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Review

Determinants of *Staphylococcus aureus* nasal carriage

Jan L. Nouwen*, Alex van Belkum, Henri A. Verbrugh

Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

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Abstract

This article aims to review what is currently known of the host and bacterial factors determining *S. aureus* nasal carriage, including recent developments and future prospects. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: *Staphylococcus aureus* nasal carriage; Host factors; Bacterial factors; Prevention

Introduction

Staphylococcus aureus is an important pathogen in human disease and the cause of infections ranging from mild, such as skin infections and food poisoning, to life-threatening, such as pneumonia, sepsis, osteomyelitis, and infective endocarditis [1]. Over the last 20 years the incidence of both community-acquired and hospital-acquired *S. aureus* infections has increased, accounting for 13% of nosocomial infections in US hospitals between 1979 and 1995 [2-4]. Despite antibiotic therapy these infections still have severe consequences, stressing the importance of prevention [5,6].

S. aureus produces many toxins and is capable of developing resistance to all available antibiotics. In 1961 methicillin resistance was first noted [7] and since the 1970s, methicillin-resistant *S. aureus*

(MRSA) has become the main cause of nosocomial infections in many countries all over the world [8-10]. Glycopeptides like vancomycin are the last resort antibiotic in these countries, however in 1997 a vancomycin-resistant *S. aureus* (VRSA) was also isolated [11-13].

S. aureus nasal carriage is the major risk factor for the development of *S. aureus* infections in various clinical settings, including post-operative wound infections [5,14], in patients undergoing continuous ambulatory peritoneal dialysis and hemodialysis [15,16], and in patients infected with the human immunodeficiency virus [17]. A large majority of these infections are of endogenous origin, in that individuals are infected by their own *S. aureus* isolate [15,16,18], as was recently confirmed by von Eiff et al. [19]. Eradication of *S. aureus* nasal carriage by application of topical mupirocin results in a reduction in endogenous infections in various risk populations [16,20-22]. In contrast, the absolute risk of developing an *S. aureus* infection as a nasal carrier is low (less than 5% for nosocomial bac-

*Corresponding author. Tel.: +31-10-463-3510; fax: +31-10-463-3875.

E-mail address: nouwen@bacl.azr.nl (J.L. Nouwen).

teremia), and in an elderly population no associated mortality was demonstrated recently [23].

Judging by the recent attention in leading medical journals, the problem of *S. aureus* is still considered an important one, and needs further research to elucidate the host-pathogen interplay and to develop effective strategies for the prevention of *S. aureus* infections [19,24-28].

***S. aureus* nasal carriage**

Humans, as other mammals, are a natural reservoir of *S. aureus* and the ecological niches of *S. aureus* strains in humans are the anterior nares, although staphylococci can be isolated from many skin sites, including axilla and perineum [29-32]. However, the elimination of *S. aureus* from the nose results in the subsequent disappearance from other areas of the body [29,33-35].

While carriage of *S. aureus* in the nose plays a key role in the epidemiology and pathogenesis of infection, and is a major risk factor for the development of both community-acquired and nosocomial infections, the biology of nasal colonization remains incompletely understood [5,15,19,24,36,37].

Cross-sectional surveys of healthy adult populations have reported *S. aureus* nasal carriage rates between 20 and 55% [32,38-43]. From longitudinal studies it became clear that *S. aureus* nasal carriage patterns differ between individuals, and that 10-35% of individuals carry *S. aureus* persistently, 20-75% carry *S. aureus* intermittently, and 5-50% never carry *S. aureus* in their nose [38,39,44-48]. Persistent carriage is more common in children than in adults, and many people change their pattern of carriage between the ages of 10 and 20 years [44]. The reasons for these differences in colonization patterns remain unknown so far.

The number of *S. aureus* colonies in the anterior nares is significantly higher in persistent carriers than in intermittent carriers [49,50], resulting in an increased risk of *S. aureus* infections [51-53]. Moreover, persistent carriers are often colonized by only one selected single strain of *S. aureus* over long time periods, while intermittent carriers carry many different strains over time [38,39,48,54,55]. Persistent carriage seems to have a protective effect on the

acquisition of other strains [56,57]. These data suggest that the basic determinants of persistent and intermittent carriage are different.

Comparison of results between studies is made difficult by the lack of conformity in the methods of ascertainment and varying criteria for the definition of persistent or intermittent carriage used, as well as the absence of information on antibiotic exposure, an important confounding variable. In clinical studies, often due to logistic reasons, only one nasal swab culture is performed to ascertain *S. aureus* nasal carriage. The result of this is that the group with one negative culture will in fact consist of a mix of true non-carriers plus intermittent carriers, while the group with one positive culture will in fact consist of a mix of true persistent carriers plus intermittent carriers. When studying determinants of *S. aureus* nasal carriage or when performing an intervention trial in this way, the differences between the positive- and negative-culture groups will become blurred by the presence of intermittent carriers in both groups (regression to the mean). In a recent study, we determined that at least two quantitative nasal swab cultures are necessary to adequately predict the nasal carrier state, while at least seven cultures are needed to discern non- from intermittent carriers [50]. The correct separation of the population into persons who are true persistent carriers versus intermittent and non-carriers is a prerequisite to adequately perform studies into the molecular and genetic basis of *S. aureus* nasal carriage, as well as intervention studies.

Determinants of *S. aureus* nasal carriage

Bacterial factors

Much research has focused on specific staphylococcal factors like cell wall components (lipoteichoic acid [58,59]), surface proteins (protein A [54], microbial surface components recognizing adhesive matrix molecules (MSCRAMM) [60-62]) and staphylococcal interactions with other host proteins and carbohydrate moieties like mucin [63,64] or other mucus components [65,66]. Other substances found in the respiratory tract, including secretory immunoglobulin A [67], glycolipids [68], gangliosides

[69,70] and surfactant protein A [71], may also constitute receptor sites for staphylococcal adherence. Hydrophobic interactions and surface charge provide forces that are probably also involved in mediating staphylococcal binding to epithelia [59,63,72].

On the basis of all these results, however, no common genetic or phenotypic characteristics segregating persistent from intermittent colonizing strains have been identified so far. However, very recently Day et al., using multilocus sequence typing, reported the presence of a number of frequently carried genotypes of *S. aureus* in the population that were disproportionately common as causes of disease [25]. They concluded that the existence of these ecologically abundant hypervirulent clones suggests that factors promoting ecological fitness, i.e. the capacity to colonize persons, also increase its virulence and that *S. aureus* is not solely an opportunistic pathogen [25]. Future studies will hopefully dissect the interrelation between colonization capacity and virulence and shed new light on the mechanisms of disease pathogenesis. The just finished '*S. aureus* genome project' would be the logical starting point [27].

Bacterial interference may be another explanation of the non-carrier state: when an ecological niche is already occupied by other bacteria, e.g. coagulase-negative staphylococci, *Corynebacterium* species or artificially with *S. aureus* 502A, wild type *S. aureus* does not seem to have the means to replace this resident bacterial population [39,73–75]. The exact mechanism for this effect has not been elucidated so far [76,77]. Cross-inhibition of the expression of various virulence factors by the recently identified accessory gene regulator (*agr*) and staphylococcal accessory regulator (*sar*), may be one mechanism by which one strain excludes others from colonizing sites including the anterior nares [78–83], although a large *S. aureus* population genetics analysis failed to confirm this suggestion [84]. Bacterial interference by active colonization using *S. aureus* 502A has been successful in nurseries during out-breaks of *S. aureus* infections in the 1960s and for treatment of patients with recurrent furunculosis [85–87]. Bacterial interference using *Corynebacterium* species has recently been reported to be successful in eradicating MRSA nasal carriage [88].

Host factors

The observation that different *S. aureus* nasal carriage patterns (non-, intermittent and persistent) can be discerned, suggests a host influence. This view is supported by the fact that persistent carriage rates vary between different ethnic groups [41,43,89], are higher in males than in females [90,91] and depend on age (higher in early childhood, lower in old age) [44,56,91–94] and hormonal status [95]. In addition, *S. aureus* seems to have a greater affinity for nasal epithelial cells obtained from carriers than from non-carriers [96] and adheres better to nasal epithelial cells from patients with eczema than to cells from patients without eczema [97].

When in an artificial colonization experiment persistent and non-carriers were both inoculated with the same mixture of *S. aureus* strains and followed-up with weekly nasal swab cultures for 26 weeks, only one of 11 persistent carriers reverted to the non-carrier state, while two out of eight non-carriers had become persistent carriers [57]. These data suggest that most non-carriers are not 'susceptible' to becoming an *S. aureus* nasal carrier even after artificial colonization.

Genetic studies have not yet provided us with a definitive answer. Two twin studies have been performed, the first showing concordant results in monozygotic twins [98], while the other could not confirm these results [99]. We recently performed a family study in which first-degree family members of non-carriers and persistent carriers were evaluated for *S. aureus* nasal carriage. No familial clustering and thus no firm genetic background could be demonstrated [100]. An earlier study that evaluated the relationship between HLA Class II haplotype and nasal carriage demonstrated HLA-DR3 to be associated with carriage, but a large proportion of the patient group suffered from an autoimmune disease, which was not adjusted for in the analysis [101].

Environmental factors can also influence the *S. aureus* nasal carrier state. Hospitalization for example, has been shown to be an important risk factor for *S. aureus* nasal carriage [42,45,102–104], while in the community household partners demonstrate highly concordant *S. aureus* nasal carriage states [105].

Many underlying diseases or conditions have been associated with a higher *S. aureus* nasal carriage and subsequent infection rate: insulin-dependent diabetes mellitus [91,106,107], hemodialysis and continuous ambulatory peritoneal dialysis [15,16,108,109], intravenous drug abuse [110,111], repeated injections for allergies [112], *S. aureus* skin infections and other skin diseases [113,114], river-rafting [115], liver cirrhosis [116,117], liver transplantation [118], human immunodeficiency virus (HIV) infection or AIDS [17,18], qualitative or quantitative defects in leukocyte function [119], Wegener's granulomatosis [120], nasal abnormalities [121], and rhinosinusitis [122]

One common factor between these seems to be the repeated violation of the skin or mucosa as anatomical barriers. However, local or systemic immune deficiencies probably also play an important role. Cole et al. reported that nasal secretions obtained from *S. aureus* nasal carriers lacked antimicrobial activity against *S. aureus* in vitro, while nasal fluid from non-carriers was bactericidal [123]. Defensins (antimicrobial peptides) as part of the innate immune system, and/or the local immune IgA response could well be involved [123–125]. Interestingly, cigarette smoking, known to cause local airway inflammation, seems to protect against carriage [91].

Future developments

Worldwide, MRSA rates have increased dramatically during the last decades. The threat of development of resistance to vancomycin, the only antimicrobial agent effective against MRSA, is alarming. The worldwide use of vancomycin has increased dramatically over the past years.

Optimization of preventive strategies is needed to control staphylococci. Therefore, new strategies have to be developed. The ability to control staphylococcal infections in the future will depend on the development of new therapeutic agents and the optimization of infection control measures. More in-depth research will be necessary to elucidate the host-pathogen interaction. The completion of both the human genome project and the *S. aureus* genome project opens new possibilities to pinpoint individ-

uals at risk, as well as 'risky' bacteria, and could thus 'personalize' our preventive options.

For now, mupirocin is the most effective drug available to achieve eradication of carriage. However, resistance to mupirocin is increasing, and it must be asked for how long this agent will be effective. One strategy that has been used successfully in the past is bacterial interference. This alternative approach to controlling staphylococcal infections could offer new opportunities if a strain with minimal virulence and maximal competition for the binding sites in the nose could be developed.

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