EDITORIAL

METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS*: WHERE ARE WE NOW?

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INTRODUCTION

An editorial in the October 1987 issue of this journal poignantly addressed the measures required to control the burgeoning problem of methicillin resistant *Staphylococcus aureus* (MRSA) in the hospital setting[1]. The passage of two and one half-years marks an opportune time to reflect on the progress toward that goal.

BACKGROUND

Two fundamental questions regarding MRSA should be answered prior to reviewing its current status: 1. Why is *Staph. aureus* so virulent? 2. How does *Staph. aureus* become resistant to penicillinase-resistant penicillins (eg. methicillin, cloxacillin, etc.)?

1. *Staphylococcus aureus* produces a variety of proteins that can cause epidermolysis (Staph scalded skin syndrome)[2] and Staphylococcal food poisoning, toxic shock syndrome[3], and increased microbial adherence to cell receptors (Staph carrier state)[4]. An additional virulence mechanism demonstrated by *Staph. aureus* is the ability to survive in leukocytes after ingestion. The intracellular environment serves as a safe haven for Staph as many antibiotics do not achieve therapeutic levels within leukocytes. This feature is a possible contributor to relapse or therapy failure[5].

2. *Staphylococcus aureus* is killed when penicillin or cloxacillin (methicillin equivalent) attaches to bacterial penicillin-binding protein (PBP) and interferes with bacterial cell wall synthesis. MRSA occurs when the target PBP is altered by the bacteria to prevent antibiotic attachment, thereby avoiding cloxacillin's or penicillin's activity. Penicillins, cephalosporins and other beta-lactams may induce the bacteria to produce both penicillinases (which destroy penicillin, but not cloxacillin) and altered PBPs. The complex interactions between *Staph. aureus* and antibiotics form an active area of investigation[6].

REASONS FOR CONCERN

Should we commit so much time, effort and resources toward this organism? MRSA is worthy of our attention on several counts.

First, it is an important contributor to nosocomial infection morbidity. Due to multiple antibiotic resistance, MRSA has a selective advantage in colonizing the more intensively treated patient. It is clear that physical debility alters a patient's "bacterial receptors" on oropharyngeal epithelial cells, allowing colonization with virulent organisms (eg. MRSA and gram negative bacilli). Once attached tothe host. organisms are able to take advantage of breaks in host defense and invade. Intravenous lines, intubation, aspiration, surgical incisions, bed sores, etc. all allow access for invasion. This theory is supported by the observation that peritoneal dialysis patients with *Staph. aureus* nasal carriage have a higher incidence of *Staph. aureus* infections[7,8].

Second, the spread of MRSA is a marker of our often inadequate efforts to prevent cross-infection between patients. We know that patients serve as reservoirs for MRSA, while medical personnel act as vectors. The environment has not been convincingly shown to be a common source for MRSA epidemics[9]. In several epidemics, the MRSA carrier rate of doctors and nurses has been very high while other ancillary personnel (respiratory therapists, phlebotomists, etc.) had minimal MRSA carriage[9]. The reason for this discrepancy is not clear, but the implications for nosocomial pathogen spread are obvious. If professionals are serving as vectors of MRSA, we are surely also serving as vectors of other pathogens (eg. multiresistant gram negative bacilli).

Finally, as noted in the previous editorial, the cost of dealing with MRSA colonization and infection is significant. In addition to the cost of effective therapy (eg. S$2,000 for 10 days of vancomycin), many other intangible expenses must be considered to obtain an accurate estimate of the total cost: patient morbidity, prolonged length of stay (LOS), added expense of isolation (single room, gloves, gowns, masks, etc.), and lost patient earnings. The spread of infection impacts the hospital in other ways: raising the average LOS for routine procedures (not always reimbursed by third-party payers)[10], obstructing bed availability for elective surgical/medical procedures, and raising patient concerns when selecting a hospital for elective procedures. The indirect costs of MRSA epidemics are ultimately borne by other health care seekers and/or taxpayers.

CURRENT SITUATION

Whether MRSA is perceived as a problem depends on one's perspective. Infection control committees look to infection trends and prevalence. Individual doctors must assess the impact of MRSA on their practices in the hospital. Hospital administrators must decide if the delivery of health care is affected. Studies performed elsewhere have found that nosocomial wound infections and pneumonias prolong hospitalization by an average of seven and six days, respectively[10].

To the best of my knowledge, a comprehensive review of MRSA's direct and indirect costs has not been performed in Singapore. In lieu of that information, I will provide a few statistics for reflection. A recent two-month review of nosocomial infection data from a large government hospital in Singapore

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revealed 16% of observed hospital-acquired infections to be due to *Staphylococcus aureus* with 55% of these isolates methicillin resistant. In another major Singapore hospital, an informal audit found 33% of single rooms of one ward, and 60% of an ICU's beds to be occupied by MRSA infected/colonized individuals. When compared to 1987, the amount of intravenous vancomycin used at these hospitals has increased 2.4 and 3.0 times, respectively[11]. Although not all hospitals are affected to the same degree, these figures suggest that MRSA is a significant problem in Singapore.

THERAPEUTIC OPTIONS

Is there hope on the horizon? We have come to rely on improvements in drug therapy for assistance. The development of newer agents with activity against MRSA has been encouraging, but the initial flush of enthusiasm must be tempered with reality.

The quinolones (particularly ciprofloxacin) have been shown to be effective against MRSA, but in locales where the drug has been widely used resistance is present in up to 40% of *Staph. aureus* isolates[12]. Additionally, therapeutic failures have been documented in many patients with deep-seated MRSA infections while receiving quinolones[13]. A recent visiting speaker to Singapore noted that sulbactam does not induce *Staph. aureus* to produce altered PBPs or penicillinases, allowing the co-drug that is given with sulbactam to destroy MRSA unimpeded by these bacterial resistance mechanisms. This interesting observation has yet to be clinically verified. Recommendations regarding sulbactam-containing regimens (eg. ampicillin/sulbactam) in treating MRSA infections must therefore await clinical trials.

Currently, the "gold standard" therapy of serious MRSA infections remains vancomycin. Alternative agents for the treatment of MRSA infectons include: trimethoprim/sulfamethoxasole (TMP/SMX), clindamycin, fusidin, quinolones, rifampicin and fosfomycin. Investigational agents not available in Singapore with *in vitro* activity against MRSA include coumermycin, pristinamycin, paldimycin, and daptomycin[9,16].

There are therapeutic limitations to many of the alternative MRSA agents that should be appreciated. For example, rifampicin, fusidin and fosfomycin when used alone result in resistance development in an unacceptable number of cases[9,14,16]. TMP/SMX has been associated with a high clinical failure rate when compared to vancomycin despite *in vitro* activity against MRSA[15]. However, there are characteristics of some of the agents that make them appealing. Clindamycin, TMP/SMX, the quinolones and rifampicin are concentrated in phagocytes. High levels of intracellular drug would be valuable in eradicating viable phagocytized MRSA, thus preventing relapse.

The above antibiotics are mentioned in the context of therapy for an established infection. There has been much work in the area of eradicating the carrier state as well. This has proved to be a stubborn problem. Combinations of oral and topical drugs have been associated with initial eradication of MRSA, but carry a high relapse rate. Recently, intranasal application of mupirocin has had some success, but there are reports of resistance developing to this drug[18,19]. Further experience is needed before recommendations can be given.

ADDRESSING THE PROBLEM

Discussing advances in antibiotic therapy does not address the basic issue. Antibiotic regimens do not affect MRSA dissemination, they only manage the consequences. The only way to control MRSA cross-contamination in our hospitals is to educate doctors and nurses regarding their roles as vectors and the means of interrupting the spread.

The steps to address MRSA epidemics were mentioned in the previous editorial but deserve repeating:

1. Isolating or cohorting patients found to be colonized/infected with MRSA.
2. Cohorting nursing personnel working with MRSA patients.
3. If strict handwashing cannot be enforced, then use disposable non-sterile latex gloves when handling patients.
4. Educating physicians, surgeons and nurses as to their role as vectors.
5. Early discharge of patients that are affected.
6. Keeping track of patients discharged with MRSA, so that on readmission they can be triaged to isolation until surveillance culture results are available. (This is a simple task in this day of computerized billing).
7. Giving authority to the Infection Control Committee to intervene when the principles of infection control are jeopardized by any member of the health care team.
8. Adequately staffing the Infection Control teams.

(Surveillance, education, monitoring, and liaison are labour intensive tasks. Studies from the 1970's reveal that one infection control nurse can provide adequate service to only 250 occupied beds.)

9. Finally, educating the public. Families should realize that MRSA is an unfortunate consequence of medical progress. Acknowledging that nosocomial infections occur and that steps are being taken to intervene is an honest, positive approach that will prevent later misunderstanding.

CONCLUSION

Methicillin resistant *Staphylococcus aureus* is not a problem we should ignore. It has the potential to disrupt the efficient delivery of health care to all Singaporeans. Since October 1987 we have furthered our understanding of the molecular basis of methicillin resistance and expanded available antimicrobial agents to counteract MRSA, yet the problem persists. The basic issue is one of **preventing** colonization and infection. Careful attention to the epidemiology of MRSA has allowed other afflicted centres to control their outbreaks[17]. Success depends on the cooperation of health care providers at all levels, intervention by doctors and nurses to prevent cross-contamination, and the realization by administrators that short-term expenditures to prevent the spread of MRSA will be more than met by long-term savings. Indifference by individuals at any level of the hospital hierarchy compromises the efforts of all the others. Until all health care providers appreciate the impact that MRSA is having or will have on the practice of medicine, the spread will continue.

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