

## FROM THE CHICAGO MEETINGS

1999

Carriage of *Staphylococcus aureus*: Epidemiology and clinical relevance

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**Abbreviations:** CAPD = continuous ambulatory peritoneal dialysis; HIV = human immunodeficiency virus; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PCR = polymerase chain reaction

**S***taphylococcus aureus* has long been recognized as an important pathogen in human disease. Between 1986 and 1996, *S. aureus* was the most commonly isolated pathogen causing nosocomial infections reported to the National Nosocomial Infections Surveillance system at the Centers for Disease Control.<sup>1</sup> Infections caused by *S. aureus* are often associated with severe complications, including death,<sup>2,3</sup> and increase the duration and cost of hospitalization.<sup>4,5</sup> The efficacy of antibiotic treatment is threatened worldwide because of the appearance and spread of MRSA strains, which are often resistant to multiple antibiotics.<sup>6,7</sup> Recently MRSA strains with decreased susceptibility to glycopeptides, such as vancomycin, have been reported.<sup>8,9</sup> The potential spread of such strains poses a serious threat to all hospitalized patients. Therefore the prevention of staphylococcal infections is now more

important than ever. *S. aureus* nasal carriage has been suggested to play a key role in the prevention of *S. aureus* infections.<sup>10-12</sup> This review aims to summarize the current knowledge on the epidemiology and clinical relevance of *S. aureus* nasal carriage and the (potential) benefits of elimination strategies.

#### EPIDEMIOLOGY

*S. aureus* can be found on the skin and mucosal surfaces of human beings and several animal species. In human beings the anterior nares serve as the ecologic niche for *S. aureus*, although it can be isolated from many skin sites, including the perineal area. It has been shown that the anterior nares area is the most consistent area of the body from which *S. aureus* is recovered.<sup>13-16</sup> Moreover, the elimination of *S. aureus* from the nares results in the subsequent disappearance of *S. aureus* from other areas of the body.<sup>15,17-19</sup>

**Definition of the carrier state.** *S. aureus* nasal carriage has been extensively studied in patients and healthy individuals.<sup>11,20</sup> Cross-sectional surveys on *S. aureus* nasal carriage have designated individuals as either carriers or noncarriers.<sup>21-31</sup> In longitudinal studies, however, the carrier state has been shown to change over time in some individuals.<sup>32-40</sup> Three carriage patterns can be distinguished: persistent carriers, intermittent carriers, and noncarriers. The criteria used to assign an individual to each of these carriage patterns have varied from study to study. Striking differences with respect to the number of nasal cultures performed, the follow-up period, and the interpretation of the culture

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Presented at the Seventieth Annual Meeting of the Central Society for Clinical Research, September 25-27, 1997, Chicago, IL.

Submitted for publication May 14, 1998; revision submitted January 22, 1999; accepted February 1, 1999.

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J Lab Clin Med 1999;133:525-34.

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0022-2143/99 \$8.00 + 0 5/1/97504

data obtained have been noted. Despite this lack of consistency, a clear distinction between persistent and intermittent nasal carriage appears to be important. The mean number of colony-forming units of *S. aureus* isolated from the anterior nares is higher in persistent carriers than in intermittent carriers,<sup>41,42</sup> resulting in more extensive dispersal of the staphylococci in the environment<sup>43</sup> and an increased risk of *S. aureus* infections.<sup>44-46</sup> Moreover, the number of *S. aureus* phage-types or genotypes that are isolated in repeated cultures is significantly lower for persistent carriers than for intermittent carriers,<sup>33,36,47</sup> indicating that the basic determinants of persistent and intermittent carriage may be different. Recent data suggest that the attribute "persistent" should be confined to individuals in the population in whom serial nasal cultures uniformly and consistently yield *S. aureus*.<sup>48</sup>

**Prevalence of *S. aureus* nasal carriage.** *S. aureus* nasal carriage rates among healthy adults vary from study to study. Cross-sectional surveys reported carriage rates between 20% and 55%.<sup>21-31</sup> Longitudinal studies indicated that between 10% and 35% of healthy adults are persistent carriers, 20% to 75% are intermittent carriers, and 5% to 70% are noncarriers.<sup>32-40</sup> This large variation in reported rates may in part be caused by differences in the populations studied. Most studies have been performed in selected populations, including medical students, hospital personnel, job applicants, and blood donors; the reported rates may therefore differ from that in unselected populations.<sup>28</sup> Differences in the procedures of nasal swabbing and isolation of *S. aureus* may also account for some of the variation observed. It has been documented that swabs from the anterior nares (ie, the vestibulum nasi) yield higher carriage rates than swabs taken proximal to this region.<sup>15,30</sup> A recent study has shown that the number of carriers found in a given population is dependent on the swab material, the transport medium, the medium for cultivation, and the incubation period.<sup>49</sup> As mentioned above, differences in reported carriage rates are also caused by varying definitions of the nasal carrier state. Because of these reasons, a direct comparison of *S. aureus* nasal carriage rates between studies is best avoided.

**Molecular typing in *S. aureus* nasal carriage.** Typing of *S. aureus* isolates has proved to be essential, as it determines the (clonal) relatedness of bacterial isolates and provides clues as to the source, transmission, and spread of *S. aureus*. Several phenotypic and genotypic methods are available for typing *S. aureus* that differ with respect to parameters such as typeability, reproducibility, discriminatory power, and ease of performance and interpretation.<sup>50-52</sup> Bacteriophage typing has long been considered the gold standard for differenti-

ating among *S. aureus* isolates. However, phage typing is time consuming and labor consuming, may not always be reproducible, and fails to type up to 30% of *S. aureus* isolates.<sup>50,51,53-55</sup> The performance of conventional typing systems has proved to be especially poor in methicillin-resistant *S. aureus*,<sup>56,57</sup> because most strains seem to be derived from a small number of ancestral clones and therefore exhibit limited genetic diversity.<sup>57-59</sup> During the last decade new typing methods—such as immunoblotting, ribotyping, plasmid and genomic DNA fingerprinting, and PCR-based methods—have been introduced. In particular, pulsed-field gel electrophoresis of DNA macro-restriction fragments and randomly amplified polymorphic DNA analysis have proved to be worthwhile. These latter techniques basically "scan" the entire genome of the microorganism and are able to cluster isolates that are epidemiologically related.<sup>50,51,53,55,56,60-66</sup> Polymorphism in genes encoding for *S. aureus*-specific proteins, such as protein A and coagulase, have also been suggested as potentially useful epidemiologic markers but so far have had only limited success.<sup>47,51,67-69</sup>

The application of typing systems in studies of *S. aureus* nasal carriage has provided evidence that a single clone of *S. aureus* may persist in the anterior nares for many years, although persistent nasal carriage is not necessarily associated with long-term residence of a single *S. aureus* clone.<sup>13,48</sup> Several investigators have reported the exchange of *S. aureus* strains over time.<sup>33,36,37,39,47,48</sup> The exchange rate appears to be higher in intermittent carriers than in persistent carriers,<sup>47,48</sup> illustrating again the distinction between these two types of carrier state (see above). Epidemiologic typing systems have also contributed to studies that have documented the risk of infection associated with *S. aureus* nasal carriage. The observation of the genetic identity of nasal carriage strains and infecting strains have provided strong evidence for an endogenous source in several types of *S. aureus* infections (see below).<sup>44,70-83</sup> It can be concluded that the recent developments in molecular typing techniques have contributed to the renewed interest in the epidemiology of *S. aureus* nasal carriage and its associated risks.

**Determinants of *S. aureus* nasal carriage.** Although numerous studies have been performed on *S. aureus* nasal carriage and the associated risks, a valid explanation for the carrier state has yet to be given. Comparative studies have suggested several host factors to be associated with *S. aureus* nasal carriage. Genetic factors (eg, race and HLA type),<sup>22-24,28,84-87</sup> sex,<sup>36,88,89</sup> age (generally decreased carriage rates with increasing age),<sup>21,28,32,89,90</sup> hormonal status in women,<sup>91</sup> and anatomic alterations of the nares<sup>30</sup> have been proposed as potential determinants. Also, increased *S. aureus* car-

riage rates have been reported in certain patient groups: patients undergoing hemodialysis<sup>92,93</sup> or CAPD<sup>94</sup>; patients with insulin-dependent diabetes mellitus,<sup>95-98</sup> rheumatoid arthritis,<sup>99</sup> HIV infection,<sup>100-102</sup> or viral infection of the upper respiratory tract<sup>103</sup>; and patients receiving repeated injections for allergies.<sup>104</sup> Moreover, intravenous drug abuse,<sup>105,106</sup> hospitalization,<sup>34,88,90</sup> antibiotic use,<sup>34,88,90,91</sup> and working conditions<sup>23,92,93</sup> have been proposed as environmental factors associated with *S. aureus* nasal carriage. A common, but still unexplained, factor seems to be repeated or long-term injury to the skin inflicted by needles or intravascular catheters. Unfortunately, only a few studies have included multivariate analyses to identify independent risk factors for *S. aureus* nasal carriage. The importance of host factors as determinants of *S. aureus* nasal carriage has been confirmed in several in vitro studies of *S. aureus* adherence. *S. aureus* was shown to have differential affinity to (nasal) epithelial cells obtained from different individuals—for example, carriers versus noncarriers,<sup>107</sup> patients with eczema versus patients without eczema,<sup>108</sup> older babies versus neonates in the first week of life,<sup>109</sup> and influenza A virus-infected volunteers versus uninfected individuals.<sup>110</sup> In addition, *S. aureus* appeared to adhere to mucin-coated epithelial cells much better than to cells without such a carbohydrate coat.<sup>111</sup>

Currently no phenotypic or genetic bacterial characteristic can segregate persistent from nonpersistent *S. aureus* strains. In vitro studies have proposed cell wall teichoic acid, lipoteichoic acid, fibronectin-binding proteins, heat-labile and heat-extractable proteins, and capsular polysaccharides as bacterial surface components that mediate binding to epithelial membranes.<sup>109,112-114</sup> Yet their role as determinants of *S. aureus* nasal carriage has not been established. Two additional *S. aureus* proteins, protein A and coagulase, have been suggested to play a role in the process of adherence of *S. aureus* to host cell structures.<sup>115,116</sup> Recent studies, however, have shown that polymorphisms in the genes encoding for these proteins were not related to the persistence of *S. aureus* nasal carriage.<sup>47,48</sup>

The presence of other bacterial flora, including *S. aureus*, in the anterior nares has been shown to prevent the (nasal) acquisition of *S. aureus* strains from the environment.<sup>117-121</sup> A recent study has suggested that certain *agr*-encoded autoinducing peptide variants in *S. aureus* strains are able to inhibit the expression of *agr* in other strains. This cross-inhibition might be correlated with the ability of one strain to exclude others from colonization sites.<sup>122</sup> However, future studies should provide more insight into the mechanisms of this so-called phenomenon of bacterial interference and its role in the *S. aureus* nasal carrier state.

At this time, knowledge on the determinants of *S. aureus* nasal carriage is limited, and its molecular basis has only partially been elucidated. However, one is currently left with the impression that it is the host and not the microorganism that determines whether an individual is a persistent, intermittent, or noncarrier of *S. aureus*.

#### CLINICAL RELEVANCE

##### *S. aureus* nasal carriage as a risk factor for infection.

The carriage of *S. aureus* has been identified as a risk factor for the development of infections in various settings. Surgical site infections remain a major source of morbidity and mortality in the surgical patient.<sup>123</sup> *S. aureus* is the most common cause of infection in clean surgical procedures.<sup>124</sup> In the late 1950s, three independent reports were published on the relationship between *S. aureus* nasal carriage and surgical site infections.<sup>74-76</sup> Since then a number of studies have followed, most of which have shown a significantly increased risk for developing a surgical site infection in *S. aureus* nasal carriers as compared with noncarriers (relative risk varying from 1.3 to 7.0).<sup>44-46,77-81,125-127</sup> The risk appeared to increase with increasing colonization density of *S. aureus* in the anterior nares,<sup>44-46</sup> and epidemiologic typing showed genetic identity of carriage strains and (subsequent) infecting strains in 30% to 100% of the cases.<sup>44,74-81</sup> suggesting a temporal relationship between *S. aureus* nasal carriage and the development of surgical site infections. A recent study that included multivariate analyses of risk factors has again confirmed *S. aureus* nasal carriage as an independent risk factor for the development of surgical site infections.<sup>128</sup>

Infection of the vascular access site with associated bacteremia is the second most common cause of death in patients undergoing hemodialysis,<sup>129</sup> and *S. aureus* is the most frequently isolated pathogen. A number of studies have, therefore, evaluated the importance of *S. aureus* nasal carriage in the development of *S. aureus* infections in patients undergoing hemodialysis. A study performed in 1975 reported higher *S. aureus* infection rates in carriers than in noncarriers, although this was not statistically significant.<sup>130</sup> In more recent studies, however, *S. aureus* infections occurred significantly more frequently in *S. aureus* nasal carriers than in noncarriers (relative risk varying from 1.9 to 4.7).<sup>73,92,131</sup> Moreover, the typing of *S. aureus* isolates has provided additional evidence that *S. aureus* infections in patients undergoing hemodialysis often are of endogenous origin.<sup>70,73</sup>

In patients undergoing CAPD, *S. aureus* is a major pathogen in exit site and tunnel infections, which may progress to peritonitis and catheter loss.<sup>132,133</sup> Since 1982, several studies have reported on the association

between *S. aureus* nasal carriage and *S. aureus* infections in patients undergoing CAPD. Infection rates at various sites (exit site, tunnel track, and peritoneum) occurred significantly more frequently in *S. aureus* nasal carriers than in noncarriers (relative risk varying from 1.8 to 14.0).<sup>72,82,94,134,135</sup> Again, the typing of *S. aureus* isolates showed that isolates from the site of infection were usually identical to previous nasal isolates.<sup>71,72,82,83</sup>

After coagulase-negative staphylococci, *S. aureus* is the second most prevalent organism causing intravascular device-related bacteremia.<sup>136</sup> The role of *S. aureus* nasal carriage as a risk factor for the development of intravascular device-related bacteremia has not yet been clearly established. However, in intensive care unit patients and HIV-positive patients with intravascular devices, *S. aureus* bacteremia was found to occur more frequently in *S. aureus* nasal carriers than in noncarriers.<sup>100,137</sup> Recent data indicate that nasal carriage of either MSSA or MRSA on admission to the intensive care unit significantly increases the risk for the development of bacteremia, surgical site infections, and respiratory tract infections.<sup>138</sup>

Anecdotal reports have stated that the relapse rate in patients with Wegener's granulomatosis, a systemic disease, is associated with *S. aureus* nasal carriage. A significantly higher relapse rate has been observed in nasal carriers as compared with noncarriers.<sup>139</sup> Moreover, the elimination of carriage by systemic treatment with sulfamethoxazole-trimethoprim appeared to have a beneficial effect on the course of the disease.<sup>140</sup>

The nasal carriage of MRSA has been suggested to pose an increased risk of infection as compared with the carriage of MSSA. Among patients undergoing CAPD, higher rates of peritonitis and exit site infections have been found in MRSA carriers than in MSSA carriers.<sup>141</sup> Also, in an intensive care setting the rate of bacteremia has been reported to be significantly increased in MRSA carriers as compared with MSSA carriers.<sup>137</sup> Whether the observed increased risk of infections in MRSA carriers resulted from an increase in the intrinsic virulence of the MRSA clone(s) involved in that particular center or from confounding by other potential risk factors for infection that also are associated with MRSA carriage remains to be determined.

In summary, *S. aureus* nasal carriage has proved to increase the risk of developing an *S. aureus* infection in various patient populations. However, the attributable risk—that is, the proportion of infections among nasal carriers that is attributable to the carriage and that might be prevented by elimination of carriage—has not yet been ascertained. The variation in reported relative risks is large; few studies have performed multivariate

analyses of risk factors, and reported relative risks may therefore be confounded. Moreover, in most studies no distinction has been made between persistent and intermittent carriers, therewith disregarding the potential impact of the type of nasal carriage on the relative and attributable risk. To determine the relative importance of *S. aureus* nasal carriage as a risk factor for the development of *S. aureus* infections, future studies should therefore include multivariate analyses of risk factors and apply strict criteria to define the three nasal carrier states.

**Elimination of *S. aureus* nasal carriage.** The elimination of *S. aureus* nasal carriage would theoretically reduce the infection rates in populations where it has been identified as a risk factor. Until today, three approaches to eliminating *S. aureus* nasal carriage have been developed: local application of antibiotics or disinfectants, systemic antibiotics, and bacterial interference.<sup>12</sup> The application of nasal ointments and sprays, sometimes combined with disinfecting agents applied to the skin, has shown limited efficacy and has resulted in the emergence of resistance to the agents used.<sup>73,74,125,142,143</sup> Recently mupirocin calcium (pseudomonic acid) ointment, a topical antibiotic with a broad spectrum of activity against gram-positive bacteria, including *S. aureus* and MRSA, has proved to be highly efficacious in eliminating *S. aureus* nasal carriage in healthy volunteers.<sup>144-146</sup> In patients undergoing hemodialysis or CAPD, however, nasal application of mupirocin was reported to have long-term efficacy only with prolonged or periodic treatment schedules.<sup>147-149</sup> Several studies have evaluated the efficacy of nasal mupirocin with respect to infection rates. In patients undergoing hemodialysis, a reduction in vascular access site infections was observed in a randomized, double-blind, placebo-controlled trial.<sup>150</sup> A recent study in patients undergoing cardiothoracic surgery has shown that perioperative application of nasal mupirocin significantly reduced the rate of surgical site infections<sup>151</sup> and was highly cost effective as a preventive strategy.<sup>5</sup> Mupirocin is well tolerated, and when it has been used appropriately (intranasally) twice daily for 5 days, mupirocin resistance has not been reported.<sup>152</sup> Resistance has been reported, however, after the application of mupirocin to skin surfaces and after prolonged or intermittent use.<sup>152-158</sup> Moreover, the over-the-counter availability of mupirocin, resulting in its widespread use, has recently been reported to have resulted in a dramatic increase in the incidence of mupirocin resistance in both wound and nasal *S. aureus* isolates (from 3.7% to 16%).<sup>159</sup> Final conclusions on the efficacy of nasal mupirocin in preventing *S. aureus* infections cannot be drawn at the moment, because only a few randomized, double-blind, placebo-controlled tri-

als have been performed. In addition, even if future studies provide additional evidence for the efficacy of nasal mupirocin in preventing *S. aureus* infections, its value may prove to be limited because of the potential spread of mupirocin resistance. Restricted and appropriate use of this valuable antimicrobial agent is therefore recommended.

Several studies have evaluated the efficacy of systemic antibiotics in the elimination of *S. aureus* nasal carriage. The results have been disappointing.<sup>29,41,160-162</sup> Of the agents studied, only rifampin has proved to be effective in randomized studies.<sup>25,73,142,163</sup> In patients undergoing hemodialysis and patients undergoing CAPD, the systemic use of rifampin significantly reduced the incidence of infections.<sup>73,142</sup> However, side effects and the rapid emergence of resistant strains have limited its use for this purpose.<sup>142,163</sup> Similar difficulties have been reported with other systemic antibiotics.<sup>160,164</sup>

The nasal acquisition of *S. aureus* has been found to be prevented by the presence of other bacterial flora, including *S. aureus*, in the anterior nares (see above).<sup>117-121</sup> Bacterial interference programs in the 1960s have appeared to be successful in the control of outbreaks of *S. aureus* infections in nurseries and in the treatment of recurrent furunculosis in adults.<sup>121,165,166</sup> *S. aureus* type 502A, which was considered to be minimally pathogenic, was used to colonize the anterior nares or the umbilical cord to prevent colonization with more-virulent strains. Unfortunately, this approach was occasionally complicated by the development of serious infections caused by *S. aureus* type 502A,<sup>167,168</sup> and one fatal septicemia has been reported in a neonate.<sup>169</sup> Although the benefits of bacterial interference programs far outweighed their hazards,<sup>169</sup> this preventive strategy was not pursued further at that time. The emergence of resistance to antimicrobial agents, including mupirocin, may hamper the effective control of staphylococcal infections in the near future. Therefore, a renewed exploration of the potentials of bacterial interference as an alternative approach seems worthwhile.

## CONCLUSIONS

*S. aureus* has long been recognized as a cause of both community acquired and nosocomial infections. The efficacy of antibiotic treatment is threatened worldwide because of the appearance of MRSA and the prospect of vancomycin-resistant *S. aureus*. The potential spread of such strains poses a serious threat to all hospitalized patients. Therefore, the prevention of staphylococcal infections is now more important than ever. *S. aureus* nasal carriage has been established as a major risk factor for the development of *S. aureus* infections. The

elimination of *S. aureus* nasal carriage has proved to be effective in reducing the incidence of *S. aureus* infections in various patient populations. Of the strategies studied, the nasal application of mupirocin calcium ointment has been the most effective in eliminating *S. aureus* nasal carriage. However, the appearance of resistance may limit the value of this elimination strategy in the near future and warrants the development of alternative preventive strategies. Strategies based on bacterial interference have been successfully applied in the past and may well hold promise in the future control of staphylococcal infections.

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