

## Gastric Acid Suppression Therapy and Its Association with Peritoneal Dialysis–Associated Peritonitis in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

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### Key Points

- In a large multinational cohort of PD patients, any GAS use was not associated with an increased risk of all-organism peritonitis.
- For peritonitis, risks were particularly high among certain classes of organisms particularly for Gram-negative, enteric, and streptococcal peritonitis episodes.
- The association with enteric peritonitis appeared to be stronger among H2RA users.

### Abstract

**Background** Peritonitis is a major peritoneal dialysis–related complication. We determined whether gastric acid suppression (GAS) (proton pump inhibitor [PPI] or histamine-2 receptor antagonists [H2RAs]) use was associated with all-cause and organism-specific peritonitis in peritoneal dialysis patients.

**Methods** In the Peritoneal Dialysis Outcomes and Practice Patterns Study (595 facilities, eight countries, years 2014–2022), associations between GAS use and time to first episode of all-cause peritonitis were examined using Cox proportional hazards models. The primary exposure of interest was GAS and secondarily PPI or H2RA use. Secondary outcomes were organism-specific peritonitis, peritonitis cure rates, and death.

**Results** Among patients ( $N=23,797$ ) at study baseline, 6020 (25.3%) used PPIs, and 1382 (5.8%) used H2RAs. Overall risks of GAS use and peritonitis risk (adjusted hazard ratio [AHR]=1.05, 95% confidence interval [CI], 0.98 to 1.13) and use of PPI (AHR 1.06 [95% CI, 0.99 to 1.14]) or H2RA (AHR 1.02 [95% CI, 0.88 to 1.18]) did not reach statistical significance. In organism-specific analyses, GAS users displayed higher peritonitis risks for Gram-negative (AHR 1.29, 95% CI, 1.05 to 1.57), Gram-positive (AHR 1.15, 95% CI, 1.01 to 1.31), culture-negative (AHR 1.20, 95% CI, 1.01 to 1.42), enteric (AHR 1.23, 95% CI, 1.03 to 1.48), and particularly *Streptococcal* (AHR 1.47, 95% CI, 1.15 to 1.89) peritonitis episodes. GAS was also associated with higher overall mortality (AHR 1.13 [95% CI, 1.05 to 1.22]).

**Conclusion** The association between GAS use and peritonitis risk was weaker (hazard ratio [HR] 1.05 [0.98 to 1.13]) than for streptococcal (HR 1.57 [1.15 to 1.89]) and Gram-negative (HR 1.29 [1.05 to 1.57]) peritonitis. A better understanding of mechanisms surrounding the differential effects of GAS subtype on peritonitis risks is needed. Clinicians should be cautious when prescribing GAS. The impact of GAS deprescribing on peritonitis risk requires further evaluation.

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### Introduction

Peritoneal dialysis (PD)–associated peritonitis contributes to significant morbidity and is a leading cause of

hemodialysis (HD) transfer.<sup>1</sup> Identifying modifiable risk factors for peritonitis is important. Gastric acid suppression (GAS), proton pump inhibitors (PPIs) and histamine-2

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receptor antagonists (H2RAs), are universally prescribed for a variety of gastrointestinal (GI) indications, such as upper GI bleeding, gastroesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* eradication.<sup>2,3</sup> Individuals receiving dialysis have a higher prevalence of GI disorders.<sup>4,5</sup> Furthermore, cardiovascular (CV) disease is prevalent among patients with kidney failure,<sup>6</sup> and for those treated with antiplatelets, prophylactic GAS is often used to mitigate GI bleeding risks. A Swedish study found higher GAS use among dialysis patients (41%) compared with hospitalized patients (13%) or patients with chronic pulmonary disease (16%).<sup>7</sup> Rates of GAS use among dialysis patients in two Canadian studies were similar to the Swedish study.<sup>8,9</sup>

Reported adverse effects associated with GAS include pneumonia, *Clostridium difficile* infection, and spontaneous bacterial peritonitis in cirrhotic patients.<sup>10</sup> Previous studies suggested that GAS is a potential risk factor of PD-associated peritonitis. Possible mechanisms for GAS-related increased peritonitis risk include gastric and small bowel bacterial overgrowth leading to alteration in the composition of the normal gut microbiota and immune system alterations. Current literature has demonstrated conflicting results, limited by small and single-center reports.<sup>11–17</sup>

Here, we sought to evaluate (1) the association between any GAS with all-cause peritonitis, (2) the risk of either PPI or H2RA on all-cause peritonitis, and (3) the impact of GAS on organism-specific peritonitis, peritonitis cure rates, and all-cause mortality.

## Materials and Methods

### Data Source

The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) is an international prospective cohort study in collaboration with the International Society for Peritoneal Dialysis.<sup>18</sup> Patients age 18 years or older receiving maintenance PD were enrolled randomly from national samples of randomly selected PD facilities treating a minimum of 20 PD patients. Study approval was obtained by a central national or institutional review board. Additional study approval and patient consent were obtained by national and local ethics committee regulations.

Study details are provided in the study by Perl *et al.*<sup>18</sup>

Data from Australia/New Zealand (A/NZ), Canada, Japan, South Korea, Thailand, the United Kingdom (UK), and the United States in PDOPPS phases 1–2 (phase 1: 2014–2018, phase 2: 2018–2022) were used. Patient demographics, comorbidities, and laboratory data were captured at study enrollment. Data for US PD patients from large dialysis organizations were extracted from electronic health records.<sup>19</sup> Remaining data were abstracted from medical charts into a web-based data collection tool.

An infection worksheet capturing the first presentation date and causative organism (or culture-negative case) was completed for each peritonitis episode during PDOPPS follow-up. Peritonitis episodes were additionally ascertained from facility-reported hospitalizations indicating a peritonitis diagnosis and assumed to have onset on the date of admission and unknown causative organism.

### Exposure Definition

The primary exposure was first reported use of all GAS (PPI or H2RA) in PDOPPS. Ninety-four percent of patients had medication data reported at the time of study entry. An additional 5% had first medication data reported in the 6-month period after study entry. Secondary exposure was individual PPI versus H2RA. Exclusion criteria were patients without medication data, patients using a combination of H2RA and PPI and hybrid therapy receipt (PD+HD).

### Outcome Definition

The primary outcome was time to first peritonitis episode (any organism) during follow-up. Repetitive or recurrent episodes of peritonitis were not included in the primary outcome as the occurrence of the first peritonitis episode may have increased the likelihood of a subsequent peritonitis episode. Therefore, we felt that time to first episode of peritonitis may be a more appropriate model to assess the association between GAS use and peritonitis risk.

Analyses were also performed using time to first organism-specific and enteric peritonitis episodes. Peritonitis organism classifications are detailed in [Supplemental Table 1](#). For organism-specific analyses, facilities not routinely reporting peritonitis organisms (defined as facilities that reported at least three peritonitis episodes but without reporting any organism type) were excluded. Secondary outcomes included all-cause mortality and the composite outcome of peritonitis or death.

### Statistical Analysis

Peritonitis time at risk for each patient started at study baseline and continued until the earliest of first peritonitis episode during the study or the end of data for a given patient (*e.g.*, because of end of data collection, patient transfer to another facility, kidney transplantation, transfer to HD [defined as permanent transfer to HD or temporary transfer with failure to return to PD within 84 days of modality switch date, censored at the date of transfer]), loss to follow-up, or death. For all-cause mortality, follow-up started at study baseline and ended at first end of data collection, kidney transplantation, permanent transfer to HD (as defined above), loss to follow-up, or death. Mortality events were included up to 60 days after study departure. In sensitivity analyses, we additionally censored patients at GAS treatment switch to reduce cross-over during follow-up: (1) We censored baseline nonusers at treatment initiation and (2) baseline users at treatment discontinuation during follow-up.

Cox proportional hazards were used to model the association between GAS use and peritonitis and death. Proportional hazards assumption was assessed by the supremum test. Models were stratified by country, US large dialysis organization, and PDOPPS phase, accounting for facility clustering using robust sandwich covariance estimators. The models were adjusted for age, sex, Black race, PD vintage, PD modality, 13 comorbidities, serum albumin, potassium, magnesium, and 24-hour urine volume. Primary results were performed with differing levels of adjustment. Subgroup analyses were performed by PD vintage, GI

comorbidity, antiplatelet medication, and country. GI comorbidity included liver disease, GI bleeding in the 12 months before the study entry, GI cancer, GI surgery, and hepatitis B and hepatitis C viral infections.

Additional sensitivity analyses stratifying patients with and without GI comorbidity was to explore possible confounding by indication because of the presence of GI conditions which may have increased the risks of GAS use and peritonitis. Similarly, we stratified by antiplatelet use in a sensitivity analysis as antiplatelet use may have been associated with both GAS and CV comorbidities, both of which may increase both peritonitis and mortality risks. We also performed sensitivity analyses censoring baseline GAS nonusers at treatment initiation and baseline GAS users at treatment discontinuation.

Peritonitis cure rates by GAS therapy were reported. Peritonitis cure was defined as the absence of a subsequent peritonitis event (relapse or recurrence, as defined previously at Al Sahlawi *et al.*<sup>1</sup>), PD catheter removal, or HD transfer (defined as permanent transfer to HD or temporary transfer with failure to return to PD within 84 days of modality switch date) or death during the 50 days after onset of a peritonitis episode.<sup>1</sup>

Missing data were imputed by the chained-equations method as implemented with IVEware for SAS.<sup>20</sup> The missingness of all variables was <8%, except for urine volume (43%) and magnesium (35%). Twenty imputations each were performed for patient-level variables and merged by replicate number. Analyses were performed separately on each imputed data set, with results combined using the Rubin method.<sup>21</sup> Data analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

## Results

### Study Participants and Clinical Characteristics

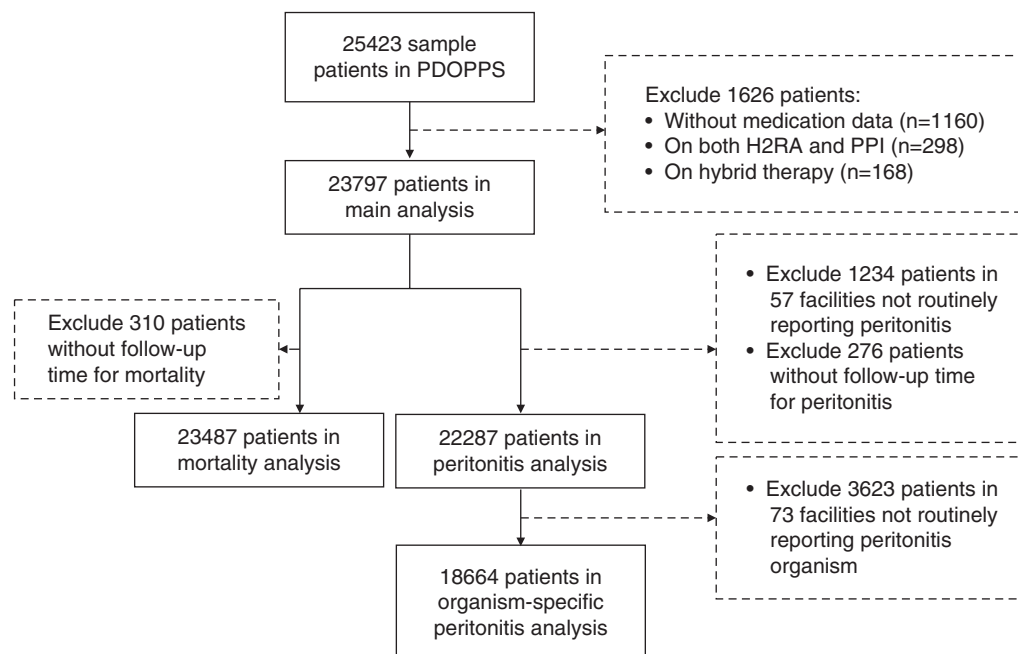
In total, 23,797 patients receiving PD were included in this study (Figure 1). Overall, 6020 (25.3%) patients were prescribed PPI, and 1382 (5.8%) were prescribed H2RA. The distribution of GAS prescription by country is shown in Figure 2. PPIs were less commonly prescribed in Thailand and South Korea.

Patients without GAS therapy were younger; less likely to have a history of CV disease, heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, neurologic disease, psychiatric disease, and malignancy; and less often prescribed antiplatelet therapy (Table 1). Other comorbidities were similar compared with GAS users. Patients prescribed PPIs were more likely to have a heart failure and coronary heart disease history compared with H2RA users or patients without any GAS treatment.

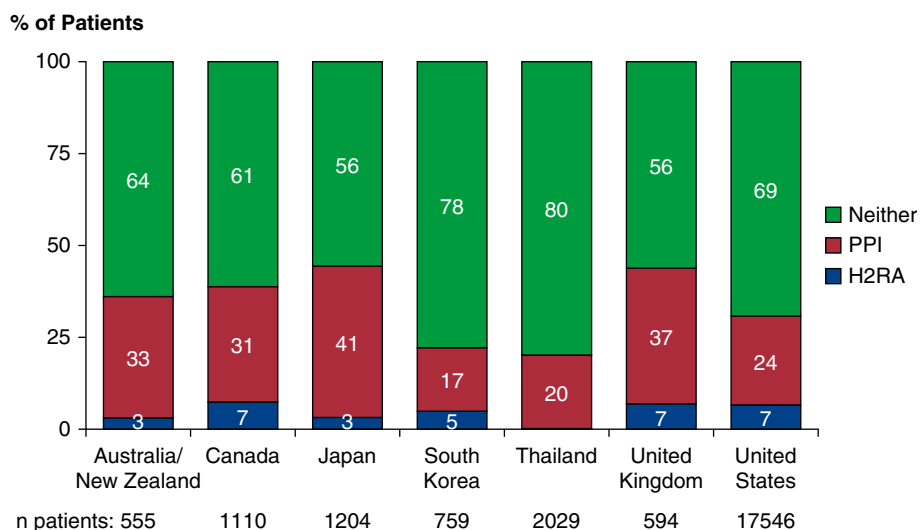
Kidney transplantation rates were similar among GAS versus non-GAS users: 4.7 per 100 patient-years among GAS users and 4.5 per 100 patient-year among nonusers. No association between GAS use and kidney transplantation (adjusted hazard ratio [AHR] 1.05, 95% confidence interval [CI], 0.93 to 1.19) was seen.

### Peritonitis Outcomes

Including 5403 peritonitis episodes, the overall peritonitis rate among GAS users was 0.24 episodes per patient-year and 0.21 among patients not taking GAS. Analysis of first peritonitis episode included 4063 episodes. The association between GAS and time to first peritonitis is shown in Figure 3A. The AHR for GAS for all-cause peritonitis



**Figure 1. Assembly of the study cohort.** H2RA, histamine 2 receptor antagonist; PDOPPS, Peritoneal Dialysis Outcomes and Practice Patterns Study; PPI, proton pump inhibitor.



**Figure 2. Cross-sectional distribution of gastric acid suppression medication use, by country at baseline.** H2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor.

was 1.05 (95% CI, 0.98 to 1.13) and with individual use of PPI and H2RA (Figure 3A) AHR 1.06 (95% CI, 0.99 to 1.14) and AHR 1.02 (95% CI, 0.88 to 1.18), respectively. Sensitivity analyses with censoring baseline nonusers at GAS treatment initiation and baseline GAS users at treatment discontinuation were consistent with our primary findings (Supplemental Figure 1A+B).

Organism-specific peritonitis risks by GAS use is presented in Table 2.

Among GAS users, there was a higher peritonitis risk for Gram-negative peritonitis (AHR 1.29, 95% CI, 1.05 to 1.57), Gram-positive peritonitis (AHR 1.15, 95% CI, 1.01 to 1.31), enteric peritonitis (AHR 1.23, 95% CI, 1.03 to 1.48), streptococcal peritonitis (AHR 1.47, 95% CI, 1.15 to 1.89), and culture-negative peritonitis (AHR 1.20, 95% CI, 1.01 to 1.42).

Compared with patients not using any GAS, the risk of streptococcal peritonitis was higher among PPI users with an AHR of 1.56 (95% CI, 1.21 to 2.02), but not among H2RA users (AHR 0.81, 95% CI, 0.42 to 1.56). The risk of enteric peritonitis was significant among H2RA users (AHR 1.70, 95% CI, 1.16 to 2.50) but did not reach statistical significance among PPI users (AHR 1.18, 95% CI, 0.98 to 1.41). Risk of Gram-negative peritonitis was higher among H2RA users (AHR 1.68, 95% CI, 1.11 to 2.54) and PPI users (AHR 1.24, 95% CI, 1.01 to 1.53).

Unadjusted peritonitis cure rates were similar in GAS users and nonusers at 75% of all episodes in patients on GAS and 78% of all episodes in patients not using GAS.

### Subgroup Analysis

Subgroup analyses are shown in Supplemental Figure 2. Country-specific analyses revealed similar trends among different countries, except Thailand, where a significant association was found between GAS use and all-cause peritonitis (AHR 1.45, 95% CI, 1.02 to 1.93). Subgroup analyses for patients with and without GI comorbidities and patients with and without antiplatelet therapy yielded similar results (Supplemental Figure 2).

### Mortality

The median follow-up for mortality was 12 months; the interquartile range was 6–22 months and was 17.6% among patients taking GAS ( $n=1285$ ) and 13.6% ( $n=2197$ ) among patients without GAS treatment. Use of GAS was associated with a higher risk of all-cause mortality (AHR of 1.13 [95% CI, 1.05 to 1.22]) in the fully adjusted model (Figure 3B, model 4). This association remained significant for PPI (AHR 1.14, 95% CI, 1.05 to 1.24) but not H2RA (AHR 1.08, 95% CI, 0.92 to 1.27).

For the combined outcome of peritonitis or death, higher risks were found among GAS users (AHR of 1.06, 95% CI, 1.01 to 1.12). Risk was consistent among PPI users (AHR 1.07, 95% CI, 1.02 to 1.13) but not H2RA users (AHR 1.02, 95% CI, 0.91 to 1.14) (Figure 3C).

Sensitivity analyses were conducted (1) censoring baseline nonusers at treatment initiation and (2) censoring baseline users at treatment discontinuation, both of which yielded similar results (Supplemental Figure 1A+B).

### Discussion

In this multinational cohort study, we observed an association between GAS use and Gram-negative peritonitis, Gram-positive peritonitis, enteric peritonitis, Streptococcal species peritonitis, and culture-negative peritonitis. Risks were especially high for H2RA use and enteric and Gram-negative peritonitis and for PPI use and Streptococcal peritonitis. Peritonitis cure rates were comparable between GAS users and nonusers. Mortality risk was higher among patients on GAS and PPI therapy.

Reduction in acid production has been associated with an increased risk of enteric infections.<sup>10</sup> Gastric acid suppressants have been linked to gastric and small bowel bacterial overgrowth and alteration in the composition of the normal gut microbiota.<sup>10,22–26</sup> Qualitative and quantitative alterations in the gut microbiota, coupled with disruptions in the intestinal epithelial barrier among those with kidney

**Table 1. Patient demographics and comorbidities by gastric acid suppression use**

Characteristic	Gastric Acid Suppression Medication Use		
	H2RA (n=1382)	PPI (n=6020)	Neither (n=16,395)
<b>Demographics</b>			
Age, yr	61±15	62±14	59±15
Sex (% male)	53%	55%	58%
Race (% US Black)	22%	22%	24%
PD vintage, yr	0.4 (0.2 to 1.6)	0.6 (0.2 to 2.0)	0.4 (0.2 to 1.5)
ESKD vintage, yr	1.1 (0.3 to 2.9)	1.3 (0.4 to 3.1)	0.9 (0.3 to 2.4)
<b>Comorbidity history</b>			
Diabetes	45%	48%	44%
Hypertension	86%	91%	90%
Coronary artery disease	23%	28%	14%
Heart failure	15%	19%	11%
Cerebrovascular disease	13%	13%	8%
Peripheral vascular disease	16%	13%	8%
Other cardiovascular diseases	17%	18%	10%
Lung disease	6%	6%	3%
Neurologic disease	4%	5%	3%
Psychiatric disorder	13%	11%	6%
Cancer	10%	10%	7%
Recurrent cellulitis/gangrene	2%	2%	0.9%
HIV	0.6%	1%	2%
GI comorbidity <sup>a</sup>	5%	7%	5%
<b>Dialysis treatments</b>			
APD	80%	72%	72%
Assisted PD	18%	28%	28%
<b>Laboratory/biometric markers</b>			
Body mass index, kg/m <sup>2</sup>	28.5±6.6	27.8±6.5	27.7±6.5
Serum albumin, g/dl	3.6±0.5	3.4±0.5	3.6±0.5
Hemoglobin, g/dl	10.9±1.6	10.9±1.6	10.9±1.6
Serum phosphorus, mg/dl	5.3±1.6	5.1±1.6	5.4±1.7
Serum calcium, mg/dl	8.9±0.8	8.7±0.8	8.8±0.8
Serum magnesium, mg/dl	2.2±0.5	2.1±0.5	2.2±0.5
Serum potassium, mEq/L	4.2±0.6	4.2±0.7	4.2±0.7
24-h urine volume, L	0.9±0.8	0.8±0.7	0.9±0.8
<b>Medication use</b>			
Antiplatelet	48%	47%	34%
Aspirin	41%	41%	30%
Clopidogrel	11%	12%	6%
P2Y platelet inhibitors	6%	5%	3%

APD, automated peritoneal dialysis; GI, gastrointestinal; H2RA, histamine 2 receptor antagonist; PD, peritoneal dialysis; PPI, proton pump inhibitor.

<sup>a</sup>GI comorbidity including liver disease, GI bleeding, GI cancer, hepatitis B and hepatitis C.

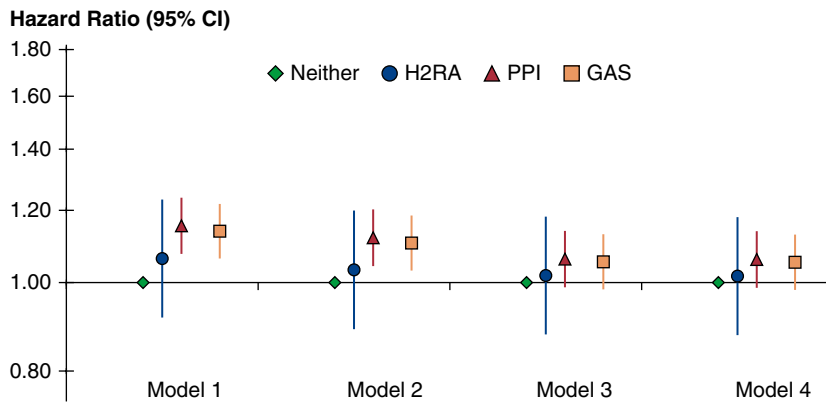
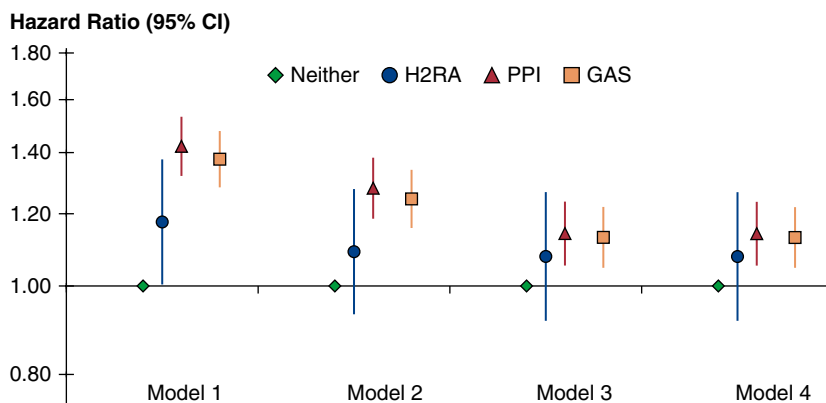
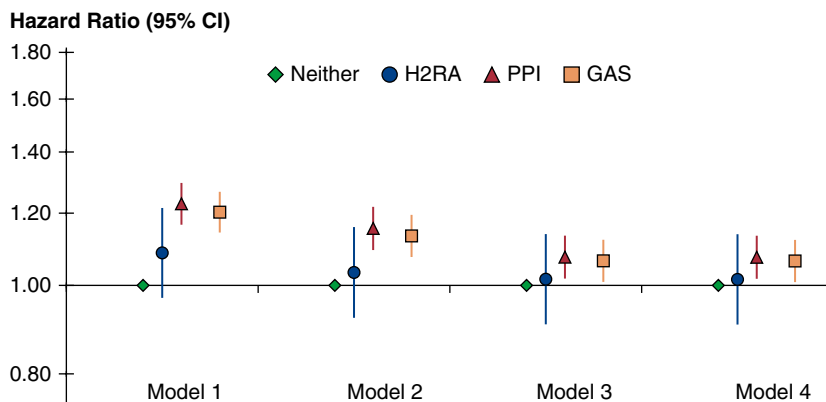
disease,<sup>27</sup> might be facilitated by GAS, resulting in bacterial translocation from the gut into the peritoneal cavity.<sup>10,28</sup> Bacterial overgrowth might occur more easily in patients using PPI, which is associated with stronger acid suppression than H2RA.<sup>10,23</sup>

Previous studies have reported the association between GAS and enteric peritonitis.<sup>11–13</sup> A meta-analysis of six nonrandomized studies involving 829 PD patients showed that GAS increased the odds of enteric peritonitis (odds ratio [OR] 1.27, 95% CI, 1.02 to 1.57). When stratified according to medication use, H2RA but not PPI use had increased odds of enteric peritonitis (OR 1.40, 95% CI, 1.01 to 1.93 and OR 1.13, 95% CI, 0.72 to 1.77, respectively). All-cause peritonitis was not evaluated in this

meta-analysis.<sup>11</sup> The main contributing study was a single-center observational cohort of Perez-Fontan *et al.*, describing 578 episodes of peritonitis in which a 33% increased risk of a first episode of enteric peritonitis was observed among GAS users. However, no association was found between all-cause peritonitis and GAS use.<sup>12</sup> Nessim *et al.* (also included in the meta-analysis) reported a case-control study of 228 peritonitis episodes. In stratified analyses, H2RA use but not PPI was associated with overall enteric peritonitis risks (as compared with nonenteric peritonitis).<sup>13</sup>

Similar to previous studies, our data showed that the association with enteric peritonitis appeared to be stronger among H2RA users, suggesting possibly that H2RA and



**A Association between GAS and peritonitis****B Association between GAS and mortality****C Association between GAS and mortality or peritonitis**

**Figure 3. Clinical outcomes by GAS prescription—results of progressive adjustment.** Outcomes shown are (A) peritonitis [ $n=22,287$  patients,  $n=4063$  events], (B) mortality [ $n=23,487$  patients;  $n=3482$  events], or (C) the composite of peritonitis or mortality. In all models, 6% of patients were prescribed H2RA, 25% PPI, 69% neither. Model 1 adjusted for patient age, sex, Black race, PD vintage, PD modality; model 2 adjusted for model 1+12 comorbidities; model 3 adjusted for model 2+serum albumin, 24-hour urine volume, potassium, and magnesium; model 4 adjusted for model 3+GI comorbidities. The estimate for GAS overall was estimated from a separate model. CI, confidence interval; GAS, gastric acid suppressants; GI, gastrointestinal; PD, peritoneal dialysis.

PPI may have differential effects on bowel flora composition and overgrowth.<sup>13</sup>

Unlike our study, other studies have demonstrated an association between GAS and all-cause peritonitis. Possible mechanisms include immune system alterations mediated

by GAS, by reducing neutrophil functions and decreasing production of proinflammatory cytokines and natural killer cell activity.<sup>10</sup> These impaired functions of the immune cells can potentially be involved in the increased incidence of infectious diseases among some GAS users and may be

**Table 2. Risk of peritonitis by GAS and causative organism classification**

Organism	No. of Events	GAS	H2RA	PPI
Gram positive <sup>a</sup>	1013	1.15 (1.01 to 1.31)	1.16 (0.88 to 1.53)	1.15 (1.00 to 1.32)
Gram negative	496	1.29 (1.05 to 1.57)	1.68 (1.11 to 2.54)	1.24 (1.01 to 1.53)
Culture negative	844	1.20 (1.01 to 1.42)	0.85 (0.56 to 1.28)	1.26 (1.06 to 1.51)
Fungal	47	1.21 (0.62 to 2.38)	2.66 (0.94 to 7.54)	1.03 (0.48 to 2.20)
Polymicrobial	159	1.20 (0.86 to 1.69)	1.08 (0.46 to 2.53)	1.22 (0.87 to 1.72)
Enteric <sup>b</sup>	624	1.23 (1.03 to 1.48)	1.70 (1.16 to 2.50)	1.18 (0.98 to 1.41)
Streptococcal species	311	1.47 (1.15 to 1.89)	0.81 (0.42 to 1.56)	1.56 (1.21 to 2.02)

Cox model stratified by country, US EHR source, and phase, adjusted for patient age, sex, Black race, PD vintage, PD modality, 13 comorbidities, serum albumin, potassium, magnesium, and 24-hour urine volume (model 4). GAS, gastric acid suppressants; H2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor.

<sup>a</sup>Includes Streptococcal species.

<sup>b</sup>Including Enterobacteriaceae, *Enterococcus* spp., and enteric anaerobes.

responsible for the trend to overall higher risk of peritonitis we observed with GAS.<sup>29</sup> A case-control study of 120 patients suggested an increased risk of all-cause first episode of peritonitis among patients on H2RA but not PPI in a multivariable analysis. No association was found between GAS and enteric peritonitis.<sup>14</sup> Maeda *et al.*, in a single-center retrospective study, described a higher all-cause peritonitis risk among users of PPI but not H2RA.<sup>16</sup> Although numbers were small, there was no difference in the distribution of Gram-positive or Gram-negative bacteria between PPI users and nonusers.

We found a particularly increased risk of streptococcal peritonitis among GAS users. A recent study evaluating peritonitis risks after gastroscopy in PD patients found higher postgastroscopy peritonitis rates among H2RA users compared with nonusers (9.4% versus 2.9%,  $P = 0.01$ ) but not PPI users (3.1% in PPI users versus 5.2% in non-PPI users,  $P = 0.29$ ).<sup>15</sup> Most of the organisms cultured in this study were enteric in origin (Gram-negative or *Enterococcus faecalis*); however, one quarter of peritonitis episodes were Gram-positive organisms from oral flora (*salivarius*, viridans streptococci, and alpha-hemolytic *Streptococcus*), postulated to be the result of transient bacteremia because of the endoscope passing through the patient's oral cavity. A possible explanation may be the increased growth of Gram-positive bacteria in the upper GI flora and oral cavity among PPI users, such as *Streptococcus* and other oral commensal flora.<sup>23,26</sup> This may also be a potential mechanism of a higher purported risk of community-acquired pneumonia among PPI users.<sup>30-32</sup> Taken together, the above may explain the higher risks of peritonitis in our study due to *Streptococcus* species.

We also observed an increased risk of mortality among PPI users. Previous studies have reported higher all-cause mortality<sup>33-35</sup> and CV risk<sup>36</sup> with PPI use in the general population. A meta-analysis found an association between PPI use and risk of all-cause mortality among HD patients.<sup>37</sup> A similar association was found in a retrospective study among PD patients in China. PPI users had a 47% higher risk of all-cause mortality and 80% more CV events.<sup>38</sup> The mechanism for higher risk of death and CV morbidity are poorly understood but may include occurrence of adverse effects, such as infections, osteoporosis and fractures, hypomagnesemia, or reduced efficacy

of some antiplatelet therapy in the context of drug-drug interactions.<sup>37,38</sup> PPIs were also found *in vivo* to affect markers of endothelial health.<sup>38</sup> However, confounding by indication can be a significant limitation, and the risks of peritonitis and mortality with PPI use across studies might be a marker of comorbidity and frailty among PPI users.

Guidelines have been developed to help clinicians decide when and how to stop PPI in the general population.<sup>39,40</sup> However, deprescribing PPI in dialysis patients is more challenging. In a single-center quality improvement study to decrease polypharmacy in HD patients, one third of the patients returned to PPI use after being deprescribed.<sup>8</sup> In another single-center interventional study stopping PPI and H2RA use, almost 50% restarted treatment because of gastroesophageal reflux, and 10% of the study participants had GI bleeding.<sup>9</sup> Clinicians should be aware of the possible higher risk of peritonitis among patients using GAS and regularly reassess treatment indications balanced against withdrawal risks.

Our study has several limitations. As with any observational analysis, we cannot fully account for unmeasured confounders and confounding by indication of GAS use may still exist. In addition, large observational studies are limited by the inability to conduct medication reconciliation. We could not evaluate the impact of dosing as PPI and H2RA doses were not available and could not capture start dates of GAS initiation before study enrollment introducing a possible prevalence use bias and potentially underestimate the risk of GAS use on patient outcomes. We partially addressed this concern considering subgroup analyses by PD vintage which yielded similar results even among those who were receiving GAS from the onset of PD. Furthermore, sensitivity analyses censoring baseline nonusers at treatment initiation and censoring baseline users at treatment discontinuation did not affect our findings. Despite concerns of prevalent user bias, a differential effect of GAS use on organism-specific peritonitis risks was demonstrated among H2RA and PPI users.

Of note, the missingness of urine volume was 43%, possibly biasing the results. However, missing data were imputed by the chained-equations method, and models were fitted separately for each imputed dataset. As long

as the data are missing at random, multiple imputation performs well at 50% missingness.

We found lower H2RA use versus PPI use. Differential effects between the two GAS may have been limited by reduced power because of fewer H2RA users. Low H2RA use is reflective of the contemporary nature of our data that decreased our power to detect other effects of H2RA on peritonitis risks. We did not include data regarding the use of nonsteroidal anti-inflammatory drugs because most are over-the-counter without prescription information, and consumption cannot be easily monitored.

Notwithstanding these limitations, we used a rich, multivariable data source and large sample size, across a diverse group of countries. To reduce confounding by indication, comprehensive model adjustments were done to include all relevant demographic data and reported comorbidities. Furthermore, sensitivity analyses were performed for particular subgroups of users yielding similar results.

In conclusion, GAS use was not associated with higher risks of first episode of all-cause peritonitis, but a significant association was found between GAS and PPI use and streptococcal peritonitis and between GAS and H2RA use and enteric and Gram-negative peritonitis. Higher mortality risk was seen among PD patients prescribed GAS. Gastric acid suppression therapy should be individualized to the patient's medical history and reevaluated periodically. Future studies assessing if deprescribing GAS in patients receiving PD has a measurable effect on reducing peritonitis rates, other infection-related risks, and mortality without increasing GI bleeding-related risks.

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#### Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

#### Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/KN9/A414>.

**Supplemental Table 1.** Peritonitis organism classifications.

**Supplemental Figure 1.** Sensitivity analysis with censoring baseline nonusers at treatment initiation and baseline users at treatment discontinuation.

**Supplemental Figure 2.** Association between gastric acid suppression use and peritonitis, subgroup analysis. Cox model stratified by country, US EHR source, and phase, adjusted for patient age, sex, Black race, PD vintage, PD modality, 13 comorbidities, serum albumin, 24-hour urine volume, potassium, and magnesium.

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