

USE OF A *STAPHYLOCOCCUS AUREUS* CONJUGATE VACCINE IN PATIENTS RECEIVING HEMODIALYSIS

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ABSTRACT

Background In patients with decreased resistance to infection, *Staphylococcus aureus* is a major cause of bacteremia and its complications. The capsular polysaccharides are essential for the pathogenesis of and immunity to *S. aureus* infection and are targets for vaccines.

Methods In a double-blind trial involving patients with end-stage renal disease who were receiving hemodialysis, we evaluated the safety, immunogenicity, and efficacy of a vaccine with *S. aureus* type 5 and 8 capsular polysaccharides conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A. Between April 1998 and August 1999, 1804 adult patients at 73 hemodialysis centers were randomly assigned to receive a single intramuscular injection of either vaccine or saline. IgG antibodies to *S. aureus* type 5 and 8 capsular polysaccharides were measured for up to two years, and episodes of *S. aureus* bacteremia were recorded. Efficacy was estimated by comparing the incidence of *S. aureus* bacteremia in the patients who received the vaccine with the incidence in the control patients.

Results Reactions to the vaccine were generally mild to moderate, and most resolved within two days. The capsular polysaccharides elicited an antibody response of at least 80 μg per milliliter (the estimated minimal level conferring protection) in 80 percent of patients for type 5 and in 75 percent of patients for type 8. The efficacy during weeks 3 to 54 was only 26 percent ($P=0.23$). However, between weeks 3 and 40 after vaccination, *S. aureus* bacteremia developed in 11 of 892 patients in the vaccine group who could be evaluated for bacteremia, as compared with 26 of 906 patients in the control group (estimate of efficacy, 57 percent; 95 percent confidence interval, 10 to 81 percent; nominal $P=0.02$).

Conclusions In patients receiving hemodialysis, a conjugate vaccine can confer partial immunity against *S. aureus* bacteremia for approximately 40 weeks, after which protection wanes as antibody levels decrease. (N Engl J Med 2002;346:491-6.)

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STAPHYLOCOCCUS *aureus* is a major cause of nosocomial and community-acquired infections, including bacteremia, metastatic abscesses, septic arthritis, endocarditis, osteomyelitis, and wound infections.¹⁻³ A study of hospitalized patients in 1995 found that the death rate, the length of stay, and the medical costs were twice as high for *S. aureus*-associated hospitalizations as for other hospitalizations.⁴ Among patients receiving hemodialysis, *S. aureus* bacteremia is a prominent cause of complications and death, with an annual incidence of 3 to 4 percent.⁵ An increasing percentage of isolates are resistant to methicillin⁶ and show relative resistance to vancomycin.⁷ Hence, immunoprophylaxis against *S. aureus* is a worthwhile objective.

The capsular polysaccharides of *S. aureus* are virulence factors in systemic infections. *S. aureus* capsular polysaccharides confer invasiveness by inhibiting opsonophagocytic killing by polymorphonuclear neutrophils; this pattern is similar to that in other encapsulated bacteria, such as *Streptococcus pneumoniae*.⁸ Of the 12 known types of *S. aureus*, types 5 and 8 account for approximately 85 percent of all clinical isolates.⁹⁻¹² Antibodies to the capsular polysaccharides of *S. aureus* types 5 and 8 induce type-specific opsonophagocytic killing by human polymorphonuclear neutrophils in vitro and confer protection in animals.^{13,14}

S. aureus capsular polysaccharides alone are poor immunogens. Their immunogenicity is enhanced by conjugation with carrier proteins.¹⁵⁻¹⁷ Monovalent vaccines containing *S. aureus* type 5 or type 8 capsular polysaccharide bound to recombinant exoprotein A, a nontoxic variant of *Pseudomonas aeruginosa* exotoxin A expressed in *Escherichia coli*, are immunogenic and well tolerated in healthy adults and in patients with end-stage renal disease.¹⁸ In a prior study

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of patients with end-stage renal disease who were receiving peritoneal dialysis, a low dose of a conjugate antistaphylococcal vaccine was not efficacious. Therefore, we evaluated a higher dose of a bivalent conjugate vaccine composed of type 5 and 8 capsular polysaccharides covalently bound to recombinant exoprotein A. The goal of this controlled study was to evaluate the vaccine in terms of safety, immunogenicity, and ability to prevent bacteremia in patients receiving hemodialysis.

METHODS

Patients

Patients were recruited at 73 hemodialysis centers in California from April 1998 to August 1999. Enrolled patients were 18 years of age or older, had end-stage renal disease, had received hemodialysis with vascular access through a native-vessel fistula or a synthetic or heterologous graft for at least eight weeks before enrollment, had a Karnofsky score of at least 50 at entry, and were expected to complete the required follow-up visits.

Criteria for exclusion were symptoms or signs consistent with an infection within two weeks before vaccination, a history of infection with the human immunodeficiency virus, hypersensitivity or previous anaphylaxis caused by polysaccharides or polysaccharide conjugate vaccines, drug abuse within one year before vaccination, use of immunosuppressive or immunomodulatory drugs, and cancer or treatment for cancer within six months before vaccination. The study protocol was approved by the institutional review boards of the Kaiser Foundation Research Institute, Southern California Kaiser Permanente, and El Camino Hospital and by the Food and Drug Administration. The study was designed by the investigators, an independent data and safety monitoring board, and the manufacturer. The data were held by the data and safety monitoring board and analyzed by a group of the authors. The manuscript was a collaborative effort of all the listed authors. All patients gave written informed consent.

Study Design

Eligible patients were randomly assigned to receive a single injection of vaccine or saline placebo. Randomization was stratified according to the type of vascular access (native-vessel fistula or synthetic or heterologous graft) and the presence or absence of persistent nasal carriage of *S. aureus*.

The vaccine (StaphVAX, Nabi, Rockville, Md.) is composed of *S. aureus* type 5 and 8 capsular polysaccharides (100 μ g per milliliter of each type) conjugated to an equal weight of recombinant exoprotein A in 0.01 percent polysorbate 80 and sodium phosphate-buffered saline (pH 7.4). The dose was selected on the basis of our previous studies in patients with end-stage renal disease (unpublished data). Vaccine and placebo (sodium phosphate-buffered saline) were supplied as 1 ml of clear liquid in identical vials, each bearing a unique code.

In two screening visits that took place approximately one week apart, subjects were evaluated for eligibility, and the anterior nares were cultured for *S. aureus*. Carriage was defined by two positive cultures. The vaccine or placebo was administered by intramuscular injection into the deltoid muscle or the anterior thigh.

Patients were evaluated 30 minutes after the injection and instructed to record local reactions (e.g., redness, swelling, aching, burning, tenderness, and heat) and systemic reactions (e.g., fever, general discomfort, muscle ache, headache, nausea, and vomiting) each day for one week. One week after injection, patients returned to the dialysis center, and reactions to the vaccine were recorded. Patients were evaluated for adverse events for up to six weeks after the injection. Deaths and all episodes of bacteremia

were recorded until the study ended or the patient withdrew. The primary outcome measure was the first occurrence of *S. aureus* bacteremia in a patient. Blood cultures were obtained before antibiotic therapy was begun.

Serum samples were obtained before and 6, 26, 54, and 67 weeks after vaccination. Antibodies to the *S. aureus* type 5 and 8 capsular polysaccharides were measured by enzyme-linked immunosorbent assay.^{15,19} A response to the vaccine was defined as an antibody level of at least 25 μ g per milliliter and at least twice the level before vaccination.

Determination of Sample Size

Surveys in the United States and Europe suggested an incidence rate of *S. aureus* bacteremia of 0.03 to 0.04 per patient-year in those receiving hemodialysis.^{5,20,22} A sample size of 900 patients per group was determined to be sufficient to detect, with 80 percent power, a 60 percent reduction in the incidence of *S. aureus* bacteremia in the vaccine group during an observation period from 3 to 54 weeks after vaccination. However, since the antibody correlate of protection was not known before the study, and since antibody levels decline rapidly in patients with end-stage renal disease, other observation periods were evaluated.

Statistical Analysis

Evaluation of efficacy was based on data obtained two weeks after vaccination. The rate of *S. aureus* bacteremia was compared between the vaccine and control groups by an exact, stratified analysis with the use of StatXact software.^{23,24} Four groups were created by the stratification of patients according to nasal-carriage status at base line and type of vascular access. The time to the first episode of *S. aureus* bacteremia was determined by the Kaplan–Meier method and compared by a stratified log-rank test.

Since the potential duration of protection that might be provided by the staphylococcal conjugate vaccine was not known a priori, the effectiveness of the vaccine was evaluated in a post hoc analysis, and nominal P values have been reported. To compute a valid P value for this analysis, a permutation analysis based on the observed data was performed. This analysis, based on a two-sample permutation test, was used to determine the time elapsed since vaccination with the highest log-rank statistic — a measure of the difference between the vaccine and placebo groups in the time to *S. aureus* bacteremia. A total of 2000 simulated data sets were generated from all 1798 subjects who received an injection and could be evaluated for bacteremia to examine the log-rank statistic in weeks 3 to 4, weeks 3 to 5, and so on up to weeks 3 to 54. The P value for the null hypothesis of no vaccine effect was calculated as the proportion of simulated data sets that yielded a log-rank statistic greater than the greatest statistic yielded by the observed data set.

The numbers of patients who had reactions to the injection and who died in the vaccine and placebo groups were compared by Fisher's exact test. No adjustments were made for the multiplicity of tests of safety. To estimate the level of antibody that conferred protection (the correlate of protection), the antibody level was interpolated from the data generated before and 6, 26, and 54 weeks after immunization to estimate the mean antibody level at the point beyond which protective efficacy was no longer observed.

RESULTS

A total of 1804 of 1991 screened patients recruited at the 73 hemodialysis centers were enrolled; 894 were randomly assigned to receive vaccine and 910 to receive placebo. Among 187 screened patients who were not immunized, 81 did not meet the eligibility criteria or did not comply with the protocol, 71 withdrew consent, 22 had a change in health status,

and 13 were not included for other reasons. The study period was from April 1998 to April 2000. The patients who received the vaccine and the control patients participated in the study for a median of 75 weeks and 74 weeks, respectively; 76 percent of the patients in each group participated in the study for at least 54 weeks. Six patients were excluded from the study after randomization; three control patients died within the first two weeks, and two patients who received the vaccine and one control patient had infections within two weeks before the injection. No patient was excluded from the analysis of safety.

The two groups were similar with regard to pretreatment demographic and clinical characteristics and were representative of the diverse population of California. Thirty-three percent of the patients were white, 31 percent were Hispanic, 23 percent were black, and 13 percent were Asian. Among the 894 patients who received the vaccine and the 910 control patients, 46 percent and 44 percent were women and 52 percent and 51 percent had diabetes, respectively. At vaccination, 69 percent of the patients in both groups had vascular access through a graft, and 22 percent had nasal carriage of *S. aureus*. The mean age in both groups was 58.3 years.

Reactions to the Vaccine and Other Adverse Events

There were no statistically significant differences in the number of deaths between the vaccine and control groups, and none of the deaths were considered to be related to the vaccine. The incidence of local reactions, malaise, and myalgia was significantly higher in patients who received the vaccine than in control patients (Table 1). Local reactions were generally mild or moderate and resolved within two days. A causal or temporal relation between *S. aureus* bacteremia and death was identified for 9 of the 152 deaths (5.9 percent) in the vaccine group and 11 of the 146 deaths (7.5 percent) in the control group ($P=0.65$ according to Fisher's exact test).

S. aureus Bacteremia

The overall trend in the incidence of infection is shown in Figure 1. In weeks 1 and 2 after vaccination and before the start of follow-up to assess the efficacy of the vaccine, there was one patient with bacteremia in the vaccine group and none in the placebo group. In terms of the primary hypothesis that the vaccine would protect against infection during weeks 3 to 54, there were no statistically significant differences between the groups; the efficacy of the vaccine for this period was 26 percent (95 percent confidence interval, -24 to 57 percent; $P=0.23$) (Table 2). We then investigated the data for other intervals during which the effect of the vaccine was more substantial. We found that during weeks 3 to 40, when

TABLE 1. SUMMARY OF REACTIONS TO THE VACCINE.*

REACTION	VACCINE GROUP (N=893)	PLACEBO GROUP (N=907)	P VALUE
	no. (%)		
Local			
Induration	121 (13.5)	40 (4.4)	<0.001
Erythema	93 (10.4)	44 (4.9)	<0.001
Pain at the injection site†	290 (32.5)	128 (14.1)	<0.001
Heat	85 (9.5)	33 (3.6)	<0.001
Any local reaction	338 (37.8)	179 (19.7)	<0.001
Systemic			
Headache	243 (27.2)	227 (25.0)	0.31
Myalgia	253 (28.3)	199 (21.9)	0.002
Malaise	226 (25.3)	188 (20.7)	0.02
Nausea	168 (18.8)	141 (15.5)	0.07
Vomiting	64 (7.2)	73 (8.0)	0.53
Fever	41 (4.6)	42 (4.6)	1.00
Any systemic reaction	431 (48.3)	393 (43.3)	0.04

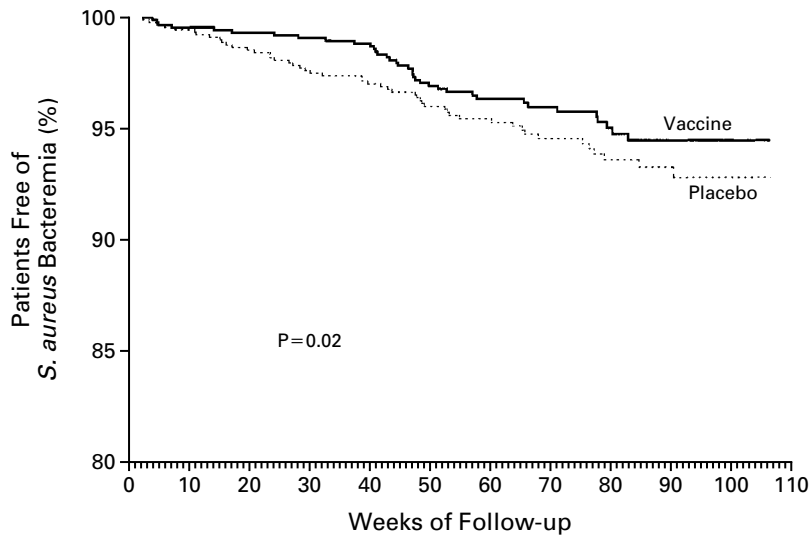
*Some patients had more than one reaction. Data were not recorded for one patient in the vaccine group and three patients in the placebo group. Fisher's exact test was used to calculate the P values.

†Pain at the injection site included ache, burning, and tenderness.

11 events occurred during 618.9 person-years in patients who received the vaccine and 26 events occurred during 627.0 person-years in control patients, the vaccine reduced the incidence of bacteremia by 57 percent (95 percent confidence interval, 10 to 81 percent; nominal $P=0.02$). With the permutation test used to account for the lack of an a priori hypothesis for a shorter interval of protection, the highest log-rank statistic was 7.03 for the interval of 3 to 32 weeks with a P value of 0.05.

Tests for homogeneity of efficacy during weeks 3 to 91 showed that efficacy was not significantly different across the four groups created by stratification ($P=0.15$ for an exact test of homogeneity). However, our study had limited power to evaluate this interaction. In both groups, patients with vascular access through a graft rather than a fistula at the start of the study tended to be at increased risk for bacteremia (Table 3). Nasal carriage of *S. aureus* also tended to be associated with an increased risk of bacteremia in control patients (7.6 vs. 3.1 per 100 person-years, $P=0.06$ according to an exact comparison of person-time rates) but not in patients who received the vaccine.

The vaccine and control groups had a similar distribution of types of *S. aureus* among patients with bacteremia. It was possible to retrieve 24 of 37 isolates from the vaccine group and 37 of 49 isolates from the control group for typing. In the vaccine group, 8 isolates (33 percent) were type 5 and 11 (46 percent)



No. AT RISK	WEEK						
	0	13	26	52	54	78	104
Vaccine	892	870	843	705	667	380	15
Placebo	906	889	850	710	661	369	10

Figure 1. Kaplan–Meier Survival Curves for *Staphylococcus aureus* Bacteremia after Week 2. The P value is for the difference between the two groups at 40 weeks. Six patients were excluded from the study after randomization (three died and three had infections within two weeks before injection).

were type 8. Five (21 percent) were type 336, a recently described surface polysaccharide.^{25,26} In the placebo group, 10 isolates (27 percent) were type 5, 20 (54 percent) were type 8, and 7 (19 percent) were type 336. Methicillin resistance was found in 7 of 37 *S. aureus* isolates in the vaccine group and 12 of 48 in the placebo group (1 isolate from a control patient was not tested). Between weeks 3 and 40, there were 37 episodes of *S. aureus* bacteremia (11 in the vaccine group and 26 in the placebo group). It was possible to retrieve 9 of 11 isolates from the vaccine group and 20 of 26 from the placebo group for typing. In the vaccine group, there were five type 5, three type 8, and one type 336 isolates. In the placebo group, there were 6 type 5, 11 type 8, and 3 type 336 isolates ($P=0.50$ according to the exact chi-square test). Between weeks 3 and 54, there were two patients who received the vaccine and six control patients who had more than one episode of bacteremia ($P=0.11$ according to the exact Cochran–Mantel–Haenszel test).

Relation between Antibody Levels and *S. aureus* Bacteremia

In our analysis, vaccine efficacy was observed for 40 weeks after receipt of the vaccine. We estimated

TABLE 2. CUMULATIVE NUMBER OF PATIENTS IN WHOM *STAPHYLOCOCCUS AUREUS* BACTEREMIA DEVELOPED AND EFFICACY OF THE VACCINE.*

WEEKS AFTER INJECTION	VACCINE GROUP		PLACEBO GROUP		EFFICACY (95% CI)	P VALUE
	NO. INFECTED	PERSON-YEARS	NO. INFECTED	PERSON-YEARS		
	%					
10	4	135.2	5	138.0	18 (–28 to 84)	1.0
20	6	300.6	13	306.6	53 (–33 to 85)	0.17
30	8	461.9	22	469.7	63 (14 to 86)	0.02
40	11	618.9	26	627.0	57 (10 to 81)	0.02
50	25	766.5	34	775.3	26 (–28 to 58)	0.30
54	27	818.4	37	827.4	26 (–24 to 57)	0.23
91	37	1165.0	49	1161.6	25 (–18 to 52)	0.24

*Data are for the first episodes of bacteremia among the 1798 patients in whom the efficacy of the vaccine was evaluated. Episodes of bacteremia during weeks 1 and 2 after injection are excluded. The efficacy of the vaccine is calculated as $100 \times (1 - [\text{incidence of } S. \text{ aureus} \text{ bacteremia in the vaccine group} \div \text{incidence of } S. \text{ aureus} \text{ bacteremia in the placebo group}])$. An exact test of the incidence ratio of 1 in comparisons between the vaccine and placebo groups was used to calculate the P values. CI denotes confidence interval.

TABLE 3. INCIDENCE OF *STAPHYLOCOCCUS AUREUS* BACTEREMIA DEVELOPED DURING WEEKS 3 TO 54, ACCORDING TO TYPE OF VASCULAR ACCESS, NASAL-CARRIAGE STATUS, AND TREATMENT GROUP.

TYPE OF VASCULAR ACCESS AND NASAL-CARRIAGE STATUS	VACCINE GROUP (N=892)		PLACEBO GROUP (N=906)	
	TOTAL NO. OF PATIENTS	PATIENTS INFECTED	TOTAL NO. OF PATIENTS	PATIENTS INFECTED
	no. (%)		no. (%)	
Graft and no nasal carriage	493	18 (3.7)	496	20 (4.0)
Graft and nasal carriage	123	6 (4.9)	129	10 (7.8)
Fistula and no nasal carriage	209	3 (1.4)	214	2 (0.9)
Fistula and nasal carriage	67	0	67	5 (7.5)

the geometric mean antibody level in patients who received the vaccine to be approximately 80 μg per milliliter at 40 weeks, and this is a crude estimate of the correlate of protection in our population. For the vaccine and placebo groups, the peak geometric mean levels of antibodies to type 5 and type 8 capsular polysaccharides were not significantly different between those patients with and those without bacteremia.

Antibody Levels

There were no statistically significant differences in antibody levels before vaccination between the vaccine and placebo groups. Antibodies remained at prevaccination levels in the placebo group. In the vaccine group, the geometric mean antibody levels were 230.0 μg per milliliter for type 5 capsular polysaccharide and 206.0 μg per milliliter for type 8 capsular polysaccharide at week 6 (the first time point evaluated), and they declined thereafter (Table 4). The percentages of patients with a peak antibody level of at least 80 μg per milliliter (the estimated minimal protective level) were 80 percent for type 5 capsular polysaccharide and 75 percent for type 8 capsular polysaccharide. Included among the patients with no response were 27 patients (3 percent) for whom data were not available.

DISCUSSION

This randomized, double-blind, placebo-controlled study demonstrates that a single injection of a conjugate vaccine containing *S. aureus* type 5 and type 8 capsular polysaccharides is safe and immunogenic and provides some protection for approximately 40 weeks against *S. aureus* bacteremia in patients with end-stage renal disease, an immunocompromised population at especially high risk for *S. aureus* bacteremia.

TABLE 4. GEOMETRIC MEAN LEVELS OF ANTIBODIES SPECIFIC FOR *STAPHYLOCOCCUS AUREUS* TYPE 5 AND 8 CAPSULAR POLYSACCHARIDES.*

TIME OF EVALUATION	VACCINE GROUP			PLACEBO GROUP		
	NO. OF PATIENTS	TYPE 5	TYPE 8	NO. OF PATIENTS	TYPE 5	TYPE 8
	$\mu\text{g/ml}$			$\mu\text{g/ml}$		
Before injection	892	5.9	8.6	910	5.7	8.6
Week 6	884	230.0	206.0	900	5.6	8.6
Week 26	838	120.0	100.0	859	5.8	8.9
Week 54	763	74.2	64.5	776	5.7	8.9
Week 67	507	78.1	65.8	512	6.2	9.4

*Pretreatment values were missing for two patients in the vaccine group because the serum was drawn after the vaccine was administered. The numbers of patients decreased over time in both groups because of attrition.

Nearly 90 percent of the patients receiving hemodialysis had a response to the vaccine, and in over 75 percent antibody levels reached at least 80 μg per milliliter (the estimated minimal level for protection). The decrease in vaccine efficacy after week 40 paralleled the decrease in levels of specific antibodies in the patient population. Antibody levels decline rapidly in patients receiving hemodialysis, and booster doses of vaccine should be evaluated.

In previous studies, vaccination with 25 μg of a monovalent conjugated *S. aureus* type 5 capsular polysaccharide induced a geometric mean level of antibody to type 5 capsular polysaccharide of 318 μg per milliliter in healthy subjects¹⁷ and 180 μg per milliliter in patients receiving hemodialysis.¹⁸ Since this vaccine was more immunogenic in immunocompetent subjects, it could in theory provide equal or better protection against systemic infection with *S. aureus* for patients about to undergo elective surgery.

We estimated the minimal level at which protection was conferred by antibodies in patients with end-stage renal disease to be 80 μg per milliliter, which is 2 to 3 logs higher than the levels at which protection is conferred by antibodies to *Haemophilus influenzae* type b capsular polysaccharide and *S. pneumoniae* capsular polysaccharides (0.15 and 1 μg per milliliter, respectively).^{27,28} The differences in the protective level of antibodies may be attributable to impaired phagocyte function and underlying disease in patients with end-stage renal disease.²⁹ Thus, identification of a protective level of antibodies for this patient population provides a surrogate for clinical efficacy of this vaccine in other at-risk patients. For immunocompetent adults, the protective levels of antibodies may be lower than those required for patients with end-stage renal disease.

The distribution of the types of *S. aureus* isolates from patients with bacteremia in this study was consistent with results reported by others.⁹⁻¹² The similar distribution of methicillin resistance among isolates from both the vaccine and placebo groups is consistent with in vitro data showing that both antibiotic-resistant and antibiotic-sensitive strains of *S. aureus* are killed by antibody-mediated opsonophagocytosis.

For 40 weeks after vaccination, the bivalent vaccine induced protection against *S. aureus* bacteremia. In addition, the efficacy of the vaccine was statistically significant during a 32-week period in the simulation model that took into account the lack of an a priori hypothesis for the duration of the vaccine effect. It is possible that efficacy will increase after the addition of the newly described type 336 to the vaccine.

The results of this study show that conjugate-induced antibodies to *S. aureus* capsular polysaccharides can provide partial protection against *S. aureus* bacteremia. Because patients receiving hemodialysis are among the least likely to have a response to immunoprophylaxis, the efficacy of the vaccine may be similar or perhaps greater in other patient populations.

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