Review Article

Methicillin-resistant *Staphylococcus aureus* Control at the National University Hospital, Singapore: A Historical Perspective

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Abstract

Introduction: The National University Hospital (NUH) was the first restructured public hospital in Singapore. As the most recently established hospital in Singapore, it has a unique record of alert organisms including methicillin-resistant *Staphylococcus aureus* (MRSA). Materials and Methods: We performed a critical review of multiple data sources including surveillance reports, task force reports, published abstracts and manuscripts concerning MRSA in NUH. Results: Three themes emerged: 1) the MRSA rates have remained relatively stable through the life of the hospital despite the increased complexity of patients and intermittent intensified control efforts; 2) the major MRSA task forces were driven by surgeons and 3) a scientific approach to epidemiology has a critical role in understanding and planning interventions. Conclusion: Although containment of MRSA can be accomplished to a certain degree through mobilisation of existing resources, higher goals such as eradication would require massive infusions of infrastructural, scientific and human resources to have a chance of success.

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Introduction

The National University Hospital (NUH) was established in 1985 as the first restructured hospital and medical centre in Singapore.[1] At its official opening in 1986, the then Director of Medical Services, Dr Kwa Soon Bee, Chairman NUH, hoped that the new teaching hospital would set the pace for "an alternative system" for the delivery of hospital care.[1] Fast forward to 2008 and now all the public hospitals are restructured and healthcare in Singapore has changed beyond recognition in the last quarter of a century. The infection control landscape has likewise changed and it is timely to review the changes that have taken place in the control of methicillin-resistant *Staphylococcus aureus* (MRSA) in the last 20 plus years at NUH.

The hospital opened on 24 June 1985 with 50 outpatients and 4 inpatients.[1] The Emergency Department did not become operational until 1987 and the hospital became fully operational in 1989. Because of its short history, NUH is unique in Singapore hospitals in having a record of alert organism surveillance from the beginning of full operations. While NUH was a newly built hospital in the late 1980s, it was not new in the sense that it began de novo in a new town with a new population. Rather, the patients and staff from the old "University" units of Singapore General Hospital (SGH) moved en bloc to Kent Ridge. All the major medical and surgical sub-specialties are currently represented in NUH ranging from paediatrics and obstetrics to transplant, neurosurgery and cardiovascular surgery with the exception of burns.

The Infection Control Committee was established in the late 1980s with 2 consultant microbiologists and an infectious diseases physician contributing substantially to the work. Right from the onset, MRSA was recognised as an important "alert" organism by the microbiology laboratory even before the Infection Control Committee organised formal surveillance. In addition, the Ministry of Health Singapore had published its guidelines for the control of MRSA in the early 1990s, which were re-issued in 1998, and these were the basis for hospitalwide policies on the control of MRSA.

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Materials and Methods

This is a critical review of the efforts to control MRSA in NUH. We reviewed surveillance data, minutes of infection control committee meetings, task force reports and published abstracts and manuscripts concerning the control of MRSA in NUH. What follows is a narrative review of the efforts undertaken to control the spread of this organism in NUH. The incidence of MRSA nosocomial infection was defined according to the Singapore Ministry of Health criteria which included only patients (not isolates) with new true nosocomial infections (i.e. excluding colonisations) detected more than 48 hours after admission to hospital. Patients with known MRSA infections who represented to hospital with relapses or recrudescences of their infections were generally excluded from the incidence data.

Results

MRSA was apparently first detected in NUH soon after the hospital began functioning from a patient transferred from another hospital. "Alert" organism including MRSA surveillance was carried out once the hospital became fully operational. The first report on antibiotic resistance surveillance was published in the NUH Therapeutics Bulletin in 1992 covering the years 1989 to 1991, i.e. the first 3 years of the hospital's full operations. These data covered 18,560 clinical isolates from all sites excluding blood, cerebrospinal fluid and stool, i.e. including respiratory samples, urine, wounds and fluids. No routine admission or pre-operative screening surveillance was done at the time so all isolates represented clinical specimens ordered by the treating physicians. *Staphylococcus aureus* accounted for 3675 isolates or 19.8% of the total. Antimicrobial susceptibility testing was done using the Kirby-Bauer method and in 1989, the year that NUH first became fully operational, 46% of the clinical isolates of *S. aureus* were resistant to methicillin. Over the 3 years of the study, the percentage of resistance of *S. aureus* to methicillin ranged from 34% to 46%.[2] The subsequent rates of MRSA isolation in the hospital from all sites and proportions of *S. aureus* isolates that were resistant to oxacillin or methicillin are charted in Figures 1 and 2.

Surgical site infection surveillance was also conducted from the beginning of hospital operations. The initial approach was based on the 2 Infection Control nurses reviewing all patients with positive wound cultures. In addition, from December 1989 to May 1990, a validation of this method was performed by active surveillance performed by a team led by a surgeon.[3] This included visual inspection of all clinician-detected infections by the trained Infection Control nurses. This method of active surveillance was found to detect twice the number of infected wounds as the passive microbiological culture driven surveillance. Overall, 4.4% of surgical wounds were determined to have

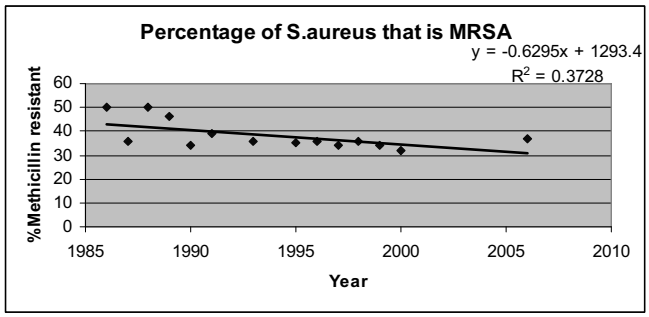

Fig. 1. Percentage of *S. aureus* that is MRSA.

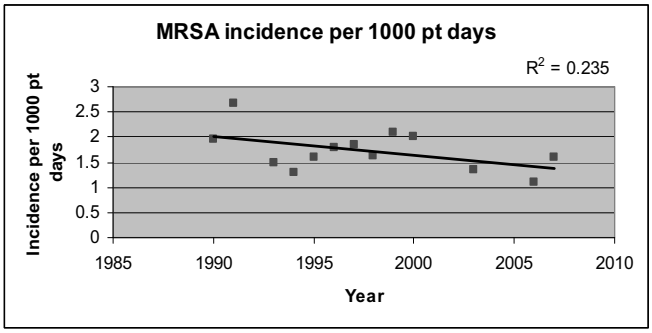

Fig. 2. MRSA incidence per 1000 patient days.

become infected. *S. aureus* was the most common cause of surgical wound infections accounting for 38% of SSI. Of these, 53% were methicillin resistant. MRSA SSI were distributed among all surgical procedures although there did seem to be some clustering with 9/16 of all SSI in urology caused by MRSA and 12/43 of all SSI following upper gastrointestinal procedures being caused by MRSA, compared with only 2/20 SSI following appendectomy due to MRSA. Sixty-eight per cent of the MRSA causing SSI in NUH in the late 1980s was found to be cotrimoxazole susceptible.[3] Interestingly enough, a recent study documented the emergence of EMRSA-15 which is often co-trimoxazole susceptible in Singapore hospitals including NUH with these strains representing 23% to 41% of all MRSA isolates.[4]

Meanwhile, microbiology laboratory-based surveillance continued and the next report published in the peer-reviewed literature was in 1995 based on a large sample of 2156 clinical isolates from 1991 including all MRSA isolates from patients in the hospital. Fusidic acid resistance was seen in 8% of MRSA isolates. There were 601 isolates of MRSA from clinical samples in that year.[5]

In addition to documenting MRSA incidence and prevalence, studies were performed to identify risk factors for MRSA infection and colonisation. In a retrospective study of 1 year's surveillance data from 1998 to 1999, the MRSA incidence rate in the intensive care units (ICUs) was 4.6 ± 2.5 per 1000 patient days compared with the general

wards with a rate of 1.4 ± 0.2 per 1000 patient days. The major risk factor identified for acquisition of MRSA in NUH was found to be the length of stay in general wards with patients staying greater than 14 days in hospital having a significantly higher risk of acquisition of MRSA.[6] A similar study found that the risk of MRSA infection and colonisation was higher in the subsidised, non-airconditioned wards compared with the non-subsidised airconditioned wards (1.84 ± 1.1 per 1000 patient days vs 0.7 ± 0.3 per 1000 patient days, P <0.005) and 8-bedded wards compared with 6-bedded wards (2.31 ± 1.4 per 1000 patient days vs 1.4 ± 0.5 per 1000 patient days, P = 0.004).[7]

Control Efforts

As with other international efforts, a 2-pronged approach of antibiotic stewardship together with infection prevention was taken. The main approach to stewardship was to use education as it was recognised that restriction using the "yellow forms" that were used in other hospitals was unsuccessful due to the ease with which the restrictions were circumvented. The first antibiotic guideline was prepared in 1991 by the Pharmacy and was widely circulated but recognised as being less widely complied with. As a result, the guidelines were re-drafted with the help of the different departments in the mid-1990s. Although the departments "owned" the guidelines, compliance was variable. To our knowledge, there was only 1 attempt to review compliance with the guidelines and this yielded an approximate 50% compliance rate for patients admitted with community-acquired pneumonia. Interestingly enough, that study found comparable outcomes but lower costs in patients whose clinicians followed hospital guidelines.[8]

On 27 November 1996, Professor Walter Tan, then deputy chairman of the Medical Board wrote to the chair of the Infection Control Committee stating that he was "deeply concerned with the rise of MRSA cases in NUH... some wards have as many as 7 MRSA cases at one time. MRSA cases in CTICU have resulted in cardiac operations being cancelled as there are inadequate isolation facilities in CTICU".

The infection control committee was directed to set up a task force to look into the MRSA problem and "to recommend urgent measures to eradicate the problem". The task force was established which included an infectious diseases physician, a microbiologist and representatives from nursing. They carried out an audit survey to monitor infection control practices in NUH. Their findings were striking and well documented for the first time – that hand hygiene was not widely practiced, that aseptic precautions were not always adhered to when intravenous devices were handled or when invasive procedures were performed or during routine patient care. A report with names of the staff involved at all levels was submitted to the Medical Board together with a series of recommendations. These included:

1. Regular infection control audits by the Infection Control nurses,
2. A mandate to the nurse managers (then referred to as "ward sisters") to "implement and supervise aseptic techniques", and
3. The building of 2 additional isolation rooms in the CTICU for patients infected or colonised with MRSA.

The report was well received by the Medical Board with a promise to support the efforts of the infection control nurses. The report without the names of the individuals concerned was also circulated to all the clinical chiefs with a strong message from the Medical Board of the importance of complying with infection control standards. The 2 isolation rooms were built in the cardiothoracic ICU and audits were put in place although it is not clear how effective these were. Nurse empowerment, an idea now being advocated by the Institute for Healthcare Improvement, among others, was probably ahead of its time.

The Ministry of Health Quality Evaluation Committee also raised the issue of MRSA control in 1998/1999 and a report was submitted by then Associate Professor Tan Chorh Chuan, Dean of the Faculty of Medicine, NUS and Chairman of the Medical Board NUH (including Dr Gamini Kumarasinghe and Associate Professor Ti Teow Yee). Several measures were considered:

1. Routine admission surveillance screening: which was rejected on the grounds of cost effectiveness at that time, adequate isolation facilities were not available to ensure that all patients infected or colonised with MRSA could be appropriately isolated or cohorted
2. Staff surveillance: at the time, the practice was to screen only nursing staff with hand lesions or dermatitis. Attempts to decolonise were only made for those with dermatitis who were colonised with MRSA. In addition, outbreaks detected through routine geographical ward based surveillance of new MRSA isolated identified through the clinical microbiology laboratory would trigger off an outbreak investigation which in most cases would involve the surveillance of both medical and nursing staff.
3. Isolation of MRSA infected and colonised patients: it was suggested that while having a dedicated MRSA ward would be ideal, there were resource constraints which limited this in practical terms. Single room isolation was then provided only for patients with respiratory isolates positive for MRSA on the basis of their theoretical risk of becoming high dispersers of MRSA. The suggestion was made to increase the number of infection control nurses to a figure close to

international norms and to deploy these nurses actively to the wards to conduct education and audits at the ward level.

4. Tagging of patients: the recognition that a large reservoir of MRSA was in patients who were frequently readmitted to the hospital, often with their MRSA status only being discovered late in their hospital admission led to the suggestion that these patients' notes be "tagged" with a sticker or electronically. This is still in the process of being implemented.
5. "Importation" of patients: as a tertiary hospital, NUH had a large number of patients transferred from other hospitals and the suggestion was made to mandate that the referring hospital inform NUH of the MRSA status of the patient. This was recognised for other pathogens as emergence of resistance to certain classes of antibiotics emerged even before these agents were used in NUH.[9] Again, this is yet to be fully operational.
6. In addition to the recommendations submitted to the Ministry of Health, internally, the committee recommended providing more prominent feedback to the clinicians on the infection rates in their own areas as well as strong efforts to develop molecular typing for the purposes of molecular epidemiology in collaboration with the Department of Microbiology in NUS.

The report from the Dean-Chairman Medical Board to the Ministry of Health concluded with a strong request for research support from the Minsitry of Health. They suggested that the Ministry of Health could allocate funds to commission research on important aspects of this problem. Some suggested priority research areas are:

1. Characterisation of the molecular epidemiology of MRSA,
2. Cost-benefit studies of current MRSA infection control programmes in Singapore, and
3. Assessement of MRSA transmission in the community and the impact of MRSA colonisation.

In 2002, the National Healthcare Group that had been established in 1999 raised the issue of infection control across the cluster and one key idea that arose was the concept of "benchmarking" in terms of certain selected outcomes. After much negotiation, the decision was made to use MRSA bloodstream infections per 1000 patient days as the marker for monitoring infection control across the NHG institutions. The significant change in the definitions was that all MRSA bacteraemias were counted and not just those occurring more than 48 hours after admission. This led to a rise in MRSA bacteraemias illustrating the importance of standardised definitions of terms (Fig. 3).

In December 2002, once again, the cardiac surgeons raised the alarm about the rate of MRSA post-surgical

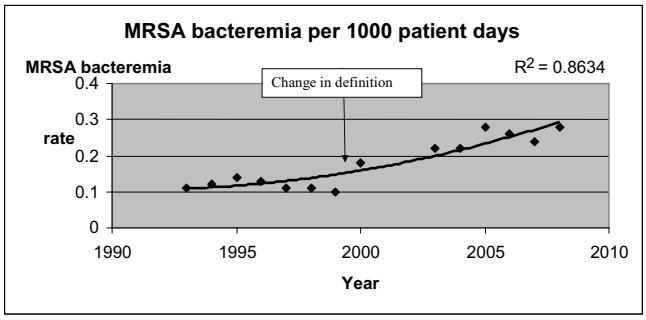

Fig. 3. MRSA bacteraemia per 1000 patient days.

wound infections following a small cluster of deep MRSA wound infections following coronary artery bypass graft surgery. Once again, a task force was assembled and the CTICU was closed for 2 days with terminal disinfection, staff screening, reinforcement of hand hygiene, aseptic procedures, operating theatre discipline, preoperative screening of all cardiac surgery for MRSA and trying to improve the isolation and cohorting of patients infected or colonised with MRSA.

While these efforts were ongoing, there was the increasing emergence of community-associated MRSA (CA-MRSA) in many parts of the world. Singapore too saw sporadic cases of typical CA-MRSA cases[10,11] with the *Staphylococcal chromosomal cassette* (SCC) types IV and V and the Panton-Valentine-Leukocidin (PVL) gene. These strains have entered hospitals and caused outbreaks and the lines between CA-MRSA and healthcare-associated MRSA have been blurred. A large survey of the source for MRSA infection and colonisation among patients with MRSA showed that using traditional definitions for nosocomial MRSA-isolates identified 48 hours after admission to the hospital would exclude more than one quarter of MRSA isolates.[12] However, almost all of these isolates came from patients in the "penumbra" of the hospital including the dialysis centres and outpatient clinics. The authors found only 1 of 383 cases of MRSA that were "true community associated MRSA". This suggests that at the time, the incidence of true community associated MRSA is about 0.3% although no molecular typing was done to confirm this. A recent survey of nasal carriage of MRSA in 400 children attending childcare centres in Singapore suggests that MRSA in the community in Singapore is also more likely to be due to a "leakage" of hospital strains of MRSA among contacts of the healthcare system, this situation is unlikely to continue in the long term and there will be the need for control of nosocomial outbreaks of CA-MRSA as has happened in other settings.[13]

The most recently published data from NUH suggest that the rate of MRSA infections among hospitalised patients[14] has not changed significantly since the hospital's opening

despite the increasing complexity of patients with the advent of transplant surgery and major increases in surgical procedures. While the overall MRSA rates have not changed, there was an increase in MRSA bloodstream infections (Fig. 3) due to the change in definitions to include those identified in the first 48 hours of hospitalisation. This indicator reflects not only MRSA control but also the efficacy of control of device-associated infections as the majority of these infections are indeed related to either short-term or long-term indwelling vascular access devices. There are also concerns about the accuracy of laboratory- based surveillance as documented in earlier studies of surgical site infections. NUH referral laboratory handles a large number of samples from regional and other local laboratories and these are occasionally aggregated into laboratory-based surveillance systems that might lead to discrepancies compared with data obtained by manual infection control practitioner driven surveillance.

Discussion

NUH is the last new hospital established in Singapore. It was also the first restructured public hospital and thus presents a unique opportunity to observe the behaviour of a major nosocomial pathogen. Several themes appear:

In terms of incidence, the MRSA rate has remained relatively constant over the past 20 years despite the increasing complexity of patients at the hospital. There are several possible reasons for this and they include the procedures put in place at the hospital's inception which were relatively successful in that the proportion of *S. aureus* that are due to MRSA has trended slightly lower than the early days of the hospital before the first infection control manuals or antibiotic guidelines were in place. In terms of incidence, the MRSA rate has also remained relatively constant. The resources devoted to infection control at the inception of the hospital were severely limited and thus there was a need to prioritise infection prevention activities. Through a step-wise process beginning with implementation of hand hygiene audits, antimicrobial guidelines and the Ministry of Health's MRSA guideline, the MRSA rate was kept relatively constant over the life of the hospital without significant reduction to the levels seen in Northern Europe, but at the same time, without the relentless rise seen in other settings.[15] Whether this was the result of infection control efforts or part of the ecological natural history of this pathogen will never be clearly known as no comparator hospital with different efforts exists in Singapore. To our knowledge, the other major academic medical centre, SGH has had a very similar history of MRSA prevalence through the past 2 decades. This would make sense seeing as the staff and even the first few patients of NUH came out of the SGH. In another similarity, we found that MRSA prevalence was highest in the 8-bedded C class wards,[7] which is similar to the epidemiology of vancomycin-resistant *enterococci* (VRE) at the SGH. A multivariable analysis revealed that the highest risk was in patients in C class wards.[16] Of concern is the apparent rise in the incidence of MRSA bacteraemias noted. This might be related to an increase in device utilisation with the greater use of intermediate and long-term vascular access devices for renal dialysis and chemotherapy which were less prevalent in the early 1990s when the data were first collected. It is clearly an area for further analysis and a good target for a multi-disciplinary approach perhaps modelled on the successful programmes rolled out in ICUs in the United States.[17]

The second theme that emerges is the role of surgeons in raising the alert over MRSA. While baseline education, surveillance and reporting were done by infectious diseases physicians and microbiologists, outbreaks tend to capture the attention of non-specialists. This also illustrates the point that in Singapore, as in many other settings, infection control has to be driven by the ownership of the problem by those who are most affected by the consequences of its failure. Cardiothoracic surgeons with the support of the infection control team prompted both major MRSA task forces in NUH. There was the recognition that severe consequences such as MRSA mediastinitis post-elective coronary artery bypass graft surgery were unacceptable and that drastic action needed to be taken. In many other countries, infection control specialists have recognised the importance of feedback to clinicians in the referring services and this has been a critical but often neglected part of many MRSA control efforts. In recent years, the increased pressure for public reporting of MRSA has reportedly led to decreases in MRSA rates in England and Wales.[18] Before we in Singapore get to public reporting, we need to ensure that our service chiefs in the major departments at least have a good understanding about the MRSA rates in our hospital.

The third theme that emerges from this review is the critical role for scholarly research into the epidemiology of all resistant pathogens including MRSA. The discipline of doing an academically rigorous study that can go through the peer review process is vital in helping to ensure the quality of data generated. It has been argued that poor data are worse than no data in that inaccurate information can lead to policies and strategies that are ill-conceived at best and full of disastrous unintended consequences in the worst case. Since the beginning of the hospital's operations, surveillance data have been collected on alert organisms and these have been published in local and international journals or presented at regional and international scientific meetings. In addition, a number of interventions have been progressively introduced at various stages, including enhancing isolation, staff screening, hand hygiene campaigns, user-generated antimicrobial use guidelines

and education at the individual ward level by nurse champions. A number of these have been evaluated in small studies. Overall, this academic approach to the problem of antibiotic resistance is perhaps part of what the pioneers of NUH had in mind when the hospital was first opened – that while service would be provided, the primary goal of the hospital would be pushing the frontiers of medical knowledge with good clinical service as a natural consequence of scientific inquiry and academic rigour. Of course, the reality is often far from these high-minded goals. Successive task forces, even those with the backing of the Dean of the School of Medicine who was at the time Chairman of the Medical Board have called for national funding for molecular epidemiology and economic analyses of the impact of MRSA more than a decade ago. These are only just beginning to happen, driven by the next generation of infectious diseases physicians, some of which are described in this edition of the *Annals*.

In summary, the task of containing MRSA has been the primary focus of the infection control efforts of the first generation of infectious diseases physicians and microbiologists at NUH. While occasionally, the dream of eradication was raised, the necessary resources were never made available. History tells us that the only successful eradication efforts for MRSA from a setting of relatively high endemicity took place several years ago in Denmark through a concerted national effort.[19] With the slow but steady rise of community-associated MRSA, it is clear that a similar effort has to take place in Singapore if we are to do more than just contain this pathogen and protect our patients.

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