Neutrophils play a central role in eliminating bacterial pathogens in sepsis, but may also contribute to end-organ damage. Interleukin-8 (IL-8), a key modulator of neutrophil function, signals through neutrophil specific surface receptors CXCR-1 and CXCR-2. In this study, a mechanistic mathematical model was used to evaluate and deploy an extracorporeal sepsis treatment which modulates CXCR-1/2 levels.

A simplified mechanistic mathematical model of IL-8 mediated activation of CXCR-1/2 receptors was developed using ordinary differential equations. The mathematical model was calibrated using experimental data from baboons administered a two-hour infusion of E. coli and followed for a maximum of 28 days. An extracorporeal intervention was then implemented by introducing a trapped receptor state which limits IL-8 signaling through CXCR-1/2.

In severe sepsis, an extracorporeal treatment which modulates CXCR-1/2 levels has therapeutic potential, but also potential for harm. Further development of the mathematical model will help guide optimal device development and determine which patient populations should be targeted by treatment.

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The model produced probabilistic predictions of the extracorporeal treatment’s impact on mortality. Treatment time of onset and duration proved to have a substantial impact on mortality. An intervention introduced within 1 hour of infection for a 72 hour duration results in the survivor population increasing from 31% to 61%. Treatment efficacy quickly diminishes if not introduced within 15 hours of infection. Treatment duration of 48 hours reduces maximal effect to 39% survival. Significant harm is possible with treatment durations ranging from 5-24 hours, which may reduce survival to 21%.

Of 16 baboons, 11 (69%) die, 6 (38%) within one day of bacterial infusion. The model was well calibrated to the data from survivors and non-survivors. Sensitivity analysis identified six model parameters, out of 21, as key determinants of mortality. Key differences between survivor and non-survivor parameters are displayed below.

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