may be required, such as surgical removal of areas of infected skin or tissue, the debridement of wound infection, and bone excision.

Next to death, surgical site infection (SSI) remains the most crucial postoperative complication. Unfortunately, SSIs account for one third of all hospital-acquired infections, and more than 29% of SSIs have been found to be MRSA-positive, underscoring the menacing complications of MRSA cutaneous infections (Manian, F. et al., 2003).

RECENT FINDINGS

Importance of differential gene expression in the evolution of USA300 virulence:

Recent research on MRSA may promise new methods of treatment for MRSA infections. One study led by Li et al. at the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) has suggested that a radical shift may be needed in how scientists should design MRSA therapeutics. This group found that USA300, a major epidemic strain of MRSA does not randomly acquire harmful genes from other MRSA strains. Rather, USA300 inherits its deadly capabilities from a forefather strain of the bacterium known as USA500.

This finding argues against the idea that targeting products of mobile genetic elements is the best way to limit MRSA spread. The NIAID researchers have
suggested that scientists should instead focus on understanding the core genome of USA300 rather than on the products of mobile genetic elements. NIAID scientists believe that this would lead to a better understanding of how increased production of certain proteins, such as toxins, affects MRSA virulence in humans. In fact, results from their study showed that USA300 and USA500 are nearly identical in virulence and their level of virulence gene production. Because USA300 has been known to carry PVL and other mobile genetic elements, while USA500 does not, this finding is important in suggesting that PVL and other mobile genetic elements actually may have no significant impact in the evolution of USA300 virulence. Thus, this study underscores the importance of differential gene expression in the pathogenesis of USA300 (Li, M. et al., 2009).

*Role of FnBP in MRSA Infection and Pathogenesis:*

In another recent study, Edwards et al. investigated how MRSA bacteria move from the bloodstream and invade endothelial cells. These scientists studied the role of fibronectin-binding protein A (FnBPA), which is a protein on the surface of the bacteria, in MRSA virulence. The interaction of FnBPA with host cell receptors, called integrins, via a fibronectin (Fn) bridge triggers the uptake of MRSA by endothelial cells. The Fn-binding region of FnBPA contains multiple non-identical repeats that mediate binding to Fn. The researchers investigated what role the FnBPA repeats play in mediating MRSA lethality.

For the first time, Edwards et al. demonstrated that the number of FnBPA repeats is central to the bacteria’s ability to invade endothelial cells. It was discovered that although only one FnBPA repeat was needed to bind to cells, altering the FnBPA protein to contain a smaller number of repeats reduced the strength of binding, thereby resulting in a less severe infection. Hence, these findings suggested that the number of repeats within FnBPA has a positive correlation with the strength of binding and the severity of MRSA infection. Experiments using a murine sepsis model demonstrated the relevance of these findings to pathogenesis; virulence was significantly reduced in bacteria expressing no or few FnBPA repeats in comparison to bacteria with a full complement of FnBPA repeats. Having established the essentiality of the FnBPA in MRSA virulence, the next step of the scientists’ research will be to develop a treatment that blocks the binding of FnBPA to cells, which could attenuate the bacterial infection spreading to the major organs in the body (Edwards, A. et al., 2010).

**Alpha-hemolysin as a potential target for therapeutics against MRSA:**

Kennedy et al. from the NIAID have identified a promising treatment method that was shown to reduce the severity of skin infections caused by USA300 in laboratory mice. The scientists investigated the effects of the bacterial toxin alpha-hemolysin (Hla), which pokes holes in a variety of different host cells, in MRSA skin infections in a mouse model. The researchers also determined whether active or passive immunization against Hla could reduce disease severity.

In their study, Kennedy et al. documented physical differences in the laboratory mice infected with different strains of MRSA, including USA300 with or without the Hla toxin. The group also immunized mice with a non-lethal version of the toxin, testing active immunity, or injected mice with Hla-specific antibodies, testing passive immunity. It was found that, in all respects of the study, when Hla toxin was either removed from MRSA bacteria or neutralized through active or passive immunization, skin lesions were significantly smaller, the mice recovered faster, and there was a substantial reduction in skin destruction (Kennedy, A. et al., 2010).

Not only do these findings implicate that Hla could be a promising target to moderate MRSA cutaneous infections, but this study also highlights the potential for
antitoxin treatment to become an efficacious alternative to traditional antibiotics. Unlike antibiotic agents that have limitations due to antibiotic resistance, antitoxins could be an effective treatment method, preventing damage caused by a specific part of a bacterial pathogen, such as Hla in MRSA, rather than trying to kill the entire pathogen, as antibiotics do. Hence, the insight gained from this investigation on the role of Hla in MRSA could lead to the development of anti-MRSA antitoxin therapeutics.

FUTURE RESEARCH

Although much knowledge on the pathogenesis of MRSA has been gained since its discovery in 1961, further investigations are needed to broaden our understanding of this deadly superbug. There are still several questions that remain unanswered. For instance, our present knowledge on the evolution of MRSA, including the origin of SCCmec, is incomplete (Deurenberg, R. and Stobberingh, E., 2008). Additional studies on the molecular events that lead to the origin of MRSA clones, in healthcare facilities and in the community, and additional epidemiological and genomic investigations of present MRSA clones could greatly expand our knowledge on the nature of MRSA propagation.

Furthermore, studies on the molecular basis of MRSA virulence, including the structure of SCCmec and the role of MRSA virulence factors, should be increased. The insight gained from such studies would provide valuable information that could be used to develop anti-MRSA therapeutics and intervention strategies. Several research groups, especially in the biotechnology and nanotechnology sectors, have already taken the first steps in this direction. One such group, Pangule et al., have recently designed highly effective antistaphylococcal nanocomposite paints based on nanotube conjugates of a cell wall degrading enzyme called lysostaphin. These paints were shown to be capable of killing staphylococci bacteria, including MRSA (>99% within two hours), without release of the enzyme into solution (Pangule, R. et al., 2010). However, although recent biotechnological advances have led to the development of potential anti-MRSA agents, such as MRSA-killing paint, the number of these developments is trifling.

In summary, further investigations are needed to fully understand the molecular epidemiology and evolution of MRSA bacteria. Until further research is conducted on MRSA virulence, pathogenesis, and genomics, MRSA will continue to be a killer microbe with high infectability among both the immunocompromised and the healthy.

REFERENCES


Methicillin-resistant Staphylococcus
aureus skin infections: implications
for patients and practitioners. Am J
Clin Dermatol 8, 259-270.

The evolution of Staphylococcus
aureus. Infection, Genetics and
Evolution 8, 747-763.

Diekema, D. et al. (2001) Survey of
infections due to Staphylococcus
species: frequency of occurrence
and antimicrobial susceptibility of
isolates collected in the United
States, Canada, Latin America,
Europe, and the Western Pacific
region for the SENTRY Antimicrobial
Clin. Infect. Dis. 32 (Suppl. 2), S114-
132.

aureus host cell invasion and
virulence in sepsis is facilitated by
the multiple repeats within FnBPA.
PLoS Pathogens 6, e1000964.

leukocidin: a marker of severity for
Staphylococcus aureus infection?

Gantz, N. et al. (2003) Methicillin-resistant
Staphylococcus aureus infections
among competitive sports
participants – Colorado, Indiana,
Pennsylvania, and Los Angeles
County, 2002-2003. Morbidity and
Mortality Weekly Report 52, 793-
795.

Groom, A. et al. (2001) Community-
acquired methicillin-resistant
Staphylococcus aureus in a rural
American Indian community. JAMA
286, 1201-1205.

and resurgence of methicillin-
resistant Staphylococcus aureus as
a public-health threat. Lancet 368,
874-885.

Ito, T., et al. (2003) Insights on antibiotic
resistance of Staphylococcus aureus
from its whole genome: genomic
island SCC. Drug Resist. Updat. 6,
41-52.

Kennedy, A. et al. (2010) Targeting of
alpha-hemolysin by active or passive
immunization decreases severity of
USA300 skin infection in a mouse

Kirkland, E. et al. (2008) Methicillin-resistant
Staphylococcus aureus and athletes.

Klevens, R. et al. (2006) Community-
associated methicillin-resistant
Staphylococcus aureus and healthcare risk factors. Emerg.

Klein, E. et al. (2007) Hospitalizations and
deaths caused by Methicillin-
resistant Staphylococcus aureus,
Infections Diseases 13, 1840-1846.

Li, M. et al. (2009) Evolution of virulence in
epidemic community-associated
methicillin-resistant Staphylococcus
aureus. Proceedings of the National
Academy of Sciences 106, 5883-
5888.

basis for the beta lactam resistance
of PBP2a from methicillin-resistant
Staphylococcus aureus. Nat Struct
Biol 11, 870-876.

of methicillin-resistant
Staphylococcus aureus: focus on
clinical and economic outcomes.
Pharmacotherapy 27, 1001-1012.

Manian, F. et al. (2003) Surgical site
infections associated with methicillin-
resistant Staphylococcus aureus: Do
postoperative factors play a role?
Clin Infect Dis 36, 863-868.

Maree, C. et al. (2007) Community-
associated methicillin-resistant
Staphylococcus aureus isolates
causing healthcare-associated
infections. Emerg. Infect. Dis. 13,
236-242.

Moran, G. et al. (2006) Methicillin-resistant
S. aureus infections among patients
in the emergency department. N.


