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## Human Fluids-Pathogen Interplay and its Impact on Cefidericol Susceptibility of Carbapenem-Resistant *Acinetobacter Baumannii*

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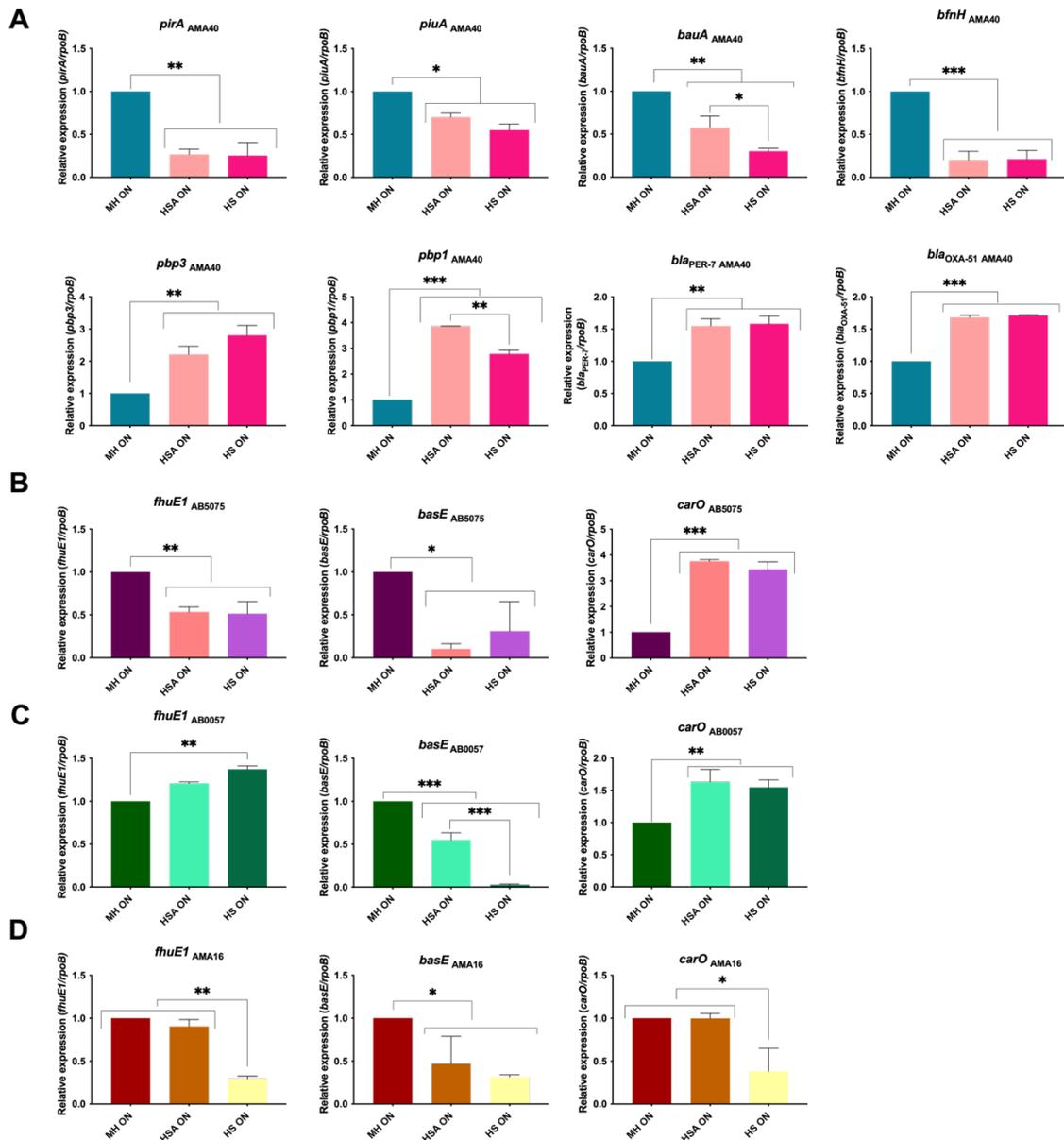
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### Abstract

Due to the increased number of antibiotic resistant bacteria that compromises our ability to treat infections, an urgent need exists to develop novel antibiotics. The recently introduced antibiotic cefiderocol (CFDC) consists of a cephalosporin component that targets cell wall synthesis and a chlorocatechol siderophore moiety that facilitates cell uptake by active iron (Fe) transporters. Using three representative CRAB isolates, we studied the expression levels of *A. baumannii* genes coding for high-affinity Fe transport systems and  $\beta$ -lactam resistance in the presence of human fluids and physiological concentrations (3.5%) of human serum albumin (HSA). Results indicated a reduced expression of iron-uptake systems and the concomitant increase expression of genes mediating  $\beta$ -lactam resistance. To further explore our observation, the CFDC minimum inhibitory concentration (MIC) of 19 CRAB strains in the presence of HSA and human fluids was assessed. Also, the expression of additional genes in the 3 representative CRAB and the CRAB AMA40 strains, which exhibited hetero-resistance in the presence of human serum components, was performed by qRT-PCR using RNA extracted from *A. baumannii* strains cultured in 100% human serum (HS) or cation adjusted Muller-Hinton supplemented with 3.5% HSA. Our results

showed an increase in the MIC values of CFDC in 12 of the tested strains. The presence of HS, or HSA, was correlated with a reduction in the expression levels of genes coding for components of Fe uptake systems and an increase the genes contributing to  $\beta$ -lactam resistance were up-regulated (Figure 1). Overall, our results show that *A. baumannii* may be unique in its response to human bodily fluids by modulating the expression of iron-uptake genes and  $\beta$ -lactam resistance associated genes that can contribute to reduce CFDC susceptibility.

Figure 1. Transcriptomic analysis of iron uptake and  $\beta$ -lactam resistance genes of AMA40 (A), AB5075 (B), AB0057 (C) and AMA16 (D) strains.



**Keyword (Complete):** acinetobacter; antimicrobial resistance, cefiderocol

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