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A reduction of the neutrophil migration into the site of infection during cecal ligation and puncture-induced sepsis increases host mortality. Inhibition of heme oxygenase (HO) prevents this neutrophil paralysis and improves host survival in the cecal ligation and puncture model. Taking into account that almost 50% of all sepsis cases are a consequence of pneumonia, we designed the present study to determine the role of HO in an experimental model of pneumonia-induced sepsis. The objective of this study was to evaluate whether the inhibition of HO improves the outcome and pathophysiologic changes of sepsis induced by an intratracheal instillation of Klebsiella pneumoniae. The pretreatment of mice subjected to pneumonia-induced sepsis with ZnDPBG (zinc deuteroporphyrin 2,4-bis glycol), a nonspecific HO inhibitor, increased the number of neutrophils in the bronchoalveolar spaces, reduced the bacterial load at the site of infection, and prevented the upregulation of CD11b and the downregulation of CXCR2 on blood neutrophils. Moreover, the pretreatment with ZnDPBG decreased alveolar collapse, attenuating the deleterious changes in pulmonary mechanics and gas exchanges and, as a consequence, improved the survival rate of mice from 0% to ~20%. These results show that heme oxygenase is involved in the pathophysiology of pneumonia-induced sepsis and suggest that HO inhibitors could be helpful for the management of this disease.