Treatment with proton pump inhibitors increases the risk of secondary infections and ARDS in hospitalized patients with COVID-19: coincidence or underestimated risk factor?

Dear Sir,

In December 2019, several cases of pneumonia of unknown origin have been reported in China, and later, SARS-CoV2 was identified as the causative pathogen for coronavirus disease 2019 (COVID-19) [1]. In some cases of COVID-19, the clinical courses are more severe and may be aggravated by secondary infections and the development of an acute respiratory distress syndrome (ARDS) with a high morbidity and mortality [1]. However, risk factors for severe clinical courses including patients' medication are poorly described. Proton pump inhibitors (PPI) play an important role in the treatment of acid-related disorders. As a result of their high efficacy, PPIs have become one of the most commonly prescribed agents. However, PPIs may trigger the development of pneumonia [2] due to the reduced gastric acid production with subsequent bacterial overgrowth in the upper gastrointestinal tract and microaspiration with following colonization of the pneumonia [2]. Therefore, we hypothesized that PPI treatment may also be a potential risk factor for the development of secondary infections and of ARDS in hospitalized patients with COVID-19.

In total, 152 patients with confirmed SARS-Cov-2 infection were included in the analysis (Figure S1). Baseline characteristics are summarized in Table 1. Sixty-two patients (40.8%) received regular treatment with PPI. Importantly, in 30 patients (48.4%), no clear reason for the PPI intake was detectable in the medical records of the patients and during assessment of patients' medical history. Forty-eight patients (31.6%) presented with a secondary infection during hospitalization. In patients with PPI treatment, 30 of 62 patients (48.4%) presented with secondary infection compared to 11 of 90 patients (20.0%) without PPI treatment ($P < 0.001$, Table 1) indicating that PPI treatment is a significant risk factor for the

[Correction added on 23 July 2020, after first online publication: The percentage, (48.4%)" has been corrected to (27.4%)" in the preceding sentence.]

development of secondary infections in patients with SARS-CoV-2 infection. After adjusting for other risk factors, especially for other predisposing comorbidities, PPI treatment remained a significant predictive factor for development of secondary infection (OR 2.37 [01.08–5.22], $P = 0.032$, Table S2). Moreover, gastroesophageal reflux disease also emerged as a significant independent predictive factor of secondary infection (OR 6.40 [1.50–35.51]; $P = 0.034$) underlining the role of microaspiration in the pathogenesis of secondary infection in these patients.

Further, PPI-treated patients developed ARDS in 17 of 62 patients (27.4%) compared to 11 of 90 patients (12.2%) without PPI treatment ($P = 0.020$, Table 1). However, development of ARDS was strongly associated with the presence of a secondary infection as only two patients (1.9%) without a secondary infection developed ARDS compared to 26 patients (54.2%) with confirmed secondary infection ($P < 0.001$). In summary, PPIs have an indirect effect on ARDS development by triggering secondary infection. In accordance with the increased risk of a secondary infection and consecutive development of ARDS, PPI-treated patients showed a significantly higher index mortality (19.4% vs. 5.6%, $P = 0.010$, Table 1).

Our hypothesis was driven by previous studies showing that PPI may lead to a higher susceptibility for infectious complications such as development of pneumonia [3]. Importantly, these studies that analysed the effect of PPI treatment on the development of pneumonia showed conflicting results [3]. However, we were able to show that PPI-treated patients with COVID-19 presented more often with secondary infections compared to patients without PPI treatment. Importantly, this effect remained statistically significant after adjusting for other possible risk factors. We also observed that secondary infections were strongly associated with the development of ARDS indicating an indirect negative impact of PPI treatment on the development of ARDS. In line with

Table 1. *Characteristics of study patients stratified according to treatment with proton pump inhibitors*

Characteristics	All patients n = 152	Non-PPI-intake n = 90	PPI intake n = 62	*P* value
Baseline data at hospital admission				
Gender				0.067
Male	86 (56.6)	45 (50.0)	41 (66.1)	
Female	66 (43.4)	45 (50.0)	21 (33.9)	
Age [years]	65 ± 17	61.9 ± 17	70 ± 17	0.004
Comorbidity				
Any coexisting diseases	104 (68.4)	55 (61.1)	49 (79.0)	0.022
Adipositas	53 (34.9)	34 (37.8)	19 (30.6)	0.391
Diabetes mellitus	44 (28.9)	28 (31.1)	16 (25.8)	0.586
Coronary heart disease	36 (23.7)	13 (14.4)	23 (37.1)	0.002
Congestive heart disease	41 (27.0)	17 (18.9)	24 (38.7)	0.009
Arterial hypertension	48 (31.6)	19 (21.1)	29 (46.8)	0.001
Liver disease	6 (3.9)	2 (2.2)	4 (6.5)	0.226
Cerebrovascular disease	20 (13.2)	10 (11.1)	10 (16.1)	0.465
Pulmonary disease	21 (13.8)	10 (11.1)	11 (17.7)	0.339
Renal disease	29 (19.1)	9 (10.0)	20 (32.3)	0.001
Cancer	33 (21.7)	20 (22.2)	13 (21.0)	0.999
Immunosuppressive treatment	17 (11.2)	5 (5.6)	12 (19.4)	0.010
Laboratory parameters[a]				
White blood count [ths μL^{-1}]	7.6 ± 5.1	7.2 ± 4.9	8.2 ± 5.2	0.116
Ferritin [ng mL^{-1}]	1108 ± 1261	1007 ± 1215	1234 ± 1318	0.595
C-reactive protein [ng L^{-1}]	122.1 ± 112.5	117.3 ± 118.5	128.9 ± 104.2	0.233
Procalcitonin [ng mL^{-1}]	1.81 ± 5.61	1.00 ± 4.69	2.89 ± 6.55	<0.001
Interleukin-6 [pg mL^{-1}]	358.3 ± 1736.7	134.2 ± 273.9	682.9 ± 2680.7	0.025
PPI treatment				
Kind of PPI				
Pantoprazole			52 (83.9)	
Esomeprazole			6 (9.7)	
Omeprazole			4 (6.5)	
Dose of PPI[b]				
20 mg per day			3 (4.8)	
40 mg per day			54 (87.1)	
80 mg per day			5 (8.1)	
Indication for PPI treatment				
Gastric ulcer			1 (1.6)	

these findings, index mortality was also higher in patients with PPI treatment.

A potential direct mechanism that links PPI treatment to the development of secondary infection is that PPI effectively suppresses gastric acid production with the result of increased gastric microbiota and small intestine bacterial overgrowth [4].

Indeed, it has been shown that microaspiration leads to bacterial colonization of the lung. Our analyses support this hypothesis as GERD was significantly associated with the development of secondary infections which was independent of PPI treatment. Further, there is growing evidence that suggests that PPI may also modulate immune responses by inhibiting neutrophil function with a

Table 1 (*Continued*)

Characteristics	All patients $n = 152$	Non-PPI-intake $n = 90$	PPI intake $n = 62$	*P* value
GERD			9 (14.5)	
NSAID/aspirin/prednisolone intake			22 (35.5)	
Unclear			30 (48.4)	
Outcome				
Secondary infection	48 (31.6)	18 (20.0)	30 (48.4)	<0.001
ARDS development	28 (18.4)	11 (12.2)	17 (27.4)	0.020
Index mortality	17 (11.2)	5 (5.6)	12 (19.4)	0.010

ARDS, acute respiratory distress syndrome; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

[a]Inflammatory parameters (C-reactive protein, procalcitonin and Il-6) are reported as maximum value within the first seven days.

[b]In patients with esomeprazole or omeprazole the dose equivalent for pantoprazole was calculated and all doses refer to pantoprazole. (20 mg omeprazole or esomeprazole is equal to 40 mg pantoprazole, 40 mg omeprazole or esomeprazole is equal to 80 mg pantoprazole).

significant anti-inflammatory activity [5]. Recently, it has been shown that the histamine 2-receptor antagonist famotidine was significantly associated with reduced risk of death or intubation in patients with COVID-19. This may be explained by reduced cytokine release and probably antiviral efficacy. In this study, PPI treatment showed no beneficial effects, but a hazard ratio > 1 was reported indicating a possible negative impact [6]. Therefore, a PPI specific effect mediated by anti-inflammatory activity may explain the negative effect compared to famotidine.

We have to acknowledge several limitations of our retrospective study. First, we only included patients who were hospitalized due to COVID-19. Patients who were treated in the outpatient unit and received follow-up by their homecare physicians were not included in our analyses. However, we decided to focus only on hospitalized patients as these patients are of special interest due to their severe course of disease. Further, due to the retrospective design, it was often difficult and in many cases not possible to assess the duration of PPI treatment before hospitalization due to COVID-19. Therefore, we are not able to analyse the effect of the duration of PPI treatment on the outcome of SARS-CoV2-infected patients.

However, with these limitations in mind, our data indicate that PPI treatment may be a negative predictive factor for development of secondary infections and consecutive ARDS in patients with COVID-19. Due to the severe courses of COVID-19,

PPI treatment should be assessed carefully. Importantly, our findings may not be generalized until external validation has been performed and to independently confirm that PPI treatment is a risk factor and not just a coincidental finding.

Conflict of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study flow chart of the included patients.

Table S1. Characteristics and definitions of suspected and confirmed secondary infections.

Table S2. Baseline characteristics of study patients stratified according to development of secondary infections.