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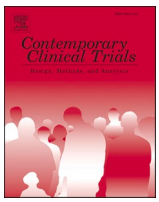

High dose esomeprazole as an anti-inflammatory agent in sepsis: Protocol for a randomized controlled trial

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ABSTRACT

Background: Sepsis is caused by dysregulated immune responses due to infection and still presents high mortality rate and limited efficacious therapies, apart from antibiotics. Recent evidence suggests that very high dose proton pump inhibitors might regulate major sepsis mediators' secretion by monocytes, which might attenuate excessive host reactions and improve clinical outcomes. This effect is obtained with doses which are approximately 50 times higher than prophylactic esomeprazole single daily administration and 17 times higher than the cumulative dose of a three day prophylaxis. We aim to perform a randomized trial to investigate if high dose esomeprazole reduces organ dysfunction in patients with sepsis or septic shock.

Methods: This study, called PPI-SEPSIS, is a multicenter, randomized, double blind, placebo-controlled clinical trial on critically ill septic patients admitted to the emergency department or intensive care unit. A total of 300 patients will be randomized to receive high dose esomeprazole (80 mg bolus followed by 12 mg/h for 72 h and a second 80 mg bolus 12 h after the first one) or equivolume placebo (sodium chloride 0.9%), with 1:1 allocation. The primary endpoint of the study will be mean daily Sequential Organ Failure Assessment (SOFA) score over 10 days. Secondary outcomes will include antibiotic-free days, single organ failure severity, intensive care unit-free days at day 28, and mortality.

Discussion: This trial aims to test the efficacy of high dose esomeprazole to reduce acute organ dysfunction in patients with septic shock.

Trial registration: This trial was registered on ClinicalTrials.gov with the trial identification NCT03452865 in March 2018.

1. Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. This condition can progress to septic shock, characterized by profound circulatory, cellular, and metabolic abnormalities, being associated with a greater risk of mortality than with sepsis alone [1]. Nowadays, sepsis still represents an elusive syndrome with high mortality rate and lack of efficacious therapies [2].

Evidence-based guidelines define a bundle of interventions that contributes to outcome improvement [3]. Despite these advances, sepsis represents a major healthcare issue and there is a huge need for drugs that can reduce morbidity and mortality in patients with sepsis and septic shock. Mortality of sepsis treated in intensive care unit (ICU) is estimated to be 42% [4]. Although the exact underlying mechanisms is not fully understood, the development and exacerbation of sepsis can be attributed to hyperinflammatory responses [2]. In addition, acidosis, which is a common finding in non-survivors septic patients, increase the release of inflammatory mediators [5].

Proton pump inhibitors (PPIs) are a widely used family of prodrugs that decrease gastric acid secretion through the inhibition of the H+/K+ adenosine triphosphatase (ATPase) enzyme system, upon activation by low pH [6,7]. Since their market release, PPIs have therefore been largely used in the treatment of peptic ulcers and reflux esophagitis, progressively eclipsing histamine H2-receptor antagonists [7,8]. The administration of PPIs was also studied in different medical fields because of their safety profile. For example, preclinical evidence supports the use of esomeprazole as novel therapeutic strategy for metastatic melanoma by modifying the acidotic environment of cancer cells [9,10]. Balza et al. hypothesized PPIs' applicability in the treatment of sepsis, since they demonstrated a selective inhibition of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) at different levels in vitro [11]. PPIs also increased survival in a murine model of endotoxic shock and esomeprazole-treated mice experienced lower mortality and inflammatory response compared to controls, when rechallenged with a sepsis-inducing agent [11].

These findings suggest that high-dose esomeprazole has immunomodulatory effects and might improve clinically relevant outcomes in patients with sepsis. Accordingly, this trial aims to evaluate esomeprazole efficacy in reducing the severity of organ failure in patients with sepsis or septic shock.

2. Methods

2.1. Study design

This is a multicenter, randomized, double blind, placebo-controlled trial investigating the effect of high dose esomeprazole administration in septic patients in terms of organ dysfunction severity. The study is registered on *clinicaltrials.gov* as NCT03452865 and Ethical Approval was obtained before the beginning of the project in each participating center (Fig. 1).

2.2. Trial population, inclusion and exclusion criteria

We plan to enroll 300 adult Emergency Department (ED) or Intensive Care Unit (ICU) patients with sepsis or septic shock, defined according to SEPSIS-3 definitions [1,12]. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. [1] Its diagnosis is established by an acute change in total Sequential Organ Failure Assessment (SOFA) score $\geq$ 2 points (Supplementary Fig. 1) from baseline, or from zero in the absence of a known baseline, consequent to infection. Septic shock is defined as sepsis plus persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) $\geq$65 mmHg and having a serum lactate level $>$ 2 mmol/L (18 mg/dl) despite adequate volume resuscitation [1,12]. Patients with little chance of survival, defined by a Simplified Acute Physiology Score (SAPS) II score $>$ 65 points (Supplementary Fig. 2) and those with sepsis for $>$36 h are excluded from the study. Table 1 shows all inclusion and exclusion criteria. Due to strong interactions with esomeprazole, patients treated with the drugs listed in Table 2 cannot be enrolled.

2.3. Recruitment and randomization

All patients who are clinically judged to be eligible for the study will be screened against inclusion and exclusion criteria, and informed consent will be obtained following the approved modality determined by the ethical committee prior to enrollment, which included deferred consent. Randomization will be performed by a computer with the use of a permuted block design. Patients will be randomized to esomeprazole versus placebo groups with a 1:1 allocation. The randomization lists are generated with a block size of 20 or 40 stratified by center. Stratifying randomization by center helps to account for potential variations or confounding factors that may be specific to each participating center.

2.4. Intervention

The experimental group will receive intravenous esomeprazole 80 mg bolus followed by continuous infusion of 12 mg/h for 72 h. After 12 h from the first bolus, patients will receive another 80 mg bolus of esomeprazole. Drug administration will be stopped after 72 h (3 days) of continuous infusion. Esomeprazole boluses will be prepared dissolving the drug into 100 ml of sodium chloride 0.9% and will be administered over 60 min. For continuous infusion, reconstituted esomeprazole at a concentration of 8 mg/ml will be injected at a rate of 1.5 ml/h (12 mg/h). Study drug infusion will be interrupted if considered necessary for patient's safety, if a clinical condition requiring the administration of any drug listed in Table 2 occurs, or if the patient or their legal representative withdraw consent for trial participation.

The control group will receive equivolume intravenous sodium chloride 0.9% in the same modalities of the intervention group (i.e., boluses and continuous infusion), without the experimental drug.

Patients can receive unblinded prescription of PPI for stress ulcer prophylaxis, if clinically indicated. All patients will receive the best available standard of care for sepsis according to latest guidelines, independently of the randomization group [13] (Fig. 2).

A web-based centralized randomization performed at the last available moment will be used to allocate subjects, in order to reduce biases. The randomization will be performed by the physician in charge of the patient. As soon as the patient is randomized, pharmacists automatically receive an e-mail containing the group allocation and instructions on how to prepare the study drug. [14] Patients, physicians, study investigators, data collectors, outcome assessors and statisticians will be unaware of group assignment for the whole duration of the trial, until database locking. Blinding is reinforced by the identical, colorless appearance of placebo and esomeprazole after syringe is prepared for administration by personnel not involved in patient's care. Considering that the study product needs multiple preparations at short time intervals, the syringe is prepared in ED and ICUs, and that patients can be enrolled (and the study product needs to be administered) 24 h a day and every day of the week, we accepted the use of vital local resources (e.g., ICU nurses not involved in the care of the patient) for preparation of the study product. [15] Data collection will be performed by blinded trained personnel who do not participate in patient care. This approach, employed within high-quality double-blind randomized trials [14,16], aligns seamlessly with the established definition of double-blind

Table 1
PPI-SEPSIS inclusion and exclusion criteria.

Inclusion criteria (All the following must be present)	Exclusion criteria (Patient is excluded if ≥1 of the following is present)
1. Age ≥ 18 years old 2. Admitted to ICU or ED 3. Sepsis* or septic shock** 4. Able to express informed consent or as requested by Ethical Committee	1. Able to express informed consent and deny it 2. Known allergy or intolerance to study drug 3. Little chance of survival, with SAPS II >65 points 4. Concomitant AIDS 5. On immunosuppressant or long-term corticosteroid therapy (>0.5 mg/kg/day of prednisone or equivalent for over 30 days) 6. Receiving lifesaving drugs known to have a strong interference with esomeprazole as stated in Table 2: *Prohibited concomitant treatments* 7. Sepsis or septic shock since over 36 h 8. Severe hepatic dysfunction 9. Ongoing pregnancy

Abbreviations: *ICU*, intensive care unit; *ED*, emergency department; *SAPS*, Simplified Acute Physiology Score; *AIDS*, acquired immunodeficiency syndrome.

* Defined as acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.

** Defined as sepsis plus persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mmHg and having a serum lactate level > 2 mmol/l (18 mg/dl) despite adequate volume resuscitation.

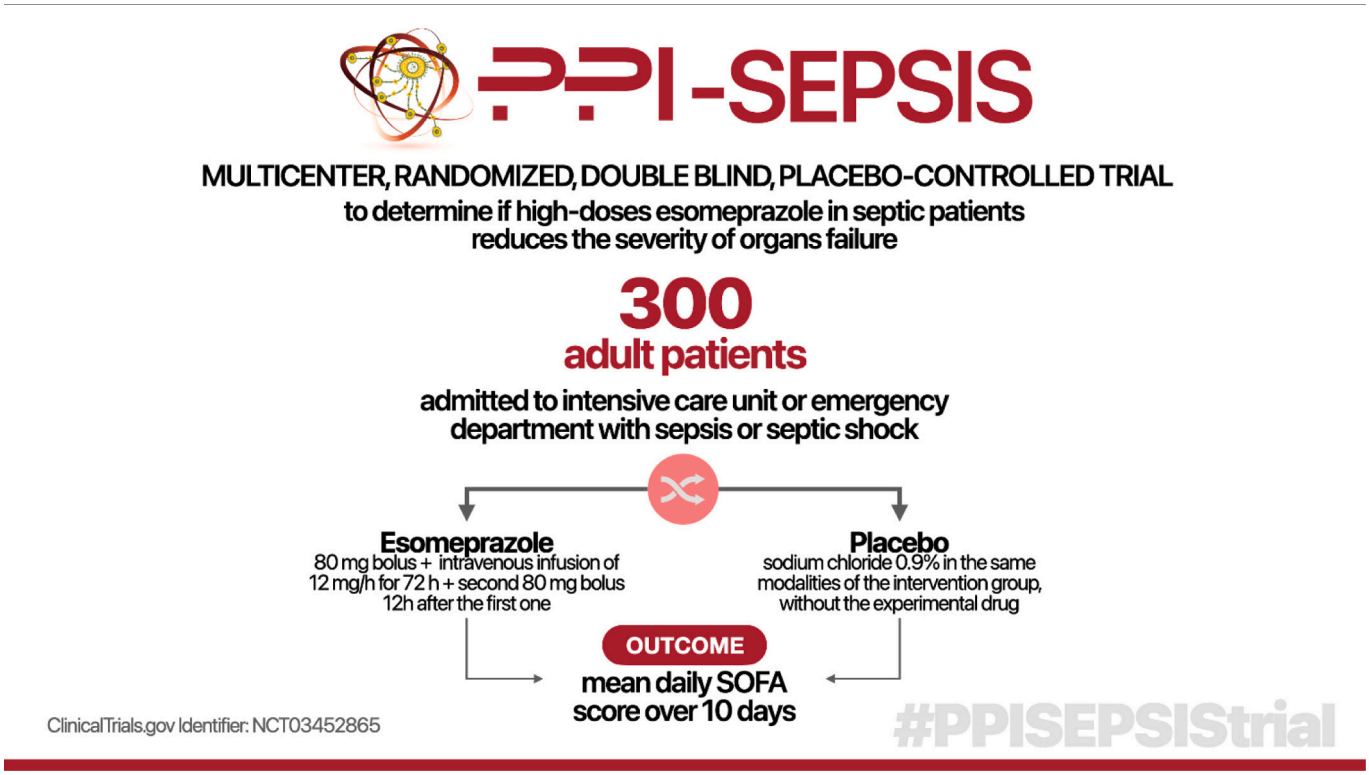

Fig. 1. PPI-SEPSIS visual abstract.

Table 2
Prohibited concomitant treatments.

Pharmacologic class	Active principle
Antiretroviral agents	Atazanavir
	Atazanavir / cobicistat
	Dolutegravir / rilpivirine
	Emtricitabine / nelfinavir / tenofovir
	Nelfinavir
	Rilpivirine
	Sofosbuvir / velpatasvir
	Sofosbuvir / velpatasvir / voxilaprevir
Tyrosine kinase inhibitors	Acalabrutinib
	Dasatinib
	Erlotinib
	Neratinib
	Pazopanib
Others	Citalopram
	Clopidogrel
	Methotrexate
	Tacrolimus

methodology [17,18].

The high dose used in our study is double the one used in previous randomized controlled trials performed in different settings [19,20]. Additionally, our choice was guided by extensive preclinical and pharmacological studies [21], taking into account pharmacodynamic and pharmacokinetic considerations, as well as the potential anti-inflammatory effects associated with this specific dosage [22,23]. Esomeprazole, administered as a continuous high-dose intravenous infusion, is a commonly used treatment in the field of gastroenterology. It is routinely prescribed for conditions such as peptic ulcer disease [24], as well as after endoscopic treatment [19]. This widespread clinical use and extensive experience with esomeprazole provided a solid foundation for its safety profile.

2.5. The SOFA score

The SOFA score was developed by the European Society of Intensive Care Medicine (ESICM) Working Group on Sepsis-related Problems in the attempt to find an immediate and objective method to universally describe individual organ dysfunction in a continuous form [25]. The score was meant to be used over time to measure the evolution of individual and aggregated organ dysfunction both in clinical trials on sepsis and by the clinician at patients' bedside [26]. The European Medicines Agency (EMA) published the "Guideline on clinical investigation of medicinal products for the treatment of sepsis" (CHMP/EWP/4713/03) in 2006, recommending SOFA for the assessment of disease severity in patients with sepsis [27]. When using SOFA score as a study outcome, the mean daily SOFA is calculated for each subject over a predefined study period [28]. The mean daily SOFA remains useful regardless of the duration of survival in case of a patient's death prior to the end of the study period, granting the advantage that no patient will be excluded from the endpoint analysis [29]. The mean daily SOFA score is also a surrogate for mortality risk assessment [30]. In their validation study published on JAMA in 2001, Ferreira et al. [31] analyzed data from 352 consecutive patients admitted to a general ICU in Belgium. They found that a 1-point increase in SOFA score was associated with a progressive mortality increase (SOFA 2.1–3.0 = 20%, 3.1–4.0 = 36.1%

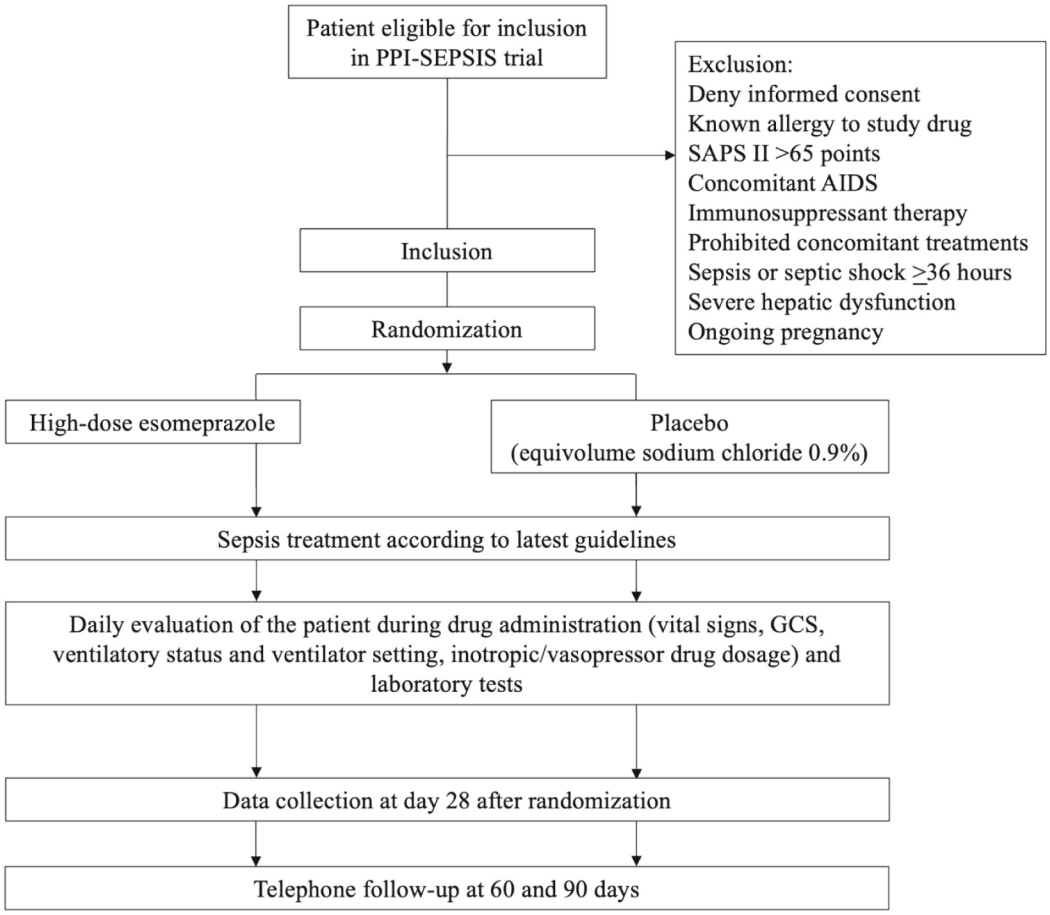

Fig. 2. PPI-SESIS flow chart.
Abbreviations: *SAPS*, Simplified Acute Physiology Score; *AIDS*, acquired immunodeficiency syndrome; *GCS,* Glasgow Coma Scale.

and 4.1–5.0 = 73.1% mortality; odds ratio 3.06, 95% confidence interval [2.36–3.97]) and had a very good discriminative power (area under the receiver operating characteristic curve = 0.88). The mean daily SOFA score holds significant prognostic value and offers valuable insights into the overall organ dysfunction and clinical trajectory of critically ill patients. It exhibits a stronger association with adverse outcomes (including mortality and length of stay) compared to other methods like delta SOFA [31]. Calculating the mean daily SOFA score over a specific period allows to avoid the potential bias introduced by mortality and obtain a comprehensive assessment of organ dysfunction during that time. The mean daily SOFA score overcomes the bias introduced by truncation due to death, ensuring a more accurate evaluation of organ dysfunction throughout the specified period [29]. Missing data for patients who died or were discharged before the completion of the study period are not imputed or replaced. The mean SOFA score, being an average measure of organ dysfunction, is calculated based on the available data within the specified timeframe, effectively capturing the inclusion of such patients in the analysis. Additionally, the mean SOFA score is more sensitive than measures like the maximum SOFA score or fixed-day SOFA in detecting changes in a patient's condition over time. By capturing the average severity of organ dysfunction over a specific timeframe, it allows for the evaluation of trends and fluctuations in the patient's clinical status [29,32]. According to a previous work [30], SOFA score represents not only a reliable measure of organ dysfunction, but it is also an independent predictor of mortality at ICU admission.

2.6. Sample size

The primary endpoint of our study is organ dysfunction measured by the mean daily SOFA score over 10 days [33]. If patients will die or will be discharged within the first post-randomization 10 days, no data imputation will be performed after the event of death or discharge. The mean daily SOFA score calculation will be interrupted before 10 days as previously described [33]. A difference of 0.5 points in mean SOFA score is considered significant [33].

Based on these data, our planned sample size is 286 patients. This will provide >80% power to detect a 0.5-point difference in mean daily SOFA score assuming a standard deviation of 1.5. We will recruit an additional 4% (14 patients) to account for potential loss to follow-up and withdrawal of consent, reaching a total planned sample size of 300 patients.

Secondary outcomes are: antibiotic-free days at day 28; single organ failure severity as per categories of SOFA score; ICU-free days at day 28 (deaths within the initial 28 days will be assigned zero ICU-free days at day 28); death from any cause at day 28, 60 and 90 after randomization.

2.7. Data collection and patient follow up

Demographic data and biometric measurements (measured or estimated), medical history, as well as vital signs, laboratory values, ventilatory status and ventilator settings, and vasopressor drug dosage of patients included in the study will be collected before the first administration of the study drug on day 0, at randomization. Patients will be evaluated daily until 28 days post-recruitment or at hospital discharge (Table 3).

Patients will be interviewed on day 28, 60, and 90 to assess survival status. If they are still in the hospital, clinicians will visit them according to the schedule, otherwise a telephone follow-up will be performed.

2.8. Statistical plan

Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Post-randomization dichotomous data will be compared through unadjusted univariate analyses, based on two tailed Chi-square (when the number of the variable is more than five) or Fisher exact test (when the number of the variable was equal to or less than five). We will calculate relative risks and 95% confidence intervals (CIs) by means of the two-by-two table method with the use of log-linear regression with a normal approximation for the standard errors. For continuous variables with non-parametric distribution, we will use the Mann–Whitney *U* test and present data with medians and interquartile ranges (IQRs). For variables with normal distribution, we will use Students' *t*-test and presented data with means and standard deviations. We will report the differences between the two groups with mean differences with 95% CIs. We will apply two-sided significance tests throughout the manuscript. Logistic regression

Table 3
Study procedures.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 28	Day 60	Day 90
Demographics	✓													
Anthropometry	✓													
Medical history	✓													
COVID-19 status	✓													
Type of hospital admission	✓													
Type of ICU admission	✓													
Antibiotics administration in the previous 3 months	✓													
Diagnosis at ICU admission	✓													
Laboratory data at baseline*	✓													
Laboratory data collected on a daily basis**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Source of infection	✓													
SAPS II score	✓													
SOFA score	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Murray Score for ARDS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
ICU-free days	✓											✓		
Antibiotics-free days	✓											✓		
Mortality	✓											✓	✓	✓

Abbreviations: *ICU*, intensive care unit; *SAPS II*, Simplified Acute Physiology Score; *SOFA*, Sequential Organ Failure Assessment; *ARDS*, acute respiratory distress syndrome.

* Sodium; potassium; calcium; chloride; total protein, prothrombin time, activated partial thromboplastin time; asparatate aminotransferase; alanine transaminase; lactate; pregnancy test.

** Arterial blood gas sample; creatinine; total bilirubin; C-Reactive Protein; procalcitonin; complete blood count.

models, adjusted for baseline values, will be used to estimate the treatment effect (and its 95% confidence intervals) on survival will also be compared with time to event analyses with the log-rank test and we will display such comparison with Kaplan-Meier survival curves. A time to event analysis with a Cox regression will be performed to adjust for key baseline characteristics. Primary data analysis will be based on intention to treat analysis. We will also perform "per-protocol" analyses, analyses excluding early deaths (patients dying within 48 h from randomization).

Data will be stored electronically via a web-based case report form and analyzed by use of STATA (Stata Statistical Software: version 16, College Station, TX, USA).

Analyses will also be conducted in predefined subgroups: ED versus ICU admission; sepsis versus septic shock at randomization; and observed SOFA score quartiles at randomization. Additional subgroup analyses will be conducted according to primary infection of surgical origin; gender; presence of active cancer. A post-hoc secondary analysis will be conducted on COVID-19 patients.

An independent safety committee conducted one ad-interim analysis which was carried out on the alpha spending models, according to Lan and De Mets, and will employ O'Brien-Fleming *Z*-test boundaries, which are very conservative early in the trial. [34–37] The efficacy stopping rules require an extremely low *P* value ($P < 0.0014$). The research team is blind to the interim analysis results.

2.9. Handling of missing data

The calculation of the mean daily SOFA score requires a SOFA score for each of the ten days. To handle missing data, we will follow the approach suggested in high-quality reviews and used in randomized controlled trials with mean daily SOFA score as the primary outcome [33,38]. By drawing from this well-established framework, we aim to ensure the integrity and validity of our results despite the potential for missing data. Given that the mean daily SOFA score is a daily value calculated over a period of ten days, the possibility of missing data needs to be considered. If necessary, missing data will be managed as follows: when only one or two consecutive days are missing, or if the missing data occurs in the last days, we will use the last available SOFA value. In case three or more days are missing, the average value of the last available and next available observation will be used. We will also conduct a sensitivity analysis including only collected data to further assess the robustness of our findings.

2.10. Safety profile

We will administer 448 mg of esomeprazole on the first day and 288 mg each day for the next two days, for a total of 1024 mg, irrespectively of patients' weight. This has to be compared with the standard prophylactic (20 mg a day, for a total of 60 mg in 3 days, about 17 times less than the dosage administered in our trial) or therapeutic dose (80 mg loading dose followed by 8 mg/h continuous infusion for three days, for a total dose of 656 mg, which is about 1.5 less than what we are studying) which is routinely administered in clinical practice [39,40].

Even if poisoning from PPI has never been described despite >20 years of everyday utilization, we introduced an exclusion criterion (receiving drugs known to have a strong interference with esomeprazole) to protect patients at theoretical risk of toxicity. Patients will be strictly monitored for efficacy and safety of the treatment. According to the FDA, in toxicity studies involving intravenous continuous administration, of esomeprazole the highest tolerable doses were reported as 48 mg/kg/day in male rats, 26 mg/kg/day in female rats, and 35 mg/kg/day in dogs. In terms of safety profile, our administered dose is approximately five times lower than the highest tolerable doses reported by the FDA in toxicity studies [41].

Reports of overdosage with esomeprazole in humans [11], with a single dose up to 2400 mg (120 times the usual recommended prophylactic dose) only produced minor clinical manifestations, including confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience for standard dose. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. [41] Single doses of 80 mg of esomeprazole, which equals our boluses administration, were uneventful [42].

In animals, a single oral dose of esomeprazole at 510 mg/kg (about 100 times the dose we will be administering in our trial), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions [41].

Proton pump inhibitors are also safe in polytherapy, and present few pharmacological interactions. So far, the major exception is represented by clopidogrel, which is converted into active metabolites by the same cytochrome involved in PPI metabolism. The competition between the two molecules might interfere with clopidogrel's efficacy, decreasing the inhibition of platelet aggregation and increasing cardiovascular events [43].

All adverse events will be assessed for likely relationship to the study drug. All serious adverse event (SAE) or a suspected unexpected serious adverse reaction (SUSAR) will be reported to the trial coordination centre within 24 h and to the relevant authorities in accordance with current regulations.

2.11. Ethical considerations

This study was approved by the Central Medical Ethics Committee at IRCCS San Raffaele Scientific Institute, Milan, Italy on March 7, 2019, in compliance to the principles of the Declaration of Helsinki and current International Conference on Harmonisation (ICH)-GCP guidelines.

A written informed consent is obtained from the patient, if competent to make a voluntary decision about whether to accept the protocol, prior to the initiation of study procedures by trained study staff members. This will include discussion about all the aspects of the study, including drug intervention, assessments, follow-up, and acquisition and storage of the data. If the patient is unconscious, a substitute decision maker (e.g., their next of kin or legal representative) will be informed and will decide. If a substitute decision maker is temporarily or permanently unavailable, the decision to enroll the patient is up to a consensus of three physicians, as per the request of Ethics Committee, in the patient's best interest. Enrollment of individuals without the ability to provide informed consent and without a surrogate is permitted to ensure that this vulnerable population is not excluded from potentially life-saving treatments. Their participation allows for a comprehensive evaluation of the intervention effectiveness and safety in real-world situations. Stringent ethical protocols are followed to protect their rights and welfare. The consent to continue the study will be asked when the clinical conditions permit it, or when a substitute decision maker will be available.

3. Discussion

Sepsis is a worldwide emergency with a high mortality rate and still represents a major healthcare problem [4]. Guidelines provide detailed definitions and a bundle of interventions which aim at reducing morbidity and mortality of sepsis and septic shock [3]. Still, a limited number of drugs proved effective in the management of these patients. They often present with severe and rapidly evolving major organ dysfunction, which can be assessed by validated prediction models such as the SOFA score [31]. An increased number of system dysfunctions – hence, an increased SOFA score – has been shown to be closely correlated with increased mortality [30,31]. Among the secondary outcomes, the assessment of antibiotic-free days is of particular significance as esomeprazole, by reducing inflammation and potentially hastening

recovery, may contribute to a shorter duration of antibiotic therapy and subsequently lower the risk of secondary infections.

Clinical manifestations of sepsis derive from a dysregulated host immune response to an infection [2], therefore drugs able to reduce inflammation have been investigated in these patients [4]. Recent literature shows that esomeprazole could reduce the secretion of inflammatory mediators such as TNF-α and IL-1β in vitro and in vivo. As a result, the administration of esomeprazole was effective in the treatment of sepsis in mice. All these effects seemed to be dose-dependent and became more evident at a dose of esomeprazole of 10 mg/kg [11]. In addition to the immediate inhibition of the early cytokine storm driven by esomeprazole administration, Balza et al. demonstrated in vivo the sustained anti-inflammatory effect of the drug. Mice that survived the endotoxic shock developed a long-lasting resistance when rechallenged with sepsis-inducing agents up to two months after the first recovery. These mice were also more resistant when challenged with a different agent, and did not show significant signs of illness after the second insult [11]. No adverse events were reported, confirming the safety of esomeprazole also for high dose, especially for short-term use [6,7,11].

The strength of this study is to repurpose a safe and effective medication (i.e., esomeprazole) as an adjuvant in the treatment of septic patients, given its immunomodulatory effects. Esomeprazole has been used as a prophylactic agent for peptic ulcer disease and reflux esophagitis for decades, while recent evidence suggests the induction of a nonspecific hyporesponsiveness to sepsis-inducing agents. Its administration in the early phases of sepsis could prevent the early cytokine storm [11]. For this reason, we decided to include patients with a state of sepsis or septic shock since $\leq$36 h, further strengthening our methodological strategy. In addition, the ability of esomeprazole to blunt acidic environments as suggested by preclinical evidence in metastatic melanoma [9,10] could imply further generalizability of this study results.

We acknowledge that we used a very high dose of esomeprazole. This represents both a limitation and a strength. We have no previous study to support the use of these doses in septic patients, but we also have the possibility to identify a new strategy in the management of sepsis and we're using a drug which has no documented dose-related adverse effects. Even if mean daily SOFA score is a validated outcome which has already been used as primary endpoint in high quality trials [33,38] we acknowledge that it is not as important as survival. If we'll identify an effect on mean daily SOFA score in these patients with early sepsis, it is reasonable to think that esomeprazole will become part of the standard of care in this setting due to its reduced cost and safety. Nonetheless, the anti-inflammatory effects of this drug in other settings (e.g., metastatic melanoma) will have to be properly studied. While efforts are made to minimize missing data, it is inevitable that some data points may be incomplete or unavailable. Furthermore, the sample size might be underpowered to detect a difference in secondary outcomes in case of loss to follow up. However, we plan to follow a rigorous method for follow up to reduce the chances of biases in the results: in case of loss to telephone follow up, provided attempts with secondary telephone numbers, we will check hospital electronic records (e.g., laboratory), patients' general practitioner, and local authorities. In case any of these strategies work, we will send a letter to the patient's home address. In acknowledgment of the inherent challenge posed by the participation of unblinded ICU nurses, it is important to note that despite our diligent efforts to maintain blinding across other key aspects of the study, the presence of unblinded nurses introduces a limitation to the strict interpretation of totally blinding.

This randomized clinical trial with high dose esomeprazole will hopefully provide clinical evidence about a novel effective drug against sepsis and septic shock. To the best of our knowledge, this is the first randomized controlled trial evaluating the effectiveness of esomeprazole in septic human patients. As shown in other studies, the SOFA score represents not only the severity of organ dysfunction, but it is per se a reliable marker of mortality [30]. In addition, PPI could become a useful anti-sepsis drug due to low-cost and the availability in most countries [10].

Trial status

The first patient was enrolled on 28th January 2020. On 30th January 2023, 213 participants were randomized in 11 centers. An a priori limit to the number of participating centers was not set. The interim analysis did not reveal any significant concerns or safety issues that would warrant a change in the trial course.

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Authors' contributions

GM, AK, SC, NB, YK, FG, GBZ, UB, FD, MBR, RL, GF, FEA, TB, FC, FL, GL, RB and AZ, contributed study conception or design. GM, AK, SC, AB, YK, FG, IR, EG, MBR, GB, FF, GB, SS, EM, RC, NB, SR, FD, GM, CG, MCP, SB, GG, FS, SS, RL, VFT, RL, MM, MM, CN, DV, GF, FEA, TB, FC, FL, GL and AZ contributed acquisition, analysis, or interpretation of data. All authors drafted and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107319.

References

[1] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA. 315 (8) (2016 Feb 23) 801–810, https://doi.org/10.1001/jama.2016.0287.

[2] D.C. Angus, T. van der Poll, Severe sepsis and septic shock, N. Engl. J. Med. 369 (9) (2013 Aug 29) 840–851, https://doi.org/10.1056/NEJMra1208623.

[3] M.M. Levy, L.E. Evans, A. Rhodes, The surviving Sepsis campaign bundle: 2018 update, Intensive Care Med. 44 (6) (2018 Jun) 925–928, https://doi.org/10.1007/s00134-018-5085-0.

[4] C. Fleischmann-Struzek, L. Mellhammar, N. Rose, A. Cassini, K.E. Rudd, P. Schlattmann, et al., Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis, Intensive Care Med. 46 (8) (2020 Aug) 1552–1562, https://doi.org/10.1007/s00134-020-06151-x.

[5] D.T. Noritomi, F.G. Soriano, J.A. Kellum, S.B. Cappi, P.J. Biselli, A.B. Libório, et al., Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study, Crit. Care Med. 37 (10) (2009 Oct) 2733–2739, https://doi.org/10.1097/ccm.0b013e3181a59165.

[6] I. Neumann, L.M. Letelier, G. Rada, J.C. Claro, J. Martin, C.W. Howden, et al., Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding, Cochrane Database Syst. Rev. (6) (2013 Jun 12), https://doi.org/10.1002/14651858.CD007999.pub2. CD007999.

[7] M.B. Forrester, Pattern of proton pump inhibitor calls to Texas poison centers, 1998-2004, J. Toxicol. Environ. Health A 70 (8) (2007 Apr 15) 705–714, https://doi.org/10.1080/15287390601188045.

[8] J.F. Barletta, D.A. Sclar, Use of proton pump inhibitors for the provision of stress ulcer prophylaxis: clinical and economic consequences, Pharmacoeconomics. 32 (1) (2014 Jan) 5–13, https://doi.org/10.1007/s40273-013-0119-5.

[9] S. Peppicelli, F. Bianchini, L. Calorini, Extracellular acidity, a "reappreciated" trait of tumor environment driving malignancy: perspectives in diagnosis and therapy, Cancer Metastasis Rev. 33 (2–3) (2014 Sep) 823–832, https://doi.org/10.1007/s10555-014-9506-4.

[10] A. De Milito, R. Canese, M.L. Marino, M. Borghi, M. Iero, A. Villa, et al., pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity, Int. J. Cancer 127 (1) (2010 Jul 1) 207–219, https://doi.org/10.1002/ijc.25009.

[11] E. Balza, P. Piccioli, S. Carta, R. Lavieri, M. Gattorno, C. Semino, et al., Proton pump inhibitors protect mice from acute systemic inflammation and induce long-term cross-tolerance, Cell Death Dis. 7 (7) (2016 Jul 21), e2304, https://doi.org/10.1038/cddis.2016.218.

[12] M. Shankar-Hari, G.S. Phillips, M.L. Levy, C.W. Seymour, V.X. Liu, C. S. Deutschman, et al., Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315 (8) (2016) 775–787, https://doi.org/10.1001/jama.2016.0289.

[13] M.M. Levy, L.E. Evans, A. Rhodes, The surviving sepsis campaign bundle: 2018 update, Crit. Care Med. 46 (2018) 997–1000.

[14] G. Monti, Marzaroli M. Bradi, A. Konkayev, E. Fominskiy, Y. Kotani, et al., Effect of continuous vs versus intermittent meropenem administration in septic critically Ill patients with sepsis: the MERCY randomized clinical trial, JAMA (2023) (in press).

[15] G. Monti, C. Galbiati, F. Toffoletto, M.G. Calabrò, S. Colombo, B. Ferrara, et al., Continuous infusion versus intermittent administration of meropenem in critically ill patients (MERCY): a multicenter randomized double-blind trial. Rationale and design, Contemp. Clin. Trials 104 (2021 May), 106346, https://doi.org/10.1016/j.cct.2021.106346. Epub 2021 Mar 6. PMID: 33684595.

[16] Ashish Khanna, et al., Angiotensin II for the treatment of vasodilatory shock, N. Engl. J. Med. 377 (5) (2017) 419–430.

[17] M. Wan, M. Orlu-Gul, H. Legay, C. Tuleu, Blinding in pharmacological trials: the devil is in the details, Arch. Dis. Child. 98 (9) (2013 Sep) 656–659, https://doi.org/10.1136/archdischild-2013-304037. Epub 2013 Jul 29. PMID: 23898156; PMCID: PMC3833301.

[18] P.J. Devereaux, B.J. Manns, W.A. Ghali, et al., Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials, JAMA. 285 (15) (2001) 2000–2003, https://doi.org/10.1001/jama.285.15.2000.

[19] E.J. Kuipers, J.J. Sung, A. Barkun, J. Mössner, D. Jensen, R. Stuart, et al., Safety and tolerability of high-dose intravenous esomeprazole for prevention of peptic ulcer rebleeding, Adv. Ther. 28 (2) (2023) 150–159, https://doi.org/10.1007/s12325-010-0095-5.

[20] Joseph J.Y. Sung, et al., Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial, Ann. Intern. Med. 150 (7) (2009) 455–464.

[21] Tommy Andersson, et al., Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole, Clin. Pharmacokinet. 40 (2001) 411–426.

[22] T.R. Koch, A. Petro, M. Darrabie, E.C. Opara, Effect of the H, K-ATPase inhibitor, esomeprazole magnesium, on gut total antioxidant capacity in mice, J. Nutr. Biochem. 15 (9) (2004 Sep) 522–526, https://doi.org/10.1016/j.jnutbio.2004.03.003. PMID: 15350983.

[23] Heba M. Eltahir, Maiiada H. Nazmy, Esomeprazole ameliorates CCl4 induced liver fibrosis in rats via modulating oxidative stress, inflammatory, fibrogenic and apoptotic markers, Biomed. Pharmacother. 97 (2018) 1356–1365.

[24] L.H. Cui, C. Li, X.H. Wang, Z.H. Yan, X. He, S.D. Gong, The therapeutic effect of high-dose esomeprazole on stress ulcer bleeding in trauma patients, Chin. J. Traumatol. 18 (1) (2015) 41–43, https://doi.org/10.1016/j.cjtee.2014.06.001 (PMID: 26169094).

[25] J.L. Vincent, R. Moreno, J. Takala, S. Willatts, A. De Mendonça, H. Bruining, et al., The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine, Intensive Care Med. 22 (7) (1996 Jul) 707–710, https://doi.org/10.1007/BF01709751.

[26] R. Moreno, J.L. Vincent, R. Matos, A. Mendonça, F. Cantraine, L. Thijs, et al., The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working group on Sepsis related problems of the ESICM, Intensive Care Med. 25 (7) (1999 Jul) 686–696, https://doi.org/10.1007/s001340050931.

[27] European Medicines Agency, Guideline on Clinical Investigation of Medicinal Products for the Treatment of Sepsis. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003459.pdf [Accessed 10 March 2023].

[28] S. Lambden, P.F. Laterre, M.M. Levy, B. Francois, The SOFA score-development, utility and challenges of accurate assessment in clinical trials, Crit. Care 23 (1) (2019 Nov 27) 374, https://doi.org/10.1186/s13054-019-2663-7.

[29] L. Minne, A. Abu-Hanna, E. de Jonge, Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review, Crit. Care 12 (6) (2008) R161, https://doi.org/10.1186/cc7160.

[30] F.L. Ferreira, D.P. Bota, A. Bross, C. Mélot, J.L. Vincent, Serial evaluation of the SOFA score to predict outcome in critically ill patients, JAMA. 286 (14) (2001 Oct 10) 1754–1758, https://doi.org/10.1001/jama.286.14.1754.

[31] A. Jain, S. Palta, R. Saroa, A. Palta, S. Sama, S. Gombar, Sequential organ failure assessment scoring and prediction of patient's outcome in intensive care unit of a tertiary care hospital, J. Anaesthesiol. Clin. Pharmacol. 32 (3) (2016 Jul-Sep) 364–368, https://doi.org/10.4103/0970-9185.168165 (PMID: 27625487; PMCID: PMC5009845).

[32] X. Qiu, Y.P. Lei, R.X. Zhou, SIRS, SOFA, qSOFA, and NEWS in the diagnosis of sepsis and prediction of adverse outcomes: a systematic review and meta-analysis, Expert Rev Anti Infect Ther 21 (8) (2023) 891–900, https://doi.org/10.1080/14787210.2023.2237192.

[33] R.M. Orme, G.D. Perkins, D.F. McAuley, K.D. Liu, A.J. Mason, A. Morelli, et al., An efficacy and mechanism evaluation study of Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS): protocol for a randomized controlled trial, Trials. 15 (2014 Jun 2) 199, https://doi.org/10.1186/1745-6215-15-199.

[34] Jerrold H. Zar, Biostatistical Analysis, Second edition, Prentice-Hall, Englewood Cliffs, New Jersey, 1984.

[35] C. Jennison, B.W. Turnbull, Group Sequential Methods with Applications to Clinical Trials, Chapman & Hall, Boca Raton, FL, 2000.

[36] Luc Devroye, Non-Uniform Random Variate Generation, Springer-Verlag, New York, 1986.

[37] M. Matsumoto, T. Nishimura, Mersenne twister: A 623-dimensionally equidistributed uniform pseudorandom number generator, in: ACM Trans. On Modeling and Computer Simulations, 1998.

[38] S. Hagel, F. Bach, T. Brenner, et al., Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial, Intensive Care Med. 48 (2022) 311–321, https://doi.org/10.1007/s00134-021-06609-6.

[39] M.M. Wolfe, G. Sachs, Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome, Gastroenterology. 118 (2 Suppl 1) (2000 Feb) S9–31, https://doi.org/10.1016/s0016-5085(00)70004-7.

[40] A.N. Barkun, M. Almadi, E.J. Kuipers, L. Laine, J. Sung, F. Tse, et al., Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group, Ann. Intern. Med. 171 (11) (2019 Dec 3) 805–822, https://doi.org/10.7326/M19-1795.

[41] Y. Chopra, J. Choudary, R. Justice, M. Furness, Pharmacology/Toxicology REVIEW AND EValuation NDA 21-689, 2004 Jun 24.

[42] R.E. Ferner, T.R. Allison, Omeprazole overdose, Hum. Exp. Toxicol. 12 (6) (1993 Nov) 541–542, https://doi.org/10.1177/096032719301200614.

[43] N. Parikh, C.W. Howden, The safety of drugs used in acid-related disorders and functional gastrointestinal disorders, Gastroenterol. Clin. N. Am. 39 (3) (2010 Sep) 529–542, https://doi.org/10.1016/j.gtc.2010.08.009.