

# Proton pump inhibitors (PPI) as a new strategy for therapy in sepsis: clinical trial to reduce severity of organ failure and in vitro experiments to search specific hallmarks in monocytes.

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**Background** Increasing evidence indicates that mitochondrial damage associated to oxidative stress and acidosis play a relevant role in acute sepsis. Proton pump inhibitors (PPI) have been recently reported to inhibit TNF- $\alpha$  and IL-1 $\beta$  secretion by blocking proton extrusion in activated monocytes. Moreover, a single administration of PPI protects mice from endotoxic shock with no adverse effects.

**Objectives** We designed a randomized, double blind, controlled clinical trial with esomeprazole in septic patients. Primary outcome is severity of multiple organ failure measured by mean SOFA scores. We will also investigate mortality and other clinically relevant outcomes. In parallel, we will evaluate changes in redox-state and functional activation of ex-vivo monocytes from septic patients.

**Methods** Inclusion criteria: adult patients; admitted to ICU or ED; sepsis or septic shock since less than 36 hours. Exclusion criteria: known allergy to esomeprazole; little chance of survival (SAPS II score > 65); concomitant AIDS; received immunosuppressants or long-term corticosteroids; severe hepatic dysfunction; receiving a life-saving drugs known to have a strong interference with esomeprazole. Patients will be randomized to receive either a bolus of 160 mg of esomeprazole followed by IV infusion of 12 mg/hour for 72 hours, or placebo. Monocytes isolated from blood samples will be assessed for basal and post-inflammatory activation ROS, antioxidants, redox-response, ATP and cytokine secretion. Epigenetic modifications and changes in expression of miRNA targeting genes involved in sepsis will be investigated. Monocytes will be differentiated in macrophages and the effect of PPI treatment in the pro- or anti-inflammatory polarization will be evaluated.

**Expected results** We expect to assess a reduction in severity of organ failure in experimental group, without safety issues. Moreover, we plan to identify a correlation between redox-stress, activation and polarization in monocytes from sepsis patient treated with esomeprazole. This study received a grant from Ministry-of-Health, Giovani-Ricercatori 2016, n. GR-2016-02363630.