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Novel approaches to battle bacterial resistance

The susceptibility and pharmacodynamic activity of ciprofloxacin & new fluoroquinolones was studied against low-level (MIC 4 ug/ml) and high-level (MIC 16 ug/ml) ciprofloxacin-resistant *Streptococcus pneumoniae*. An *in vitro* pharmacodynamic model simulating free fluoroquinolone (protein unbound) serum concentrations using Cp_{max} & $AUC_{0\text{-}24h}$ achieved after standard oral doses for community acquired respiratory infections was used to compare bacterial killing by 5 fluoroquinolones. Against 6 ciprofloxacin-resistant *S. pneumoniae* isolates (4 different resistance mutant phenotypes; ParC, efflux, ParC with efflux & ParC & GyrA) obtained from an ongoing Canadian respiratory organism surveillance study. The potency (MIC only) of fluoroquinolones was gemifloxacin>moxifloxacin>gatifloxacin>levofloxacin> ciprofloxacin. Ciprofloxacin (free $AUC_{0\text{-}24h}$/MIC 0.9-3.5) produced no reduction of growth at 6, 24 or 48 hours compared to the initial inoculum against all six strains. Levofloxacin (free $AUC_{0\text{-}24h}$/MIC 35) was bactericidal (≥3 log10 killing) at 6, 24 and 48 hours for the ParC as well as the efflux mutants, but only bactericidal at 24 hours for the ParC with efflux strain. Levofloxacin (free AUC 0-24h/MIC 4.4) demonstrated no reduction of growth relative to the initial inoculum against the ParC and GyrA mutants. Gatifloxacin and moxifloxacin (free $AUC_{0\text{-}24h}$/MIC of 48 and 60, respectively) were bactericidal at 6, 24 and 48 hours against the ParC, efflux and ParC with efflux mutants, but demonstrated little to no growth reduction (free $AUC_{0\text{-}24h}$/MIC of 6 and 7.5, respectively) against ParC and GyrA mutants. Gemifloxacin (free AUC24/MIC 67-133) was bactericidal (≥3 log10 killing) at 6, 24 and 48 hours against all low-level ciprofloxacin-resistant *S. pneumoniae* mutants. Against 2 of the ParC and GyrA mutants gemifloxacin (free AUC 0-24h/MIC of 32) was bactericidal at 6, 24 and 48 hours but against one ParC and GyrA mutant (free AUC 0-24h/MIC of 16) gemifloxacin demonstrated reduced activity with initial killing at 24 hours but with subsequent regrowth. These data suggest that ciprofloxacin produces no inhibition in growth against low or high level ciprofloxacin-resistant *S. pneumoniae*, while gatifloxacin, levofloxacin and moxifloxacin (moxi>gati>levo) were bactericidal against low-level resistant strains but produced little to no inhibition vs. high-level resistant strains. Gemifloxacin when simulating free AUC0-24h/MIC ≥32 was bactericidal against low and high level resistant strains. When simulated free AUC0-24h/MIC was ≥16 gemifloxacin allowed regrowth of high-level ciprofloxacin-resistant strains.

Biography

Ayman Noreddin received his PhD in Pharmaceutical Sciences from the University of the Pacific, California and received research training as a visiting scholar at the Department of Medicine, Stanford University. He had Postdoctoral fellowship (Pharmacokinetics and Pharmacodynamics of Antimicrobials), Department of Medical Microbiology, University of Manitoba followed by an American College of Clinical Pharmacy postdoctoral fellowship (Infectious Diseases). His research interest includes Pharmacoklinetic/Pharmacodynamic modeling of anti-infective and anti-cancer therapy, clinical simulation and Monte Carlo analysis and bacterial resistance in biofilm studies. He has outstanding records of scientific and academic accomplishments with multiple research funding, numerous publications in highly prestigious journals and various presentations in both national and international conferences. He served as a scientific reviewer for the NIH as well as other national and international research institutions.

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