

Dialysis

Aspirin Treatment Is Associated With a Significantly Decreased Risk of *Staphylococcus aureus* Bacteremia in Hemodialysis Patients With Tunneled Catheters

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Background: Hemodialysis patients with tunneled catheters are at increased risk of bacteremic *Staphylococcus aureus* infections. In vitro and in vivo studies showed that aspirin has direct antistaphylococcal effects by inhibiting expression of α -toxin and matrix adhesion genes through activation of sigma factor B stress-induced operon. We hypothesized that long-term treatment with aspirin may decrease the frequency of *S aureus* bacteremia in such patients.

Methods: We retrospectively analyzed electronic medical records for a variety of clinical parameters, including catheter dwell times, blood culture results, and aspirin use in our dialysis population.

Results: A total of 4,722 blood cultures were performed in 872 patients during more than 476 patient-catheter-years. There was a lower rate of catheter-associated *S aureus* bacteremia in patients treated with aspirin versus those not treated with aspirin (0.17 versus 0.34 events/patient-catheter-year, $P = 0.003$), whereas no such difference was observed for other bacteria. This association was dose dependent, seen mostly with the 325-mg aspirin dose. Using the Cox proportional hazard method, risk to develop a first episode of *S aureus* bacteremia decreased by 54% in patients using aspirin (confidence interval, 24 to 72; $P = 0.002$). Aspirin was associated with decreased risk of: (1) a first episode of methicillin-resistant *S aureus* bacteremia and (2) metastatic complications during the first episode of catheter-related *S aureus* bacteremia.

Conclusion: These data are consistent with our clinical hypothesis that aspirin has a clinically useful antistaphylococcal effect in the dialysis population.

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INDEX WORDS: Hemodialysis; tunneled catheter; catheter infection; catheter sepsis; bacteremia; *Staphylococcus aureus*; methicillin-resistant *Staphylococcus aureus*; aspirin; salicylic acid.

The incidence of bacteremia has increased in hemodialysis patients, primarily because of increased rates of serious *Staphylococcus aureus* infection in this population.¹ Long-term hemodialysis patients experience an annual incidence of *S aureus* bacteremia of 3% to 4%.² Use of tunneled dialysis catheters is a major risk factor for developing such blood-borne infections in hemodialysis patients. Despite Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines recommending the use of permanent vascular access for dialysis, the prevalence of hemodialysis catheter use in the United States is increasing and approaching 30% of all hemodialysis patients.³ In an environment of increasing antibiotic resistance patterns among *S aureus* strains, new approaches for the prevention and treatment of catheter-related *S aureus* bacteremia are urgently needed.⁴

In vitro investigations, as well as in vivo studies of experimental infective endocarditis in rabbits, showed that aspirin has direct antistaphy-

lococcal effects mediated by salicylic acid, its major biometabolite. Salicylic acid inhibits the expression of 2 key *S aureus* virulence genes involved in endovascular pathogenesis (α -toxin [*hla*] and fibronectin-binding adhesin [*fnbA*])

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through activation of genetic pathways involving the major stress response operon, sigma factor B.⁵ These aspirin-mediated effects on sigma factor B were observed at concentrations normally achieved by standard clinical dosages of aspirin in humans.^{5,6} Because these factors have a major role in *S aureus* virulence by facilitating the attachment and propagation of *S aureus* within the vascular system, we hypothesized that aspirin may be effective clinically in decreasing the incidence of *S aureus* bacteremia in such high-risk patient groups as hemodialysis patients with tunneled catheters.

METHODS

We retrospectively studied all patients who underwent hemodialysis at our main dialysis unit and a satellite dialysis unit during a 10-year period from 1995 to 2005. Our hospital is a tertiary-care medical center offering dialysis in northern New Hampshire and eastern Vermont, serving a population of about 400,000 people. The medical center uses a proprietary central electronic record system for medical records and billing. This system contains the complete records of all radiological and surgical procedures; all laboratory, pathology, and microbiology data, including data from our dialysis unit; and office and admission notes, discharge summaries, and medication lists. All patients who were dialyzed through a tunneled catheter during the study period were included in our investigation. All tunneled catheters were placed by the interventional radiology service at our main hospital using standard aseptic protocols, and nearly all catheter removals were performed by the same service. Temporary catheters were excluded because of the high variability in circumstances of placement, greater risk of infection, and difficulty tracking them. For patients with tunneled catheters, no difference was made between "acute" and "chronic" dialysis because this distinction often is arbitrary, depending mainly on administrative factors, and is determined in part by patient survival from catheter infection.

We collected the following data from the electronic medical record system:

1. Dates of catheter insertion and removal, from which catheter dwell times were calculated.
2. Reason(s) for catheter removal (obtained from radiology procedure notes).
3. Results of all blood cultures performed in patients with a tunneled catheter in place. All data were obtained from the electronic medical record system with 1 exception: blood cultures from our satellite dialysis unit in another hospital were processed at the local in-house microbiology laboratory, and results were obtained by review of hard copy dialysis charts. Catheter tip cultures were collected separately when available. Blood cultures were performed when the usual signs and symptoms suggestive of infection were present. The number of blood cultures obtained was determined by the primary team.
4. Medication use, including aspirin, was determined by reviewing computerized medication lists, office notes, admission notes, and discharge summaries. The focus of our study was treatment with aspirin and other medications during the events leading to catheter failure, which we arbitrarily defined as treatment for a minimum of 4 weeks before catheter removal. Outpatient medication lists for long-term dialysis patients were updated routinely on a monthly basis per unit policy. Omission of a medication from a medication list was not counted as a discontinuation unless clearly documented in a physician's note. Because the pharmacological effects of aspirin in the body may last for weeks, we considered discontinuation of aspirin treatment only if it was documented to have occurred at least 4 weeks before catheter removal. Data were organized into aspirin-treated and non-aspirin-treated groups. The aspirin group was subdivided further into an 81-mg/d and 325-mg/d category according to the most common dosage used in the United States.
5. Patient demographic data and medical diagnoses obtained from discharge summaries, admission notes, and office notes. The same data sources were used to determine the incidence of metastatic infections as endocarditis, osteomyelitis, and septic arthritis in patients with *S aureus* bacteremia.

Catheter-associated bacteremia was defined as 1 or more positive blood culture result in a patient with a tunneled catheter. Because other sources of infection or contamination could not be excluded in retrospect, all blood culture results obtained in the presence of a tunneled catheter were included in our study. Blood cultures obtained after catheter removal were excluded. We did not require evidence of catheter tunnel infection (eg, purulent drainage and erythema of the access site), although this frequently was present. A subsequent episode of bacteremia was considered a new event only if the first catheter had been removed and replaced by a new catheter in the interim (tunneled catheters that are a suspected source of bacteremia usually are removed in our practice, and negative culture results usually are required before a new tunneled catheter is placed). Repeated events in the same patient were included for the purpose of estimating overall rates of catheter-associated bacteremia, but were excluded in multiple logistic regression and Cox proportional hazard analyses. We used the latter statistical methods to estimate overall and time-dependent risks of a patient to develop the first episode of catheter-associated *S aureus* bacteremia. The interval between catheter insertion and removal constituted the follow-up interval. The end point for the analysis was catheter removal associated with *S aureus*-positive blood culture results. Censoring events were catheter removal for any other reason, not related to *S aureus* bacteremia. Poisson regression with log link was used to compare infection rates. Fisher exact test and unpaired Student *t*-test were used as appropriate to compare clinical parameters of the aspirin-treated and non-aspirin-treated groups. Statistical significance was defined as *P* less than 0.05. Statistical analysis was performed using Statview 5.0.1 and JMP 6.0.3 software

(both from SAS Institute, Cary, NC). This retrospective study was approved by our local institutional review board committee for the protection of human subjects.

RESULTS

We identified 872 patients during the 10-year study period with a total of 1,853 tunneled catheters placed and who accumulated more than 476 patient-catheter-years. During this time, 4,722 blood cultures were performed. The overall incidence of bacteremia was 7.2 episodes/100 patient-catheter-months, with an incidence of *S aureus* bacteremia of 2.1/100 patient-catheter-months and an incidence of *S aureus* endocarditis of 0.16/100 patient-catheter-months. The principal reason for catheter removal was suspected infection (19%), followed by poor catheter blood flow (14%) and presence of a mature permanent vascular access (14%). Other reasons for catheter removal included patient death, transplantation, change to peritoneal dialysis therapy, recovery of renal function (5%), inadvertent removal, puncture, fracture, uncontrollable bleeding after insertion, and manufacturer recall. Of note, the fate of only 8 of 1,853 tunneled catheters (<0.5%) remained unaccounted for.

Table 1 lists unselected microbiological data for the 10-year study period that include polymicrobial

infections and repeated episodes. Gram-positive bacteria accounted for the majority of bacteremic episodes, with staphylococci the most common pathogens isolated from blood cultures. There was a significantly lower rate of catheter-associated *S aureus* bacteremia in patients using aspirin (0.17 versus 0.34 events/patient-catheter-year in non-aspirin-treated patients; $P = 0.003$). No such difference was observed for other bacterial isolates, including coagulase-negative staphylococci. When all positive blood culture results were considered, no statistically significant difference between patients receiving or not receiving aspirin was found.

In addition to blood cultures, 369 catheter tip cultures were performed, 53 of which grew *S aureus*. If positive catheter tip culture results were considered as indirect evidence for *S aureus* bacteremia and added together with bona fide blood cultures, the result was statistically more significant: 83 instances of *S aureus* bacteremia (0.36 event/patient-catheter-year) were observed in the non-aspirin-treated group versus 45 (0.18 event/patient-catheter-year) in the aspirin-treated group ($P = 0.001$).

If repeated episodes of *S aureus* bacteremia in the same patient were excluded, the difference

Table 1. Number of Episodes and Rates of Catheter-Associated Bacteremia in a 10-Year Period From 1995 to 2005

	No Aspirin		Aspirin		P
	No.	Rate (/patient-catheter-y)	No.	Rate (/patient-catheter-y)	
All positive	232	1.02	207	0.83	0.30
Gram-positive					
Coagulase-negative <i>Staphylococcus</i>	96	0.42	93	0.37	0.85
<i>S aureus</i>	77	0.34	43	0.17	0.003*
MRSA	19	0.08	11	0.04	0.16
<i>Enterococcus</i> species	21	0.09	30	0.12	0.18
<i>Corynebacterium</i> species	7	0.03	6	0.02	0.82
<i>Streptococcus</i> species	4	0.02	7	0.03	0.34
<i>Bacillus</i> species	4	0.02	4	0.02	0.97
Gram-negative					
<i>Enterobacter</i> species	20	0.09	21	0.09	0.81
<i>Pseudomonas</i> species	11	0.05	13	0.05	0.64
<i>Serratia</i> species	12	0.05	9	0.04	0.55
<i>Klebsiella</i> species	9	0.04	10	0.04	0.77
<i>Escherichia coli</i>	7	0.03	4	0.02	0.39
<i>Acinetobacter</i> species	4	0.02	4	0.02	0.97
<i>Bacteroides</i> species	3	0.01	3	0.01	0.78

Note: Multiple bacterial isolates and repeated episodes were included in this table. Fungal isolates and bacterial species found fewer than 5 times during the 10-year study period were omitted.

*Significant difference by Poisson regression.

Table 2. Association Between Aspirin Dose and Rates of Catheter-Associated *S aureus* and MRSA Bacteremia

	No Aspirin		81 mg Aspirin		325 mg Aspirin	
	No.	Rate (/patient-catheter-y)	No.	Rate (/patient-catheter-y)	No.	Rate (/patient-catheter-y)
	978 Catheters/227.4 Patient-Catheter-Years		367 Catheters/116.2 Patient-Catheter-Years		508 Catheters/133.1 Patient-Catheter-Years	
<i>S aureus</i>	77	0.34	26	0.22	17	0.13
			$P = 0.26$			
					$P < 0.001^*$	
MRSA	19	0.08	10	0.09	1	0.01
			$P = 0.62$			
					$P = 0.001^*$	

*Significant difference by Poisson regression.

was even more significant: 64 first episodes of *S aureus* bacteremia (0.57 event/patient-catheter-year) in patients not administered aspirin versus 28 first episodes (0.23 event/patient-catheter-year) in patients treated with aspirin ($P < 0.001$).

We further examined the association between aspirin dosage and rate of *S aureus* bacteremia (Table 2). The lowest rate of *S aureus* bacteremia was found in patients treated with the 325-mg dose. Comparing only patients administered 81 mg of aspirin versus patients not administered aspirin, the difference in rates of *S aureus* bacteremia was not statistically significant (0.22 versus 0.34 event/patient-catheter-year; $P = 0.26$). Catheter-associated bacteremia with methicillin-resistant *S aureus* (MRSA) occurred less frequently than with methicillin-sensitive *S aureus*. However, the 325-mg dose of aspirin was associated with a lower number of catheter-associated MRSA bacteremia than the 81-mg dose because during the 10-year study period, only 1 such event occurred (Table 2).

Table 3 lists patient characteristics and prevalences of different risk factors for patients in the aspirin-treated and non-aspirin-treated groups. As anticipated, coronary artery disease, peripheral vascular disease, history of stroke, hypertension, and diabetes mellitus were more prevalent in patients treated with aspirin, who were on average 10 years older than patients not treated with aspirin.

Using Cox proportional hazard analysis, we studied risk factors for developing a first episode of

Table 3. Patient Characteristics and Distribution of Covariates for the Cox Proportional Hazard Analysis

	No Aspirin (454 patients)	Aspirin (418 patients)	<i>P</i>
Age (y)	59 ± 19*	68 ± 13*	<0.0001
Time on dialysis (d)	362 ± 810	346 ± 542	0.73
Catheter no.	1.8 ± 1.8	1.9 ± 1.7	0.70
Female sex	194 (42)	186 (44)	0.54
Tobacco use	205 (45)*	225 (54)*	0.01
Diabetes mellitus	170 (38)*	236 (56)*	<0.0001
Hypertension	333 (74)*	364 (87)*	<0.0001
COPD	92 (20)*	117 (28)*	0.009
Coronary artery disease	159 (35)*	309 (79)*	<0.0001
Peripheral vascular disease	113 (25)*	200 (48)*	<0.0001
Stroke	66 (15)*	99 (24)*	0.007
Arthritis	141 (31)*	164 (39)*	0.01
Cancer	102 (23)	80 (19)	0.24
Previous transplant	50 (11)*	14 (3)*	<0.0001
Clopidogrel	12 (3)*	40 (10)*	<0.0001
Warfarin	61 (14)	60 (14)	0.77
Statin	69 (15)*	172 (41)*	<0.0001
B-Blocker	248 (55)*	315 (75)*	<0.0001
ACE inhibitor/ARB	136 (30)*	187 (45)*	<0.0001
Calcium channel blocker	216 (48)	216 (52)	0.28
Aspirin	0	418	<0.0001

Note: Values expressed as mean ± SD or number (percent).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Statistically significant difference between aspirin-treated and non-aspirin-treated groups by means of Fisher exact test or unpaired Student *t*-test, as appropriate.

Table 4. Risk of a First *S aureus* Bacteremia Episode in 872 Dialysis Patients With a Tunneled Catheter by Using Cox Proportional Hazard Analysis

	Relative Risk (95% CI)	P
Age (y)	1.0 (1.0-1.0)	0.99
Time on dialysis (d)	1.0 (1.0-1.001)	0.88
Catheter no.	0.95 (0.83-1.09)	0.45
Female sex	1.19 (0.76-1.86)	0.45
Tobacco use	0.78 (0.49-1.24)	0.30
Diabetes mellitus	1.65 (1.02-2.67)	0.04*
Hypertension	1.36 (0.74-2.51)	0.33
COPD	0.49 (0.24-0.97)	0.04*
Coronary artery disease	0.80 (0.48-1.34)	0.40
Peripheral vascular disease	1.01 (0.62-1.65)	0.97
Stroke	1.11 (0.63-1.96)	0.72
Arthritis	1.22 (0.78-1.92)	0.39
Cancer	1.04 (0.59-1.83)	0.89
Previous transplant	1.19 (0.55-2.55)	0.66
Clopidogrel	1.06 (0.40-2.83)	0.91
Warfarin	1.79 (1.03-3.10)	0.04*
Statin	1.08 (0.63-1.85)	0.79
B-Blocker	1.13 (0.70-1.83)	0.62
ACE inhibitor/ARB	0.79 (0.50-1.25)	0.31
Calcium channel blocker	0.73 (0.46-1.15)	0.17
Aspirin	0.46 (0.28-0.76)	0.002*

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Statistical significance in Cox proportional hazard model.

catheter-associated *S aureus* bacteremia (Table 4). The presence of diabetes mellitus increased the odds, whereas the presence of chronic obstructive pulmonary disease (COPD) decreased the odds of developing a first episode of *S aureus* bacteremia. Aspirin was statistically the most significant factor and decreased the odds of developing a first episode of *S aureus* bacteremia by 54% (confidence interval [CI], 72 to 24; $P = 0.002$). No other cardiovascular medication in our analysis had a significant effect. Interestingly, the risk of a first episode of *S aureus* bacteremia increased in patients treated with warfarin, while being unaffected by treatment with clopidogrel.

Multiple logistic regression analysis yielded a similar result: risk of ever developing a first episode of catheter-associated *S aureus* bacteremia decreased by 60% in patients using aspirin (CI, 75 to 33; $P < 0.001$). In addition, stratification of the analysis according to different aspirin doses confirmed that the decreased odds to develop *S aureus* bacteremia was associated mainly with use of the 325-mg dose of aspirin, whereas no

statistically significant effect was found with the 81-mg dose. Using multiple logistic regression analysis, risk of *S aureus* bacteremia significantly increased in patients with diabetes mellitus (relative risk, 2.2; CI, 1.3 to 3.6; $P = 0.002$) and decreased by the presence of COPD (relative risk, 0.42; CI, 0.21 to 0.84; $P = 0.01$), whereas contrary to results of the Cox analysis, warfarin had no significant impact. Aspirin decreased the risk of developing a first episode of MRSA bacteremia by 65% (CI, 9 to 87; $P = 0.03$). The risk of developing metastatic infection with a first episode of *S aureus* bacteremia decreased by an estimated 78% in patients treated with aspirin, although the CI was very large (3 events with aspirin versus 11 events without aspirin; CI, 7 to 95; $P = 0.04$).

Figure 1 shows the cumulative failure plot of tunneled catheters associated with *S aureus* bacteremia, obtained using the Kaplan-Meier method. Grouping by aspirin treatment resulted in 2 divergent graphs, with the risk of catheter failure caused by *S aureus* infection significantly increased in the non-aspirin-treated group ($P < 0.001$ by log-rank test).

DISCUSSION

Our data constitutes one of the largest studies of dialysis catheter-associated bacteremia. The incidence of catheter-related bacteremia in our population is within the previously reported range of 3.9 to 16.7 episodes/100 patient-months.^{7,8} Incidences of *S aureus* bacteremia and *S aureus* endocarditis in our population are similar to those reported in the literature.⁹ Because catheter tip cultures and differential central and peripheral-blood cultures were not performed systematically, our study definition of catheter-associated bacteremia is not identical to the definition of the Hospital Infection Control Practices Advisory Committee.¹⁰ However, growth of *S aureus* from a peripheral-blood culture, which is the focus of our study, is particularly likely to be associated with a catheter-related blood-borne infection in this population.¹¹ Even when *S aureus* was cultured from the tip of a suspect catheter only, but blood cultures either were not obtained or remained negative, the risk of *S aureus* bacteremia is very high and treatment often is recommended.¹² For this reason, we included catheter tip cultures in a separate analysis. Because inclu-

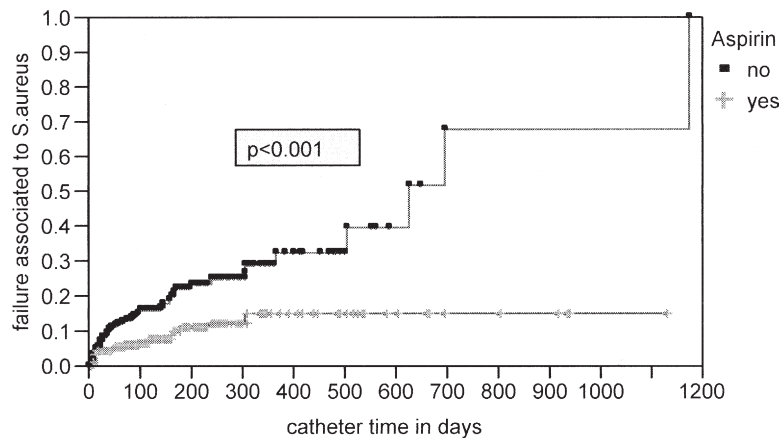


Figure 1. Cumulative plot of tunneled catheter failure associated with *S aureus* bacteremia. The failure plot was obtained using the Kaplan-Meier method. Tics represent censoring of catheter removal unrelated to *S aureus* bacteremia. Log-rank test was used to calculate *P*.

patients at risk:

ASA	417	142	66	35	25	16	9	6	5
no ASA	452	118	61	37	22	11	6	3	2

sion of patients with multiple episodes of bacteremia is a potential source of bias, we performed data analysis considering only first episodes of *S aureus* bacteremia.

The principal result of our study is that treatment with a daily 325-mg dose of aspirin is associated with significantly less *S aureus* bacteremia in at-risk patients with tunneled dialysis catheters. Of particular importance, we observed a similar association with MRSA, a notoriously difficult-to-treat subgroup of *S aureus* infection. Aspirin dosage appeared to be pivotal because the statistical effect derived only from the 325-mg regimen, whereas the 81-mg “baby aspirin” dose had little, if any, effect.

Although the antistaphylococcal effects of aspirin were studied extensively in the laboratory setting, there exists little prior clinical data to such effects in humans. A study of embolic complications of patients with endocarditis found a decreased rate of embolic events in patients with native valve infections who were on long-term aspirin treatment (11% versus 47%), although the numbers were too small to be conclusive.¹³ Adjunctive treatment of established infective endocarditis with aspirin was found to be beneficial in 1 study involving 9 patients,¹⁴ but this result was not confirmed in a randomized trial by Chan et al.¹⁵ Of note, only 25% to 30% of patients in this trial had a *S aureus* infection and aspirin was added to already established

disease, thus not allowing to assess for changes in incidence.

In our study, no difference in number of episodes of bacteremia was found with pathogens other than *S aureus*, particularly coagulase-negative staphylococci. This observation is consistent with the putative importance of downmodulation of α -toxin production by aspirin in its protective effects because coagulase-negative staphylococci possess a sigma factor B operon, but no α -toxin homologue. Consistent with the notion that the putative antistaphylococcal effects of aspirin are not related to its antiplatelet properties are: (1) the 325-mg, but not the 81-mg, dose was associated with decreased risk of *S aureus* bacteremia, although both these dose regimens exert equivalent antiplatelet effects¹⁶; (2) the antiplatelet agent clopidogrel was not protective; and (3) prior studies confirmed the antistaphylococcal effects of salicylic acid itself, which has no antiplatelet properties.⁵

Colonization is the initiating event of catheter-associated bacteremia.¹¹ Nasal carriage of *S aureus* is recognized as an endogenous source for initiating bacteremic infection,¹⁷ and it is known from prospective studies that the interval between catheter placement and staphylococemia can be very short, with 23% of episodes of catheter-related bacteremia occurring less than 1 week after catheter insertion.¹⁸ It therefore is conceivable that aspirin decreases colonization

and nasal carriage. Figure 1 illustrates another measure of the putative prophylactic benefit of aspirin against *S aureus* bacteremia: delayed onset of infection.

Diabetes mellitus previously was recognized as a risk factor for *S aureus* bacteremia in dialysis patients, also confirmed in our study.¹⁹ A potential explanation for the reduced risk of catheter-associated *S aureus* bacteremia in patients with COPD could be more frequent antibiotic use and hence decreased *S aureus* carriage in this patient group. A greater incidence of *S aureus* bacteremia was reported in patients with cardiovascular disease.¹ That we observed the opposite, lower numbers of bacteremia in this patient group treated with aspirin, emphasizes the potential clinical importance of its antistaphylococcal effects. In addition, aspirin is recommended for dialysis patients by the 2005 KDOQI guidelines because of its beneficial cardiovascular effects.²⁰

A major limitation of our study resides in its retrospective and observational nature, with the impossibility to eliminate bias resulting from changes in practice patterns. However, we believe our data to be robust because a single geographic area with no competing dialysis center was queried, a centralized electronic medical record system was used, and close to 100% catheter follow-up was achieved. In addition, the number of observations was large. The design of our study with inclusion of all blood cultures in all patients with tunneled catheters minimized selection bias. Potential noncompliance with daily aspirin treatment regimens raises the possibility of misclassifications of patients between the non-aspirin-treated versus aspirin-treated groups. Thus, our study may still have underestimated the clinical antistaphylococcal effect of aspirin in such noncompliant patients.

Aspirin has been on the market for more than 100 years, is widely used, and is available without prescription. Conversely, conventional antibiotics have been available for only much shorter periods, require prescription for use, and were associated with relatively rapid development of bacterial resistance. That we still observe an impressive negative association of aspirin treatment with *S aureus* bacteremia in at-risk patients may be testimony to the mechanism of action of this agent being different from traditional antibiotics. Of note, in

vitro studies of aspirin did not show either a growth-inhibitory or bactericidal impact at clinically achievable human serum levels.²¹ Therefore, it seems unlikely that rapidly developing resistance to aspirin's antimicrobial effects will occur in the future. Our findings strongly support the need for a prospective analysis of aspirin treatment in hemodialysis patients and other populations at increased risk of staphylococcemia.

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