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Proton-pump inhibitors do not influence clinical outcomes in patients with *Staphylococcus aureus* bacteremia

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Abstract

Background: Proton-pump inhibitors (PPIs) are commonly used in clinical practice for gastric acid suppression. However, these agents have also been associated with certain negative clinical outcomes. We evaluated the real-world effects of incident PPI use on clinical outcomes in patients with *Staphylococcus aureus* bacteremia.

Methods: This retrospective cohort study included patients admitted to Veterans Affairs hospitals with positive *S. aureus* blood cultures collected between 2002 and 2013 that received appropriate antibiotics within 48 hours of culture collection. Clinical outcomes among three PPI exposure groups, each compared to nonusers, were assessed with propensity-score-matched Cox proportional-hazard regression models: pretreated PPI users initiating therapy in the 30 days prior to culture and either (a) continuing PPI therapy after culture, or (b) not continuing after culture, and (c) *de novo* users initiating at culture.

Results: Clinical outcomes, including inpatient mortality, intensive care discharge, 30-day mortality, 30-day readmission, and 30-day *Clostridium difficile* infection (CDI) were similar among PPI users and nonusers. Though length of stay was longer in pretreated, continuing PPI users [time-to-discharge hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.65–0.93], 14-day mortality was significantly lower than in nonusers (HR 0.66, 95% CI 0.50–0.87).

Conclusions: In our large national cohort study, PPIs were not associated with an increased risk of negative clinical outcomes, including mortality and CDI, in patients with *S. aureus* bacteremia.

Keywords: bacteremia, *Clostridium difficile*, mortality, proton-pump inhibitors, *Staphylococcus aureus*

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Introduction

Proton-pump inhibitors (PPIs) are commonly used in clinical practice for gastric-acid suppression, particularly for the prevention of stress ulcers in critically ill patients. However, an increased risk of some negative clinical outcomes has been reported, including kidney disease, hypomagnesemia, bone fractures, pneumonia, and *Clostridium difficile* infections (CDIs).[1,2] A recent study raised alarm by suggesting that initiating PPIs during hospital admission could increase the risk of inpatient mortality by about 90%.[3] While older data have suggested that acid suppression allows for increased intestinal bacteria, some analyses found this overgrowth occurred less with histamine antagonists, conceivably related to less potent gastric-acid suppression from histamine antagonists when compared with PPIs.[4] Moreover, PPIs have been associated with decreased leukocyte antimicrobial activity *in vitro*, as well as attenuated innate immune responses *in vivo* that may be beneficial in clearance of bacterial infection.[5] We thought it would be important to examine if

these reported immunomodulatory effects described for PPIs translated into any clinical outcome differences in patients with invasive infection. Among the most common of invasive bacterial infection in humans, *Staphylococcus aureus* affects broad patient populations exhibiting high diversity in baseline host innate immune status. This study sought to evaluate the real-world effects of incident PPI use on clinical outcomes in patients with *S. aureus* bacteremia.

Methods

Data source

We utilized national Veterans Affairs (VA) databases, which contain health and administrative data captured from electronic medical records. The databases used included diagnoses and procedures from outpatient and inpatient care, laboratory and microbiology results, vital signs and vital status, and pharmacy data, including inpatient and outpatient administration and dispensing, and medications prescribed by non-VA providers or purchased by patients at non-VA pharmacies.

Study population

This retrospective cohort study included adult patients (age ⩾ 18 years) admitted to VA hospitals with positive blood cultures for *S. aureus* between 1 January 2002 and 1 December 2013. Initial antibiotic regimens within 48 hours of culture collection were reviewed and only those with appropriate regimens were selected for inclusion: intravenous β-lactam therapy (ampicillin-sulbactam, nafcillin, oxacillin, piperacillin–tazobactam, cefazolin, cefotetan, cefoxitin, ceftazidime, ceftriaxone, ceftaroline, ertapenem, doripenem, imipenem–cilastatin, or meropenem) or vancomycin for methicillin-susceptible *S. aureus* (MSSA) and vancomycin or ceftaroline for methicillin-resistant *S. aureus* (MRSA). If patients were discharged within 1 day of culture or died in that same timeframe, they were excluded. Once these criteria were applied, the first admission was selected for analysis.

This study was approved by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center.

As this study utilized existing health data, a waiver of informed consent was granted by the Institutional Review Board of the Providence Veterans Affairs Medical Center.

PPI use

Incident PPI use was defined as initiation of a PPI within the 30 days prior to culture or at culture, without PPI use in the previous year. Those initiating prior to culture were further categorized as continuing after culture and not continuing after culture, to assess whether lasting effects were observed after discontinuation. Nonusers were those with no record of PPI use in the year prior to culture or during the entire admission and served as the comparison group for all three PPI user groups (pretreated with continuation, pretreated without continuation, and *de novo* at culture).

Outcomes

The primary outcome was mortality as assessed within 30 days of the culture collection date and the secondary outcomes included 14-day mortality, inpatient mortality, hospital discharge, intensive care unit (ICU) discharge, 30-day readmission, and 30-day CDI (International Classification of Diseases, 9th edition, 008.45). We calculated time for each endpoint from the culture collection date to the event date, and censoring was used in the assessments of discharge, readmission, and CDI for patients who died.

Statistical analysis

We developed three separate propensity-score models for each PPI exposure group that controlled for initial antibiotic treatment, treating facility, treating specialty, infection source, previous healthcare exposures, demographics, current comorbidities, medical history, and other clinical characteristics, such as MSSA/MRSA (Appendix 1 in the Supplementary Material). We confirmed goodness of fit and absence of multicollinearity in the propensity-score models. Nonusers were then matched to users on their propensity score using nearest neighbor matching within 0.005 caliper. Lastly, Cox proportional hazard regression models were used to quantify the hazard ratio (HR) and 95% confidence interval (CI) for all outcomes. Analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Our study included 653 pretreated PPI users without continuation, 642 pretreated PPI users with continuation, 900 *de novo* PPI users, and 11,840 nonusers, all with *S. aureus* bacteremia (Figure 1). Table 1 lists demographics and clinical characteristics of patients in each of these

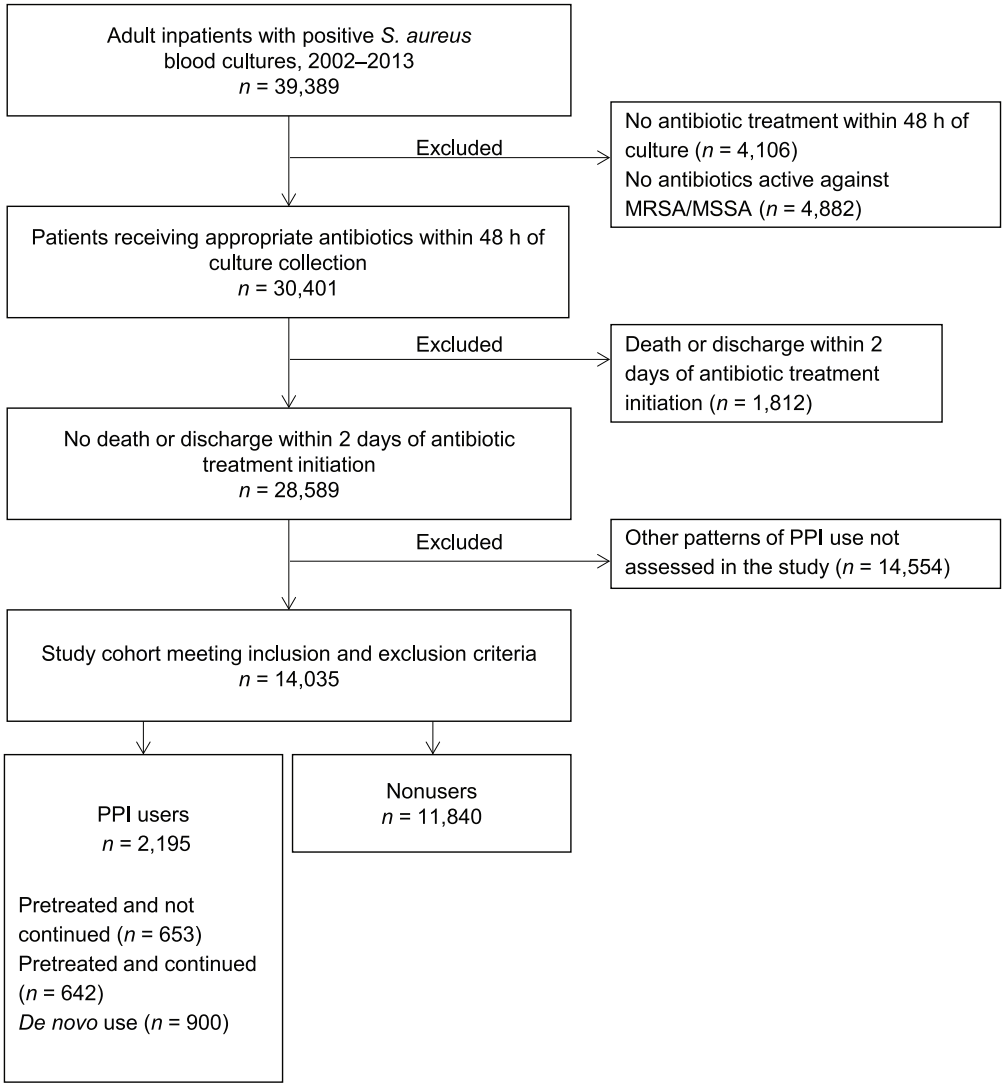


Figure 1. Study cohort identification.
MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PPI, proton-pump inhibitor.

groups prior to implementation of propensity-score matching. PPI users differed considerably from nonusers, in terms of demographic characteristics, source of infection, comorbidity burden, and medical history. Due to these significant differences, these variables were included in the propensity-score models. Each model demonstrated goodness of fit, allowing strong discrimination between the groups, with high C statistics of 0.82–0.90, and due to the small caliper used for identifying matches, complete overlap in propensity-score distributions between PPI users and nonusers was obtained.

In propensity-matched analyses of the aforementioned clinical outcomes, there were few differences observed between PPI users and nonusers (Table 2). Inpatient mortality, intensive care discharge, 30-day mortality, 30-day readmission, and 30-day CDI were similar among PPI users and nonusers. In pretreated PPI users with continuation, the 14-day mortality rate was significantly lower (HR 0.66, 95% CI 0.50–0.87) despite a lower discharge rate (HR 0.78, 0.65–0.92). This lower discharge rate, which reflected a longer length of stay, was also observed in *de novo* PPI users (HR 0.85, 95% CI 0.74–0.97) as compared with nonusers. Similar results were observed in sensitivity analyses that excluded patients with a *C. difficile* diagnosis code during the *S. aureus* bacteremia admission, where 14-day mortality was significantly lower (HR 0.62, 95% CI 0.42–0.92) among pretreated PPI users

Table 1. Demographic and clinical characteristics in proton-pump inhibitor users and nonusers.

Characteristics	Unexposed (n = 11,840)	Pretreated without continuation (n = 653)	Pretreated with continutation (n = 642)	*De novo* (n = 900)
Age (years)	68.8 ± 11.8	68.8 ± 11.6	67.6 ± 12.6*	68.4 ± 12.6
Body mass index	28.0 ± 7.4	26.9 ± 6.7*	26.7 ± 7.4*	26.9 ± 7.1*
Male sex	11605 (98.0)	647 (99.1)	627 (97.7)	884 (98.2)
White race	7623 (64.4)	407 (62.3)	402 (62.6)	593 (65.9)
Hispanic ethnicity	723 (6.1)	26 (4.0)*	37 (5.8)	51 (5.7)
Year				
2002–2005	4558 (38.5)	264 (40.4)*	273 (42.5)*	296 (32.9)*
2006–2009	3824 (32.3)	242 (37.1)*	225 (35.1)*	368 (40.9)*
2010–2013	3458 (29.2)	147 (22.5)*	144 (22.4)*	236 (26.2)*
Intensive care at culture	1953 (16.5)	174 (26.7)*	146 (22.7)*	251 (27.9)*
Region of facility				
Midwest	2406 (20.3)	125 (19.1)*	128 (19.9)*	173 (19.2)*
Northeast	1449 (12.2)	100 (15.3)*	125 (19.5)*	148 (16.4)*
South	5233 (44.2)	300 (45.9)*	274 (42.7)*	395 (43.9)*
West	2752 (23.2)	128 (19.6)*	115 (17.9)*	184 (20.4)*
Source of infection§				
Catheter	226 (1.9)	19 (2.9)	29 (4.5)*	11 (1.2)
Endocarditis‡	380 (3.2)	15 (2.3)	2 (0.3)*	65 (7.2)*
Respiratory culture site	593 (5.0)	73 (11.2)*	81 (12.6)*	60 (6.7)*
Skin and soft tissue culture site	1896 (16.0)	65 (9.9)*	43 (6.7)*	102 (11.3)*
Urine	1392 (11.8)	49 (7.5)*	73 (11.4)	147 (16.3)*
Other culture site	213 (1.8)	11 (1.7)	9 (1.4)	15 (1.7)
S. aureus pathogen				
MRSA infection	5336 (45.1)	359 (55.0)*	352 (54.8)*	411 (45.7)
MSSA infection	6504 (54.9)	294 (45.0)*	290 (45.2)*	489 (54.3)
Median time to antibiotic treatment initiation from culture collection (days)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Median length of antibiotic therapy (days)	9 (5–14)	8 (5–14)	11 (7–16)*	12 (8–18)*
Median time to culture collection from admission (days)	0 (0–3)	4 (0–14)*	6 (2–15)*	0 (0–1)*

Table 1. (Continued)

Characteristics	Unexposed ($n = 11,840$)	Pretreated without continuation ($n = 653$)	Pretreated with continuation ($n = 642$)	*De novo* ($n = 900$)
Surgery during the current admission	4288 (36.2)	251 (38.4)	260 (40.5)*	314 (34.9)
Comorbidity during current admission				
Charlson score	3.2 ± 2.5	3.7 ± 2.9*	3.6 ± 2.9*	2.8 ± 2.5*
Elixhauser score	3.6 ± 1.9	3.9 ± 2.0*	3.8 ± 1.9	3.6 ± 1.9
Sepsis	9814 (82.9)	516 (79.0)*	487 (75.9)*	773 (85.9)*
Shock	498 (4.2)	45 (6.9)*	36 (5.6)	91 (10.1)*
Coagulation and hemorrhagic disorders	56 (0.5)	3 (0.5)	10 (1.6)*	4 (0.4)
Peptic ulcer disease	89 (0.7)	26 (4.0)*	37 (5.8)*	16 (1.8)*
Peptic ulcer disease excluding bleeding	33 (0.3)	8 (1.2)*	10 (1.6)*	7 (0.8)*
Gastrointestinal hemorrhage	65 (0.6)	21 (3.2)*	34 (5.3)*	7 (0.8)
Medical conditions prior to current admission§				
Charlson score	3.3 ± 2.9	3.5 ± 3.2	2.9 ± 3.2*	2.3 ± 2.7*
Elixhauser score	3.9 ± 2.7	4.1 ± 2.7	3.3 ± 2.0*	2.8 ± 2.5*
S. aureus infection	530 (4.5)	30 (4.6)	24 (3.7)	32 (3.6)
Influenza vaccination	1516 (12.8)	92 (14.1)	72 (11.2)	85 (9.4)*
Surgery	3574 (30.2)	193 (29.6)	152 (23.7)*	201 (22.3)*
Hospitalization	6106 (51.6)	395 (60.5)*	318 (49.5)	328 (36.4)*
Nursing home stay	908 (7.7)	64 (9.8)*	54 (8.4)	63 (7.0)

Data are mean ± standard deviation, number (%) of patients, or median (interquartile range).
*$p < 0.05$ for pairwise comparison between PPI exposure group and non-user group.
§Culture-confirmed source of infection ± 24 hours from culture collection unless indicated otherwise.
‡Source of infection identified from ICD-9-CM diagnosis codes ± 24 hours from culture collection.
§Present in the 1 year prior to the *Staphylococcus aureus* bacteremia hospitalization.
ICD-9-CM, International Classification of Diseases, 9th edition, clinical modification; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; PPI, proton-pump inhibitor.

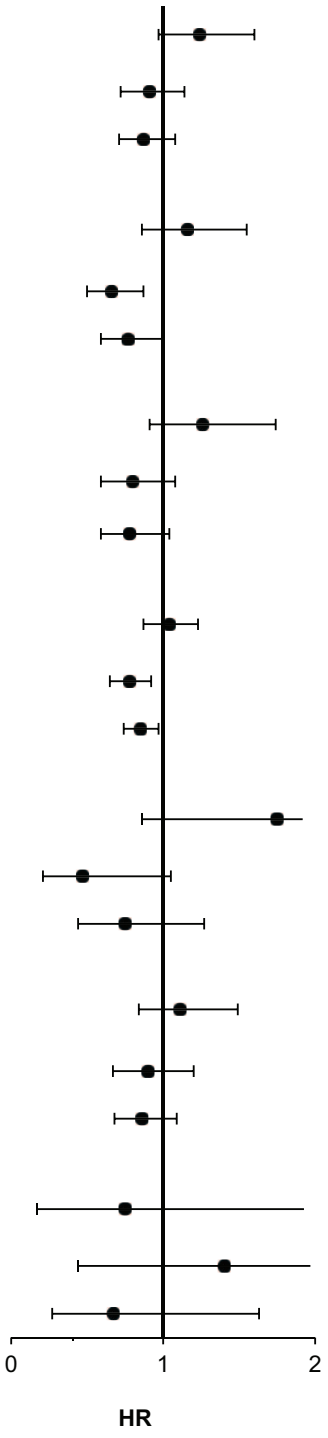
with continuation, despite a lower discharge rate (HR 0.74, 0.60–0.90), and a lower discharge rate was also observed for *de novo* PPI users (HR 0.75, 95% CI 0.64–0.87; data not presented in tables).

Discussion

PPIs have been shown in various studies to inhibit neutrophil functions that are critical in bacterial clearance, including production of reactive oxidative species, chemotaxis, and phagolysozome acidification.[6,7] In addition, certain PPIs are reported to reduce expression of integrins CD11b and CD18 on the neutrophil surface and expression of adhesion molecules ICAM-1 and VCAM-1 on endothelial cells, potentially compromising transcytosis of the immune cells to tissue foci of infection.[8] Consistent with such laboratory data is

Table 2. Clinical outcomes in propensity-matched proton-pump inhibitor users and nonusers.

Outcomes	Events, *n*/patients, *n*		HR (95% CI)
	PPI users	Nonusers	
30-day mortality			
Pretreated without continuation	153/632	129/632	1.24 (0.97–1.60)
Pretreated with continuation	168/683	169/683	0.91 (0.72–1.14)
De novo	178/1006	190/1006	0.87 (0.71–1.08)
14-day mortality			
Pretreated without continuation	100/632	92/632	1.16 (0.86–1.55)
Pretreated with continuation	97/683	136/683	**0.66 (0.50–0.87)**
De novo	100/1006	126/1006	0.77 (0.59–1.00)
Inpatient mortality			
Pretreated without continuation	127/632	110/632	1.26 (0.91–1.74)
Pretreated with continuation	142/683	139/683	0.80 (0.59–1.08)
De novo	166/1006	169/1006	0.78 (0.59–1.04)
Discharge			
Pretreated without continuation	505/632	522/632	1.04 (0.87–1.23)
Pretreated with continuation	541/683	544/683	**0.78 (0.65–0.92)**
De novo	840/1006	837/1006	**0.85 (0.74–0.97)**
ICU discharge			
Pretreated without continuation	123/167	121/165	1.75 (0.86–3.56)
Pretreated with continuation	113/151	114/152	0.47 (0.21–1.05)
De novo	204/262	201/272	0.75 (0.44–1.27)
30-day readmission			
Pretreated without continuation	137/505	132/522	1.11 (0.84–1.49)
Pretreated with continuation	127/541	131/544	0.90 (0.67–1.20)
De novo	181/840	208/837	0.86 (0.68–1.09)
30-day *Clostridium difficile* infection			
Pretreated without continuation	5/505	6/522	0.75 (0.17–3.35)
Pretreated with continuation	12/541	7/544	1.40 (0.44–4.41)
De novo	8/840	13/837	0.67 (0.27–1.63)



Propensity score matched within a 0.005 caliper range. The propensity score was derived from an unconditional logistic regression model and controlled for the variables listed in Appendix 1 in the Supplementary Material.
Bold text indicates statistical significance.
CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

previous clinical evidence suggesting poorer clinical outcomes in patients treated with PPIs, including increased risk for *C. difficile* infections and mortality.[2,3]

Seeking to determine whether PPIs influence clinical outcomes in patients with *S. aureus* bacteremia, we found similar outcomes between PPI users with varying exposure patterns as compared with nonusers, in agreement with a recent meta-analysis of 19 randomized trials conducted among critically ill patients.[9] As the included randomized trials evaluated prophylactic PPI use, these studies most likely reflect a *de novo* exposure pattern, however the number of studies excluding patients with preadmission PPI use was not reported. Pneumonia, mortality, and ICU length of stay were similar among those randomzied to PPIs *versus* histamine-2-receptor antagonists (H2RAs), with a relative risk of 1.12 (95% CI 0.86–1.46) and 1.05 (95% CI 0.87–1.27) for pneumonia and mortality, respectively, and a mean difference in ICU length of stay of −0.38 days (95% CI −1.49 to 0.74). None of the included 19 studies reported CDIs.

While multiple meta-analyses have found an association between PPI use and CDIs, heterogeneity among studies evaluated has been consistently high ($I^2 > 85\%$) reflecting variability in the associated risk among studies, and significant limitations of existing studies have been noted.[10,11] A recent study evaluating the risk of CDI among intensive care unit patients suggests some patient populations may not have the same associated risk, consistent with our results.[12] In this large multicenter study among 18,134 patients, PPI use did not lead to a significant increase in CDI [adjusted hazard ratio (aHR) 1.56; 95% CI 0.72–3.35] among patients not receiving antibiotics and was protective in those receiving antibiotics (aHR 0.64; 95% CI 0.48–0.83). Further studies should seek to determine in which patient populations PPIs may be safely used without conferring increased CDI risk.

Several limitations to our study should be noted. First, over-the-counter use of PPIs may not have been reported during clinical visits and hospitalizations. Second, we utilized diagnosis codes to operationally define certain conditions, such as CDI, which may result in misclassification. For example, presence of diagnosis codes may not always reflect active problems and may be used to reflect history of the condition, or even colonization in the case of *C. difficile*. Third, residual confounding may be present due to unmeasured confounders, despite our efforts to control for many confounders using propensity-score methods. Fourth, our study was conducted among patients receiving care at VA hospitals, and included mostly older males.

Conclusion

Rates of negative clinical outcomes were similar among PPI users and nonusers in our large, national, real-world cohort study. As this is one observational study from a single-study population, our results should be substantiated in other study populations. If rates of negative clinical outcomes, such as mortality and CDI, are found to be similar between PPI users and nonusers with serious infections then the clinical benefits of PPI use under appropriate indications may outweigh the potential risk of certain other adverse events that have been attributed to PPI use.

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Conflicts of interest statement

Aisling Caffrey has received research funding from Pfizer, Merck (Cubist), and The Medicines Company. Tristan Timbrook has received honoraria for speaking and/or consulting from BioFire Diagnostics, GenMark Diagnostics, and Roche Diagnostics. Syed Raza Ali has no conflicts to disclose. Victor Nizet has received research funding or acted as an advisor for InhibRx, Centauri

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Supplemental material

Supplemental material for this article is available online.

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