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Nasal Carriage of *Staphylococcus aureus*: Epidemiology, Underlying Mechanisms, and Associated Risks

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INTRODUCTION

Staphylococcus aureus has long been recognized as an important pathogen in human disease. Staphylococcal infections occur regularly in hospitalized patients and have severe consequences, despite antibiotic therapy (89, 216). Due to an increasing number of infections caused by methicillin-resistant *S. aureus* (MRSA) strains, which are now most often multiresistant, therapy has become problematic (203). Therefore, prevention of staphylococcal infections is now more important than ever. Carriage of *S. aureus* in the nose appears to play a key role in the epidemiology and pathogenesis of infection. This review discusses the literature on the epidemiology of nasal carriage and the risks associated with it. In addition to presenting what is known at present, it focuses on studies that need to be performed to develop optimal preventive strategies.

CARRIAGE OF *S. AUREUS*

Epidemiology

The ecological niches of *S. aureus* strains are the anterior nares. Elegant studies have shown that the nares are the most consistent area from which this organism can be isolated (208). Moreover, when the nares are treated topically to eliminate nasal carriage, in most cases the organism also disappears from other areas of the body (142, 156). Over time, three patterns of carriage can be distinguished. Approximately 20% of individuals almost always carry one type of strain and are called persistent carriers. A large proportion of the population (±60%) harbors *S. aureus* intermittently, and the strains change with varying frequency. Such persons are called intermittent carriers. Finally, a minority of people (±20%) almost never carry *S. aureus* and are called noncarriers (208). Persistent carriage is more common in children than in adults, and many people change their pattern of carriage between the age of 10 and 20 years (10). The reasons for these differences in colonization patterns are unknown. Persistent carriage seems to have a protective effect on the acquisition of other strains, at least during hospitalization (136). This barrier to colonization is reduced when carriers are treated with antibiotics (136). These findings suggest that the acquisition and transmission of antibiotic-resistant *S. aureus* in the hospital mainly concern intermittent carriers and persistent carriers treated with antibiotics.

The prevalence and incidence of *S. aureus* nasal carriage vary according to the population studied. The results of studies on nasal carriage as determined in cross-sectional surveys are shown in Table 1. In the general population, a mean carriage rate of 37.2% was found. However, the range of carriage rates

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TABLE 1. Rates of *S. aureus* nasal carriage in various populations[a]

Population type	No. of people	Carriage rate (%)		References
		Mean	Range	
General	13,873	37.2	19.0–55.1	26, 37, 54, 61, 64, 65, 82, 97, 113, 121–123, 133, 135, 160, 176, 184, 211
Health care workers	2,568	26.6	16.8–56.1	36, 45, 96, 98, 116, 144, 160
Patients on admission[b]	21,842	35.7	10.2–85.0	36, 69, 98, 136, 158, 161, 182, 210
Patients hospitalized	3,879	29.8	14.3–52.5	13, 96, 98, 100, 106, 144, 151
Diabetes mellitus				
Insulin dependent	454	56.4	24.1–76.4	14, 105, 120, 176, 192
Non-insulin dependent	434	29.0	11.1–35.0	26, 105, 176, 192
Controls	1,035	32.2	9.1–44.3	26, 105, 176
Dialysis				
Hemodialysis	454	51.5	30.1–84.4	14, 60, 84, 87, 129, 157, 191, 215
CAPD	605	43.3	16.8–51.4	38, 108, 140, 148, 169, 170
Chronic renal failure only	38	21.1	14.3–33.3	60, 87, 191
Drug addicts				
Intravenous	288	55.2	33.8–61.4	14, 193
Nonintravenous	603	25.9	9.1–49.0	14, 193
S. aureus skin lesions	1,439	65.9	42.0–100	71, 99, 132, 180
HIV/AIDS				
HIV positive	664	35.5	26.9–54.7	9, 12, 58, 155, 205
Controls (HIV negative)	508	20.9	17.2–30.8	9, 12, 58, 155, 205

[a] Only studies in which prevalence rates of nasal carriage of *S. aureus* were determined are included.
[b] For admission rates in surgical patients, see also Table 3.

reported is large. This may be due partly to differences in the quality of the sampling and of the culture techniques used in these studies. Also, the studies were reported between 1934 and 1994, and changes in *S. aureus* nasal carriage may have occurred over the years. The older studies tended to find higher carriage rates. The rates in the general population are comparable to those found in health care workers and in patients on admission and during hospitalization (Table 1). Some studies, however, reported increased carriage rates when patients were hospitalized (see Table 3). Subgroups of patients with significantly increased carriage rates include those with insulin-dependent diabetes mellitus, those on hemodialysis, those on continuous ambulatory peritoneal dialysis (CAPD), intravenous drug addicts, patients with *S. aureus* skin infections, and those with human immunodeficiency virus (HIV) infection or AIDS (Table 1). In the first four groups, the common factor seems to be repeated or long-term puncture of the skin by needles and/or intravascular catheters. To confirm this association, higher carriage rates were also found among relatively healthy patients receiving repeated injections for allergies (88). It is predictable that high nasal carriage rates are found in patients with *S. aureus* skin infections since nasal cultures were taken at the time the *S. aureus* infection was present. However, the reason for the higher carriage rates in HIV-positive patients is unclear. The studies on HIV cited in Table 1 have excluded HIV-positive intravenous drug addicts, since their carriage rate would be expected to be high even in the absence of HIV infection. Furthermore, the stage of HIV disease did not seem to influence the carriage rate. To control for hospitalization as a risk factor, Weinke et al. (205) selected patients with other types of chronic disease as controls; nevertheless, the carriage rate in HIV-positive patients was higher. The authors proposed that immunological defects were the basis for the higher carriage rate in HIV patients. However, the exact nature of these defects remains to be elucidated. In addition to the groups mentioned above, there have been some anecdotal reports on other groups with high *S. aureus* carriage rates. Decker et al. (39) found a carriage rate of 65.6% in river-rafting guides, and the *S. aureus* infection rates were also high in this group. Maceration of the skin caused by prolonged contact with water, together with repeated small skin injuries, were the proposed reasons. Finally, Gittelman et al. (59) found high carriage rates in patients with rhinosinusitis.

Molecular Basis of the Carrier State

Although *S. aureus* can be cultured from multiple sites of the skin and mucosal surfaces of carriers, the primary reservoir of staphylococci is thought to be the vestibulum nasi (anterior nares), i.e., the nostrils of the nose. Inside, this part of the nose is lined by a fully keratinized epidermis with hairs, sebaceous glands, and sweat glands. The vestibule is limited above and behind by a ridge, the limen nasi, over which the skin becomes continuous with the nasal mucous membrane. Apparently, the staphylococcal cells flourish here in the relative absence of human defenses and/or are capable of withstanding the local antibacterial defenses. To adhere, bacterial cells need to establish firm interactions with human cell surfaces, to prevent their rapid elimination by physicochemical mechanisms. To establish successful colonization, it is thought that surface components of the staphylococcal cell interact with complementary components on the eukaryotic host cell membranes. Bacterial adherence may be nonspecifically mediated by physicochemical forces including hydrophobic interactions (34). Alterna-

TABLE 2. Factors that may influence the rate of *S. aureus* nasal carriage

Factor	Reference(s)
Adherence to epithelia which is mediated/influenced by:	
Lipoteichoic acid in *S. aureus* cell wall	2, 29
Surface associated proteins in *S. aureus* cell wall	49, 55
Carrier versus noncarrier state	5
Viral infections of the upper respiratory tract	50
Nasal abnormalities	82
HLA type	86
Ecology of nasal flora	102, 114
Race	123, 133, 160
Age	10, 136
Genetic makeup	76
Immunological status	46
Repeated needle injections	87, 88, 193
Hormonal status in women	211
Hospitalization	61, 134, 144, 174, 210

tively, adherence may be more specifically accomplished through binding of certain bacterial cell surface moieties (adhesins) to defined structural receptors in the membrane of the host cell. A wide array of staphylococcal and host cell determinants has been studied at the molecular level in a similarly diverse array of test systems. Table 2 shows factors that have been found to be associated with carriage of *S. aureus*. There appear to be differences in adherence between *S. aureus* strains and nasal epithelial cells from different individuals. *S. aureus* has a greater affinity for nasal epithelial cells obtained from carriers than from noncarriers (5). In addition, *S. aureus* adheres better to nasal epithelial cells from patients with eczema than to cells from patients without eczema (3). Also, nasal carriage may be associated with certain HLA antigens, such as DR3, but not with others (86).

This section will focus on the interaction of *S. aureus* with epithelia, especially from the airways. Also included are studies of staphylococcal interaction with other epithelial cells including the endothelial and mesothelial cells that line the vascular bed and major body cavities, respectively, and studies on the bovine mammary gland epithelium. The studies on nonnasopharyngeal epithelium are discussed because mechanisms of adherence may be shared. The adherence of microorganisms to extracellular matrices of the body was recently reviewed elsewhere (143).

Adherence to airway epithelium. Staphylococci adhere well to cells scraped from the anterior nares of healthy volunteers (5, 8, 167, 175, 204), patients with dermal abnormalities (6) and geriatric patients (159). The molecular basis of staphylococcal adherence to this site has been only partially elucidated. Host factors are important, since early studies showed that recolonization with strains that had recently colonized is virtually impossible. This failure to recolonize is indicative of a local immune response (46). The role of age and genetic background was shown in several studies (7, 86). Epithelial antibiotic substances have recently been discovered, and they may play a role in the prevention of the *S. aureus* carrier state (166).

Eukaryotic surface glycoproteins and proteoglycans, present on the mucous membranes, contribute to the adhesion of bacteria. There is considerable heterogeneity among nasal cells in participation in the adherence of bacteria. Staphylococci seem to adhere to mucin-coated cells much better than to cells without such a carbohydrate coat (175). Staphylococci will bind to bovine mucin and to mucus in a ferret model of adherence (164, 189) but do not seem to adhere to the ciliated cells of the airway epithelium. Other substances found in the respiratory tract, including secretory immunoglobulin A (15), glycolipids (95), and surfactant protein A (118), may also constitute receptor sites for staphylococcal adherence. Interestingly, *S. aureus* was recently found to adhere better to a cystic fibrosis bronchial cell line (genotype ΔF508/w1282X) than to matched rescued control cells. Increased binding to the tetrasaccharide (Galβ1-3GalNacβ1-4Galβ1-4Glc) of the asialoganglioside 1 (aGM1) was found. More aGM1 is produced and excreted apically by epithelia from cystic fibrosis patients because these cells have impaired sialyltransferase activity (81). The importance of carbohydrates as receptor molecules on the surface of epithelial cells is further evidenced by the loss of staphylococcal adherence to periodate-treated mucins (175). However, hydrophobic interactions and surface charge provide forces that are probably also involved in mediating staphylococcal binding to epithelia (29, 167, 175).

There is significant variation among individuals, with higher rates of staphylococcal binding being observed to cells from carriers than noncarriers of *S. aureus* (5), older babies than neonates in the first week of life (8), influenza A virus-infected volunteers than control uninfected individuals (50), and moderately ill geriatric patients than seriously ill elderly patients (159). The dynamic processes underlying these variations in staphylococcal adherence are largely unknown. Sanford et al. (163) found that influenza A virus induced more and new plasma membrane receptors for *S. aureus* binding in an in vitro system involving canine kidney cells; these receptors were distinct from the hemagglutinin receptors that are also induced by the virus.

There is no consensus about the surface components of *S. aureus* that mediate binding to epithelial membranes. Cell wall teichoic acid, lipoteichoic acid, fibronectin-binding proteins, heat-labile and heat-extractable proteins, and even type 5 and type 8 capsular polysaccharides have been proposed as major ligands (8, 29, 111, 163, 179). Purified capsular polysaccharides bound well to a human epithelial carcinoma cell line in vitro and induced these cells to produce cytokines (179). However, there is no direct evidence for capsule-mediated adherence of staphylococci to epithelial cells. In studies with nasal epithelial cells, free teichoic acid blocked the binding of staphylococci to fully keratinized cells whereas fibronectin partially blocked the adherence to keratinized cells but not to spinous or low granular epithelial cells (8), probably by masking teichoic acid binding sites. Staphylococci adhere better to fully matured, i.e., keratinized, cells than to granular or spinous cells present deeper in the epidermis (8). However, pretreatment of the bacteria with proteolytic enzymes, with heat (>100°C), or with the protein synthesis-inhibiting antibiotic clindamycin will reduce their adherence to epithelia and to mucin, indicating that surface proteins may be involved as well (5, 29, 172, 175). *S. aureus* protein A is probably not involved since isogenic *spa*-negative mutants adhered as well as the parent strain to HEp-2, Vero, and mesothelial cell monolayers (152). Knockout mutation of the accessory gene regulator, however, increased staphylococcal adherence twofold, indicating that a cellular product is involved that is produced during the exponential phase of growth; the gene for this product is in the vicinity of the *mec* gene (152). In contrast to the adhesins for cellular surfaces, protein A and other surface proteins that are adhesins for extracellular matrix proteins have been characterized in detail; these adhesins recognize, among others, fibronectin, fibrinogen, and collagen, and they have been de-

scribed as microbial surface components recognizing adhesive matrix molecules (143).

Adherence to bovine mammary gland epithelium. Since *S. aureus* is one of the major pathogens causing mastitis in cattle, its adherence to bovine mammary epithelia has been studied in some detail. *S. aureus* adheres well, better than most other bacterial species, to these epithelial cells, especially to cells higher up in the gland (57). Again, not all cells participate in the binding of staphylococci; staphylococci attach only to the nonvillous, dome-shaped, hexagonal cells that seem capable of secretion (57). The adherence of bacteria to the keratinized cells of the teat canal varies with the origin of the cell type (185) and is reduced by pretreatment of the bacteria with proteolytic enzymes. Recently, a cell wall protein of 145 kDa was isolated from a strain of *S. aureus* that could bind to mammary epithelial cells (103). Interestingly, the adhesion of the bacteria becomes enhanced when bacteria are grown in milk whey instead of broth. In this circumstance, adherence is trypsin resistant but periodate sensitive, indicating that the putative adhesin(s) is of a largely carbohydrate nature (112). Adhesion of staphylococci to fat globules in milk has also been demonstrated, and it is proposed that such binding promotes dissemination of the bacteria in the mammary gland. Although antibody against whole bacteria can block staphylococcal adherence to epithelial cell lines derived from high ductular tissues, the surface epitopes involved in binding have not been further delineated (139). Thus, the relative contributions of nonspecific physicochemical interactions and specific interactions between staphylococcal cell wall-associated moieties and host receptors remain unknown.

Adherence to endothelium and mesothelium. Staphylococci have the potential to invade the bloodstream and the large body cavities, where they encounter endothelial and mesothelial cells, respectively. Again, *S. aureus* avidly binds to these cellular surfaces and may even enter the cells (68, 138). Early studies by Gould et al. showed extensive staphylococcal adherence to canine and human cadaveric heart valves (62). Binding to the surface of endothelial cells is probably mediated to a large extent by fibronectin, since this endothelium-derived molecule is ubiquitous in the vascular space and *S. aureus* has adhesins for this protein (199, 201). Fibronectin seems to bind a uronic-amine exopolysaccharide at some distance from the electron-dense cell wall (10). Fibronectin binding to teichoic acid has been reported (8). Interestingly, data suggest that efficient binding of *S. aureus* to endothelium is an active process which probably requires the synthesis of proteins by the endothelial cells (188). Thus, staphylococcal adherence is reduced at 4°C and after preincubation with a protein inhibitor, e.g., dactinomycin, whereas it is increased when cells are prestimulated with interleukin-1. Adherence can also be modulated by host cell growth factors (19).

The role of fibronectin in mediating *S. aureus* adherence to mesothelial cells is in doubt (68, 152). It has been shown that antifibronectin antibody reduces the adherence of *S. aureus* to fibronectin to a greater extent than to mesothelial cells, suggesting that an additional receptor site is present on mesothelial cells (49). Free lipoteichoic acid consistently interfered with staphylococcal binding to mesothelial cell monolayers, making this cell wall component a likely adhesin candidate (68).

In summary, one can conclude that the molecular determinants of *S. aureus* adherence to human epithelia remain to be fully described. As long as such insight into *S. aureus* adherence is lacking, a valid explanation for the carrier state in some individuals but not in others cannot be given.

Carriage of MRSA

Risk factors for acquisition of MRSA include the administration of multiple antibiotics (25, 35, 145). The nasal bacterial flora is modified when systemic antibiotics are given (4). Interestingly, older data indicate that increased environmental contamination with penicillin was an important risk factor for colonization of the nares of hospitalized patients with penicillin-resistant staphylococci and for the transmission of penicillin-resistant *S. aureus* to other patients (136). It has also been shown that administration of tetracycline to patients colonized with a tetracycline-resistant strain of *S. aureus* induced the dispersal of this organism in the environment (47), thus contributing to further spread. MRSA strains are usually resistant to several groups of broad-spectrum antibiotics that are used on a large scale in the hospital. This mechanism of increased spreading under antibiotic pressure may have contributed to the worldwide increase in the prevalence of MRSA in hospitals (203).

Molecular Typing of *S. aureus* Strains from Carriers

An important topic in nasal colonization studies concerns the population characteristics and dynamics of the resident *S. aureus* strain(s). Major questions are whether a persistently colonized individual is always inhabited by the same strain, whether strain exchange or replacement can be observed, and whether persistent strains share certain genetic characteristics that set them apart from the strains that display intermittent colonization only. To answer these questions, medical microbiologists have a broad spectrum of technical instruments at their disposal. These vary from techniques that monitor phenotypic characteristics to those that involve genetic procedures that highlight DNA polymorphisms (for a review, see reference 115). Among the phenotypic procedures, testing of susceptibility to restriction-sensitive bacteriophages is considered to be the gold standard. Unfortunately, most laboratories are not equipped to handle phage typing, and this technique can be used successfully only if it is performed in an experienced reference laboratory (115). Even in this setting, a number of strains cannot be evaluated since they are nontypeable. DNA-typing procedures are easier to perform, and most are able to type all strains. Although more easy to perform than phage typing, these tests are not yet available in most routine microbiology laboratories (190). Genotypic procedures can lead the way to elucidating the molecular genetics of colonizing *S. aureus* populations. DNA-typing procedures are being applied with increasing frequency and have proven quite valuable for assessing clonality among given strains of many bacterial species including *S. aureus* (131). For staphylococci in general, comparative molecular typing has been the subject of a number of recent studies (33, 187, 195). From these studies, it was deduced that DNA analysis, either by PCR-mediated techniques or by pulsed-field gel electrophoretic separation of large DNA restriction fragments, can be applied successfully once the techniques have reached a sufficient level of reproducibility. These tests allow an excellent degree of resolution among nonrelated strains, whereas epidemiologically clustered isolates are identified as being identical. The use of these relatively novel techniques in studies of nasal populations of *S. aureus* may provide interesting new insights. At present, these types of studies are still limited in number (see below). Although most epidemiological studies on *S. aureus* focus on monitoring the spread of particular strains (91, 171), strains isolated from the nasal cavities of multiple persons have sometimes been analyzed. A recent Japanese study revealed that within individual carriers, the same strain could be identified in

every positive culture (79). Although this contradicts old data obtained by phage typing of staphylococcal isolates (70), the authors suggest that recolonization of the anterior nares rarely occurs. They also suggested that bacterial interference may lead to the noncarrier state: when an ecological niche is already occupied, for instance by coagulase-negative staphylococci, *S. aureus* does not have the means to replace the resident bacterial population. A recent study from our laboratory (196) revealed that in Danish volunteers who were longitudinally examined for nasal carriage of *S. aureus*, several "carrier states" could be distinguished. Persons could be classified as persistent (>8 positive cultures in 10 examinations), intermittent (60 to 80% positive cultures), or occasional (10 to 40% positive cultures) carriers. All the strains were analyzed phenotypically by phage typing and by measuring the amount of surface-exposed protein A. Genetic typing was done by random amplification of polymorphic DNA and restriction fragment length polymorphism analysis of the coagulase and protein A genes (56, 168). On the basis of all the results, no common genetic or phenetic characteristics segregating persistent from intermittent or occasional colonizing strains could be identified. Neither protein A nor coagulase gene polymorphisms correlated with the type of carrier state. Apparently, polymorphisms in these genes do not play a significant role in the propensity of *S. aureus* to colonize the human nasal epithelium.

Studies on the molecular epidemiology and population dynamics of nasal populations of *S. aureus* are still limited in number. Additional analyses are required, and their results may suggest novel pathways for elimination of resident strains.

Application of Molecular Typing Techniques for Prevention of Nosocomial *S. aureus* Infections

Another application of typing techniques is to elucidate the epidemiology of *S. aureus* infections in the hospital environment. Historically, *S. aureus* has been an example of a microorganism involved in cross-infection (209). Carriers among health care workers or patients have been identified frequently as the source of outbreaks. However, other data show that many *S. aureus* infections have their origin in the patients' endogenous flora (see elsewhere in this review). How can one deal with *S. aureus* infections in the hospital setting? The basis of infection control is surveillance. This means that the rates of nosocomial infections should be monitored on a permanent or semipermanent basis (93). In the presence of increased infection rates, either epidemic or endemic, the isolates cultured from patients with infections should be typed. To do this, the microbiology laboratory should store all relevant clinical isolates of staphylococci routinely, for some time (e.g., 6 months). When typing results show that there is a high level of clonal relatedness among the strains, the investigation should be aimed at identifying a common source. However, if there is no relatedness among the strains, it is unlikely that there is a common source, and therefore the investigation should be directed another way, for instance, looking for breaks in hygiene or surgical techniques. For these kinds of investigations, molecular typing methods have proven to be reliable techniques. Also, it is possible to type nearly all kinds of pathogenic microorganisms by only one procedure (random amplification of polymorphic DNA) (197, 198). The application of typing procedures has enabled epidemiologists and infection control practitioners to target epidemiological investigations, and they are important instruments in the prevention of nosocomial infections.

CARRIAGE OF *S. AUREUS* AS A RISK FACTOR FOR INFECTION

Carriage of *S. aureus* has been identified as a risk factor for the development of infections in various settings (see Tables 3 and 4). This has been studied extensively in surgical patients, in patients undergoing hemodialysis, and in patients on CAPD. Also, anecdotal reports on intravascular device-related bacteremia (154, 178) and *S. aureus* bacteremia in HIV-positive patients (205) and on a higher relapse rate in patients with Wegener's granulomatosis (181) have been published. Carriage of MRSA constitutes a special problem with regard to prevention and treatment of infection. Elimination of nasal carriage would theoretically reduce the infection rates in populations in which it has been identified as a risk factor. The literature available on these subjects will be reviewed in the following sections.

Surgery

Probably one of the first observations pointing to the endogenous source of bacterial wound infection was made in 1915 by Sir Almroth Wright (214). In a report on wound infection during World War I, he made the following statement: "During this war every wound is heavily infected. The chain of cause and consequence seems to be as follows: The clothes and skin of the soldier on war service become contaminated with all manner of filth containing pathogenic organisms and spores; the projectile takes these in with it, and it implants them far in—in point of fact, far beyond the reach of any prophylactic applications of antiseptics." This description is not entirely of an endogenous infection because it implies that most of the infecting organisms were contaminating the skin and clothes before they were inserted and, thus, were not part of the soldiers' endogenous flora. Nevertheless, the description of the route of infection is clearly endogenous. In surgical procedures, this transmission route is prevented largely by disinfecting the surgical site before incision and covering the patient with sterile drapes. Despite these preventive measures, a clear correlation exists between the carriage of *S. aureus* and the development of *S. aureus* surgical wound infections. This relationship was first established in the late 1950s. The major reason for the studies in those years was a pandemic of serious staphylococcal infections both in the community and in hospitals (126), which involved strains that were resistant to many of the antibiotics available at that time. Resistance was considered to enhance the spread and virulence of *S. aureus* in the hospital (47, 209). A great number of studies were performed to gain insight into the epidemiology of *S. aureus* in both the community and the hospital to develop preventive strategies. For those purposes, it was important that phage typing was available to enable a comparison of *S. aureus* isolates. Cross-infection was the primary focus of attention, and much was learned about the relative importance of patients, health care workers, and the environment (both fomites and air) in the transmission of *S. aureus* (for a comprehensive review, see reference 209). In the late 1950s, the observation was made that some patients developed infections with *S. aureus* strains that had been isolated previously at other sites on the same patient and not from other potential sources in the environment. In 1959, three independent reports were published which had investigated primarily the relationship between nasal carriage of *S. aureus* and the development of surgical wound infections (32, 206, 210). In the next decade, a number of studies followed, most of which showed a significantly increased risk for development of a wound infection by nasal carriers, as shown in Table 3. The causal relationship was

TABLE 3. Nasal carriage of *S. aureus* as a risk factor in surgical patients

Reference		No. of patients	*S. aureus* carriage-rate (%)	No. of infections/no. of patients		Relative risk	95% confidence interval	% of identical types in carriers
No.	Yr			Carriers	Noncarriers			
32	1959	348	30	15/104	5/244	7.0	2.6–18.9	100
206	1959	125	34	16/43	9/82	3.4	1.6–7.0	91.7
210	1959	1,319	52	47/687	13/632	3.3	1.8–6.1	59.6
153	1960	3,056	27	73/821	158/2,235	1.3	1.0–1.6	42.9
72	1961	413	46	15/190	4/223	4.4	1.5–13.0	ND[a]
110	1961	187	40	12/74	11/113	1.7	0.8–3.6	ND
11	1963	520	85	24/442	6/78	0.7	0.3–1.7	58
		2,480	55	30/1,371	25/1,119	1.0	0.6–1.7	30
73	1963	100	68	6/68	2/32	1.4	0.3–6.6	50
78	1963	330	17	6/57	12/273	2.4	0.9–6.1	33.3
85	1963	430	42	57/181	15/249	5.2	3.1–18.9	94.7
207	1963	451	23	20/106	28/345	2.3	1.4–4.0	ND
			9 L[b]	4/42	28/345	1.2	0.4–3.2	
			6 M	5/26	28/345	2.4	1.0–5.6	
			8	11/38	28/345	3.6	1.9–6.6	
104	1967	146	46	25/67	16/79	1.8	1.1–3.2	ND
28	1969	269	36	16/96	16/173	1.8	0.9–3.4	100
			11 L	2/29	16/173	0.7	0.2–3.1	
			12 M	3/31	16/173	1.0	0.3–3.4	
			13 H	11/36	16/173	3.3	1.7–6.5	
27	1970	2,260	48	104/1,093	28/1,167	4.0	2.6–6.0	ND
			15 H	65/336	28/1,167	8.1	5.3–12.3	
124	1993	306	15	8/47	4/259	9.4	2.9–30.2	91
89	1995	1,980	13	21/264	19/1,716	7.2	3.9–13.2	100
162	1996	1,049	24	15/248	8/801	6.1	2.6–14.1	87
92	1996	255	27	6/69	2/186	8.1	1.7–39.1	ND
			9 L	0/23	2/186	NA[c]		
			18 H	6/46	2/186	12.1	2.5–65.4	

[a] ND, not done.
[b] L, light; M, moderate; H, heavy.
[c] NA, not applicable.

strengthened by showing a correlation between the colonization density of *S. aureus* at the carriage site and the risk for the development of infection, as demonstrated by Calia et al. (28), White (207), Bruun (27), and Kluytmans (92). Typing of *S. aureus* showed that a variable proportion (30 to 100%) of infections was due to endogenous strains (Table 3). The variations between the risk ratios and proportions of infections due to endogenous strains in different studies may be due to differences between the patient populations, the types of surgery performed, and the perioperative care such as preoperative length of hospitalization, antisepsis, asepsis, and the use of systemic antibiotic prophylaxis. These factors can influence the overall infection rate by modifying either the risk of cross-infection or the risk of endogenous infection. For example, when the number of endogenous infections is considered constant, in a setting where hygiene measures are inadequate, resulting in a large number of infections caused by cross-infection, the risk of endogenous infection will be relatively low. However, when the number of cross-infections is reduced, the relative importance of endogenous infection will increase. Besides the variables mentioned above, the sensitivity of the culture technique employed has to be taken into account. As mentioned above, the risk of infection correlates with the number of staphylococci in the nose. Therefore, studies that use a very sensitive culture technique will identify more carriers who are not at increased risk, which will result in a lower relative risk.

In spite of these differences, it is clear that there is a certain amount of endogenous infection with *S. aureus* in nearly every surgical setting. Considering the results of the most recent studies, the proportion of endogenous *S. aureus* infection as opposed to cross-infection may even be higher today than formerly. If the results from the 14 studies performed up to 1970, as shown in Table 3, are combined, there were 467 *S. aureus* infections in 5,030 carriers and 348 in 6,844 noncarriers. This results in a relative risk of 1.8 with a 95% confidence interval from 1.6 to 2.1 for carriers. In the four studies performed in the 1990s, 50 infections were observed in 628 carriers and 33 were observed in 2,962 noncarriers, giving a relative risk of 7.1 with a 95% confidence interval from 4.6 to 11.0. It is not unreasonable to state that the risk of cross-infection in the setting of modern hospitals is lower than that in the earlier investigations. Important improvements have been made in the design of the operating theater, the surgical procedures, the administration of perioperative antibiotic prophylaxis, and aseptic perioperative care. Therefore, the current importance of nasal carriage of *S. aureus* as a risk factor in various populations of surgical patients deserves further evaluation, since it could have important implications for prevention of infection.

Hemodialysis

Infection is a major cause of morbidity and the second most common cause of death in hemodialysis patients (166), and *S. aureus* is the most frequently isolated pathogen, causing infection at the vascular access site which is often associated with bacteremia. Table 4 shows four studies which evaluated the importance of nasal carriage for the development of *S. aureus* infections in patients on hemodialysis. The infection rate was higher in carriers in all the studies, with relative risks varying

TABLE 4. Nasal carriage as a risk factor in categories other than surgical patients

Category and reference		No. of patients	Carriage rate (%)	Site or type of infection	No. of infections/no. of patients		Relative risk	95% confidence interval	Remarks
No.	Yr				Carriers	Noncarriers			
CAPD									
170	1982	30	33	Exit site	8/10	4/20	4.0	1.6–10.1	
				Peritonitis	7/10	1/20	14.0	2.0–98.7	
38	1989	87	23	Exit site	14/20	7/67	6.7	3.1–14.3	
169	1989	43	65	Peritonitis	16/28	0/15	NA[a]		
108	1990	140	45	Exit site	22/63	2/77	13.4	3.3–55.0	
				Peritonitis	11/63	0/77	NA		
				Tunnel	5/63	2/77	3.1	0.6–15.2	
150	1993	138	51	Exit site	81/71	31/67	2.1	1.7–2.8	
				Peritonitis	38/71	9/67	4.0	2.1–7.6	
				Tunnel	23/71	12/67	1.8	1.0–3.3	
109	1993	167	17	All	24/28	18/139	6.6	4.2–10.5	MRSA carriage and infections only
Hemodialysis									
157	1975	32	84	Access site	8/27	1/5	1.8	0.3–11.7	
60	1978	40	35	All	10/14	10/26	1.9	1.1–3.3	Skin carriage evaluated
215	1986	86	70	All	12/26	3/26	4.0	1.3–12.5	34 carriers not included because of treatment
84	1988	70	51	Access site	5/36	1/34	4.7	0.6–38.4	
HIV/AIDS									
205	1992	136	53	Bacteremia	8/72	0/64	NA		
Intravascular device-associated bacteremia									
178	1990	107	14	Bacteremia	7/15	6/86	6.3	2.6–17.2	
154	1996	488	30	Bacteremia	32/147	6/341	12.4	5.3–29.0	
MRSA in long-term care									
127	1991	197	16	All	8/32	6/132	5.5	2.0–14.7	
MRSA in intensive care									
119	1994	484	4	All	5/19	6/465	20.4	6.8–61.0	
154	1996	488	13	Bacteremia	24/63	8/84	4.0	1.9–8.3	MRSA versus MSSA carriers
					24/63	6/341	21.7	9.2–50.8	MRSA versus noncarriers
Wegener's granulomatosis[b]									
181	1994	57	63	Relapse rate	21/36	2/21	6.1	1.6–23.6	

[a] NA, not applicable.
[b] Data for relapse rates.

from 1.8 to 4.7. In another study, *S. aureus* isolates from carriers and those from the site of *S. aureus* infection were phage and plasmid typed (48). In 12 infectious episodes, 11 *S. aureus* isolates were identical to the ones previously isolated from the patients' nares. It can be concluded that patients on hemodialysis have an increased *S. aureus* carriage rate and that most *S. aureus* infections in this setting are of endogenous origin.

CAPD

In patients treated by CAPD, *S. aureus* infections constitute frequent and serious problems, being the leading cause of exit site and tunnel infection and often leading to catheter loss (107, 149, 218). The first study reporting an association between the carriage of *S. aureus* and an increased infection rate in CAPD patients was performed by Sewell et al. in 1982 (170). Several others followed; the results are shown in Table 4. The observed relative risks for carriage are even higher than in hemodialysis patients (range, 1.8 to 14.0). As shown in Table 4, several studies investigated the risk of infection at various sites (catheter, exit site, peritoneum, and tunnel track). All these sites were at increased risk in carriers. In addition, some studies used typing methods to compare *S. aureus* isolates from carriage sites with isolates from infections. Luzar et al. (108) found identical isolates in 85% of the patients with infections. Pignatari et al. (147, 148) showed that in six patients with eight episodes of peritonitis caused by *S. aureus*, all isolates from the site of infection were identical to strains isolated previously from carriage sites. The same observation was made by Sesso et al. (169) in eight patients with *S. aureus* peritonitis. These results show that patients on CAPD are like those on hemodialysis in that the carriage rate is high and *S. aureus* carriage is an important risk factor for the development of *S. aureus* infections.

HIV, ARC, and AIDS

In patients with AIDS-related complex (ARC) and AIDS, increased rates of *S. aureus* bacteremia, deep soft tissue infections, and recurrent *S. aureus* infection have been observed

(83, 177, 212). In one of these studies, observations were made in a group of patients without other known risk factors for *S. aureus* infection (e.g., no intravenous drug abuse). Theoretically, the higher infection rates may be due, in part, to impaired B-cell immune function. However, Ganesh et al. (58) found a higher carriage rate of *S. aureus* in asymptomatic HIV-positive homosexuals than in HIV-negative homosexuals (49 and 27%, respectively; $P < 0.05$). Weinke et al. (205) studied the carriage rates in 136 HIV-positive patients with various stages of progression of disease (23.5% asymptomatic, 26.5% ARC, and 50% AIDS [compared to asymptomatic, $P < 0.05$]). The carriage rate was somewhat lower in homosexuals (40.2%) than in intravenous drug addicts (52.9%), giving an overall rate of 44.1%. The rate was not influenced by the CD4 cell count or by granulocytopenia. Nevertheless, a higher rate was observed in patients with ARC or AIDS than in HIV-positive, asymptomatic patients. In other hospitalized patients with various chronic diseases, a carriage rate of 30.8% ($P > 0.05$) was found, and in hospital staff the rate was 23.4% ($P < 0.05$). In the same study, it was found that *S. aureus* septicemia occurred only in carriers (Table 4), which statistically was highly significant. Therefore, in HIV-positive patients, the carriage rates are increased, and this is a risk factor for subsequent infection with *S. aureus*. It should be noted that the carriage rates in HIV-positive patients may even be higher than those actually observed if there was not such a widespread use of antibiotic prophylaxis (e.g., co-trimoxazole for *Pneumocystis carinii*) and antibiotic therapy in this particular group of patients. The growing number of HIV patients warrants more studies to establish the importance of nasal carriage for the development of infection. Furthermore, the underlying mechanism of increased carriage in this group of patients remains to be elucidated.

Intravascular Device-Associated Bacteremia

After coagulase-negative staphylococci, *S. aureus* is the second most prevalent organism causing intravascular device-associated bacteremia (111, 165). However, no study has been performed with the primary aim of establishing the role of *S. aureus* nasal carriage in this important setting. Lipsky et al. (106) have studied the relationship between nasal carriage and intravenous therapy-related phlebitis. They did not find a correlation but commented that most of their cases of phlebitis were not infectious but physicochemical phenomena. In Table 4, the results of a study by Snydman et al. (178) are shown. This study evaluated the incidence and risk factors for the development of nosocomial bacteremia in patients treated intravenously with interleukin-2. Of 107 patients, 20 (19%) developed sepsis, and *S. aureus* was the causative organism in the majority of these (13 of 20 patients). Carriage of *S. aureus* increased the risk of *S. aureus* bacteremia 6.3-fold. Desquamation of the skin at the catheter insertion site increased the risk 2.0-fold. If both desquamation of the skin and carriage of *S. aureus* were present, a relative risk for *S. aureus* bacteremia of 14.5 (95% confidence interval, 4.1 to 50.9) was found. Thus, in this specific population with an extremely high rate of bacteremia, the role of carriage has been clearly established. In general, insertion of intravenous devices is not associated with such a high rate of bacteremia, but it is likely that carriers of *S. aureus* will have a higher rate of *S. aureus* bacteremia. Pujol et al. (154) investigated bacteremia in an intensive care unit. Most of the *S. aureus* bacteremias were caused by an intravascular device. In this study, carriers of *S. aureus* had a relative risk of 12.4 for the development of *S. aureus* bacteremia (Table 4). Again, this correlation should be investigated in further studies because it may have important implications for prevention.

Wegener's Granulomatosis

Wegener's granulomatosis is a systemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract in combination with vasculitis and focal necrotizing crescentic glomerulonephritis (52). Treatment with cyclophosphamide and corticosteroids has proven to be successful. After remission is achieved, the clinical course is highly variable and relapses occur in most patients at variable intervals. Stegeman et al. (181) have recently reported a significant association between nasal carriage of *S. aureus* and a higher relapse rate of disease (Table 4). Also, some anecdotal reports have stated that treatment with sulfamethoxazole-trimethoprim had a beneficial effect on the course of the disease (194), which could be due to the reduction of *S. aureus* carriage by the antibiotic treatment. The underlying pathophysiological mechanisms remain to be elucidated, and the effects of elimination of nasal carriage on the relapse rate should be studied more specifically.

MRSA

The difference between MRSA and methicillin-susceptible *S. aureus* (MSSA) is resistance to β-lactamase-stable β-lactam antibiotics. Often this is associated with resistance to multiple other antibiotics, which limits the therapeutic options. MRSA has become an important pathogen in many hospitals. In the United States, the proportion of MRSA has rapidly increased from below 5% in the early 1980s to 29% in 1991 (141). In that study, it was also shown that the prevalence generally increased with the size of the hospital. In Europe, an interesting variation in the geographic distribution of MRSA is found. The prevalence of MRSA increases significantly from northern to southern countries (202).

The fact that carriage of MRSA poses an increased risk of infection over the risk of carriage of MSSA has been suggested by several authors. Lye et al. (109) found that among CAPD patients, MRSA carriers were at increased risk for MRSA infection compared with noncarriers (Table 4). Comparing MRSA carriers with MSSA carriers, they found a higher rate of peritonitis and exit site infection in MRSA carriers. Moreover, in the group of MRSA carriers, there was a significantly larger number of catheter losses and CAPD patient dropouts. Muder et al. (127) studied the consequences of MRSA carriage in a long-term care facility and found that MRSA carriers were at increased risk for the development of *S. aureus* infections. The occurrence of *S. aureus* infections in MSSA carriers was comparable to that in noncarriers. Mest et al. (119) found that perioperative colonization with MRSA significantly increased the risk for postoperative MRSA infection in patients in the intensive care unit. Pujol et al. (154) studied the rate of bacteremia in patients admitted to the intensive care unit. Patients colonized with MSSA in the nares were at a significantly increased risk for the development of *S. aureus* bacteremia (relative risk 5.4 and 95% confidence interval 1.9 to 15.2 compared with noncarriers), but patients colonized with MRSA were at a much higher risk (relative risk 21.7, 95% confidence interval 9.2 to 50.8 compared with noncarriers). The risk for MRSA carriers was significantly higher than the risk for MSSA carriers (relative risk 4.0, 95% confidence interval 1.9 to 8.3). After adjusting for other predictors of bacteremia, the relative risk for *S. aureus* bacteremia was 3.9 with a 95% confidence interval of 1.6 to 9.8 for MRSA carriers compared with MSSA carriers. The conclusion of these studies

was that MRSA carriage constitutes a greater risk for the development of *S. aureus* infection than does MSSA carriage. This could be a result of the resistance itself, of an increased intrinsic virulence of MRSA compared with MSSA, or of a more vulnerable category of patients being colonized by MRSA. A number of studies have failed to show that the virulence of MRSA differs from that of MSSA. These studies involved the in vitro production of extracellular hemolysins, enzymes, or toxins (145); intraleukocyte survival or phagocytic destruction (145, 200); and animal mortality studies (75, 145). Also, a clinical evaluation comparing the outcomes of MRSA and MSSA infections did not reveal significant differences (74). Since these studies indicate that there is no increased virulence of MRSA over MSSA, it is most likely that the increased infection rate observed in carriers of MRSA is primarily due to the selection of a population of patients who become carriers of MRSA. In view of the rapid increase in the prevalence of MRSA and the problems associated with its control and therapy, more insight into the epidemiology of MRSA colonization and infection is needed to develop more effective preventive strategies. Typing methods are important tools in these kind of investigations.

PATHOGENESIS OF ENDOGENOUS INFECTION

The nose is regarded as the major site of *S. aureus* carriage from where the organisms can spread to other parts of the body (207, 209). Reagan et al. (156) have shown that elimination of nasal carriage by using topical mupirocin also eliminates hand carriage. From these observations, it can be concluded that the nose provides an environment in which *S. aureus* can propagate and maintain itself for prolonged periods. The proposed pathogenesis for a number of endogenous infections would be that from the nose, the skin becomes colonized, causing subsequent infection in patients with impaired skin sites, e.g., in hemodialysis (20) and CAPD patients and in patients with intravascular catheters. For surgical patients, there are other possibilities to be considered. First, most patients are intubated prior to surgery, traumatizing the epithelial lining of the throat, which may cause hematogenous spreading of *S. aureus* to the surgical site. However, many surgical procedures include the use of antimicrobial prophylaxis, which should protect against this route of infection. Another possibility is that *S. aureus* is dispersed from the nose into the air of the operating room and then contaminates the surgical site during surgery. This route of transmission could certainly have played a role in the early days of surgery, when the air flow in the operating room was not as well controlled as at present. A recent study on endogenous infection as a major cause of surgical wound infections (89) was conducted in an operating theatre with a laminar downflow unit positioned directly over the patient. Therefore, this route is not considered likely in the setting of the modern operating room. Finally, skin carriage of *S. aureus* in patients who are nasal carriers could be an explanation for endogenous infection. In nasal carriers, the skin is often colonized by *S. aureus*. Preoperative disinfection may not be effective in the deeper layers of the skin, and *S. aureus* may thus become a source of infection during surgery. It should be emphasized that these are only hypotheses on the pathogenetic mechanisms of *S. aureus* infection, all of which should be confirmed or refuted in further studies. These studies are needed because an optimal preventive strategy can be developed only when the pathogenesis is fully understood.

EFFECTS OF ELIMINATION OF CARRIAGE ON INFECTION RATES

Elimination Strategies

It is conceivable that in populations in which *S. aureus* nasal carriage is identified as a risk factor for infection, elimination of carriage would reduce the infection rate. Three approaches to the elimination of carriage are available. The first is the local application of antibiotics or disinfectants. Most often used are nasal ointments or sprays, sometimes combined with the application of disinfecting agents to the skin. In general, the results have been disappointing. Both a low efficacy and a rapid emergence of resistance to the agents used were observed. Results of such studies have been reviewed by others (30, 128, 209). Recently, mupirocin (Bactroban; SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.), a new antibiotic, has become available for topical use. This agent has been shown to posses excellent efficacy for the elimination of *S. aureus* carriage and therefore has offered a new opportunity to eliminate *S. aureus* nasal carriage. Mupirocin is well tolerated, and when it was used for short courses (application to the nose twice daily for 5 days, as recommended by the manufacturer), development of resistance was not reported. The results from a limited number of exemplifying studies are reported here. A more extensive review of the literature on mupirocin has been published recently by Hudson (80). In a randomized, double-blind placebo-controlled multicenter study, Doebbeling et al. (40) found that application of mupirocin to the nose twice daily for five consecutive days resulted in elimination of carriage in 91% of stable nasal carriers. At 4 weeks posttreatment, 87% of the subjects remained free of nasal carriage. In the placebo group, the posttreatment elimination rates were 6 and 7%, respectively ($P < 0.0001$). A subgroup was followed up for 1 year to determine the long-term efficacy of mupirocin (41). At 6 months, the nasal carriage rate in the treated group was 48% and that in the placebo group was 72% ($P = 0.054$). At 12 months, the rates were 53 and 76%, respectively ($P = 0.056$). Hand carriage at 6 months was significantly reduced in the treated group relative to the controls (15 and 48%; $P = 0.04$). The recolonizing strains were subjected to plasmid typing. A total of 36% of the patients were recolonized with a new strain at 1 year, whereas 34% had the original strain. Resistance to mupirocin was not observed. Comparable results were found by Fernandez et al. (53).

In the studies mentioned above, mupirocin was applied to healthy volunteers (health care workers). In patients on hemodialysis, mupirocin was less effective (23). A reduction from 90 to 33% directly after treatment and to 66% after 4 months was observed. Apparently, in this group of patients, other sites exist where *S. aureus* can maintain itself. The question remains if recolonization by an identical strain is the result of inadequate treatment with mupirocin. This would mean that the microorganism is able to persist at other sites of the body. Another possibility is that successfully treated subjects are recolonized from external sources, which would not be considered a treatment failure. Although the development of resistance to mupirocin was not observed in clinical studies for eradication of carriage, resistance has been reported repeatedly in the literature. Generally, it was found in patients with prolonged use of the skin preparation (80). There are two types of resistance, a low-level type and a high-level type. The low-level form (MIC, 8 to 256 mg/l) results from modifications in the target enzyme. The high-level form (MIC, >500 mg/l) results from a plasmid-encoded mupirocin resistant enzyme (125). This transmissible mechanism causes concern about the future spread of mupirocin resistance when it is used on a large scale. Therefore,

restricted use of this valuable and unique antimicrobial agent is recommended. Appropriate use would be in selected groups of persons and for short courses (up to 7 days) only.

A second approach to eliminating nasal carriage is administration of systemic antibiotics. The results have been disappointing for most agents. To date, only rifampin has proven to be an effective agent, but side effects and the rapid emergence of resistant strains have limited its use for this purpose. Chow and Yu have written a comprehensive review on this subject (30).

The third strategy is bacterial interference, i.e., active colonization with a strain of *S. aureus* (type 502A) which is considered to possess minimal pathogenic properties but is able to prevent colonization by more virulent strains, presumably by competition for the binding sites in the nose. However, the exact mechanism for this effect has never been elucidated (1). Interference was used successfully in nurseries during outbreaks of *S. aureus* infections in the 1960s and for treatment of patients with recurrent furunculosis (24, 101, 173, 183). However, this approach was occasionally complicated by serious infections due to *S. aureus* 502A (17, 43), and even a fatal infection has been reported (77). Although the report documenting a fatal outcome concluded that, "The benefits of *S. aureus* 502A programs far outweigh their hazards," this strategy was not pursued further at that time.

In conclusion, most strategies to eliminate the carriage of *S. aureus* have been disappointing. Mupirocin has offered a new opportunity for this purpose and is considered by far the most effective agent available.

Surgery

The concept of elimination of *S. aureus* carriage in surgical patients was studied when the risk of carriage became evident. These early attempts were generally hampered by a lack of effective elimination methods available. In a report by Gould and Allan in 1954 (63), a nasal ointment containing tetracycline was used to treat nasal carriers among hospital staff members. After this intervention, a reduction of the *S. aureus* infection rate was observed, which was due to a reduction in the number of infections with "hospital staphylococci." When the carriage rate among staff members increased after the topical therapy was stopped, the number of infections with hospital staphylococci also increased. In 1959, Weinstein (206) reported a study of patients who underwent chest surgery. The mean duration of preoperative hospitalization in this group was extremely long (4 months). Most patients were treated for tuberculosis. Nose swabs were taken when surgery was being planned. When *S. aureus* was cultured, topical treatment of the nose with bacitracin-neomycin ointment three times a day was started and continued until the fourth to fifth postoperative day. The overall infection rate in carriers was significantly higher despite the treatment. However, these results are difficult to interpret because of the high failure rate of the elimination therapy. Nineteen carriers who were treated adequately and had follow-up cultures taken were considered evaluable. Twelve of them converted to negative nasal cultures, whereas seven remained positive. The infection rate in the unsuccessfully treated carriers was much higher (5 of 7) than that in the successfully treated carriers (0 of 12). Although the numbers are small, these findings suggest a beneficial effect of elimination of nasal carriage on the infection rate.

The first double-blind, placebo-controlled trial of nasal disinfection with naseptin cream was reported by Henderson and Williams in 1961 (72). They observed no effect on the postoperative *S. aureus* wound infection rate in 850 patients (5.0% among treated patients and 4.6% among patients given a placebo). Again in this study, a high failure rate of elimination of *S. aureus* nasal carriage was found. Another outcome in this study was a higher *S. aureus* infection rate in the noncarriers in the treated group compared with those in the nontreated group, which approached statistical significance (4.6% versus 1.1%; $P = 0.07$). A similar trial was performed by Stokes and Milne (182). They found an *S. aureus* infection incidence of 12 (3.9%) among 308 treated patients compared with 16 (5.6%) among 285 placebo-treated patients ($P = 0.34$). Also, the infection rate in noncarriers who were treated was slightly higher than in noncarriers who were not treated (4 of 207 versus 2 of 193; $P = 0.69$) and the failure rate of successful eradication of carriage was high. Rountree et al. (161) also used naseptin but did not use a placebo in the control group. They found a significant reduction of the *S. aureus* infection rate in the treated group (3 of 84 patients [3.5%] versus 16 of 99 patients [16.0%]; $P = 0.007$). The differences in the effects observed in these studies may be caused by differences in the local epidemiology of *S. aureus* infections, such as the presence of environmental reservoirs not influenced by elimination of nasal carriage. The major drawback of these studies, however, is the poor efficacy of the treatments used to achieve the primary target, i.e., elimination of nasal carriage of *S. aureus.*

As stated above, this problem of efficacy has now been largely overcome by the introduction of mupirocin ointment in the late 1980s. By using mupirocin as a perioperative prophylaxis in a surgical population where the risk factor of nasal carriage was clearly established, a highly significant reduction in the surgical wound infection rate was found (90). All patients underwent thoracic surgery in the same department and were under prospective surveillance for the development of infections. A historical control group ($n = 928$) was compared with an intention-to-treat group ($n = 868$), of whom 752 were actually treated. Treatment started on the day before surgery and was applied twice a day for five consecutive days. Follow-up nasal cultures, taken 6 to 8 days after the day of surgery, showed that eradication was achieved in 93% of the patients. The surgical wound infection rates in the control group and the intention-to-treat group were 7.3 and 2.8%, respectively ($P < 0.0001$). The reduction was even greater in the treated group (1.7%). In the not-treated group after the intervention, the rate (7.4%) was comparable to that in the control group. Resistance to mupirocin was not observed, and the strategy was highly cost-effective (92). These results look promising and await confirmation in a randomized, placebo-controlled, double-blind trial.

Hemodialysis

Several oral and topical antibiotics for the eradication of *S. aureus* nasal carriage in hemodialysis patients have been studied. These studies were summarized by Chow and Yu (30). Rifampin has been the most effective oral agent used for this purpose. Yu et al. (215) used rifampin in conjunction with nasal bacitracin and obtained a significant reduction in the *S. aureus* infection rate in their population of hemodialysis patients. However, a rapid emergence of rifampin-resistant strains was observed. Mupirocin has been evaluated in hemodialysis patients in six studies reviewed by Boelaert (20). By using a short-term course of therapy of 5 to 10 days, a high elimination rate immediately posttherapy was found (mean, 87%; range, 76 to 100%). However, in some studies, the nares were sampled at 3 months posttherapy and a relapse rate of 20 to 77% was found. Therefore, a schedule of continuous mupirocin was proposed by Boelaert et al. (21). In a randomized,

double-blind, placebo-controlled trial, they treated stable nasal carriers with mupirocin three times a day for 2 weeks and then thrice weekly for a total of 9 months. A highly significant reduction in the carriage rate in the treated group (only 6% of the cultures were positive) was observed, accompanied by a significant reduction in the *S. aureus* infection rate (1 of 104 patient-months in the treated group and 6 of 147 patient-months in the not-treated group [$P < 0.05$]). The administration of mupirocin to nasal carriers was later adjusted to an initial course of 5 days three times a day and thereafter once a week during the remaining period on hemodialysis. This schedule resulted in a highly effective elimination of carriage accompanied by a four- to sixfold reduction in the *S. aureus*-bacteremia rate (22, 94). Although resistance to mupirocin was observed in only one patient (22), it is a point of concern with these prolonged treatment schedules. In conclusion, elimination of nasal carriage with mupirocin in hemodialysis patients significantly reduces the *S. aureus* infection rates but carries a risk for the development of resistance.

Bloom et al. (18) performed an analysis of the cost-effectiveness of mupirocin in the hemodialysis setting. Two preventive strategies were compared. The first was to screen all patients by a nasal culture every 3 months and to treat those with *S. aureus* by using mupirocin for 5 days twice daily (strategy 1). The second was to treat all patients irrespective of their carrier state with mupirocin weekly for 3 days twice daily (strategy 2). These strategies were compared with each other and with no mupirocin applications, called treat infection only. The annual savings of strategies 1 and 2 per 1,000 dialysis patients were $784,000 and $1,117,000, respectively. Also, both preventive strategies prevented death and improved the quality of life. Although from this analysis it could be concluded that treating all patients is preferable, the authors comment that the risk of development of resistance with such a widespread use of mupirocin is increased. Therefore, strategy 1 may be the better choice. Further studies are needed to determine which strategy gives maximal efficacy and minimal development of resistance.

CAPD

Zimmerman et al. (217) studied the effects of intermittent administration of rifampin to patients on CAPD in a randomized controlled trial. A total of 64 patients were randomized, irrespective of their carrier state, to receive 300 mg of rifampin twice a day for 5 days which was repeated every 3 months or to receive nothing. No significant differences between the *S. aureus* colonization rates were observed. Also, there were no significant difference between the *S. aureus* peritonitis rates. In the treated group, a statistically significant reduction was observed in the time to the first catheter-related infection and the catheter infection rate (both the rate of infections caused by *S. aureus* and the overall rate). However, resistance to rifampin emerged in four patients in the treated group compared with none in the control group. Dryden et al. (44) found a reduction of the infection rate after an intervention program which included elimination of nasal carriage and stringent aseptic care of the exit site. Because a number of measures were taken at the same time, the effect of elimination of nasal carriage could not be established. To date, two reports have been published studying the effects of mupirocin on the infection rate in CAPD patients. Perez-Fontan et al. (146) used a historical control group and compared it with the results from a group from which samples were cultured three times at monthly intervals. If *S. aureus* was isolated, a 7-day course of mupirocin three times a day was given. Seven days after this treatment and monthly thereafter, a control culture was performed. If recolonization was found, a new course of mupirocin was given. The initial efficacy was 100%, but recolonization occurred frequently, especially after 3 months. The *S. aureus* peritonitis rate was significantly reduced, but the overall peritonitis rate was not, mainly due to a significantly higher rate of peritonitis caused by gram-negative bacteria in the treated group compared with the not-treated group. Similar observations were made for catheter exit site infections. Due to the severity of the *S. aureus* catheter exit site infections, there was a significantly lower catheter loss due to exit site infections in the treated group. During the 2-year study period, a gradual increase in the resistance of *S. aureus* isolates to mupirocin was observed, which gives great cause for concern for the future development of resistance in this setting. Although a historical control group was used, a reduction in *S. aureus* infections is likely to result from the application of mupirocin. However, the unexplained observation that the rate of infection due to other microorganisms was increased makes these results difficult to interpret. Therefore, a randomized, placebo-controlled, double-blind multicenter study was performed (51). Nasal carriers were treated with mupirocin or placebo ointment twice daily for 5 days. This was repeated every 4 weeks. In 1,144 patients screened, 267 carriers were identified (23.3%). The *S. aureus* exit site infection rate was significantly lower in the treated group (1 in 99.3 patient-months versus 1 in 28.1 patient-months; $P = 0.006$). There was no significant increase in the number of gram-negative infections, and development of resistance to mupirocin was not observed. Why resistance was observed in the previous study and not in this one is not clear. Nevertheless, the possibility of development of resistance should be taken seriously when mupirocin is used for prolonged periods such as in CAPD patients. It can be concluded that elimination of *S. aureus* nasal carriage in patients on CAPD decreases the exit site infection rate. The effect on the peritonitis rate remains unclear.

MRSA

In their consensus review, Mulligan et al. (128) state that indications for eradication of MRSA are elimination of an outbreak in a health care setting and prevention of recurrent infections in an individual. In settings where MRSA is endemic, elimination of carriage has not been found to be cost-effective and is therefore considered not indicated by these authors. In an outbreak situation, the first goal should be to identify all carriers, including patients and health care workers. Then elimination of carriage should be achieved in all identified carriers (31, 91, 128). Most reports on the effects of elimination of MRSA carriage in outbreak situations also mention that other infection control measures were taken concomitantly. These other interventions may have played a significant role in controlling these outbreaks. One report mentioned the complete control of an outbreak when only simple infection control measures were taken (67), while several others found that only extensive modification of local infection control practices were effective (16, 25, 91, 130). Therefore, infection control measures should be accompanied by identification of carriers and, subsequently, elimination of *S. aureus* carriage (213). The effects of elimination strategies in settings where MRSA is endemic have not been studied extensively. One study in a surgical intensive care unit reported a significant decrease of the colonization and pulmonary tract infection rate when all patients were treated during the first week after admission (186).

GENERAL CONCLUSIONS

"Among the more chastening chapters in the annals of microbiological research is the story of our apparently dismal failure to control the depredations of the staphylococcus. Repeatedly, fresh light has been shed upon the habits and habitats of these minute clustered spherules, and once outmoded hypotheses about their metabolic mechanisms have been refurbished. Yet three quarters of a century after Koch first noted their presence in pus, the staphylococci (like Francis Thompson's angels) 'keep their ancient places', no less ubiquitous but still elusive, and (like Lucifer at least) shockingly endowed with apparently new, malign propensities." This quote is from a manuscript describing the first seven decades of staphylococcal research by Dolman, published in 1955 (42). Since then, four decades of extensive research have passed, and it seems that nothing has really changed. New staphylococcal diseases have been recognized, like the toxic shock syndrome, and we are still unable to control the spread of staphylococci and the development of resistance. 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. At the same time, resistance in other gram-positive microorganisms has increased significantly. The resistance of enterococci in intensive care units of U.S. hospitals may serve as an example. In 1989, <0.5% of enterococci were resistant. In 1992, resistance had increased to nearly 8% (66). It has been shown both in vitro and in animal studies that high-level vancomycin resistance can easily be transferred from enterococci to *S. aureus* (137). Therefore, it seems inevitable that this will also happen in clinical settings. This totally resistant microorganism would have dramatic impact on morbidity and mortality in the hospitalized patient. Optimization of preventive strategies is needed to control staphylococci. Therefore, new strategies have to be developed or, as Dolman stated, "old methods have to be refurbished."

The ability to control staphylococcal infections in the future will depend on many factors, e.g., development of new therapeutic agents, optimization of infection control measures, and introduction of new medical devices with a reduced risk of infection. In this review, the importance of nasal carriage has been summarized. Nasal carriage of *S. aureus* plays a key role in the development of *S. aureus* infections. It has been clearly established that it is a major risk factor for the development of infection in certain groups of patients (e.g., patients undergoing hemodialysis, CAPD, and surgery, and patients with intravascular devices and HIV infection). The underlying mechanisms of nasal carriage are unknown. In view of the benefits to be expected from the elimination of nasal carriage in groups at risk, the pathogenesis of endogenous infection has to be elucidated. Only then can the most effective elimination strategy be developed. 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 unique 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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