Review

Epidemiology, surveillance and control of methicillin-resistant *Staphylococcus aureus*: an Overview

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Abstract

Staphylococcus aureus (*S. aureus*) is one of the most common human pathogens, causing a wide range of afflictions from minor infections of the skin to serious wound infections, bacteraemia, pneumonia and endocarditis. Methicillin, the first semisynthetic derivative of penicillin, was a new hope to treat penicillin resistant *S. aureus* in the early 1960s. Nevertheless, only one year after its introduction, the first methicillin-resistant *S. aureus* (MRSA) strains were detected. There is no golden rule in the control of MRSA. Nevertheless, using surveillance cultures of patients and healthcare personnel, strictly enforced contact precautions, and judicious use of broad-spectrum antibiotics have helped several countries, including Finland, Denmark, and the Netherlands to keep MRSA at a very low level. Conversely, countries including China, Japan, US, Italy, Greece, UK, where stringent counter-measure were not able to be installed, MRSA have become hyper-endemic. Control of MRSA in those countries were obliged to concentrate available resources to prevent MRSA infections only at patients at high risk of serious morbidity and mortality.

Keywords: *Staphylococcus aureus*; methicillin; surveillance

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is one of the most common human pathogens, causing a wide range of afflictions from minor infections of the skin to serious wound infections, bacteraemia, pneumonia and endocarditis. Methicillin, the first semisynthetic derivative of penicillin, was a new hope to treat penicillin resistant *S. aureus* in the early 1960s. Nevertheless, only one year after its introduction, the first methicillin-resistant *S. aureus* (MRSA) strains were detected. Over the past sixty years, MRSA has evolved into one of the most challenging scourges of modern medicine, first in hospitals, then in the community.

In the United States (US), since the first case of MRSA reported in 1968, MRSA has become a persistent problem in hospitals. Data from the National Nosocomial Infections Surveillance (NNIS) System indicated that the proportion of *S. aureus* isolates that was methicillin resistant increased from 2% in 1975 to 29% in 1991 at NNIS hospitals[1]. MRSA percentage among intensive care units (ICU) patients increased significantly in the last decade from less than 40% in 1995 to over 60% in 2004[2]. An increasing proportion of MRSA isolates are susceptible only to vancomycin, the last therapeutic option for patients with MRSA. It is therefore alarming to the whole world when vancomycin resistant *S. aureus* (VRSA) isolates were first reported in 2002 in the United States. At least three *S. aureus* isolates fully resistant to vancomycin have been reported among US patients in the past years[3-5]. In a recent study, data collected by the Active Bacterial Core surveillance system (ABCs) identified 5, 287 cases of invasive MRSA infection and 988 deaths in 2005[6]. Based on the findings, the researchers calculated that MRSA was striking 31 out of every 100000 Americans, which translated into 94360 cases and 18650 deaths nationwide. In comparison,

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the AIDS virus killed about 12500 Americans in 2005.

A similar pattern has been observed among most countries in the world. In the Far East in China, MRSA has become a major public health problem, where resistance among hospital-acquired infections reached almost 90% in 2001[7]. In Japan, approximately 70% of all *S. aureus* bloodstream isolates were methicillin resistant in 2001[8]. In Europe, the overall prevalence of MRSA increased from 16% in 1999 to 24% in 2004. In some southern European countries, over half *S. aureus* isolates are methicillin resistant, with the highest MRSA proportion (70%) in Romania. Even though some of the Scandinavian countries had witnessed the lowest MRSA rates worldwide, a recent increase in MRSA incidence rate has also been reported. Denmark and the Netherlands reported MRSA proportion higher than 1%, and Finland reported an MRSA proportion exceeding 3%[9].

Equally if not more disturbing is the emergence and rapid dissemination of community-acquired MRSA (CAMRSA). Since the first study of CAMRSA among patients without predisposed risk factors of MRSA in 1998[10], CAMRSA infections have been reported among patients from a variety of community settings, including children in day care centers[11], competitive athletes[12], Native Americans[13] and military recruits.[14] The death of four previously healthy children indicated the potential severity of CAMRSA infections[15]. Figure 1 illustrated the key events of *S. aureus* resistance over time and its epidemic spread worldwide.

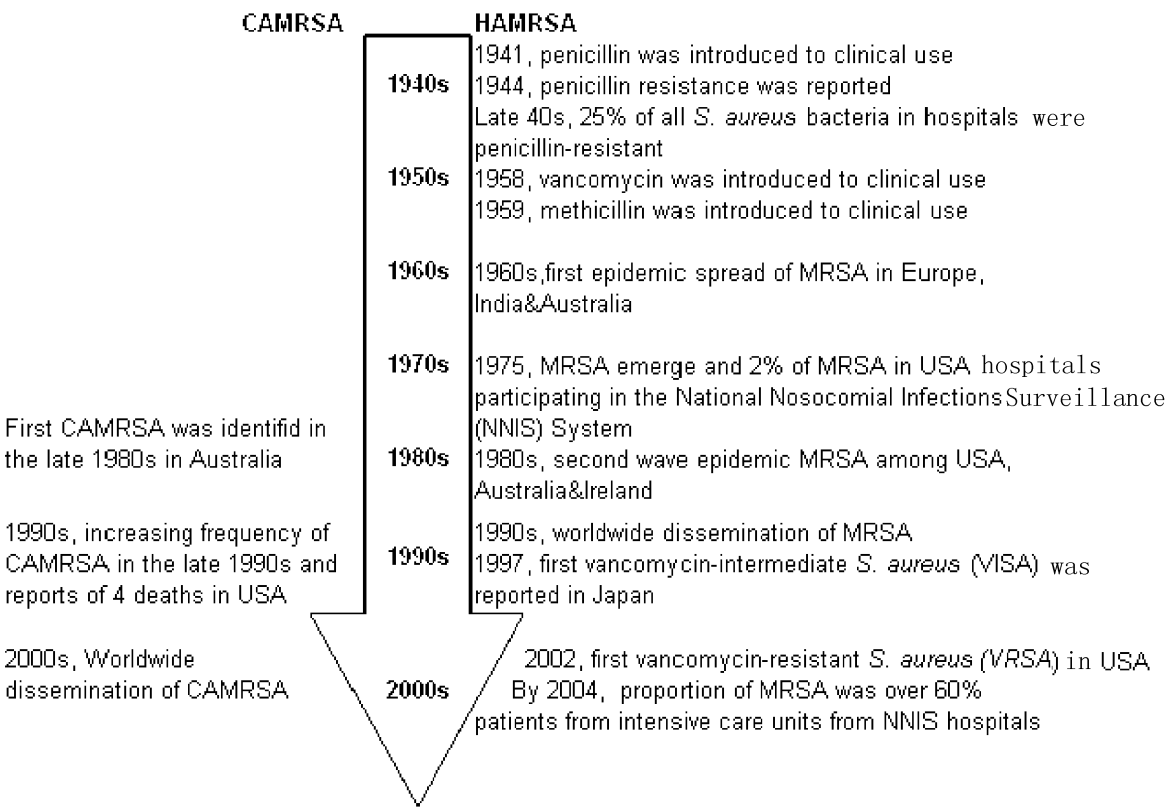

Figure 1 Timeline of hospital-acquired methicillin-resistant *Staphylococcus aureus* (HAMRSA) and community-acquired methicillin-resistant *Staphylococcus aureus* (CAMRSA)[1-4, 16, 17].

SURVEILLANCE OF MRSA

In response to the increasing threat of MRSA, control of MRSA is high on both the political and scientific agenda in several leading industrial countries, including both the US and United Kingdom (UK). Central to all national, international, and global efforts against antimicrobial resistance is a focus on well-designed surveillance systems. A search of the WHO AR Info Bank conducted in August 2005 documented 70 national and 12 international antimicrobial resistance surveillance networks[18], many of

which has incorporated MRSA. Most of the large-scale, global surveillance systems have been either funded by the pharmaceutical industry or by the federal government. In contrast, surveillance studies at regional and local levels face greater challenge of fund shortage. The approach of centralized testing is usually unrealistic for regional or local efforts. Instead, alternative approaches such as aggregation of institutional antibiograms or analysis based on retrospectively collected antimicrobial susceptibility testing (AST) data were often used at a regional or local level for some organisms, including MRSA. Surveillance studies based on AST data take the advantage of extensive data that are readily being collected and could include all clinical laboratories[19]. On the other hand, inclusion of duplicate data was and remains one of the major problems in the interpretation of surveillance studies based on routine AST data or combining institutional antibiograms[20].

To address this situation, the Clinical and Laboratory Standards Institute (CLSI, formerly known as National Committee for Clinical Laboratory Standards) proposed to using AST results from the first species isolate per patient, per period of data analysis, to calculate susceptibility frequencies[21]. Several other approaches widely in use for identifying and removing duplicate isolates included no removal of any isolates (NR), counting only the most susceptible (MS) or most resistant (MR) isolate from an individual per surveillance period, and the Cerner® laboratory management system, a widely used software program[22,23]. Employing data from a statewide, population-based antimicrobial resistance surveillance system, Li *et al*[24]. for the first time compared the effect of thirteen duplicate isolate removal strategies on *S. aureus* susceptibility to oxacillin. The study found that no removal produced the lowest estimates of susceptibility. NCCLS and Cerner methodologies produced similar estimates of susceptibility for any given analysis period and the difference in susceptibility percentage between a 90-day and 365-day time period was less than 1% by either of the two criteria and was statistically insignificant. Greater impact of duplicate isolate removal was observed among inpatient settings. For example, when comparing NCCLS365 to NR, an increase of 7% in the susceptibility proportion was observed in the inpatient environment; this same comparison resulted in an increase of only 1% in the outpatient setting. These finding can be seen in Table 1. For the ease of implementation and comparability of results, the authors recommend using the NCCLS guideline for surveillance of MRSA.

Table 1 The impact of duplicate isolate removal on *Staphylococcus aureus* susceptibility to oxacillin, by clinical setting, Hawaii, 2002

Methods of duplicate isolates, removal*	Inpatient				Outpatient			
	No. Total	No. S	% S	95% CI	No. Total	No. S	% S	95% CI
NR	4737	2436	51	48 - 55	9858	7281	74	73 - 75
C3	4075	2092	51	48 - 55	9590	7101	74	73 - 75
NCCLS3	4036	2066	51	48 - 55	9559	7078	74	73 - 75
C10	3719	1969	53	49 - 57	9500	7045	74	73 - 75
NCCLS10	3654	1936	53	49 - 57	9461	7020	74	73 - 75
C30	3438	1914	56	52 - 60	9280	6907	74	74 - 75
NCCLS30	3346	1875	56	52 - 60	9222	6875	75	74 - 75
MR	2971	1672	56	52 - 60	8427	6295	75	74 - 76
C90	3255	1864	57	53 - 61	8905	6667	75	74 - 76
NCCLS90	3121	1815	58	54 - 62	8802	6617	75	74 - 76
C365	3142	1821	58	54 - 62	8589	6444	75	74 - 76
NCCLS365	2971	1752	59	55 - 63	8427	6368	76	75 - 76
MS	2971	1802	61	57 - 65	8427	6433	76	75 - 77

*NCCLS: National Committee for Clinical Laboratory Standards; NR: No removal; C3: Cerner 3 d; NCCLS3: NCCLS 3 d; C10: Cerner 10 d; NCCLS10: NCCLS 10 d; C30: Cerner 30 d; NCCLS30: NCCLS 30 d; C90: Cerner 90 d; NCCLS90: NCCLS 90 d; C365: Cerner 365 d; NCCLS365: NCCLS 365 d; MR: Most resistant; MS: Most susceptible; S: Susceptible; CI: Confidence interval. Adapted with permission from Li[24].

MRSA CONTROL

As the first and critical step to detect and describe the current situation of the existing problems, surveillance of antimicrobial resistance serves as the core tool in understanding the nature and scope of the problem while assisting in controlling the spread of resistance [25-27]. The information gained from surveillance system is expected to inform those capable of identifying effective public health interventions in the prevention and containment of the spread of resistant organisms. For the past five decades, MRSA has preoccupied policy makers, members of the academic community, and more recently, professionals and the lay public at all levels. To summarize, attempts to control the spread of MRSA in hospital settings have relied principally on three measures: the detection and isolation of infected or colonized patients, hand hygiene among healthcare workers, and restriction of antibiotics.

The detection and isolation of infected or colonized patients has been central to most national guidelines[28]. In the Netherlands, a timely implementation of national policy of stringent control policy was successful in bringing down MRSA prevalence in *S. aureus* bacteremia from approximately 20% at the end of 1960s to less than 1% throughout the 1980s and 1990s[29]. The "search and destroy" policy successfully adopted for at least 20 years in Western Australia has prevented the establishment of epidemic MRSA in any of the Western Australian hospitals and a relatively lower MRSA prevalence (3%) in Perth, compared to a much higher rate of MRSA, e. g., 35% in Sydney where the "search and destroy" policy was not adopted[30].

Nevertheless, the effectiveness of such strict isolation measures remained controversial in the hospital management of MRSA, particularly in regions where MRSA was already highly endemic[28-31]. In a recent review by Cooper *et al*[31], only 6 out of 46 studies examined provided sufficient evidence. While four of the six studies providing convincing evidence that isolation of MRSA patients controlled spread, the remaining two revealed control failure in spite of the employment of intensive isolation measures[32,33]. Nevertheless, the author warned that the absence of evidence for effectiveness should not be mistaken for evidence of lack of effect. Isolation measures recommended in national guidelines should continue to be applied until further research establishes otherwise.

In order to determine cost of the MRSA 'search and destroy' policy, Rijen *et al*[34]. carried out a study in a teaching hospital with 1370 beds from 2001 until 2005. They found that a successful MRSA control policy was maintained at a cost of £ 2.16 (around US $ 4.22) per admission. During the study period, no patients had a bacteremia caused by MRSA and only one patient developed an invasive infection with MRSA. More studies are needed to determine the cost effectiveness of such policies in places of highly endemic MRSA.

Hand decontamination has been considered the most effective and cost-effective means in the prevention and control of hospital acquired infections[35,36]. Promoting hand hygiene to improve patient safety and decrease health-care-associated infections constitutes a core component of control of MRSA. Nevertheless, adherence with hand hygiene and barrier techniques was inadequate, with a median 31% rate reported in several studies[37,38]. Traditional interventions aimed at increasing hand washing compliance were found to have little or no sustained effect[39]. Fortunately, with strong institutional commitment, the University Hospital Geneva was successful to ensure continuing high levels of compliance with hand washing protocols, which subsequently brought a reduction in hospital-acquired infections [40].

Health care regulations were also successful in the reduction of inappropriate antimicrobial use in some countries. Interdiction of over-the-counter sales of antimicrobial agents in Chile has a sustained impact on antimicrobial use in the outpatient settings. Sales of orally used antimicrobial agents decreased by 43% from US $ 45.8 million in 1998 to US $ 26.1 million in 2002[41]. Restriction of preoperative antimicrobial prophylaxis in Belgium has a continued effect on the use of antimicrobial prophylaxis in Belgium[42]. Separation of dispensing and prescribing in South Korea decreased overall prescribing of antimicrobial agents and selectively reduced inappropriate prescribing[43]. Denmark's national program of strict infection control measures and low consumption of antibiotics introduced in the 1970s have kept its incidence of MRSA infections extremely low[44].

Nevertheless, a large-scale educational program to promote appropriate antimicrobial drug use in the state of Wisconsin did not generate greater antimicro-

bial prescribing reductions despite improved knowledge[45]. Even though some studies focusing on the restriction of antimicrobial use were capable to change physicians´behavior, there was limited evidence of subsequent effect of antimicrobial resistance[46]. Given the fact the antibiotics actually foster the emergence of resistant strains, strict policies to limit their use are not enough to reverse the trend, once MRSA has gained a foothold. In the case of MRSA, little correlation was found between its prevalence and parsimonious use of antibiotics. For example, Finland, UK, and Italy all consume roughly the same amount of antimicrobial agents, yet, they have big differences in the proportion of MRSA isolates.

In conclusion, with all the uncertainness, there is no golden rule in the control of MRSA. Nevertheless, using surveillance cultures of patients and healthcare personnel, strictly enforced contact precautions, and judicious use of broad-spectrum antibiotics have helped several countries, including Finland, Denmark, and the Netherlands to keep MRSA at a very low level. Conversely, countries including China, Japan, US, Italy, Greece, UK, where stringent counter-measure were not able to be installed, MRSA have become hyper-endemic[8]. Control of MRSA in those countries were obliged to concentrate available resources to prevent MRSA infections only at patients at high risk of serious morbidity and mortality[47]. Implementation of well- designed interventional studies to inform the choice of control measures should be of high research priority for the future.

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