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CLINICAL INVESTIGATION

A Multinational Randomized Trial of Mega-Dose Esomeprazole as Anti-Inflammatory Agent in Sepsis

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OBJECTIVES: Proton pump inhibitors have dose-dependent immunomodulatory effects. We tested the hypothesis that mega-dose esomeprazole therapy would reduce organ dysfunction in patients with sepsis or septic shock.

DESIGN: A multinational, randomized, double-blind, placebo-controlled clinical trial.

SETTING: Seventeen ICUs or emergency departments in three countries.

PATIENTS: Adult patients with sepsis or septic shock.

INTERVENTIONS: Mega-dose (1024 mg) esomeprazole or placebo over a 72-hour period.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was mean daily Sequential Organ Failure Assessment (SOFA) score to day 10. Secondary outcomes included antibiotics-free days, ICU-free days at day 28, and all-cause mortality. We also conducted a mechanistic study of the in vitro effects of esomeprazole in sepsis. We randomized 307 patients and assigned 148 to esomeprazole and 159 to placebo. Mean age was 71 years; 166 patients (54%) had septic shock and median SOFA score at randomization was 7. The median mean daily SOFA score in the first 10 days post-randomization was 5 (interquartile range [IQR], 3–9) in the esomeprazole group and 5 (IQR, 3–8) in the placebo group (risk difference, 0.1; 95% CI, −0.8 to 1.0; $p > 0.99$). No differences were observed in secondary outcomes. Monocytes isolated from patients' peripheral blood and activated with a toll-like receptor agonist exhibited a pro-inflammatory phenotype, which was not affected by esomeprazole therapy.

CONCLUSIONS: Among patients with sepsis or septic shock, mega-dose esomeprazole did not reduce organ dysfunction or other patient-related or biological secondary outcomes.

KEYWORDS: critical care; esomeprazole; proton pump inhibitors; sepsis; septic shock

Sepsis is characterized by a dysregulated host response to infection (1) and is a global healthcare challenge due to its increasing incidence (2, 3). Although incompletely understood, hyperinflammation plays a pivotal role in its pathogenesis and clinical course (4, 5).

Proton pump inhibitors (PPIs) are commonly used to suppress gastric acid secretion (6, 7) and are generally considered safe (8). However, hypochlorhydria from both short- and long-term use may increase the risk of infections and the development of *Clostridium difficile* associated diarrhea (9, 10). PPIs can also cause vitamin B12 deficiency due to cobalamin malabsorption, potentially leading to neuropsychiatric and hematologic

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KEY POINTS

Question: Does an early administration of mega-dose esomeprazole reduce the severity of organ dysfunction among patients with sepsis and septic shock?

Findings: In this multinational randomized clinical trial enrolling 307 patients with sepsis and septic shock, early administration of mega-dose esomeprazole, compared with placebo, did not reduce median mean daily Sequential Organ Failure Assessment score in the first 10 days post-randomization (5 [interquartile range (IQR), 3–9] in the esomeprazole group vs. 5 [IQR, 3–8] in the placebo group).

Meaning: Early administration of mega-dose esomeprazole did not reduce organ dysfunction among patients with sepsis and septic shock.

complications (9, 10). Additionally, evidence is inconclusive regarding PPIs' potential interference with clopidogrel activation (9, 11, 12).

The usual PPI dosage varies between prophylactic (20 mg daily) or therapeutic use (up to 80 mg loading dose followed by 8 mg/hr by continuous infusion for 3 d) (13, 14). Beyond gastric acid suppression, preclinical in vivo studies suggest PPIs reduce pro-inflammatory mediators expression, protect against acute systemic inflammation, increase vascular repair, reduce mortality, and improve long-term cross-tolerance (15–19). Very high-doses esomeprazole demonstrated mortality reduction in murine models of endotoxic shock (15), with mice also developing a reduced inflammatory response upon reexposure to sepsis-inducing agents (15). PPIs may, therefore, suppress excessive immune activation, prevent secondary sepsis-induced immunological activation, and potentially reduce organ dysfunction.

Accordingly, we designed the PPI-SEPSIS trial to test the hypothesis that early administration of mega-dose esomeprazole would reduce organ dysfunction in terms of mean daily Sequential Organ Failure Assessment (SOFA) score to day 10, single organ failure severity, antibiotics-free days, ICU-free days at day 28, and all-cause mortality among patients with sepsis and septic shock. In addition, we explored in vitro PPIs' anti-inflammatory effects in monocytes from septic patients.

MATERIALS AND METHODS

Trial Design

PPI-SEPSIS was a multinational, randomized, double-blind, placebo-controlled clinical trial conducted in 17 centers in Italy, Russia, and Kazakhstan and was registered on ClinicalTrials.gov (NCT03452865). The trial protocol (16) was conducted in accordance with the principles of the Helsinki Declaration of 1975 and was approved by the Ethics Committee of San Raffaele Hospital, as well as by Ethical Committees of all participating centers (**Table S5**, https://links.lww.com/CCM/H731).

Participants and Randomization

Adult patients admitted to the emergency department (ED) or the ICU with a confirmed diagnosis of sepsis or septic shock made within less than 36 hours from first evaluation were eligible for inclusion. Sepsis and septic shock were defined according to the Sepsis-3 definitions (1). Key exclusion criteria included patients with little chance of survival, defined by a Simplified Acute Physiology Score

II score greater than 65 points (**Table S2**, https://links.lww.com/CCM/H731) (20), patients meeting sepsis criteria for greater than 36 hours, and patients treated with drugs with known strong interactions with esomeprazole (**Table S3**, https://links.lww.com/CCM/H731). **Table S4** (https://links.lww.com/CCM/H731) shows the complete list of inclusion and exclusion criteria.

Informed consent was obtained from patients or their legally responsible representatives as per local ethical committee instructions.

Randomization was performed by computer-based permuted block design (block sizes of 20 or 40), stratified by center, with a 1:1 allocation ratio for receiving mega-dose esomeprazole or placebo. After randomization, only dedicated pharmacists and trial nurses received automated treatment assignment via email; they were not involved in data collection or analysis. Patients, treating physicians, study investigators, and statisticians were blinded to treatment allocation.

Data collection and outcome assessment were performed by trained personnel who did not participate in patient care and were blinded to group allocation.

Interventions

Patients were randomly assigned to receive a blinded infusion of either mega-dose esomeprazole or equivalent volume saline as boluses and continuous infusion. All patients received the best available standard of care for sepsis according to the latest Surviving Sepsis Campaign guidelines, independently of their randomization group (1, 21).

Patients in the esomeprazole group received an 80 mg bolus followed by continuous infusion of 12 mg/hr for 72 hours, with an additional 80 mg bolus at 12 hours of IV esomeprazole (total dose: 1024 mg). Drug administration was stopped after 72 hours (3 d) or discontinued in case of safety reasons or consent withdrawal. Esomeprazole boluses were prepared by dissolving the drug into 100 mL of saline solution and administered over 60 minutes. The continuous infusion of reconstituted esomeprazole at a concentration of 8 mg/mL was administered at a rate of 1.5 mL/hr (12 mg/hr). If clinically indicated, unblinded 40 mg esomeprazole was allowed for stress ulcer prophylaxis.

Daily peripheral blood samples were collected at baseline and for 10 days post-randomization. Additional blood tests and cultures were performed as needed. Blood samples from both groups were also used for monocytes isolation and in vitro tests, with further details provided in the **Supplemental Online Content** (In vitro studies section, https://links.lww.com/CCM/H731).

Outcome Measures

The primary outcome of the study was organ dysfunction measured as the mean daily SOFA score during the first 10 days (**Table S1**, https://links.lww.com/CCM/H731).

Secondary outcomes were antibiotics-free days at 28 days post-randomization, single organ failure severity measured via single SOFA score variables, ICU-free days at 28 days post-randomization, and death from any cause at day 28, 60, and 90 post-randomization. Deaths within the initial 28 days were assigned zero ICU-free days and zero antibiotic-free days at day 28. A post hoc secondary outcome was the incidence of *C. difficile* infection.

We investigated the biological effects of esomeprazole in vitro. In 26 patients (esomeprazole = 14, placebo = 12), we measured inflammatory markers and oxidative status in monocytes; correlation between redox stress and altered cytokine production; effect of esomeprazole on redox stress and cytokine production in monocytes; changes of redox stress; and cytokine production in monocytes (Supplemental Online Content, https://links.lww.com/CCM/H731).

While safety was not a predefined secondary outcome, all adverse events were systematically recorded in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (22) to provide a comprehensive safety profile of PPIs in this population.

Data Collection

Data were stored via a web-based case report form. On day 0, demographic, clinical, and laboratory data were collected.

Demographic, biometric, and clinical data (vital signs, laboratory, ventilation, and vasopressor) were collected on day 0 before the first administration of the study drug. For the primary outcome, SOFA scores were

recorded daily for 10 days or until discharge or death. Patients were monitored daily for 28 days or until discharge/death and followed up (on site if they were still admitted to the hospital or by means of a telephone follow-up) at days 28, 60, and 90 to assess survival.

Statistical Analysis

A 0.5 difference in SOFA score was associated with an estimated 1.4–1.7-fold increase in mortality (23–26). The study aimed for 286 patients to achieve 80% power in detecting a 0.5-point difference in mean daily SOFA score, assuming a 1.5 SD (23). To account for loss to follow-up, 21 extra patients were enrolled, totaling 307 participants. An independent data and safety monitoring committee of clinical trial experts and epidemiologists conducted a planned interim analysis after 150 patients completed 28-day follow-up. Responsibilities and procedures of the committee were established before the study initiation. As no safety concerns emerged, the trial proceeded unchanged. Investigators remained blinded to interim results.

Dichotomous data were analyzed using the chi-square test or Fisher exact test, whereas continuous variables were compared using the Mann-Whitney *U* test for nonparametric data and the *t* test for normally distributed data. Results are reported with 95% CIs, and all analyses used two-sided significance tests. Multiplicity adjustment was not applied to secondary outcomes. The statistical analysis plan was prepublished (Supplemental Online Content, https://links.lww.com/CCM/H731) (16).

Prespecified subgroup analyses included comparisons by admission type (ED vs. ICU), sepsis severity, SOFA quartiles, infection origin, gender, and active cancer status. A per-protocol analysis excluded patients who did not receive the assigned drug or failed inclusion criteria. A sensitivity analysis was conducted using only collected data to assess the robustness of our findings. A post hoc time-to-event analysis assessed death from any cause, and the hazard ratio and 95% CI were calculated and used for a stratified log-rank test.

RESULTS

Trial Population

A total of 584 patients with sepsis or septic shock admitted to the ED or ICU were screened between January 28, 2020, and May 21, 2023, with 307 randomized (148 to esomeprazole, 159 to placebo). All 307 patients were included in the primary outcome analysis (**Fig. 1**), and no patient was lost to follow-up at 90 days.

Baseline characteristics (**Table 1**) were balanced, with a median age of 71 years (interquartile range [IQR], 61–78 yr) and 64% males. The proportion of sepsis vs. septic shock was similar between groups, ensuring consistent administration of additional therapies, such as corticosteroids. However, active cancer was more frequent in the esomeprazole group, whereas cerebrovascular disease was more common in the placebo group.

The COVID-19 pandemic caused periods of low recruitment (**Fig. S1**, https://links.lww.com/CCM/H731). An infection site was identified in 58% of patients (mainly respiratory, gastrointestinal, and genitourinary).

Study Drug Administration

Patients in the experimental group received a median esomeprazole dose of 1075 mg. Unblinded PPI prophylaxis for stress ulcer was administered to 272 patients (88.6%), with similar use in both groups (89.2% in the esomeprazole group vs. 86.8% in the placebo group). The median (IQR) duration of mega-dose esomeprazole or placebo treatment was 3 (3–3) (**Table 2**). Study drug administration was not interrupted and unblinding occurred in only 4% of cases due to error.

Primary Outcome

At 10 days, there was no difference in the median mean daily SOFA score: 5 (IQR, 3–10) in the mega-dose esomeprazole and 5 (IQR, 3–9) in the placebo groups (risk difference [RD], 0.1; 95% CI, –0.8 to 1.0; $p > 0.99$). There was no difference in the mean daily SOFA for the first 10 days (**Fig. S2**, https://links.lww.com/CCM/H731).

Secondary Outcomes

There was no difference in single organ failure severity measured via single mean daily SOFA score variables over 10 days (**Table 3**).

At day 28, the median antibiotic-free days were 15 (IQR, 0–21) in the mega-dose esomeprazole group vs. 13 (IQR, 0–21) in the placebo group ($p = 0.62$), and ICU-free days were 7 (IQR, 0–22) vs. 8 (IQR, 0–21),

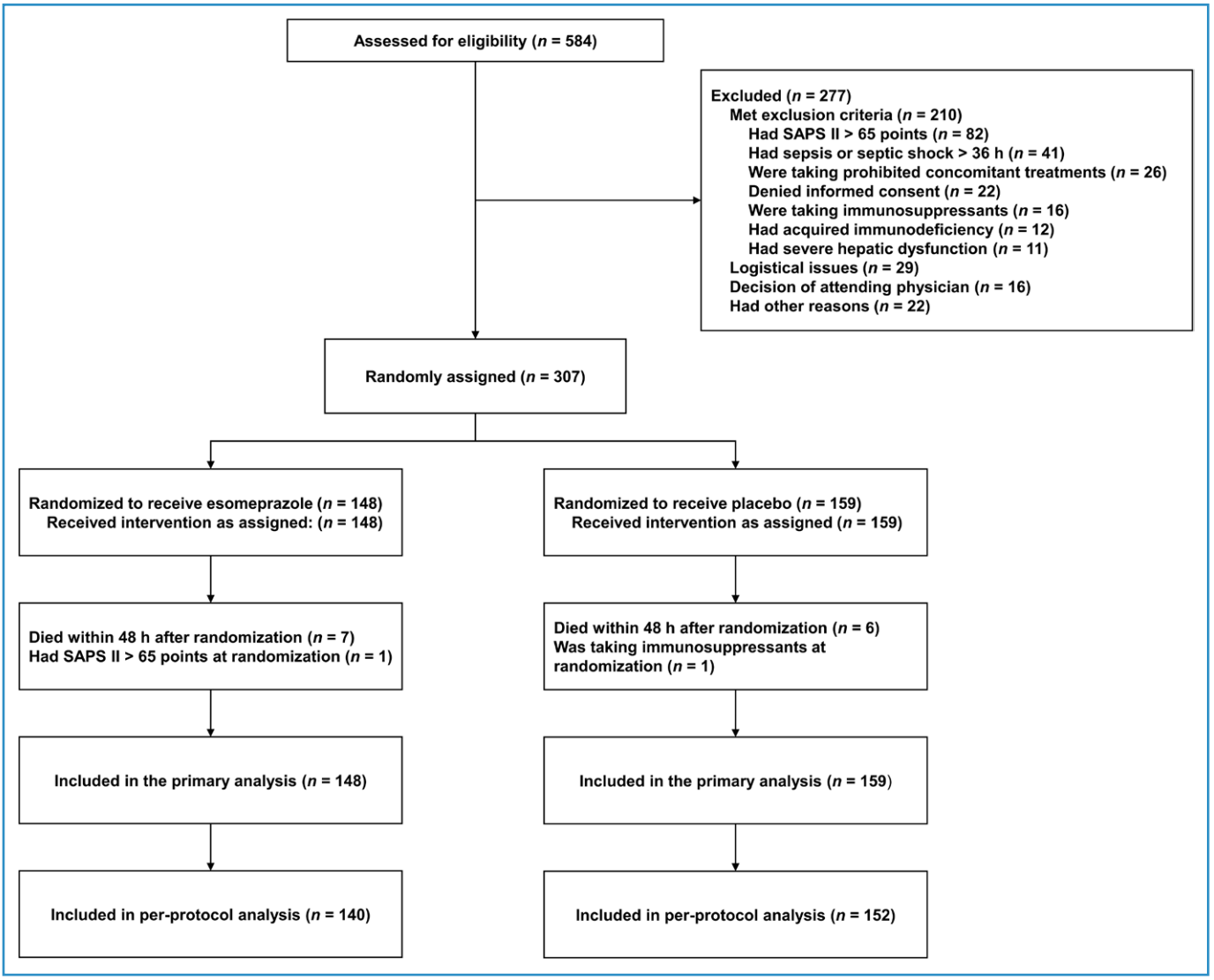

Figure 1. Assessment, exclusions, and randomization for the PPI-SEPSIS trial. SAPS II = Simplified Acute Physiology Score II.

respectively ($p = 0.91$). Length of hospital stay was 15 days (IQR, 9–27 d) vs. 17 days (IQR, 11–36 d; $p = 0.18$). *C. difficile* infection rates were similar between groups.

All-cause mortality at 28 days was 25% in the mega-dose esomeprazole group and 20% in the placebo group (RD, 4.9; 95% CI, –4.5 to 14.2; $p = 0.31$). Kaplan-Meier survival analysis to day 90 showed no difference between groups (**Fig. S3**, https://links.lww.com/CCM/H731). No adverse events or allergic reactions related to the study drug were reported.

The absence of significant differences across all outcomes suggests no impact on the findings.

Secondary Analysis for the Primary Outcome

Subgroup analyses confirmed the primary analysis (**Fig. S4**, https://links.lww.com/CCM/H731). Univariate and multivariate analyses for the association of baseline variables with 90 days mortality showed no significant effect for mega-dose esomeprazole (**Tables S5** and **S6**, https://links.lww.com/CCM/H731). Per-protocol analysis and sensitivity analysis (including only data without imputation) were consistent with the findings of the primary analysis (**Tables S7** and **S8**, https://links.lww.com/CCM/H731). Trial center stratification revealed no significant interaction (**Fig. S5**, https://links.lww.com/CCM/H731).

In Vitro Results

Monocytes from patients at baseline, activated in vitro with toll-like receptor agonist, exhibited downregulated pro-inflammatory cytokines secretion, reduced levels of anti-inflammatory cytokines, and altered redox status

TABLE 1.
Baseline Characteristics

Variable	Mega-Dose Esomeprazole Group ($n = 148$)	Placebo Group ($n = 159$)
Age, yr, median (IQR)	72 (64–77)	69 (57–78)
Female, sex, *n* (%)	53 (35.8)	58 (36.5)
Age ≤ 55 yr	5 (26.3)	11 (33.3)
Body mass index[a,b], kg/m^2, median (IQR)	26.2 (24–29)	26.5 (24–30)
Sepsis, *n* (%)	77 (52.0)	89 (56.0)
Septic shock, *n* (%)	71 (48.0)	70 (44.0)
Race or ethnic group, *n* (%)		
White	144 (97.3)	152 (95.6)
Asian	2 (1.4)	3 (1.9)
Hispanic	2 (1.4)	3 (1.9)
African American	0 (0.0)	1 (0.6)
Comorbidities[b], *n* (%)		
Hypertension	94 (63.9)	101 (63.9)
Dyslipidemia	49 (33.3)	61 (38.6)
Diabetes	46 (31.3)	39 (24.7)
Peripheral vascular disease	26 (17.7)	23 (14.6)
Coronary artery disease	24 (16.3)	25 (15.8)
Other chronic disease	35 (23.8)	48 (30.4)
Chronic kidney disease	19 (12.9)	24 (15.2)
Chronic obstructive pulmonary disease	20 (13.6)	22 (14.0)
Active cancer	19 (12.9)	11 (7.0)
Cerebrovascular disease	8 (5.4)	23 (14.6)
Congestive heart failure	13 (8.8)	17 (10.8)
Hepatic impairment	1 (0.7)	1 (0.6)
Hematologic malignancy	2 (1.4)	5 (3.2)
Connective disease	7 (4.8)	6 (3.8)
Asthma	2 (1.4)	4 (2.6)
Hepatic cirrhosis	6 (4.1)	12 (7.7)
HIV infection	0 (0.0)	0 (0.0)
Randomized in the emergency department, *n* (%)	44 (29.7)	45 (28.3)
Randomized in the ICU, *n* (%)	104 (70.3)	114 (71.7)

IQR = interquartile range.

[a]Calculated as weight in kilograms divided by height in meters squared.

[b]The proportion of missing values was < 5%.

compared with healthy controls (**Figs. S6** and **S7**, https://links.lww.com/CCM/H731). In vitro, esomeprazole (200 μM) suppressed interleukin-1β secretion and reduced reactive oxygen species production and cysteine release (**Fig. S8**, https://links.lww.com/CCM/H731).

After 72 hours of esomeprazole therapy, we observed a reduction in serum antioxidant capacity (**Fig. S9**, https://links.lww.com/CCM/H731). However, post-treatment monocytes analysis showed no significant differences between placebo

TABLE 2.
Study Drug Doses, Use of Concurrent Proton Pump Inhibitor, and Adverse Events

Variable	Mega-Dose Esomeprazole Group (*n* = 148)	Placebo Group (*n* = 159)
Median study drug dose (IQR), mg		
Day 0[a]	218 (176–316)	212 (140–316)
Day 1[b]	288 (288–368)	328 (288–368)
Day 2[c]	288 (288–288)	288 (288–288)
Day 3[d]	161 (132–223)	180 (138–240)
Median study drug dose corrected for body weight (IQR), mg/kg		
Day 0[a]	3 (2–5)	3 (2–4)
Day 1[b]	4 (3–5)	4 (3–5)
Day 2[c]	4 (3–4)	4 (3–4)
Day 3[d]	2 (2–3)	2 (2–3)
Treatment duration[e], d	3 (3–3)	3 (3–3)
Receiving concurrent proton pump inhibitor, *n* (%)	132 (89.2)	138 (86.8)
Protocol deviations, *n* (%)		
Methodological issues	4 (2.7)	6 (3.8)
Mistakes in enrollment	0 (0.0)	0 (0.0)
Minor deviations	5 (3.4)	4 (2.6)
Interruption of study product	6 (4.1)	6 (3.8)
Other protocol deviations	6 (4.1)	8 (5.1)
Consent withdrawal before administration, *n* (%)	0 (0.0)	0 (0.0)
Deaths during treatment (< 48 hr), *n* (%)	7 (4.7)	6 (3.8)
Adverse events, *n* (%)	0 (0.0)	0 (0.0)

IQR = interquartile range.
[a]Data missing from 34 and 62 subjects in the treatment and placebo group, respectively.
[b]Data missing from 33 and 58 subjects in the treatment and placebo group, respectively.
[c]Data missing from 41 and 60 subjects in the treatment and placebo group, respectively.
[d]Refers to the proportion of patients receiving continuous infusion from midnight to the end of the 72 hr.
[e]The proportion of missing values was < 5%.

and esomeprazole-treated patients when stimulated in vitro with lipopolysaccharide (**Fig. S10**, https://links.lww.com/CCM/H731).

DISCUSSION

In this double-blind, multinational, randomized controlled trial, we found no significant difference in mean daily SOFA score over 10 days between septic patients receiving mega-dose esomeprazole and patients receiving placebo. Additionally, no significant differences were observed in clinically relevant secondary outcomes and in vitro studies showed no differential monocyte response to stimulation according to treatment allocation.

Prior preclinical studies suggested that very high-dose esomeprazole increases survival in murine models of sepsis and reduces inflammation and hypoxia/reoxygenation injury (15–19, 25). Balza et al (15) hypothesized a therapeutic potential of PPIs in sepsis, with evidence administration of very high-dose esomeprazole before septic insult reduced pro-inflammatory cytokines, improved survival, and a favorable safety profile in animal models (17–19, 27, 28). In addition, studies in animal models using similar dosing regimens for short periods did not identify

TABLE 3.
Primary and Secondary Outcomes

Variable	Mega-Dose Esomeprazole Group (*n* = 148)	Placebo Group (*n* = 159)	Absolute Risk Difference (95% CI)	*p*
Primary outcome				
Median of mean Sequential Organ Failure Assessment score over 10 d[a] (IQR)	5 (3–10)	5 (3–9)	0.1 (–0.8 to 1.0)	> 0.99
Secondary outcomes				
Median of single organ failure severity[a,b] (IQR)				
CNS	0 (0–2)	0 (0–2)	0 (–0.3 to 0.3)	0.87
Cardiovascular	3 (0–4)	3 (0–4)	0.1 (–0.3 to 0.5)	0.39
Respiratory	2 (1–3)	2 (1–3)	0 (–0.2 to 0.2)	> 0.99
Coagulation	0 (0–1)	0 (0–1)	0.1 (–0.1 to 0.2)	0.76
Liver	0 (0–1)	0 (0–0)	0 (–0.1 to 0.2)	0.95
Renal function	0 (0–2)	1 (0–1)	0.1 (0.1–0.4)	0.53
Follow-up at day 28				
Median antibiotic-free days (IQR), d	15 (0–21)	13 (0–21)	0.7 (–1.6 to 3.0)	0.62
Median ICU-free days[c] (IQR), d	7 (0–22)	8 (0–21)	0.4 (–2.3 to 3.0)	0.91
Early death within 24 hr, *n* (%)	5 (3.4)	3 (1.9)	1.5 (–2.1 to 5.1)	0.49
Median length of ICU stay[c] (IQR), d	9 (4–19)	12 (4–24)	–3.4 (–8.1 to 1.3)	0.26
Median length of hospital stay[a] (IQR), d	15 (9–27)	17 (11–36)	–2.8 (–7.8 to 2.2)	0.18
Median LOS in ICU among survivors[c] (IQR), d	9 (5–16)	12 (5–24)	–2.1 (–7.9 to 3.8)	0.29
Median LOS in hospital among survivors (IQR), d	16 (10–27)	18 (12–37)	–2.8 (–8.5 to 3.0)	0.15
Readmission to ICU[a], *n* (%)	9 (6.3)	11 (7.2)	–1.0 (–6.7 to 4.7)	0.74
Clostridioides difficile infection[d], *n* (%)	2 (2.2)	3 (2.8)	–0.6 (–5.0 to 3.7)	0.77
Mortality, *n* (%)				
At 28 d	37 (25)	32 (20.1)	4.9 (–4.5 to 14.2)	0.31
At 60 d	46 (31.1)	42 (26.4)	4.7 (–5.5 to 14.8)	0.37
At 90 d	52 (35.1)	49 (30.8)	4.3 (–6.2 to 14.8)	0.42

IQR = interquartile range, LOS = length of stay.

[a]The proportion of missing values was < 5%.

[b]Measured by single mean daily Sequential Organ Failure Assessment score variables over 10 d.

[c]Data missing from 33 and 31 subjects in the treatment and placebo group, respectively.

[d]Data missing from 56 and 53 subjects in the treatment and placebo group, respectively.

Data are presented as risk difference for dichotomous outcomes and as absolute mean differences for continuous outcomes. The risk difference is calculated as the event probability in the mega-dose esomeprazole group minus the event probability in the placebo group. The absolute mean difference is calculated as the mean of the mega-dose esomeprazole group minus the mean of the placebo group. The 95% CIs presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.

harm (10). Furthermore, reports of esomeprazole overdose in humans, including doses up to 2400 mg, have shown only transient adverse effects (i.e., confusion, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth) similar to those observed at standard doses. Notably, single doses of 80 mg, equivalent to our bolus administration, were well-tolerated without complications (8).

In contrast to the abovementioned preclinical evidence, despite the administration of 1024 mg of

esomeprazole over 3 days (17 times the standard prophylactic dose), the current trial did not demonstrate clinical benefits in sepsis (13, 14). This discrepancy between preclinical and clinical findings may stem from differences in murine vs. human physiology, variations in sepsis models, or the limited post-administration effects of PPIs (29–31). While the anti-inflammatory properties of PPIs were evident in animal studies, their therapeutic impact in human sepsis remains unproven, highlighting the challenges in translating preclinical findings into clinical success (29, 32). However, the in vivo preclinical evidence provided key insights into the anti-inflammatory effects and dose-dependent benefits of PPIs, forming a rationale for further clinical investigation. Additional factors that may contribute to this discrepancy include interspecies genetic and immunological differences, which influence inflammatory cascades and drug metabolism (33, 34). Furthermore, human sepsis is a highly heterogeneous condition with diverse etiologies, comorbidities, and host responses, which are not fully replicated in animal models (35). Timing of drug administration relative to disease progression, and variability in host-pathogen interactions, may also impact therapeutic efficacy (36). These complexities highlight the need for refined translational models and personalized approaches in sepsis research.

This study is the largest clinical evaluation of mega-dose esomeprazole in the early stages of sepsis in humans. Its multinational, double-blind design enhances both external and internal validity. Strict inclusion criteria ensured that only critically ill patients in early stages of sepsis were enrolled, excluding those in the late-stage sepsis. We included patients within 36 hours of sepsis onset, unlike other trials that focused on hospital-acquired sepsis. Notably, the 1-month mortality rate in our study (22%) aligned with previous studies (37).

The trial enrolled critically ill patients in the early stages of sepsis both in ED and ICU, reflecting real-world clinical practice, where ED patients often present with severe instability and a high risk of deterioration, requiring intensive monitoring and organ support. The classification of critically ill patient is primarily determined by clinical status, including organ dysfunction severity and need for urgent intervention, rather than solely by the setting of care (38). By enrolling patients within 36 hours from sepsis onset, the study aimed to assess the potential therapeutic effect of PPIs before organ dysfunction developed (39).

We acknowledge several limitations. First, clinicians could co-administer PPIs at prophylactic doses in both groups, risking contaminating the comparator group. However, the dose used in the comparator group was much less than in the intervention group. The comparator arm reflected the standard of care, and the study drug was administered on top of it. Since prophylactic PPI use is routinely part of standard care, both groups exhibited a similarly high rate of administration (89.2% vs. 86.8%). Additionally, study drug administration could be interrupted based on clinical judgment. Second, while all patients were diagnosed with sepsis within 36 hours, there was variation in infection site, and no standardized treatment protocol was provided. Nonetheless, there were no significant differences between groups in primary infection site, and patient treatment. Third, although mean daily SOFA score is commonly used in ICU trials, mortality is a more critical endpoint and represents a competing risk in assessing organ dysfunction (40, 41). Patients who die early may have less time to develop worsening organ failure, potentially biasing treatment effect interpretation. A treatment that affects mortality can indirectly influence SOFA scores, not necessarily by altering organ function, but because fewer patients survive long enough for assessment. However, mortality was numerically higher with esomeprazole. In addition, the trial might have been underpowered to detect effects on mean SOFA score difference less than 0.5. However, given the consistent findings across all outcomes, any PPIs' impact on organ dysfunction is likely limited. The sample size estimate was based on limited available data from prior studies evaluating similar endpoints in critically ill patients, although not specifically investigating PPIs in sepsis (23). While this approach has limitations, it represented the best available data to estimate the sample size for our phase 2 trial. Nevertheless, our study remains the largest randomized controlled trial on this intervention, and the lack of effect is clear in all analyses. Sepsis and septic shock represent a continuum of severity, but inflammatory burden and treatment timing may alter PPIs' effect in these subpopulations. Therefore, we conducted predefined subgroup analyses to compare their response to PPIs, revealing no significant differences. We did not separately analyze the exact timing between sepsis/septic shock diagnosis and

treatment initiation. However, we enrolled patients within 36 hours of confirmed diagnosis to ensure a narrow therapeutic window. The SOFA score, used as the primary outcome, presents limitations due to its composite nature and risk of missing data, but there was a predefined strategy for handling missing data (reported in the statistical analysis plan). Finally, our hypothesis was rooted in preclinical evidence, which has inherent limitations when applied to human septic shock. While animal models cannot fully replicate the complexity of sepsis in critically ill adults, they remain invaluable for studying pathophysiological mechanisms and testing interventions like mega-dose PPIs under controlled conditions.

This study demonstrated that PPIs do not reduce organ failure in advanced sepsis. Future research could investigate PPIs in sepsis prevention, particularly in high-risk surgical patients (e.g., esophagectomy), to determine whether they modulate the inflammatory response and reduce sepsis incidence or severity. This study used a high-dose PPI regimen consistent with clinical practice for gastrointestinal bleeding prevention in critically ill patients. However, experimental models often use single-dose PPIs. Future research should focus on dose optimization through structured dose-finding studies. A phase 2 trial incorporating dose escalation, similar to early-phase drug development (phase 1 or 2a), could help define the most biologically active and clinically relevant dose (if any), assessing pharmacokinetics and pharmacodynamics. A phase 2b trial could then evaluate safety and preliminary efficacy before moving to larger confirmatory studies.

CONCLUSIONS

In sepsis patients, mega-dose esomeprazole did not reduce organ dysfunction (as measured by mean SOFA score over 10 d) or improve secondary outcomes, despite demonstrating in vivo immunomodulatory effects. These findings do not justify further investigation of mega-dose esomeprazole as an adjunctive treatment for sepsis.

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