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Comparative *in vitro* efficacy of antibiotics against the intracellular reservoir of *Staphylococcus aureus*

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Abstract

Staphylococcus aureus (SA) is a leading cause of bloodstream infection. The liver represents the sentinel immune organ for clearance of bloodstream pathogens and eradication of intracellular SA from liver-resident macrophages (Kupffer cells, KCs) eliminates the likely pathogenic reservoir that contributes to persistent bacteraemia.

Objectives

We assessed antimicrobial activity at phagolysosome-mimicking pH, intracellular penetration, and SA eradication within KCs *in vitro* for clinically prescribed antistaphylococcal agents alone or in combination: vancomycin, daptomycin, ceftaroline, ceftobiprole, oritavancin, oxacillin, cefazolin; rifampin and fosfomycin.

Methods

pH-adjusted broth microdilution assays, intracellular bioaccumulation assays, and intracellular killing assays against clinical bloodstream isolates were performed using a murine KC line with study agents.

Results

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(2- to 32-fold MIC increase in order of least to greatest potency reduction). All agents evaluated had poor to modest intracellular to extracellular concentration ratios (0.024–7.8), with exceptions of rifampin and oritavancin (intracellular to extracellular ratios of 17.4 and 78.2, respectively). Finally, we showed that the first-line treatment for SA bacteraemia (SAB), vancomycin, performed worse than all other tested antibiotics in eradicating intracellular SA at human C_{max} concentration (0.20 log cfu decrease), while oritavancin performed better than all other agents alone (2.05 versus 1.06–1.36 log cfu decrease).

Conclusions

Our findings raise concerns about the efficacy of commonly prescribed antibiotics against intracellular SA reservoirs and emphasize the need to consider targeting pathogen eradication from the liver to achieve early control of SAB.

Topic: antibiotics, vancomycin, rifampin, staphylococcus aureus, bacteremia, cefazolin, daptomycin, fosfomycin, keratoconjunctivitis sicca, kupffer cells, oxacillin, liver, persistence, minimum inhibitory concentration measurement, oritavancin, bloodstream infections, ceftobiprole, ceftaroline

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