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In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes

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Shareable abstract (@ERSpublications)
In an observational study of 3032 mechanically ventilated patients, early anti-anaerobic antibiotics increased mortality risk. In secondary studies, anti-anaerobic antibiotics disrupted patients' gut microbiota and worsened outcomes in mouse models. https://bit.ly/3BLbpvz

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Abstract

Background Critically ill patients routinely receive antibiotics with activity against anaerobic gut bacteria. However, in other disease states and animal models, gut anaerobes are protective against pneumonia, organ failure and mortality. We therefore designed a translational series of analyses and experiments to determine the effects of anti-anaerobic antibiotics on the risk of adverse clinical outcomes among critically ill patients.

Methods We conducted a retrospective single-centre cohort study of 3032 critically ill patients, comparing patients who did and did not receive early anti-anaerobic antibiotics. We compared intensive care unit outcomes (ventilator-associated pneumonia (VAP)-free survival, infection-free survival and overall survival) in all patients and changes in gut microbiota in a subcohort of 116 patients. In murine models, we studied the effects of anaerobe depletion in infectious (*Klebsiella pneumoniae* and *Staphylococcus aureus* pneumonia) and noninfectious (hyperoxia) injury models.

Results Early administration of anti-anaerobic antibiotics was associated with decreased VAP-free survival (hazard ratio (HR) 1.24, 95% CI 1.06–1.45), infection-free survival (HR 1.22, 95% CI 1.09–1.38) and overall survival (HR 1.14, 95% CI 1.02–1.28). Patients who received anti-anaerobic antibiotics had decreased initial gut bacterial density (p=0.00038), increased microbiome expansion during hospitalisation (p=0.011) and domination by Enterobacteriaceae spp. (p=0.045). Enterobacteriaceae were also enriched among respiratory pathogens in anti-anaerobic-treated patients ($p<2.2\times10^{-16}$). In murine models, treatment with anti-anaerobic antibiotics increased susceptibility to Enterobacteriaceae pneumonia (p<0.05) and increased the lethality of hyperoxia (p=0.0002).

Conclusions In critically ill patients, early treatment with anti-anaerobic antibiotics is associated with increased mortality. Mechanisms may include enrichment of the gut with respiratory pathogens, but

increased mortality is incompletely explained by infections alone. Given consistent clinical and experimental evidence of harm, the widespread use of anti-anaerobic antibiotics should be reconsidered.