

# Impact of Early Valve Surgery on Outcome of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis: Analysis in the International Collaboration of Endocarditis–Prospective Cohort Study

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(See the Editorial Commentary by Karchmer and Bayer on pages 750–2.)

**Background.** The impact of early valve surgery (EVS) on the outcome of *Staphylococcus aureus* (SA) prosthetic valve infective endocarditis (PVIE) is unresolved. The objective of this study was to evaluate the association between EVS, performed within the first 60 days of hospitalization, and outcome of SA PVIE within the International Collaboration on Endocarditis–Prospective Cohort Study.

**Methods.** Participants were enrolled between June 2000 and December 2006. Cox proportional hazards modeling that included surgery as a time-dependent covariate and propensity adjustment for likelihood to receive cardiac surgery was used to evaluate the impact of EVS and 1-year all-cause mortality on patients with definite left-sided *S. aureus* PVIE and no history of injection drug use.

**Results.** EVS was performed in 74 of the 168 (44.3%) patients. One-year mortality was significantly higher among patients with *S. aureus* PVIE than in patients with non-*S. aureus* PVIE (48.2% vs 32.9%;  $P = .003$ ). *Staphylococcus aureus* PVIE patients who underwent EVS had a significantly lower 1-year mortality rate (33.8% vs 59.1%;  $P = .001$ ). In multivariate, propensity-adjusted models, EVS was not associated with 1-year mortality (risk ratio, 0.67 [95% confidence interval, .39–1.15];  $P = .15$ ).

**Conclusions.** In this prospective, multinational cohort of patients with *S. aureus* PVIE, EVS was not associated with reduced 1-year mortality. The decision to pursue EVS should be individualized for each patient, based upon infection-specific characteristics rather than solely upon the microbiology of the infection causing PVIE.

**Keywords.** endocarditis; prosthetic valve; surgery; 1-year mortality.

Received 19 February 2014; accepted 16 September 2014; electronically published 10 November 2014.

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Clinical Infectious Diseases® 2015;60(5):741–9

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DOI: 10.1093/cid/ciu871

*Staphylococcus aureus* (SA) prosthetic valve infective endocarditis (PVIE) is associated with some of the highest mortality rates observed in bacterial infections, ranging from 40% to 80% [1–10]. In a number of reports, in-hospital mortality rates of SA PVIE were significantly higher in patients who had not undergone valve surgery [4–6, 8, 9, 11–13]. These observations have prompted some authors to conclude that early valve surgery (EVS) should be considered standard treatment for any patient with SA PVIE, especially those with early-onset (within 2 months of prosthetic valve insertion) infection [9]. For instance, after a comprehensive review of the literature, Attaran et al concluded recently that infection with *S. aureus* should be considered an indication for surgery in prosthetic valve endocarditis even without cardiac or valvular complications. They even suggested that these patients should undergo surgery as soon as possible before cerebral complications develop [14].

By contrast, the literature and the experience of the International Collaboration on Endocarditis (ICE) group indicate that decisions about EVS in patients with SA PVIE should be made on a careful, case-by-case basis [7, 15–17]. In this respect, a study performed by Hill et al is quite instructive [17]. Patients who received medical-only treatment were divided into 2 subgroups of patients: those with no indication for surgery and those in whom surgery was contraindicated. The highest survival rate was observed in the subgroup with no surgical indication. These results implied that selected patients with SA PVIE could actually be cured without valve surgery.

Although a randomized controlled trial could definitively establish the impact of valve surgery on the outcome of SA PVIE, such a trial would be difficult or impossible to complete [18, 19].

In the current investigation, we reevaluated the relationship between EVS and outcome of SA PVIE using appropriate analytical methods to examine data from the ICE Prospective Cohort Study (PCS).

## METHODS

### Study Population and Clinical Data

The ICE-PCS is a prospective, multicenter, international (64 sites from 28 countries) registry of patients with infective endocarditis (IE) [2]. Between January 2000 and December 2006, data were prospectively recorded using standard definitions during the index hospitalization and 1 year after through national death records, medicals records, and/or patient contact as available. Informed consent (oral/written) was obtained from all patients according to local institutional review boards or ethic committee guidelines at all sites. We extracted the data of patients with SA PVIE and a definite diagnosis of IE according to the modified Duke criteria from the ICE-PCS database, which contained 5668 cases by December 2006 (see sample

acquisition in Figure 1) [20]. Cases with the following characteristics were excluded: native-valve IE, right-sided IE, intravenous drug use, as well as cases with missing values for any of the following variables: sex, receipt and/or date of surgery, length of initial hospitalization, and survival status at 1-year follow-up. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used. When essential data were missing in the database, sites and their investigators were queried to complete data collection.

### Definitions

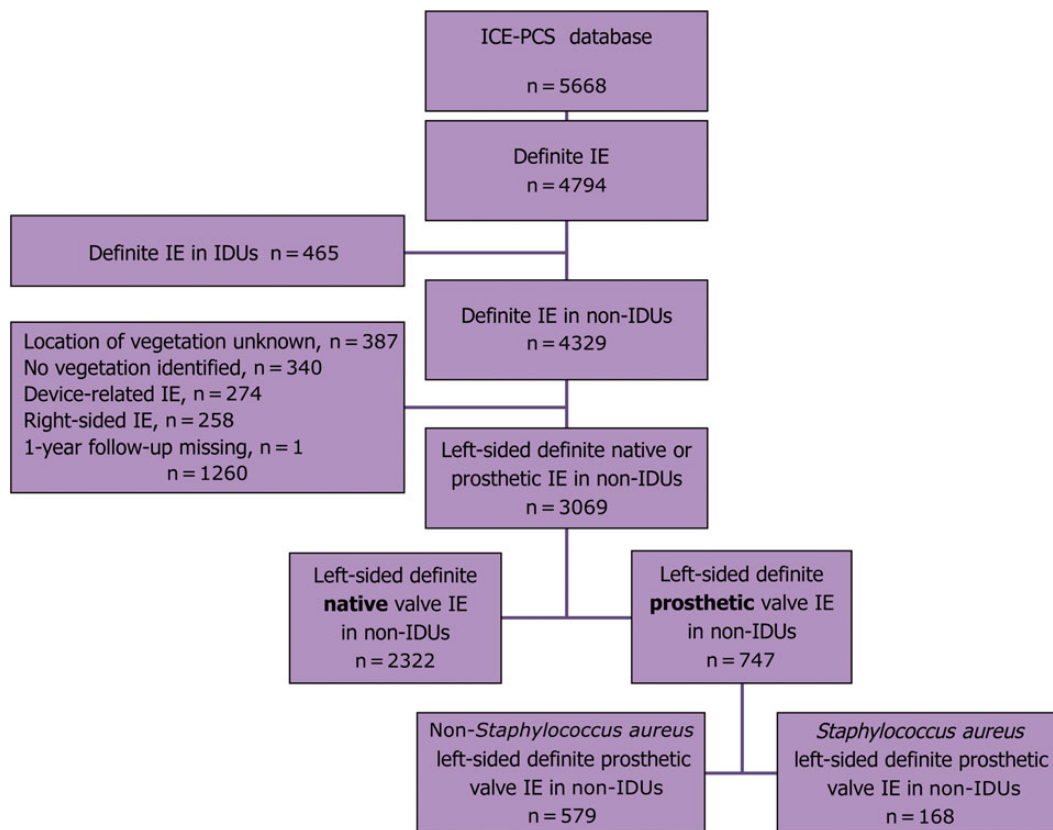
The definitions used in the ICE-PCS cohort have been reported in detail previously [21]. EVS was defined as replacement of the infected prosthetic valve within the first 60 days after admission for PVIE. Chronic illness was defined as the presence of comorbidities such as diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, and cirrhosis. Severity of heart failure was categorized according to New York Heart Association (NYHA) functional classification. Paravalvular complication was defined as transthoracic or transesophageal echocardiographic evidence of intracardiac abscess or fistula and prosthetic valve complication as evidence of dehiscence or new moderate-to-severe paravalvular regurgitation by transthoracic or transesophageal echocardiography.

Systemic embolization included embolism to any major arterial vessel, excluding stroke defined by acute neurological deficit of vascular origin lasting >24 hours. Healthcare-associated endocarditis consisted of either nosocomial or nonnosocomial healthcare-associated infection, using prior definitions [22, 23].

### Analytical Methods

The primary endpoint was all-cause mortality 1 year after discharge from the hospitalization for the treatment of IE. We used 1-year mortality as the primary endpoint because it has been shown that a period of at least 6 months is necessary to offset the early high postoperative mortality related to valve surgery [24] and because information on 1-year follow-up was systematically recorded in the ICE-PCS database. We also looked at all-cause in-hospital mortality as a secondary endpoint.

We first compared in a univariate analysis SA PVIE patients with patients with PVIE due to any other pathogens. We then compared outcomes of SA PVIE patients between those who had undergone EVS and those who had not. Baseline characteristics and outcomes of patients with SA PVIE who underwent EVS were compared to those receiving medical therapy alone, using both univariate and multivariate analyses. A nonparsimonious multivariable logistic regression model was constructed to search for independent predictors of EVS. Adjusted risk estimates for EVS were presented as odds ratios and 95% confidence intervals (CIs).



**Figure 1.** Sample acquisition. Abbreviations: ICE-PCS, International Collaboration on Endocarditis–Prospective Cohort Study; IDUs, intravenous drug users; IE, infective endocarditis.

In a next step, we identified factors associated with both in-hospital and 1-year mortality using both univariate and multivariate analyses through an adjusted Cox proportional hazards regression model, without entering the EVS variable into the models.

Finally we assessed EVS as a prognostic factor by evaluating the relationship between EVS and 1-year mortality through a Cox model adjusted to prognostic factors and predictors of EVS (propensity factors) identified in previous steps. Two Cox proportional hazard models that included all relevant covariates (to control for treatment selection bias) as well as EVS as a time-dependent variable (to control for survival bias) were constructed. In the second model, EVS was time-partitioned into 2 time-dependent covariates (because the proportional hazard assumption is not satisfied, related to a higher postoperative mortality in the surgery group than in the nonsurgery group that reversed after 7 days): the first indicated whether the patient had undergone EVS within the prior 7 days, which reflects the short-term effect of EVS; the second indicated whether the patient had had EVS >7 days before, which reflects the long-term effect of EVS. Thus, adjustment for short-term surgical effect can reveal long-term surgical effect. Results of

prognosis analyses were expressed as risk ratios with 95% CIs; a 2-sided  $P$  value < .05 was considered significant. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

## RESULTS

After exclusion of cases in intravenous drug users, cases of right-sided and native valve IE, and cases with missing data, a total of 747 patients with left-sided definite prosthetic valve IE, among whom 168 cases were due to *S. aureus* and 579 cases were due to other pathogens, were selected from the 5668 cases of IE in the ICE-PCS database (Figure 1). Susceptibility to methicillin was characterized in 149 patients (missing information for 19 patients); 48 strains were resistant to methicillin (32.2%). Patients with SA PVIE had a shorter time from onset to admission, were more often on hemodialysis, had more frequently healthcare-associated IE, and presented with or developed more often a stroke than patients with non-SA PVIE. Echocardiography evidenced more frequently a prosthetic valve dehiscence in SA PVIE than in non-SA PVIE. EVS was performed less frequently in patients with SA PVIE, although

the difference was not statistically significant (44.3% vs 51.5;  $P = .1$ ). One-year mortality was significantly higher in patients with SA PVIE compared with patients with non-SA PVIE (48.2% vs 32.9%;  $P = .003$ ).

Patients with SA PVIE who received EVS were younger, more often had paravalvular complications, prosthetic dehiscence, or an intracardiac abscess and had a significantly lower 1-year mortality rate (33.8% vs 59.1%;  $P = .001$ ) than patients with SA PVIE who did not receive EVS (Table 1).

Table 2 shows the results of the propensity analysis of the factors associated with EVS. The existence of paravalvular complications was significantly associated with EVS both in univariate analysis and in the multivariate model (odds ratio, 4.1 [95% CI, 1.9–8.6]). We therefore decided to use “paravalvular complications” as an adjustment variable in the multivariate prognosis model discussed below.

Multivariate prognosis analysis in SA PVIE patients (without considering EVS as a potential prognostic factor) identified the following 3 variables to be associated with 1-year mortality: age, stroke, and congestive heart failure, defined by NYHA class III or IV, with the following adjusted hazard ratios [HRs]: age (per 1-year increment: HR, 1.03 [95% CI, 1.01–1.05];  $P = .002$ ); stroke (time-dependent: HR, 2.56 [95% CI, 1.62–4.05];  $P < .0001$ ); and congestive heart failure (HR, 2.06 [95% CI, 1.29–3.30];  $P = .002$ ).

Table 3 shows results of the intermediate model that indicated no impact of EVS on in-hospital mortality. The results of the final adjusted models are displayed in Tables 4 and 5. They show that, overall, EVS was not significantly associated with 1-year mortality. However, the time-partitioned coding revealed an interaction between HR of death and time: within 7 days following intervention, mortality was higher in the surgery group

**Table 1. Compared Characteristics of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis Patients by Performance of Early Valve Surgery**

Characteristic	No EVS (n = 93 [55.7%])			EVS (n = 74 [44.3%])			P Value
	No.	%	SD	No.	%	SD	
Male sex	56	60.2		42	56.8		.65
Age, y, mean (SD)	93	64.0	14.9	74	59.2	14.8	.0434
Duration of symptoms >1 mo prior to presentation	5	5.4		12	16.7		.04
Associated conditions and comorbidities							
Hemodialysis dependence	12	13.5		3	4.1		.04
Diabetes mellitus	22	24.7		9	12.7		.06
Cancer	5	5.6		7	9.9		.30
Charlson index, mean (SD)	46	1.8	1.6	33	2.0	2.1	.58
Place of acquisition							
Community	40	43.0		33	44.6		
Healthcare: hospital	39	41.9		33	44.6		
Healthcare: nonhospital	11	11.8		3	4.1		
Unknown	2	2.2		5	6.8		
Prior history of IE	18	19.6		14	19.2		.95
Intracardiac device	18	19.4		9	12.3		.22
Echocardiographic findings							
Evidence of new regurgitation	37	40.2		36	48.6		.28
Paravalvular complications	18	19.6		36	48.6		<.0001
Prosthetic valve dehiscence	3	3.3		12	16.4		.004
Complications							
CHF (NYHA class III or IV)	26	28.0		17	23.0		.46
Stroke	30	33.0		27	37.0		.59
Embolic event	12	13.3		14	19.4		.29
Intracardiac abscess	15	16.7		29	40.3		.0008
Outcome							
Days to death, mean (SD)	55	46.0	81.5	25	229.6	560.9	.02
In-hospital death	45	48.4		18	24.3		.001
1-year mortality	55	59.1		25	33.8		.001

Abbreviations: CHF, congestive heart failure; EVS, early valve surgery; IE, infective endocarditis; NYHA, New York Heart Association; SD, standard deviation.

**Table 2. Factors Associated With the Performance of Early Valve Surgery in *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis Patients (Propensity Analysis)**

Characteristic	SA PVIE (n = 167)	EVS (n = 74)		Univariate Analysis			Multivariate Analysis	
	No.	No.	%	OR	95% CI	P Value	OR	95% CI
Male sex	98	42	42.9	1		.65		
Female sex	69	32	46.4	1.2	.6–2.1			
Age ≤ 65 y	84	42	50.0	1		.14		
Age >65 y	83	32	38.6	0.6	.3–1.2			
Duration of symptoms >1 mo prior to presentation	17	12	70.6	3.3	1.1–9.8	.04		
Chronic hemodialysis	15	3	20.0	0.3	.1–1.0	.03		
Diabetes mellitus	31	9	29.0	0.4	.2–1.0	.05		
Cancer	12	7	58.3	1.9	.6–6.1	.30		
Charlson index, per 1 unit	79	33	41.8	1.1	.8–1.4	.58		
Nosocomial IE	72	33	45.8	1.2	.7–2.3	.53		
Prior history of IE	32	14	43.8	1.0	.4–2.1	.95		
Intracardiac device	27	9	33.3	0.6	.2–1.4	.22		
Evidence of new regurgitation	73	36	49.3	1.4	.8–2.6	.28		
Paravalvular complications	54	36	66.7	3.9	2.0–7.7	<.0001	4.1	1.9–8.6
Prosthetic valve dehiscence	15	12	80.0	5.8	1.6–21.3	.003		
CHF (NYHA class III or IV)	43	17	39.5	0.8	.4–1.6	.46		
Stroke	57	27	47.4	1.2	.6–2.3	.59		
Embolic event	26	14	53.8	1.6	.7–3.6	.29		
Intracardiac abscess	44	29	65.9	3.4	1.6–7.0	.0008		

Abbreviations: CHF, congestive heart failure; CI, confidence interval; EVS, early valve surgery; IE, infective endocarditis; NYHA, New York Heart Association; OR, odds ratio; PVIE, prosthetic valve infective endocarditis; SA, *Staphylococcus aureus*.

than in the nonsurgery group (nonsignificant statistical association); but thereafter, mortality was significantly lower in the surgery group than in the nonsurgery group (risk ratio, 0.53 [95% CI, .30–.97];  $P = .04$ ).

## DISCUSSION

Although guidelines may help clinicians decide whether and when patients with IE should undergo surgery, such decisions

can be extremely difficult in individual and unique patients, and particularly in patients with PVIE [25–28]. Patients with SA PVIE who undergo EVS are younger, have more severe cardiac complications, and appear to have significantly lower in-hospital and 1-year mortality rates than patients with SA PVIE who do not undergo EVS. However, EVS was not an independent predictor of better outcome, whether considering in-hospital or 1-year mortality, if appropriately designed prognostic models are utilized to examine outcomes.

**Table 3. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery—Endpoint: In-Hospital Mortality**

Variable	RR	95% CI	P Value
Age (per 1-year increment)	1.03	1.01–1.05	.0075
Female sex	1.17	.68–2.01	.58
Stroke (time-dependent)	2.94	1.68–5.14	<.0002
Cardiac failure (NYHA class III or IV)	2.00	1.13–3.50	.0163
Early valve surgery (time-dependent)	0.82	.41–1.62	.5645

Model is based on 166 patients, after exclusion of 2 cases due to missing data. Abbreviations: CI, confidence interval; NYHA, New York Heart Association; RR, risk ratio.

**Table 4. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery—Endpoint: 1-Year Mortality**

Variable	RR	95% CI	P Value
Age (per 1-year increment)	1.03	1.01–1.05	.002
Female sex	1.43	.91–2.40	.12
Stroke (time-dependent)	2.54	1.58–4.09	<.0001
Cardiac failure (NYHA class III or IV)	2.02	1.25–3.26	.004
Paravalvular complications	1.20	.74–1.96	.46
Early valve surgery (time-dependent)	0.67	.39–1.15	.15

Model is based on 150 patients, after exclusion of 18 cases due to missing data. Abbreviations: CI, confidence interval; NYHA, New York Heart Association; RR, risk ratio.



**Table 5. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery (Partitioned)—Endpoint: 1-Year Mortality**

Variable	RR	95% CI	P Value
Age (per 1-year increment)	1.03	1.01–1.05	.002
Female sex	1.44	.92–2.26	.11
Stroke (time-dependent)	2.53	1.57–4.08	<.0001
Cardiac failure (NYHA class III or IV)	2.05	1.27–3.32	.003
Paravalvular complications	1.23	.75–2.01	.41
EVS (time-dependent, partitioned, D0–D7)	1.34	.59–3.02	.49
EVS (time-dependent, partitioned, D8–D365)	0.52	.28–.96	.04

Model is based on 150 patients, after exclusion of 18 cases due to missing data. Abbreviations: CI, confidence interval; D0–D7, day 0 to day 7; D8–D365, day 8 to day 365; EVS, early valve surgery; NYHA, New York Heart Association; RR, risk ratio.

Our findings and conclusions are similar to those by Lalani et al who addressed the same questions in all patients with prosthetic valve IE within the same ICE registry [29]. A specific finding of our analysis is that patients with SA PVIE who underwent EVS and survived the first 7 postoperative days had a better survival rate at 1 year. In our study, the long-term protection of ESV did not compensate for the early postoperative excess mortality. It must indeed require longer follow-up to offset the effect of postoperative mortality and to show an overall protective effect [24].

Our findings contradict conventional assumptions and suggest that EVS may not always improve outcome in patients with SA PVIE [14]. EVS is certainly beneficial to a selected group of SA PVIE patients, as those with clear indications for surgery [6]. But we currently do not have a way to specifically identify individual patients who would actually benefit from EVS, nor do we know the optimal timing of EVS. Our data as well as others' provide no evidence to support the routine performance of EVS in patients with PVIE, including SA PVIE. We can only confirm that, as in previous studies when there is a clear indication for valve surgery (cardiac failure, valve destruction, prosthesis dehiscence), patients' outcome is better when surgery is performed [17, 28, 29].

The major strength of this observational study is that every effort was made to minimize the impact of potential biases, especially treatment selection and survivor biases. Indeed, it has been shown that a proper analysis of the relationship between EVS and outcome in IE should fulfill at least the following criteria: using Cox models adjusted on both potentially prognostic variables and predictors of EVS (propensity factors), choosing long-term (1 year or more) mortality as the primary endpoint, and minimizing survivor selection bias by coding surgery as a time-

dependent variable [24]. The latter point is critical as the likelihood of receiving EVS may be influenced by longer survival; that is, patients who die early during hospitalization may be considered as dying with medical therapy with indications for surgery.

Our study has several limitations. The study sample size might be too small to evidence a positive impact of EVS on mortality in IE even though the ICE-PCS database is the largest registry ever built in this field. Also ICE-PCS data have been collected between 2000 and 2006 and may reflect practices—especially surgical—that have changed in the recent years. Despite the efforts we made to minimize biases, we may have been unable to identify the confounding effect of some variables. In addition, we cannot exclude that referral bias may have played a role as most institutions participating in the ICE cohort are tertiary-care centers. More importantly, neither our study nor any other prior observational study has addressed the myriad of factors that affect surgical decision making in IE (and notably we could not analyze the well-validated indications of surgery), the impact of the expertise of the IE dedicated team, or the impact of surgeon skill on patient outcome. Likewise, we could not make an analysis of the attributable causes of death in each individual case. Although it would be useful to separate deaths due to complications of surgery vs endocarditis in patients who underwent EVS and to clearly identify the cause of death in nonoperated patients, this information was not available in the ICE database.

Although mortality associated with SA PVIE is among the highest observed in patients with IE, and although mortality rates are lower in patients who undergo EVS than in those who do not, our study showed that EVS is not an independent predictor of reduced mortality in patients with SA PVIE. Consequently, we believe that decisions about EVS in patients with SA PVIE should be individualized for each patient and be based on a careful clinical multidisciplinary evaluation, exactly as in any other patient with IE. Further research to define the effect and optimize the timing of surgery in patients with SA PVIE and more generally, PVIE, should in the future rely on well-designed multicenter interventional trials.

## Notes

**Financial support.** This work was supported in part at Hospital Clinic of Barcelona (Spain) by grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III (Madrid, Spain); the Spanish Network for Research in Infectious Diseases (REIPI RD06/0008); Fondo de Investigaciones Sanitarias (Madrid, Spain) (grant FIS 1101131); and Fundación Máximo Soriano Jiménez (Barcelona, Spain).

**Potential conflicts of interest.** J. M. M. has received consulting honoraria and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, GlaxoSmithKline, Gilead Sciences, Pfizer, Roche, Theravance, and ViiV. N. F.-H. was supported by Ministerio de Economía y Competitividad, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund “A way to achieve Europe,” Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015). V. G. F. was supported by the National Institutes of Health (grant number R01-AI068804). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## APPENDIX

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