Nasal carriers are more likely to acquire exogenous *Staphylococcus aureus* strains than non-carriers

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Abstract

We performed a prospective observational study in a clinical setting to test the hypothesis that prior colonization by a *Staphylococcus aureus* strain would protect, by colonization interference or other processes, against *de novo* colonization and, hence, possible endo-infections by newly acquired *S. aureus* strains. Three hundred and six patients hospitalized for >7 days were enrolled. For every patient, four nasal swabs (days 1, 3, 5, and 7) were taken, and patients were identified as carriers when a positive nasal culture for *S. aureus* was obtained on day 1 of hospitalization. For all patients who acquired methicillin-resistant *S. aureus* (MRSA) or methicillin-susceptible *S. aureus* via colonization and/or infection during hospitalization, strains were collected. We note that our study may suffer from false-negative cultures, local problems with infection control and hospital hygiene, or staphylococcal carriage at alternative anatomical sites. Among all patients, 22% were prior carriers of *S. aureus*, including 1.9% whom carried MRSA upon admission. The overall nasal staphylococcal carriage rate among dermatology patients was significantly higher than that among neurosurgery patients (n = 25 (55.5%) vs. n = 42 (16.1%), p 0.005). This conclusion held when the carriage definition included individuals who were nasal culture positive on day 1 and day 3 of hospitalization (p 0.0001). All MRSA carriers were dermatology patients. There was significantly less *S. aureus* acquisition among non-carriers than among carriers during hospitalization (p 0.005). The mean number of days spent in the hospital before experiencing MRSA acquisition in nasal carriers was 5.1, which was significantly lower than the score among non-carriers (22 days, p 0.012). In conclusion, we found that nasal carriage of *S. aureus* predisposes to rather than protects against staphylococcal acquisition in the nose, thereby refuting our null hypothesis.
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Introduction

The recent introduction of metagenomic technologies has highlighted the great diversity of bacterial species that live in or on the human body. These bacteria play an important role in balancing our health status. However, this natural balance may be disturbed, and some species can transform from colonizers into invasive pathogens. The causes of such changes are ill-

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defined, and both human and microbial physiology will be influential, as are bacterial interspecies interactions. Certain species may preclude the presence of others, and the dynamics of such interactions may be important in homeostasis. *Staphylococcus aureus* is one of the best-known human (nasal) colonizers that is also very capable of pathogenic behaviour.

Being the flexible opportunist that it is, *S. aureus* is a well-recognized nosocomial pathogen. Of all nosocomial infections, *S. aureus* accounts for approximately 15% [1–4]. This includes bacteraemia and wound infections, which lead to increased hospital stay, additional antibiotic use, and elevated costs, morbidity, and mortality [4–9]. Patients who are nasal carriers (20–50%) are at increased risk of developing autoinfection [8,10–14]. Thus, eradication of *S. aureus* nasal carriage may prevent nosocomial infections, and such interventions have been proven to be clinically effective [8,14–17]. For instance, mupirocin treatment combined with chlorhexidine washings was effective in eliminating *S. aureus* from both the nares and skin [18,19], which reduced the number of nosocomial *S. aureus* endo-infections.

Whether prior nasal colonization with a methicillin-susceptible *S. aureus* (MSSA) strain protects against acquisition of exogeneous MSSA or methicillin-resistant *S. aureus* (MRSA) is still largely unknown [20,21]. Consequently, the effect of prior colonization on *S. aureus* endo-infection vs. exo-infection is unclear. It was shown that patients re-admitted to hospital benefited from a protective effect of being colonized with MSSA [22,23]. The protective efficacy of such colonization in the prevention of acquisition of MRSA was calculated to be 78%. The studies lacked information on real hospital-based events, including the occurrence of infections, and were considered to be inconclusive.

In this study, we investigated the frequency of *de novo* colonization by *S. aureus* in patients in a single hospital where a highly endemic MRSA clone was circulating. We studied whether patients who carried *S. aureus* upon admission were more susceptible to or protected from acquisition of another *S. aureus* strain.

Materials and methods

Study design

We performed a single-centre prospective observational follow-up study. The study involved patients admitted to Hospital Kuala Lumpur (HKL), which is a 2200-bed acute-care and teaching hospital in Malaysia. The current study covered two departments: neurosurgery, which has three wards (intensive-care unit; male ward A; and female ward B); and dermatology. The majority of the neurosurgery patients were trauma cases without underlying diseases. Patients in all departments previously showed a higher rate of *S. aureus* (MSSA and MRSA) colonization and infections and more extended hospitalization periods than patients in other but clinically similar wards (unpublished data). Patients were followed until the moment at which they left the hospital.

Inclusion criteria

Adult patients (aged $\geq$18 years) were included in the study, after informed consent had been obtained, when the patient was not pregnant, did not have obvious staphylococcal infection upon admission, was not hospitalized in the 6 months before, had a hospital stay of $\geq$7 days at the end of the study period, and provided the possibility of performing frequent microbiological culture. Patients diagnosed with staphylococcal infection within <24 h after hospitalization were excluded from the study.

Ethics and informed consent

The study was performed according to the rules of Good Clinical Practice and according to the Malaysian statutory definition of clinical trials. Patients received verbal and written information on screening for nasal carriage with *S. aureus* by nursing personnel. Patients or relatives provided oral consent, which was noted in the nursing record. Patients had to be mentally and physically capable of taking the decision to take part in the study. For patients unable to make such a decision, guardians were informed, and their initial agreement was obtained. Before official participation, either the patients or their guardians had to provide official written consent. Patients could stop participating at any time without having to provide a particular reason. Furthermore, the study investigator ended the participation whenever the patient's wellbeing was considered to be at risk.

Definition of staphylococcal carriage state

In the current study, we chose the simplest of carriage definitions: carriers were those subjects who had a positive nasal culture taken on their admission day (day 1 of hospitalization). All other patients were defined as non-carriers, irrespective of whether they had one or more positive cultures for the nasal swabs taken on days 3, 5 and 7 after admission (Fig. 1). The likelihood of acquiring one or more new *S. aureus* strains during hospitalization in carriers and non-carriers was examined.

Extranasal and nasal *S. aureus* acquisition

S. aureus isolation from the nose at >48 h after hospitalization and acquisition of a strain with a different *spa* type among non-carriers was considered to be proof of *de novo* nasal acquisition. To determine acquisition of *S. aureus* during hospital stay, data

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