

**Title:** *Application of Osteopathic Manipulative Medicine to Ameliorate Sepsis Induced Ileus*

**Author:** Kevin T. Keating, Brandon G. Beck, Sarah A. Robinson, Anthony J.M. Bauer

**Abstract:**

Background. Sepsis is a systemic inflammatory response to infection frequently caused by endotoxin releasing gram negative bacteria. The mortality rate of sepsis is nearly 30% in the U.S., and is much higher in the developing world. Currently only antibiotics and supportive therapy are used for treatment. Sepsis is listed as the most expensive treatment in the U.S. costing over \$20 Billion in 2011.

Objective. Our objective was to explore the application of a novel therapeutic osteopathic intervention to ameliorate the sequelae of sepsis.

Methods. C57Bl/6 were injected with lipopolysaccharide (LPS) and sacrificed 24 hours later. Osteopathic repetitive abdominal compressions (ORAC) were performed 100 times in five increments 24, 12, 6, 3, and 1 hour prior to injection with 1 or 2.5 mg/kg of LPS and sacrificed 24 hours later. Spatial distribution of neutrophil infiltrates were quantified using a muscularis externa (ME) whole-mount preparation stained with myeloperoxidase. Gastrointestinal transit distribution histograms and geometric centers were generated by orally feeding a liquid non-digestible/non-absorbable FITC-dextran (15 $\mu$ l of 5mg/ml, 70,000 MW, excitation 495nm/emission 519 nm) and determining its distribution in 15 segments of the gut (lower esophageal sphincter to rectum) after a period of 80 minutes of in vivo transit. Organ bath jejunal circular muscle strip contractility responses to bethanechol were quantified for the control, LPS and ORAC.

Results. Analysis of neutrophilic infiltrates demonstrated ORAC sepsis-induced muscularis externa whole-mounts had less neutrophils compared to untreated LPS sepsis-induced mice. The average gastrointestinal transit geometric center revealed a significant improvement of ORAC compared to untreated LPS sepsis-induced mice (LPS=3.5 $\pm$ 0.63, vs ORAC+LPS=8.2 $\pm$ 0.39; N=5 each). Additionally, the average gastrointestinal transit geometric center of ORAC alone was comparable to control mice (ORAC=9.9 $\pm$ 0.06 vs. control=10.1 $\pm$ 0.13, N=5). Spontaneous jejunal circular smooth muscle contractions from control mice was robust, but significantly

suppressed after endotoxin injection. In contrast, ORAC pretreatment significantly ameliorated the LPS-induced suppression in spontaneous jejunal circular muscle contractions.

Conclusion. The data demonstrate the application of osteopathic manipulative medicine as a pre-treatment to ameliorate sepsis-induced ileus. We hypothesize that ORAC activates the enteric nervous system which prepares the gastrointestinal system for future stresses associated with a bacterial infection inducing sepsis. On-going experiments will characterize the protective mechanism of the osteopathic manipulative procedure, which could provide a novel treatment for patients suffering from sepsis.