MRSA: Historical Perspective

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Staphylococcus aureus (SA) has been a plague of mankind since the dawn of history. In fact, an outbreak of staphylococcal skin disease may even be mentioned in the Bible. The book of Exodus, chapter 9, recounts the sixth plague of Egypt, when Moses and Aaron were commanded by God to take two handfuls of soot from a furnace and then scatter the ashes skyward (Figure 1). The Egyptian men and livestock developed festering eruptions known as *shhin*, a term translated as "boils," a festering malady that was extremely difficult to heal.

The modern recognition of *S. aureus* dates back to the late 19th century. Sir Alexander Ogston, a Scottish surgeon and early advocate of antisepsis, first described the organism in 1881 as a bacterial cause of "acute suppuration." He named the organism, "*Staphylococcus pyogenes aureus*, taking clues from its microscopic morphology, purulent nature, and tendency to form golden colonies on plated media.

For much of the next half-century, this bacterium remained a notable cause of severe morbidity and death among patients. During World War I, post-influenza staphylococcal pneumonia occurred in young, healthy military personnel producing "dirty salmon-pink anchovy sauce" colored sputum, ultimately leading to "cherry-red indigo-blue cyanosis" and rapid progression to death (2). Skin and soft tissue infections also frequently progressed to sepsis without effective antibiotic therapy to halt their spread. In 1941, an 82% mortality was documented for patients who were treated for *Staphylococcus aureus* septicemia in the pre-antibiotic era (1). The survival rate in the over-fifty population in their sample was only 2% (3).

The introduction of penicillin G in 1941 was revolutionary, and mortality rates due to staphylococcal infections dropped precipitously. However, nonsusceptible strains of *S. aureus* were described almost immediately, and resistance to chloramphenicol, erythromycin, and the tetracyclines also emerged within the next decade (4). Within 5 years, approximately 50% of *S. aureus* isolates expressed resistance to penicillin via production of the beta-lactamase enzyme. Vancomycin, a glycopeptide antibiotic, was introduced in 1956, and methicillin, the first semisynthetic antistaphylococcal penicillin, was introduced in 1961, both in an attempt to combat penicillin-resistant *S. aureus*. (Table 1) (5). However, the availability of these agents did not stem the tide of resistance. The first case of methicillin resistant *Staphylococcus aureus* was described in the United Kingdom in 1961 (5), and MRSA was widespread in Europe by the 1970s and in the U.S. by the late 1980s (3). The decade of the 1990s saw nosocomial MRSA rates almost double from approximately 30% in 1990 to nearly 57% in 2000 (Figure 2). Currently, nosocomial MRSA rates approach 60% or more in many areas of the country (6).

The increasing prevalence of MRSA among *S. aureus* strains resulted in a significant increase in the utilization of vancomycin. By the mid 1990s, *S. aureus* strains less than susceptible to vancomycin began to emerge (Figure 3). In 1997, the first *S. aureus* strains possessing reduced susceptibility to vancomycin, known as VISA (vancomycin-intermediate *Staphylococcus aureus*), were documented in Michigan and New Jersey in patients on peritoneal dialysis who were administered vancomycin for prolonged duration (7). The first case of vancomycin resistant *Staphylococcus aureus* (VRSA) was subsequently documented in Michigan in 2002 in a patient administered vancomycin for almost 6 weeks. Subsequent studies have documented progressive overall decreasing vancomycin susceptibility among clinical isolates of *Staphylococcus aureus* (i.e., "susceptibility creep") (Figure 4) as well as the emergence of heteroresistant strains *S. aureus* strains (hetero-VRSA). These strains form subpopulations of vancomycin-resistant daughter cells in a larger population of more susceptible *S. aureus* strains which may be selected out in the presence of vancomycin therapy.

MRSA has also become a prominent pathogen outside the healthcare setting. In the late 1980s, reports surfaced of MRSA cases occurring in the community in patients without exposure to hospitals or nursing homes. These cases affected younger individuals, ethnic minorities, and often involved severe skin or soft tissue infections. Outbreaks were associated with certain higher risk groups, including individuals who used IV drugs, participants in close contact sports, and residents living together in crowded conditions, such as inmates, military recruits, and disabled individuals in group homes. In the late 1990s, four pediatric deaths attributable to "community acquired MRSA" (CA-MRSA) was documented involving previously-healthy children (9). CA-MRSA infections differ from healthcare-associated MRSA infections in a number of ways. CA-MRSA infections are predominantly skin and soft tissue infections, are often susceptible to other non-β-lactam antimicrobial drugs, and carry a type IV or V staphylococcal cassette chromosome (SCC) with the *mec*A gene (10). In contrast, healthcare-associated MRSA infections are found at multiple body sites, are usually multidrug resistant, and carry the SCC*mecc* types I, II and III. In the United States, 2 major clones of CA-MRSA have been identified by pulsed-field gel electrophoresis (PFGE) and designated USA300 and USA400 by the CDC. Toxin expression of the CA-MRSA strains carry the intracellular toxin Panton-Valentine leukocidin (PVL), which is known for pore formation on polymorphonuclear cells of the host. In addition, the USA300 clone appears to be emerging as the predominant strain of MRSA nationwide in both community and hospital-acquired settings, with outbreaks of skin and soft tissue disease (Figure 5), community and hospital-acquired pneumonia (Figure 6), and bacteremic syndromes (11,12,13). CA-MRSA rates in some areas of the country now exceed 75% of the strains, especially in the pediatric population (14).

Thus, trends in the second half of the current decade include the increasing role of MRSA as a community-acquired pathogen, the re-emergence of surgical debridement as a therapeutic modality in managing *Staphylococcus aureus* skin and soft tissue infection, and the waning use of vancomycin, as other gram positive antibiotic agents take a more prominent role in the treatment of MRSA skin infections, pneumonia, bacteremia, and endocarditis.

References

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Table 1: Time required for prevalence rates of resistance to reach 25% in hospitals.

Drug	Year Drug Introduced	Years to report of resistance	Years until 25% rate in hospitals	Years until 25% rate in the community
Penicillin	1941	1-2	6	15-20
Vancomycin	1956	40	?	?
Methicillin	1961	<1	25-30	40-50 (projected)

Chambers H. Emerging Infect Dis. 2001;7:179.

Figure 1: The sixth plaque of Egypt-the plague of boils (Exodus IV), 1483. From the woodblocks of the Great Cologne Bible, 1483.

Figure 2: Increasing incidence of MRSA infection in the United States.

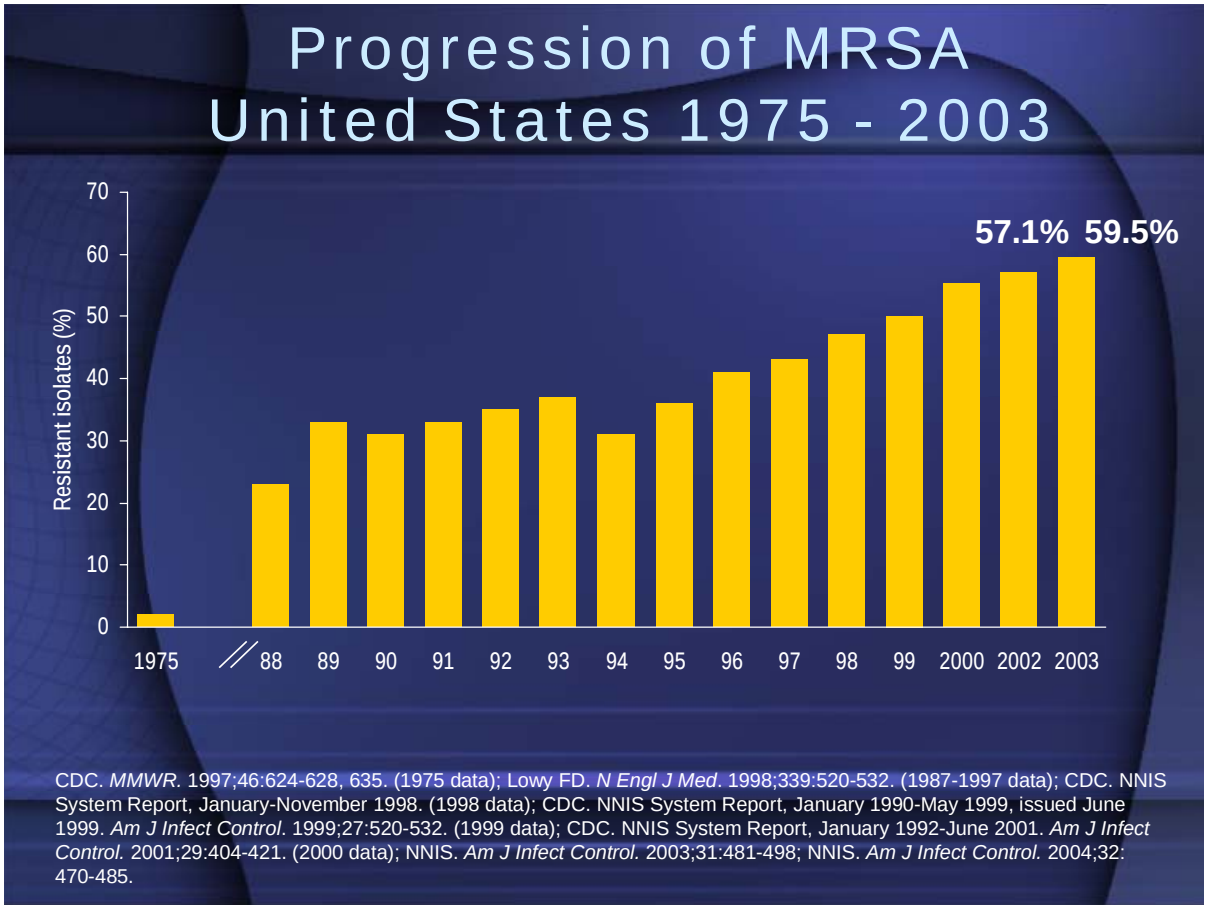
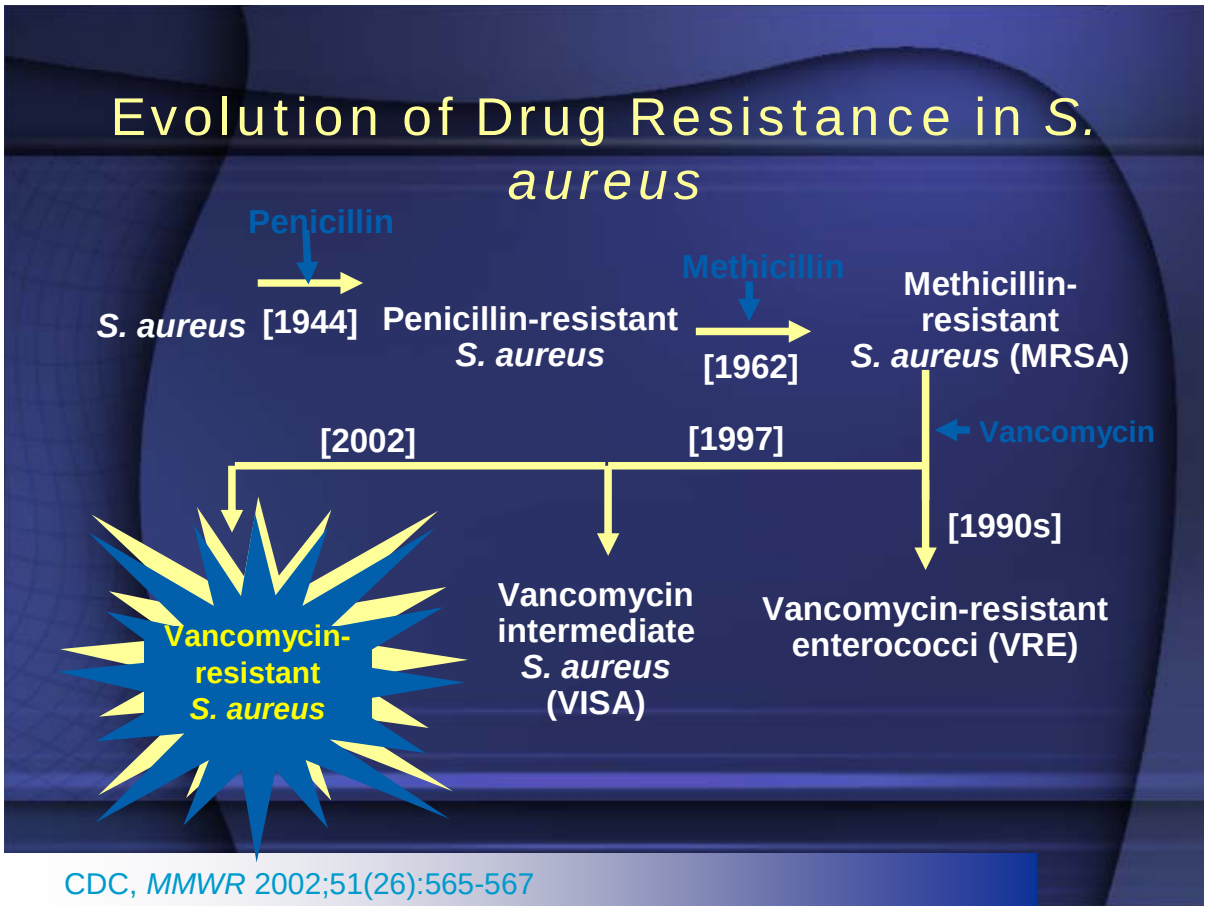


Figure 3: Chronologic evolution of resistant *Staphylococcus aureus*



Adapted from: CDC's 12 Steps to prevent antimicrobial resistance in hospitals. http://www.cdc.gov/drugresistance/healthcare/tools.htm#slides

Figure 4

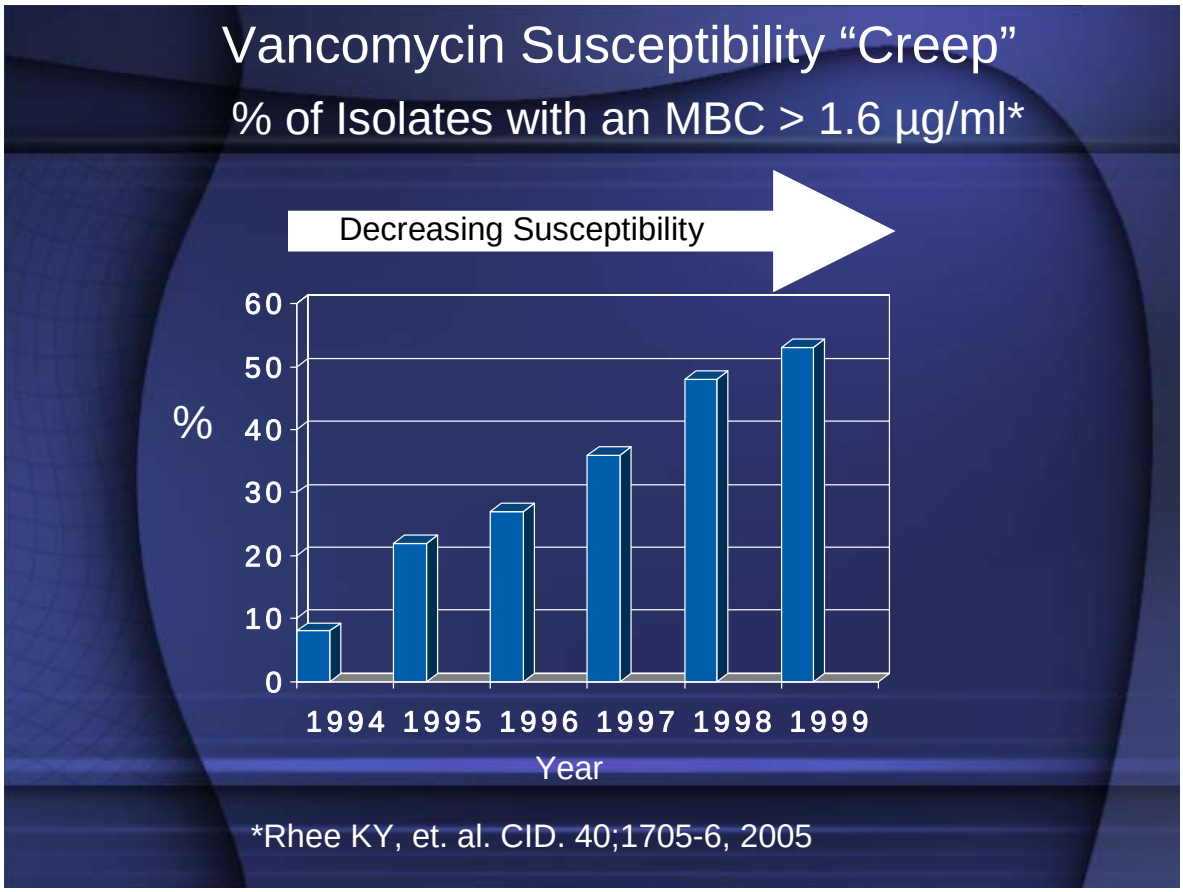

Vancomycin Susceptibility "Creep"
% of Isolates with an MBC > 1.6 µg/ml*
Decreasing Susceptibility
%
60
50
40
30
20
10
0
1994 1995 1996 1997 1998 1999
Year
*Rhee KY, et. al. CID. 40;1705-6, 2005

Figure 5: Community-acquired MRSA skin infection in a patient after obtaining a tattoo. MMWR. 55(24):677-9. 2006. June 23

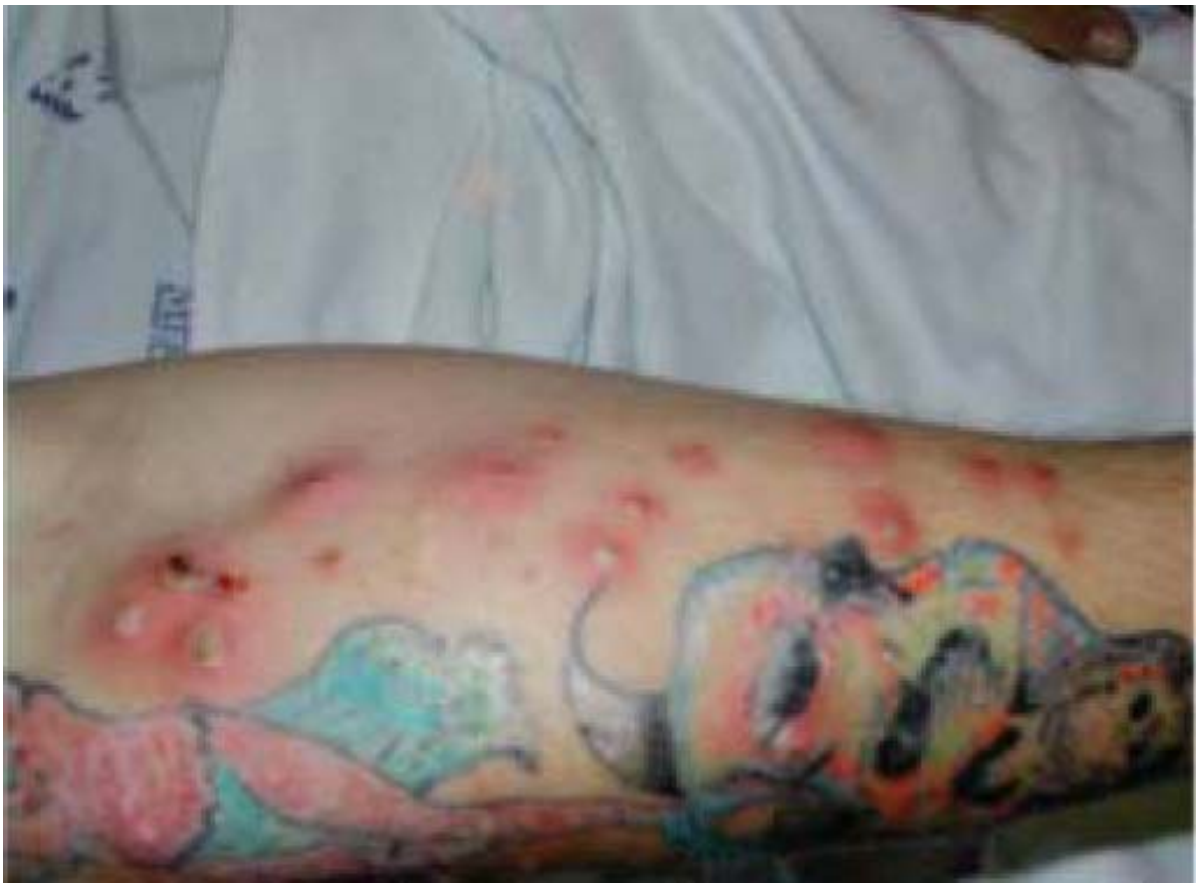


Figure 6: Nosocomial necrotizing MRSA pneumonia with spontaneous right pneumothorax in ICU patient (Photo courtesy of the author)